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Unseen Influences: The Pervasive Impact of Environmental Volatiles on Eukaryotic Gene Expression and Physiology

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Dedication

I dedicate this work to God, my family, friends, and loved ones that have helped me reach where I am today. A mis padres, Rogelio Nuñez Vallin and Rosa Georgina Nuñez, gracias por su amor, apoyo y guía. A mi primo, Jose Guadalupe Gomez, gracias por su amor, apoyo y guía. To my siblings, Wendy Nuñez Flores and Jovanni Jesus Nuñez, thank you budderinos for being there to support me and inspire me with your own excellence and perseverance. To Gregory Luevano, thank you friend for the coffees and being present. To my loving partner Dr. Gladys Ornelas, thank you for your unwavering love, patience, and support through this process. In loving memory of my High School math teacher, Mrs. Gemma O'Grady Nohilly, whose wisdom, kindness, and encouragement have shaped me in more ways than words can express. Thank you to all my past educators and mentors who have educated and supported me throughout my academic career.

ABSTRACT OF THE DISSERTATION

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by

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Dr. Anandasankar Ray, Chairperson

Eukaryotes are frequently exposed to microbes and their secreted metabolites, including volatile odor compounds (VOCs). However, the effects of long-term exposure to these microbial volatiles, and other environmental volatiles remain largely unexplored. This study uses *Drosophila melanogaster, Arabidopsis thaliana,* and human cell lines as model systems to investigate the impact of VOCs such as diacetyl, a volatile emitted by yeast found around fermenting fruits. The findings reveal that exposure to diacetyl vapors alone can alter gene expression in the antenna of *Drosophila*. Diacetyl and related compounds also inhibit human histone-deacetylases (HDACs), increase histone-H3K9 acetylation in human cells, and induce widespread changes in gene expression in both *Drosophila* and mice. Notably, diacetyl crosses the blood-brain barrier and modulates gene expression in the brain, indicating its potential as a therapeutic agent.

The study further explores the physiological effects of volatile exposure using two disease models responsive to HDAC inhibitors. Diacetyl vapors were found to inhibit the proliferation of human neuroblastoma cells in culture and slow neurodegeneration in a

Drosophila model of Huntington's disease. These findings suggest that certain environmental volatiles can profoundly impact histone acetylation, gene expression, and physiology in animals, potentially without our awareness.

In addition to animals, volatile odor compounds play a significant role in plant communities, influencing development and stress responses. The study demonstrates that specific VOCs can cause notable changes in plant root growth, leaf development, and flowering time by altering gene expression through HDAC inhibition pathways. These epigenetic changes also affect how plants respond to abiotic stressors such as freezing. The research highlights a potentially conserved pathway in eukaryotes, including plants, for responding to environmental volatiles.

Furthermore, we study interaction of odorants with transmembrane odorant receptor proteins. Using *Aedes aegypti* co-receptor mutants for two different chemoreceptor gene families, *Gustatory Receptors (Gr3), Ionotropic Receptors (Ir76b* and *Ir25a).* Specifically, I assessed how the maxillary palp CO_2 receptor neurons rely on these co-receptors to detect different chemicals. Through in vivo electrophysiology, we found that CO_2 detection and inhibition in these neurons rely solely on *Gr3*, while *Ir25a* modulates the response to specific odors, indicating its role in fine-tuning odor detection.

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CHAPTER I: Introduction

Chemosensation

Chemosensation is what allows all living organisms to detect environmental chemicals and allow them to distinguish them for means of survival and reproduction. Animal olfaction, for example, detects airborne molecules and distinguish them through the use of odorant receptors and associated sensory neurons (Bargmann, 2006). In mammals, odorant signals are detected by binding of volatile ligands to odorant receptors that belong to heterotrimeric G-proteins, that signal through canonical second-messenger cascades (Buck & Axel, 1991b). Olfaction has diverged greatly between vertebrates and invertebrates (Ache & Young, 2005). By contrast, insects detect volatile chemicals using three receptor families: Odorant receptors (Ors), Ionotropic receptors (Irs), and Gustatory receptors (Gr), contribute to insects' ability to detect a wide variety of volatile compounds. Ors are unique class of odor-gated ion channels consisting of two subunits: a conserved co-receptor (Orco) subunit and highly divergent odorant receptor (Or) subunit that contains odorant-binding site and confers chemical sensitivity to heteromeric complex (Hallem & Carlson, 2006; Sato et al., 2008; Wicher et al., 2008). Ionotropic receptors are an ancient chemoreceptor family found across the Protostomia branch of the animal kingdom and like Ors, also function as odorant-gated ion channels. Irs, an expansion of ionotropic glutamate receptor(iGluR) family, respond to acids, amines, aldehydes, and humidity. Irs, much like Ors, have what can be described as co-receptors that are required for odor-evoked responses (Pask & Ray, 2016). In addition, Gustatory receptors contribute to volatile detection by being able to detect CO_2 (Kwon et al., 2007). Different classes of olfactory receptor neurons detect differing volatile chemicals with various degrees of specialization.

Odors can be identified and distinguished due to each receptor being sensitive to specific sets of odors and activate combination of ORs, known as combinatorial coding. Or repertoires vary considerately in size between species: ≈1200 OR genes in rodents, ≈400 in humans, and ≈127 receptors in *Drosophila melanogaster* (Mombaerts, 1999; Robertson et al., 2003; Saberi & Seyed-Allaei, 2016). Mammalian olfaction is mediated by Odorant receptors (Ors), a large family of GPCRs from the rhodopsin-relates super-family (Buck & Axel, 1991b). Even between humans and mice the number of functional Or genes greatly differ and orthologous genes rarely can rarely be found due to quick diversification between species (Niimura & Nei, 2005).

Chemosensation in Humans

Human olfaction follows a stereotypical anatomy consisting of three primary stages: the olfactory epithelium, the olfactory bulb, and olfactory cortex. The olfactory epithelium in the nose/olfactory cleft is the peripheral organ for the sense of smell in humans. A large range of small organic compounds, generally with a hydrophobic region, can be perceived by humans, often at very small concentrations (Breer, 2003; Katada et al., 2005). Odorant binding specificity occurs due to specific OR proteins expressed by the OSN, from a repertoire of approximately 400 possible genes (Billesbolle et al., 2023; Bjarnadóttir et al., 2006). Selectivity of these OR proteins maybe narrow or broadly tuned, however most ORs can be activated by a range of structurally similar compounds.

In humans, the bipolar-shaped neurons extend a dendrite to epithelial surface airspace while extending an axon through the base of the epithelium to join other axons,

into respective glomerulus, forming the first cranial nerve (CN I). Multiple immotile cilia extend from each dendritic knob into the mucus layer extending the membrane surface area for chemosensing/recognition via the ORs at the neuronal cilia membranes (Williams et al., 2014). For each odor, a specific pattern of neuronal signals are generated comprising of the strength of the signal, time period, and quality of the odorant stimuli (Breer, 2003). Based from quantitative models, the number of compounds that are considered odorous may be in the billions (Mayhew et al., 2022). From the primary olfactory cortex, neuronal signals are sent to the higher cortical areas and the limbi system. It is these higher cortical areas that allows the conscious perception of odors, and the limbic system governs analogous emotions, memory, behavioral, and sensational effects. In addition to the flow of information leaving the olfactory bulb and targeting diverse regions involved with behaviors, there is extensive feedback projections targeting every level of the primary olfactory pathway. This is notably understood in how the olfactory bulb's response to food odors is modulated by hunger and satiety with hunger promoting higher neural activity (Pager et al., 1972; Sachse & Beshel, 2016).

Olfactory Processing in the brain

In mammals there are two different olfactory systems: the main olfactory epithelium (MOE) projecting to the main olfactory bulb (MOB) and Vomeronasal organ (VNO) which projects to the accessory olfactory bulb (AOB). The VNO contributes to detection of pheromones while the MOB detects volatile odors, including pheromones. The VNO in mice for instance detect opposite-sex urinary volatiles, while the MOB detects

volatiles from both sexes (Baum, 2012; Martel & Baum, 2007). However, while these VNOs of humans and old-world monkeys are non-functional, they still play important roles in social and reproductive behavior(Brennan & Zufall, 2006; Liman & Innan, 2003; Zhang & Webb, 2003). In humans, the MOB maybe responsible for pheromone detection (Preti et al., 2003; Wysocki & Preti, 2004) .

In the MOE, the glomerular layer of the MOB forms OR maps which correspond to individual molecular features and the behavioral effects they produce(Kobayakawa et al., 2007; Mainen, 2007; Matsumoto et al., 2010; Mori & Sakano, 2011; Mori et al., 2006).

Odors also have an impact on behavior via emotions. Learned or experiences tied with select odorant stimuli can produce an explicit behavioral response both in a positive or negative effect (Kauffman, 2015). In humans, the link to smells with memories is largely attributed to the brain's limbic system, particularly the hippocampus and the amygdala. The olfactory bulb has direct connections to both areas associated with emotion and memory(Rolls, 2004; Royet et al., 2003; Zald & Pardo, 1997). The amygdala plays a role in processing of emotions, particularly pleasure and fear. The hippocampus is crucial in new memory formation and consolidating short-term memory into long-term(Olsen et al., 2012; Rolls, 2010; Small et al., 2011). The amgydala projects to the hypothalamus which allows for olfactory stimuli to potentially influence the autonomic and endocrine systems(Barbas et al., 2003; Gabbott et al., 2012; Pitkanen et al., 2000).

Amygdala-lesioned animals demonstrated loss of freezing/autonomic responses to fear conditioned stimuli and a reduction in neophobia(Helmstetter, 1992; Murray et al.,

1996; Phillips & LeDoux, 1992; Rolls & Rolls, 1973; Sananes & Davis, 1992; Weiskrantz, 1956).

Through associative learning or even traumatic events, certain smells can become associated to certain memories and become triggered by the presence of these odors in the future through the development of neural pathways. The amygdala plays a role in associative learning, with some of its neurons encoding odor cues associated with positive or negative taste (Schoenbaum et al., 1999).

The hippocampus is relayed olfactory information from the amygdala and the entorhinal cortex which receives inputs from the MOB and piriform cortex. The hippocampus plays a fundamental role in episodic memory(Lemogne et al., 2006; Olsen et al., 2012; Rolls, 2010; Small et al., 2011). Hippocampal damage has been shown to impair odor-place associated learning and temporal order memory for odor information(Kesner et al., 2002; Rolls & Kesner, 2006). Select hippocampal neurons are responsible for place of odor-related reward(Rolls, 2010; Tort et al., 2011). Hippocampal stimulation has been demonstrated to affect autonomic responses such as decreasing heart rate and blood pressure (Ruit & Neafsey, 1988).

VOC's Cognitive/Learning

Odors can also gain aversive and rewarding properties via associated learning. In both invertebrates and vertebrates, odors play an important role in recognition of kin and mates. In social insects, odors play an essential role in identifying group members from non-group members. Ant bodies are covered by a layer of cuticular hydrocarbons that apart

from preventing desiccation, functions as a means for recognition, even at a distance (Brandstaetter et al., 2008). The pattern of cuticular hydrocarbons can be complex and dynamic, allowing for them to function as identifiers of colony members or non-group members (Guerrieri et al., 2009). In honeybees (*Apis mellifera*), unsaturated molecules, such as alkenes, seem to play the more prominent role in nest-mate recognition (Châline et al., 2005; Dani et al., 2005). Mouse pups' approach to maternal odors influenced by neonatal learning, not only forms the basis for nest localization and parent-progeny recognition, but also future mate selecting with differing major histocompatibility complex (MHC) genotype (Yamazaki et al., 2000). Strong evidence found in mice demonstrated ability to discriminate between the urine odors of congenic mice that differed genetically only at the H2 locus of their MHC(Yamaguchi et al., 1981; Yamazaki et al., 1994). Humans too can discriminate and recognize odors from different individuals, identifying odors of a related infant compared with an unrelated one even without prior experience (Porter et al., 1986). Odor profiles help facilitate recognition of kin and even highlight prospective mates with genetic diversity.

Evidence shows odors are linked to emotional memory, with responses to odors including positive or negative associated emotions (Rolls, 2005). For example, a predator's odor can cause flight reaction in prey and the odor of mother's promotes newborn babies to breastfeed (Varendi & Porter, 2001) . Certain odors have been shown to impair working memory, reducing anger, or even improving mood (Habel et al., 2007; RÉTiveau et al., 2005; Schiffman et al., 1995; Schneider et al., 2006). Citrus fragrances were even shown to improve psychological states and immune system in patients with depression(Komori et

al., 1995). Green odors, specifically from oak leaves, have been seen to become necessary for polyphemus moths to promote mating (Riddiford, 1967). In humans, such natural green odor smells have been shown to elicit pleasantness, attenuation of stress-induced elevations of plasma adrenocorticotropic hormone, and body temperature (Nakashima et al., 2004; Sano et al., 2002). Skin-barrier disruption was shown to be resulting in rats and humans through certain natural odor exposures(Fukada et al., 2007; Fukada et al., 2012).

Odor-evoked memory is powerful in reminding humans about past emotional experiences that they associate with respective odors. This odor associated learning begins in early life, even in-utero the pregnant mother's diet can influence the odors liked by the offspring(Schaal et al., 2000). Rodents in experiments conditioning odors with foot shock stimulus, aversive and fear responses are commonly observed(Sacco & Sacchetti, 2010; Sullivan et al., 2000). In human patients suffering from posttraumatic stress disorder, imaging demonstrate the activation of the amygdala and prefrontal cortex when exposed to odor related to traumatic memory(Vermetten et al., 2007). The hippocampus and the prefrontal cortex are shown to be activated by odors associated with autobiographical memory retrieval process(Larsson & Willander, 2009). Based on gene homology, flies and mammals share many genes, suggesting shared molecular mechanisms of behavior plasticity(Rubin et al., 2000). It offers the possibility of relating analysis from the genetic, molecular, electrophysiological, and network levels to behavior (Sokolowski, 2001).

Behavior detect/avoid danger

VOCs effect on odor-guided reward and aversion can be seen, even without prior experience. For example, rodents avoid or freeze in response to predator urine odors, even in laboratory-bred animals with generations of non-exposure to such threats (Adduci et al., 2021; Bolbroe et al., 2000; Fendt et al., 2005; Horii et al., 2010; Osada et al., 2013; Staples et al., 2008; Wallace & Rosen, 2000). The vomeronasal organ is one of the major sensory input channels in which predator cues are detected and thus mediate freezing behaviors in mice (Rocha et al., 2024). Cat saliva has been shown to activate the V2R-A4 subfamily of vomeronasal receptors and differentially react to fresh and old saliva odors (Nguyen et al., 2024). Considering how conspecific urine has been shown to increase voluntary wheel running in wild-derived mice, external chemosensory cues and its detection may modulate exercise activity (Drickamer & Evans, 1996). Olfaction seems to play a significant role for voluntary exercise in mammals such as mice, with selective breeding for high runners producing mice with significantly different vomeronasal receptor gene expression than controls (Nguyen et al., 2020).

Drosophila melanogaster is innately aversive to CO_2, a component released by stressed flies, even at 0.1% exposure (Suh et al., 2004). *Drosophila* also have a functionally segregated olfactory circuit, based off a single class of sensory neurons expressing Or56a, dedicated for detecting geosmin, the odor associated with the smell after rain. While pleasant for people, this odor is important for *Drosophila* to detect and avoid as it is commonly emitted by toxic microbes on spoiled foods (Stensmyr et al., 2012). Avoidant

behavioral response for both mammals and insects demonstrates olfaction's contribution towards beneficial innate response in response to select volatiles.

Behavior Mate and food selection

Similarly, sex pheromones and food odors are innately attractive to invertebrates and vertebrate species without prior exposure. *Drosophila melanogaster* are innately attracted to the scent of vinegar from rotting fruit, their main food source (Zhu et al., 2003). 11-*cis*-vaccenyl acetate, a known volatile pheromone produced by male *Drosophila* acting via Or67d receptor, regulates mating behavior (Howard & Blomquist, 2005; Kurtovic et al., 2007; Sengupta & Smith, 2014). Odors are prevalent in mammals mate selection as well, contributing to sexual attraction. Many factors such as hormone levels, age, diet, and other individual components play a role in affecting an individual's scent mark attractiveness. Urinary protein found in male mice was found to invoke female sexual attraction (Roberts et al., 2010). In addition, scents marks deposited by female mice during estrus or behavioral estrus are more attractive to males, thus advertising their sexual receptivity (Ferkin, 2018; Kavaliers et al., 1994).

Human Health Impact

Exposure to VOCs is an important research issue due to their prevalence in our environment and potential impacts on human health through prolonged exposure. Volatile odor compounds are naturally present in many consumables or artificially added to enhance scents, flavors, cosmetics, etc. Anthropogenic air pollution also contains several VOCs and

has a recognizable impact on health both inside and outside our homes. Negative health effects of environmental VOCs are well documented within consumables such as tobacco products via direct, secondhand, and thirdhand tobacco smoke exposure contributing to acute and chronic lung diseases, cardiovascular disease, and various cancers. Cigarette smoke exposure is a primary risk factor for lung cancer, chronic obstructive pulmonary disease and bronchitis, and is considered the fifth leading cause of death globally (Prevention, 2021). Taking account of the growing popularity of electronic cigarettes (e-cigarettes), the deleterious effect of smoking remains prevalent and enduring (Zhu et al., 2014). The dangers go beyond nicotine, with the flavoring chemicals displaying cytotoxic effects in human embryonic stem cells and not due to nicotine (Bahl et al., 2012). E-cigarette refills with a variety of artificial flavorings and means of highly efficiently aerosolizing them have shown to be cytotoxic to human lung cells (Behar et al., 2018). VOCs have far-reaching effects as they can be carried over long distances and easy envelop spaces due to high volatility. One acclimates to smoke, pollution, body odor, cosmetics, food odors, and more if you are exposed to it long enough, but this does not mitigate their presence and its health impact.

Volatile exposures surround us, including within our enclosed motor vehicles which expose us to various VOCs that long-term may increase health risks (Chen et al., 2014; Kim et al., 2016). While inside the automobile cabins, 17 volatiles compounds (6 aromatics, 6 aldehydes, 2 ketones, 1 volatile fatty acid, 1 alcohol, and 1 ester) were generally ± 2 ppb of the exterior air concentrations, 3 VOCs (acetaldehyde, acetone, and formaldehyde) were significantly higher than ambient exterior air irrespective of engine

and ventilation settings. Long-term effects from cell permeable VOCs are important to account for considering their impact on health. Clearly, the consequences of VOC exposure requires a concerted effort to assess all downstream mechanisms to inform about prevention and intervention of possible diseases.

Long term effects of odor exposure

While the impact is known on how certain odorants play important roles in altering behavior in regard to survival, selecting mates, and finding resources, it is still not very understood how certain compounds may impact eukaryotes at a genetic level. The way environmental volatile odor compounds (VOCs), commonly secreted by microbes, can alter eukaryote gene expression and phenotypes, is not well understood. What happens when you are chronically exposed to certain odorants, even at low concentrations, beyond the point one habituating to them? Odor habituation is a phenomenon in response to prolonged exposure to an odor which causes decrease response to it. Odor habituation allows the endurance of malodorous environments and the ability to distinguish any new odors from the constant background odors (Kadohisa & Wilson, 2006; Linster et al., 2007; Pellegrino et al., 2017). This ubiquitous feature of an animal's response to an odorant is that it declines when the odorant is continuously or frequently encountered such as in *Drosophila melanogaster* (Twick et al., 2014). This makes observations of chronic odorant exposure necessary to observe if their effects go beyond their roles in behavior.

Volatile odor compounds (VOCs) consist of small volatile organic compounds that are usually gaseous at room temperature due to their low boiling point. VOCs, responsible

for the odors we smell, are ubiquitous and vary greatly from place to place. The sense of smell, modulated by the olfactory system, detects select environmental volatile cues and changes in odor concentrations that are crucial to an animal's survival and reproduction. The olfactory system in insects works hard to detect environmental variations in VOCs and uses that information to identify food sources, a potential mate, or a suitable egg-laying site (Pask & Ray, 2016). In some animals and most plants, VOCs are involved in social communication as chemoattractant and chemorepellents (Brosset & Blande, 2022; Ninkovic et al., 2021; Smeets et al., 2020). Microbial volatiles emitted by fungi impact ecological interactions between fungi and other organisms, altering growth, development, and even plant pathogen resistance (Schulz-Bohm et al., 2017). These compounds can act as long distance, intra- and inter-kingdom communication signals to influence the behaviors of animals involved in antagonisms or mutualisms with fungi. Eukaryotes coevolve with microbiomes and respond to their secreted soluble metabolites(Lee et al., 2019; Ryu et al., 2003). However, little is known about eukaryotic responses to various common environmental volatile chemicals in long term exposures, several of which, are emitted by microbes. Therefore, we became interested in how exposure to common environmental volatile compounds can affect eukaryotic organism.

Epigenetic changes with VOC exposure

Histones, which play a major role in chromatin conformation and regulating gene expression, undergo acetylation and deacetylation by Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs), respectively. Acetylation of histones by HATs

promote an open chromatin structure that make it more accessible by transcription factors, while removal of acetylation by HDACs promote a condensed chromatin structure. HDAC inhibitors modulate transcriptional activation and thus alter gene expression. The delicate balance in acetylation/deacetylation by HATs and HDACs may have an unknown role in VOC exposure effect on eukaryote gene expression.

HDACs

Histone deacetylases (HDACs), also called Lysine deacetylases (KDACs) to better describe their function, are involved in many biological processes contributing to epigenetic changes via histone modulation and deacetylation of non-histone proteins. They alter gene expression through removal of acetyl groups from lysine chains on histones, proteins involved in DNA packaging into chromatin. Epigenetics is a reversible change in gene expression caused by modifications outside of permanent DNA alterations. Epigenetic regulation is essential for establishing the gene expression patterns defining cell identity, differentiation, and response to environmental stimuli(Allis & Jenuwein, 2016). Due to its mechanistic variability and variety, it has received increasing attention as a potential factor in neurodegeneration pathogenesis. Histone modifications are a type of reversible epigenetic change that alters gene expression. This has sparked interest in the use of HDAC inhibitors as a means of altering gene expression, because histone deacetylases are known to be involved in many debilitating human diseases. This has risen interest with neurodegenerative diseases such as Alzheimer's, Huntington's, and

Parkinson's Disease which all involve protein aggregates pathogenesis (Chuang et al., 2009).

Gene expression in eukaryotic cells is dependent on how the DNA is packaged, and the accessibility of transcription factors to DNA sequences (Chuang et al., 2009). DNA is packaged into nucleosomes, a protein-DNA complex composed of an octamer of four core histones (H3/H4 tetramer) and two dimers (H2A/H2B). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two enzyme classes that participate in the acetylation and deacetylation of lysine residues found on histones and several non-histone proteins, respectively, and are the main contributors to DNA modification. HAT acetylation of histones generally enhances interactions with DNA and other proteins involved in transcription, while HDACs generally hinder this process. Chromatin associated processes that are directly affected by this acetylation balancing act involve replication, site-specific recombination, and DNA repair. These processes affect signal transduction pathways such as cell differentiation, cell apoptosis, vascular remodeling, inflammation, immune responses, neuronal plasticity, and metabolic reprograming. This delicate balance in acetylation by HATs and HDACs play a major role in overall cell fate and have been found to be impaired in several neurodegenerative diseases (Goldberg et al., 2007).

HDAC Classification

HDACs are evolutionarily conserved enzymes and are found within many species, including humans. In humans, there are 18 identified HDAC enzymes that have been

classified into 4 classes based on their homology to yeast HDACs (**Table 1**). Class I HDACs include HDAC1, 2, 3 and 8, and are related to the yeast enzyme Rpd3. Class II HDACs include HDAC4, 5, 6, 7, 9 and 10, and are related to the yeast protein HDA1. Class II HDACs are further divided into two subclasses by their structural similarities, IIa (HDAC4, 5, 7 and 9) and IIb (HDAC6 and 10). Class I and II HDACs have been extensively investigated for their roles in the central nervous system (CNS). Class III HDACs are referred to as sirtuins owing to their homology to the yeast HDAC Sir2. This class includes SIRT1–SIRT7 show dependence of nicotinamide adenine dinucleotide (NAD+). Class IV HDAC only includes HDAC11, which due to its distinct structure, is in its own class. Class I, II, and IV are zinc-dependent enzymes(de Ruijter et al., 2003). It is important to note that HDACs target many non-histone proteins and thus promotes their suggested name change to lysine deacetylase (KDACs) (Van Dyke, 2014). For the purpose of this dissertation, we will continue to refer to them as HDACs.

Non-histone proteins that are known to interact with HATs and HDACs include those found in **Table 2**. HDAC enzymes have over 60 nonhistone protein substrates, including gene transcription factors and coregulators (e.g., p53, c-myc, and BCL-2), chaperones (e.g., heat-shock protein [HSP] 70 and HSP90), signaling mediators (e.g., STAT3, Smad7, and β-catenin), DNA repair proteins (Ku70 and Ku86), and proteins involved in cell motility (e.g., **α** tubulin) (Licciardi et al., 2012). HDACs act through the formation of large multiprotein complexes. They act as a scaffold for a wide variety of spatially and temporally regulated interactions, altering downstream protein profiles by

means outside of histone modulation. When it comes to the net-balance of acetylation profiles, HDACs and HATs play a balancing act with one another (Saha & Pahan, 2006).

HDAC inhibitors Mechanism of Action

The general pharmacophore structures of Histone deacetylase inhibitors (HDACis) consist of a Cap, Linker, and Zinc Binding Group (ZBG). Zinc Binding Groups (ZBG) play a crucial role in targeting HDACi to the active site of histone deacetylases, determining its potency. A common ZBG is hydroxamic acid, the most used ZBG in the structure due to its high affinity to zinc ion compared to alternatives (Giannini et al., 2012; Zhang et al., 2018). The cap and linker's roles serve to bind to residues in the active site of HDACs, contributing to ligand-receptor interactions contributing towards HDACi selectivity. The ZBG binding to the zinc ion and surrounding residues play the decisive role in inhibitory activity (Manal et al., 2016).

HDACi have emerged primarily as a new class of anticancer therapeutics. Currently suberoylanilide hydroxamic acid (SAHA; Vorinostat; Zolinza) and depsipeptide (FK228 and FR901228; Romidepsin; Istodax) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma in 2006 and 2009, respectively (Suraweera et al., 2018) (**Table 3**). The potential utility of HDACi has been extended to non-oncologic applications, including autoimmune disorders, inflammation, diseases of the CNS, and malaria (Licciardi et al., 2012). There are at least 15 potential HDACi currently in clinical trials either as stand-alone therapeutics or in combination with other modalities(Licciardi et al., 2012). However, many of these inhibitors are broad

spectrum and inhibit other HDAC classes. This can lead to unforeseen side effects that can hinder efficacy of treatment (Roche & Bertrand, 2016). Current progress is working towards developing more specific HDACi. Tubacin, one of the few known selective HDACi against HDAC6 discovered through High Throughput compound screening of over 7000 compounds, displayed inhibitory effect on tubulin deacetylation (Haggarty et al., 2003; Namdar et al., 2010). Tubacin inhibits the second active deacetylase domain (Haggarty et al., 2003).

HDACs in Cancer

Early use of HDAC inhibitors were focused on their potential anticancer use. Hyperacetylation, from inhibiting HDAC activity, was associated with increased expression of pro-apoptotic genes such as Bax and P21 and pro-survival genes like Bcl-2 and growth factors protective in other cell types. This could potentially explain how HDAC inhibitors may seem lethal in certain cancers and benign in other cell types(Saha & Pahan, 2006). While HDAC inhibitors have been predominantly limited to hematological malignancies. FDA-approved HDAC inhibitors for cutaneous T cell lymphomas (vorinostat, romidepsin), peripheral T cell lymphoma (belinostat), and multiple myeloma (panibostat), and many other clinical candidates are being studied in solid and hematological malignancies(O'Connor et al., 2015; San-Miguel et al., 2016; Whittaker et al., 2010). Limitations for HDAC inhibition in treating solid tumors highlight the issue of targeting common essential genes, which have a narrow therapeutic window due to target proteins being crucial for both healthy and cancer cell survival. Targeting HDACs has the

added benefit of the large number of redundancies between HDAC enzymes. Specificities for individual HDACs vary between small molecules, with off-target effects potentially mediating added therapeutic effects(Eckschlager et al., 2017; Lechner et al., 2022). While HDAC3 is predicted to be a shared essential HDAC involved in chromatin remodeling/gene regulation in most cell types, HDAC1 and HDAC2 are paralogs that are lethal in cells when simultaneously knocked out or inhibited (Najm et al., 2023). Through development of more selective HDAC inhibitors, targeting such paralogs HDAC1 or HDAC2 could provide therapeutic effects while mitigating off-target toxicity(Dharia et al., 2021; Zhang et al., 2023).

HDACs in Neurodegeneration

Multiple roles have been shown if HDAC inhibition in neurodegenerative conditions, including Huntington's Disease (**HD**). Huntington's Disease (HD) is a rare genetic autosomal dominant neurodegenerative syndrome caused by expanded CAG repeats in the huntingtin gene, leading to pathological elongated huntingtin protein with polyglutamine tract. This condition leads to cognitive, motor, and psychiatric symptoms, and shrinkage in basal ganglia and cerebral cortex (Illarioshkin et al., 2018; Wright et al., 2017). Transcriptional dysregulation has been suggested to be a significant mechanism of HD pathogenesis (Sharma & Taliyan, 2015). Hypoacetylation of histones, a result of increase HDAC activity, have been associated with downregulated genes in HD mice models. HDAC inhibitor treatment increased the association of acetylated histones with downregulated genes, helping to correct mRNA abnormalities suggesting a potential

therapeutic value (Sadri-Vakili et al., 2007). Several HD models have been shown to demonstrate therapeutic values via HDAC inhibition (Sadri-Vakili et al., 2007; Sadri-Vakili & Cha, 2006). An overall decrease in H3 acetylation was observed in HD mice models treated with HDAC inhibitors (McFarland et al., 2012). Select HDAC6 inhibition increased acetylation of microtubules, compensating for the transport deficit observed in HD (Vaughan et al., 2008). Improvement in motor skills was seen in HD mice models treated with HDAC inhibitors (Ellrichmann et al., 2017; Thomas et al., 2008). In *Drosophila* HD models, expressing the mutant huntingtin protein in the fly rhabdomeres resulting in degeneration, the use of HDAC inhibitors SAHA and Sodium butyrate were shown to slow the progression of neurodegeneration (Steffan et al., 2001).

HDACs in Plant growth and development

HDACs are widely conserved in Eukaryotes, including plants. HDACs play key roles in regulating plant growth, development, and stress responses. Altered expression of HDAC genes such as Arabidopsis AtHDA19 have shown various developmental abnormalities, including early senescence, serration, aerial rosette formation, and floral delay/ abnormalities(Tian & Chen, 2001). In Arabidopsis, Flowering Locus C (FLC), a MADS-box transcription factor, acts as a flowering repressor that inhibits transition state from vegetative growth to reproductive development. AtHDA6 can repress the expression of FLC to control flowering time with *Athda6* mutants or *fld-6* mutant plants displaying late-flowering phenotype (Yu et al., 2011).

With certain abiotic stresses such as cold, Arabidopsis histone deacetylase 2C (HD2C) plays a role in promoting cold-responsive COR genes necessary for cold tolerance. Through the degradation pathway of HD2C in the presence of cold, hyperacetylation of H3 on COR chromatin induces *CORs* expression and cold tolerance (Park et al., 2018). The functions of HDACs, especially AtHDA6 and AtHDA19, were most well studied in Arabidopsis. AtHDA6 and AtHDA19 were recently reported to be involved in abscisic acid response and are required for salt stress tolerance (Chen et al., 2010). HDACs seem to play a role for modulating chromatin accessibility in response to environmental conditions and stressors in order to adapt.

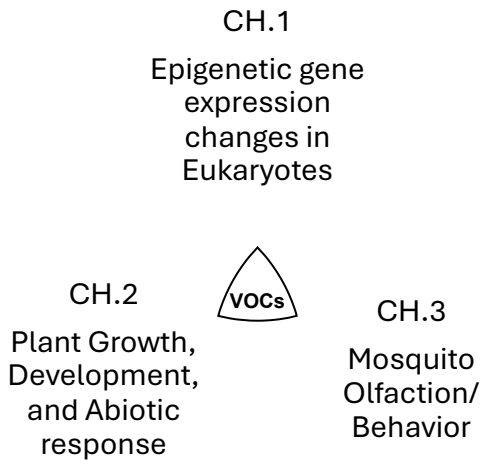


Figure 1.1 Thesis Chapters: The connection between all my dissertation chapters highlight the multiple roles environmental VOCs play in eukaryotes.

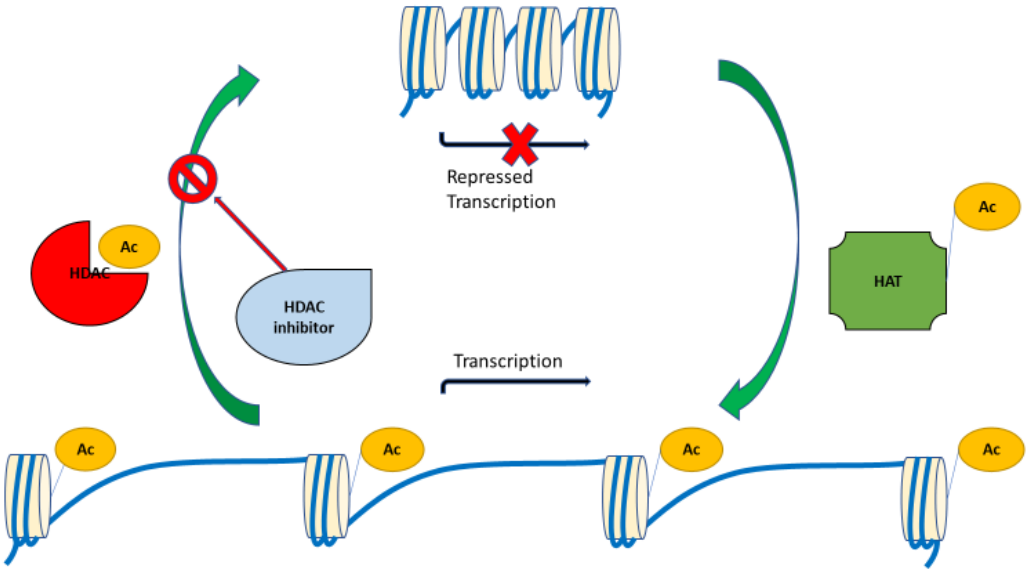


Figure 1.2 Histone Acetylation and Epigenetic Modulation

HATs and HDACs share an important role in acetylation homeostasis of histones which regulate accessibility of tightly wound DNA to transcription factors and subsequent gene expression.

CLASS	Protein Structure (*S. cerevisiae*)	Human HDACs (18 proteins)	HDAC Class Tissue Association	Cellular Localization	Dependent Group	Ref
I	**Rpd3, Hos1, Hos2, Hos3-like**	HDAC1,2,3, & 8	Ubiquitous	Nucleus	Zn2+	(Seto & Yoshida, 2014)
IIa	**Hda1-like**	HDAC4,5,7, & 9	Heart, Skeletal Muscle, Brain, Placenta, Pancreas	Nucleus/Cytoplasm	Zn2+	(Seto & Yoshida, 2014)
IIb	**Hda1-like**	HDAC6 & 10	Heart, Brain, Liver, Kidney, Pancreas, Spleen	Cytoplasm	Zn2+	(Seto & Yoshida, 2014)
III	**Sir2, Hst1, Hst2, Hst3, Hst4,-like**	Sirtuins 1-7	Liver, heart, brain, pancreas, muscle, skeletal muscle, adipose tissue, kidney, vascular smooth muscle, spleen	Nucleus/Cytoplasm/Mitochondria	NAD+	(Seto & Yoshida, 2014; Sudhakar et al., 2018)
IV		HDAC11	Brain, Heart, Skeletal Muscle, Kidney	Nucleus/Cytoplasm	Zn2+	(Seto & Yoshida, 2014)

Table 1.1 HDAC Classifications:

This shows Human HDAC classifications, their class associated tissues, and cellular localizations. These associated tissues and localizations can vary between HDACs within the same class.

Proteins	Acetylation of these proteins affected by HAT/HDAC balance promotes:	Ref
p53	Increases DNA binding affinity; transcriptional activation; protein stability	(Gu & Roeder, 1997)
SRY	Increases DNA binding affinity	(Thevenet et al., 2004)
STAT3	Increases DNA binding affinity; transcriptional activation; protein stability	(Wang et al., 2005; Yuan et al., 2005)
GATA1	Increases DNA binding affinity; transcriptional activation	(Boyes et al., 1998; Caldwell et al., 2013)
GATA2	Increases DNA binding affinity; transcriptional activation	(Hayakawa, 2003; Ozawa et al., 2001)
E2F1	Increases DNA binding affinity; transcriptional activation	(Martinez-Balbas et al., 2000)
YY1	Decreases DNA binding affinity	(Yao et al., 2001)
HMG-A1	Decreases DNA binding affinity; Increases Transcriptional activation	(D'Angelo et al., 2014; Munshi et al., 1998)
HMG-N2	Decreases DNA binding affinity	(Luhrs et al., 2002)
p65	Decreases DNA binding affinity	(Kiernan et al., 2003)
HMG-A1	Decreases DNA binding affinity; Increases Transcriptional activation	(Munshi et al., 2001)
AR	Increases transcriptional activation; protein stability; promotes protein-protein interaction	(Fu et al., 2000; Fu et al., 2002; Gaughan et al., 2005)
ER α	Decreases transcriptional activation; increases protein stability	(Kawai et al., 2003; Wang et al., 2001)
GATA3	Increases transcriptional activation	(Yamagata et al., 2000)
EKLF	Promotes protein-protein interaction	(Chen & Bieker, 2001; Zhang et al., 2001)
MyoD	Increases transcriptional activation	(Polesskaya et al., 2000; Sartorelli et al., 1999)
HIF1α	Decreases Protein stability	(Jeong et al., 2002)
c-MYC	Increases Protein stability	(Nebbioso et al., 2017; Patel et al., 2004)
Smad7	Increases Protein stability	(Emori et al., 2012; Gronroos et al., 2002)
Importin α	Promotes protein-protein interaction	(Bannister et al., 2000; Liu et al., 2012)
NF-κB	Disrupts protein-protein interaction	(Chen et al., 2001)
Ku70	Disrupts protein-protein interaction	(Cohen et al., 2004)
Hsp90	Disrupts protein-protein interaction	(Kovacs et al., 2005)
α-tubulin	Microtubule function and cell motility	(Palazzo et al., 2003)
IRS-1	Facilitation of insulin signaling	(Kaiser & James, 2004)

Table 1.2 Notable proteins that interact with HAT/HDACs and the outcomes of their acetylation.

HDAC inhibitor	Target HDAC Class
Vorinostat (SAHA)	**Class I, IIa, IIb, IV**
Panobinostat (LBH589)	**Class I, IIa, IIb**
Belinostat (PXD101)	**Class I, IIa, IIb, IV**
Romidepsin (FK288)	**Class I**
ITF2357	Class I, IIa
PCI-24781 (Abexinostat)	Class I, IIa, IIb
Entinostat	Class I
MGCD0103	Class I
Phenyl Butyrate	Class I, IIa
Valproic acid	Class I, IIa
Trichostatin A	Class I, IIa, IIb, IV
LAQ824	Class I, IIa, IIb, IV
Mocetinostat	Class I, IV
Pracinostat	Class I, IIa, IIb, IV
Nicotinamide	Class III
Cambinol	Class III
Tenovin 1	Class III
Tenovin 6	Class III
Sirtinol	Class III
EX-527	Class III
Tucidinostat	Class I, IIb
Citarinostat	HDAC6
KA2507	HDAC6
Fimepinostat	Class I, IIa, IIb
Quisinostat	Class I, IIa, IIb, IV
Ricolinostat	HDAC6
Nanatinostat	Class I
Ivaltinostat	Class I, IIa, IIb, III, IV
CUDC-101	Class I, II
MPT0E028	Class I, IIb

Table 1.3 Table of some known HDAC inhibitors and their associated target HDAC classes.

Most of the FDA approved HDAC inhibitors, shown in BOLD, are broad HDAC inhibitors used to treat T-cell lymphoma (Mabe et al., 2024; Suraweera et al., 2018).

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CHAPTER II: Plasticity of gene expression in the nervous system by exposure to environmental odorants that inhibit HDACs

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Abstract

Eukaryotes are often exposed to microbes and respond to their secreted metabolites, such as the microbiome in animals or commensal bacteria in roots. Little is known about the effects of long-term exposure to volatile chemicals emitted by microbes, or other volatiles that we are exposed to over a long duration. Using the model system *Drosophila melanogaster* we evaluate a yeast emitted volatile, diacetyl, found in high levels around fermenting fruits where they spend long periods of time. We find that exposure to just the headspace containing the volatile molecules can alter gene expression in the antenna. Experiments showed that diacetyl and structurally related volatile compounds inhibited human histone-deacetylases (HDACs), increased histone-H3K9 acetylation in human cells, and caused wide changes in gene expression in both *Drosophila* and mice. Diacetyl crosses the blood-brain barrier and exposure causes modulation of gene expression in the brain, therefore has potential as a therapeutic. Using two separate disease models known to be responsive to HDAC-inhibitors, we evaluated physiological effects of volatile exposure. First, we find that the HDAC inhibitor also halts proliferation of a neuroblastoma cell line in culture as predicted. Next, exposure to vapors slows progression of neurodegeneration in a *Drosophila* model for Huntington's disease. These changes strongly suggest that unbeknown to us, certain volatiles in the surroundings can have profound effects on histone acetylation, gene expression and physiology in animals.

Introduction

Multicellular organisms evolve in the presence of microbial volatiles and metabolites (Dorrestein et al., 2014; McFall-Ngai et al., 2013), often for prolonged periods of time. Human-associated microbes have incredible metabolic diversity, encoding 100x as many genes as the human genome itself(McFall-Ngai et al., 2013). It is estimated that about half of the thousands of metabolites found in mammalian blood are either produced or altered by microbes (Wikoff et al., 2009). Microbial metabolites are an important mechanism by which the microbiome influences host immunity amongst other things (Dorrestein et al., 2014; Rooks & Garrett, 2016). Many volatiles are generated from the metabolism of a variety of food components, including triglycerides, sugars and amino acids (Shibamoto, 2014). Some chemicals are also produced by microorganisms such as yeasts and lactic bacteria during fermentation in many foods and beverages (Shibamoto, 2014).

In the model system *Drosophila melanogaster*, prolonged exposure to CO_2 showed an increase in volume of the CO_2-sensing glomerulus in the antennal lobe, which can lead to adaptations in fly behavior (Devaud et al., 2001; Sachse et al., 2007). Carbon dioxide is a common byproduct of yeast fermentation in overripe fruits, the preferred food source. In order to study the physiological effects of long-term exposure to other volatiles emitted during fermentation, we exposed flies for 5 days to diacetyl, a buttery odorant made by yeast in fermenting fruits at high levels (1350 ppb in ripe banana), and is also found in many commonly consumed foods such as butter, yoghurt, wine, fruits, beer, popcorn (Hughes, 2001; Martineau, 1995; Nykanen, 1991; Shibamoto, 2014). Diacetyl was selected

for two reasons: first, *Drosophila melanogaster* use fermenting fruits as their favored food source, oviposition site and spend long durations of time exposed to it. Second, diacetyl is known to be an inhibitory odorant of the CO_2 receptor and therefore an opposite effect is expected on the V-glomerulus from the previous study (Turner & Ray, 2009). Follow up experiments revealed that diacetyl acts as an HDAC inhibitor in vitro. We found that volatiles structurally similar to diacetyl have similar HDAC-inhibitory properties as well. Subsequent analyses with two different model systems: *Drosophila melanogaster* and *Mus musculus* showed gene expression changes in tissues caused by odor exposure from a distant source. We found expression of hundreds of genes to be modulated upon exposure to the volatile, as would be expected from an inhibitor of HDACs. HDACs are histone-modifying enzymes involved in the removal of acetyl groups from lysine residues and the remodeling of chromatin structure as a means to regulate gene expression (Graff & Tsai, 2013; Shahbazian & Grunstein, 2007). With large-scale roles in gene regulation, HDACs are promising targets in drug development for many diseases such as cancers and neurodegenerative disorders (Chuang et al., 2009; Kazantsev & Thompson, 2008; Minucci & Pelicci, 2006). Several classes of orally administered HDAC inhibitors have been found to attenuate the progression of certain cancers and neurodegenerative diseases including Alzheimer's disease and Huntington's disease (Chuang et al., 2009). We find that exposure to diacetyl volatiles can substantially alter gene expression in the mouse brain, presumably by crossing the blood-brain barrier. The exposure slows degeneration of photoreceptor cells in a Huntington's disease model in *Drosophila*. Additionally, exposure to diacetyl shows dramatic reduction in proliferation of a neuroblastoma cell line in culture. Our

discovery of a family of volatile odorants that also act as HDAC inhibitors highlights a need to understand how small molecules present in our environment interact with and alter eukaryotic gene expression.

Results

Activity-dependent expression modulation of chemosensory receptors

Previous studies have demonstrated that prolonged exposure of ~5 days to elevated CO_2, can cause an increase in volume of the CO_2-sensitive V-glomerulus in the antennal lobe, which can lead to adaptations in fly behavior(Devaud et al., 2001; Sachse et al., 2007) . To assess the effect of CO_2 response inhibitor diacetyl on the antennal lobe, flies were exposed to the odorant during the first days immediately following eclosion. The CO_2-detecting ab1C neuron was labelled using the promoters of the CO_2 receptors, *Gr63a-Gal4;UAS-mcd8GFP* and *Gr21a-Gal4; UAS-mcd8GFP*, and the flies were exposed to headspace above a 1 % (V/V) diacetyl solution in an air-tight container. The flies were then imaged for expression of GFP in the ab1C neurons of the antenna, as well as the V glomerulus, which receives axonal input from ab1C neurons in the antennal lobe (Jones et al., 2007). Surprisingly, the *Gr63a* promoter driven GFP signal in the V glomerulus is completely abolished after 5 days of exposure to the odor for all brains imaged (**Figure 2.1A, 2.1B**). However, there is also a concomitant decrease in GFP signal in ab1C neurons in the antenna (**Figure 2.1A**). Similar results were seen for *Gr21a* driven expression, where expression of GFP was lost in both the V-glomerulus

and ab1C neurons (**Figure 2.11A, 2.11B**). Interestingly, after five days of recovery in clean air the GFP expression is regained in the V-glomerulus as well as in ab1C neurons in the antenna , indicating that both *Gr21a* and *Gr63a* expression has been restored (**Figure 2.12**). Because olfactory neurons do not regenerate in the fruit fly (Berdnik et al., 2006; Sigg et al., 1997), these results suggest that changes in GFP levels are likely due to changes in the promoter expression and not due to neuronal cell death.

In order to test whether expression of *Gr63a* and *Gr21a* is being down regulated by diacetyl we relied on quantitative-PCR along with a few members of the *Odorant receptor (Or)* family genes. Apart from *Gr63a* and *Gr21a* we also evaluated receptors where diacetyl has no activity (Or47a, Or88a) and the broadly expressed co-receptor (Or83b). Wild-type flies that were exposed to diacetyl for 6 days showed dramatic down regulation in all genes tested. However, after a 5-day recovery period expression of all but one of the genes recovered, including *Gr63a* (**Figure 2.11C**). This form of plasticity in gene expression is unexpected and therefore mechanistically interesting to investigate.

Diacetyl and structurally related odorants act as HDAC inhibitors in vitro

Diacetyl is structurally related to a soluble metabolite secreted by the gut microbiome and liver, β-hydroxybutyrate, which is known to inhibit zinc-dependent HDACs (Shimazu et al., 2013) (**Figure 2.1C**). It is also structurally related to another known HDAC inhibitor Sodium butyrate (**Figure 2.1C**). Diacetyl is present widely in nature as a pH-neutral fermentation product of microorganisms such as yeasts in over-ripe fruit, the favorite food for *Drosophila*, and also from lactic acid bacteria, and is found in

many foods and beverages (Shibamoto, 2014). In humans, diacetyl is also produced by microbes on the skin, in the oral cavity, and is found in breath (Whiteson et al., 2014). Interestingly, this volatile is known to traverse the cell membrane (Krogerus & Gibson, 2013).

Soluble metabolites from the gut microbiome like short chain fatty acids are known to affect histone modifying enzymes gene expression, and physiology in various parts of the host (Krautkramer KA et al., 2017; McFall-Ngai et al., 2013). It is presumed that these dissolved compounds absorbed in the blood circulate to various parts of the body. Additionally, microbes in our skin microbiome, mouth microbiome, and environment also emit a diverse repertoire of volatile metabolites that can traverse much greater distances away from the source (James et al., 2013). To examine if diacetyl can directly modulate HDACs like β-hydroxybutyrate, we performed in vitro acetylation assays with recombinant human HDACs. We found that indeed, diacetyl inhibited all four purified human Class I HDACs (HDAC1, 2, 3 and 8) and the one Class II HDAC (HDAC6) tested. The inhibition occurred in a dose-dependent manner. The IC_{50} values for HDAC1, 2, 3, 8 and 6 were 7.3 mM, 23.1 mM, 7.5 mM, 14.3 mM and 24.5 mM respectively (**Figure 2.1C**). The levels of inhibition as observed from IC_{50} values for HDAC1 and HDAC3 are comparable to those of β-hydroxybutyrate whose IC_{50} values for HDAC1 and 3 were previously reported as 5.3 and 2.4 mM, respectively (Shimazu et al., 2013).

To test other odorants for their ability to inhibit HDACs, we identified a list of volatile odorants structurally similar to diacetyl using the similarity search feature on Pubchem (**Figure 2.1D & Figure 2.8A-D**) and cross-referenced as odorants and tested

them on four purified human HDACs, from Class I (HDAC1 and HDAC3) and Class II (HDAC4 and HDAC6). Each compound was tested at 15 mM, the concentration at which diacetyl inhibits HDAC1, 3, and 6 with more than 50% efficacy (**Figure 2.1D & Figure 2.8A-D**). All compounds tested reduced the activity of at least one of the HDACs (**Figure 2.1D**). Ethyl pyruvate, methyl pyruvate, 2,3-hexanedione, 2,3-heptandione, 2,3-pentandione inhibited HDAC1, 3 and 6 with more than 70% efficacy. Methyl pyruvate and ethyl pyruvate dose response curves also demonstrated 13.78mM and 4.049 mM IC_{50} values against HDAC6, respectively (**Figure 2.9A & 2.9B**). Allyl butyrate also similarly inhibited those HDACs but with lower efficacy. 1-acetoxyacetone, and 2,3-butanediol inhibited HDAC6 more than 70% but inhibitory effects against HDAC1 and 4 were lower. Moreover, propyl formate strongly inhibited HDAC 6 but did not inhibit HDAC1, 3, and 4. Taken together, these results indicate that microbial volatiles and structurally related odorants have the ability to inhibit human HDACs, and that each compound has specific HDAC inhibitory properties.

Microbial volatile increases histone acetylation in human cell nuclei

In order to directly examine histone acetylation at the cellular level, we used human HEK293 cells which offer a tractable system to prepare nuclear extracts and picked one volatile to test in more detail. We exposed the cells to different doses of diacetyl for 2 or 6 hours and monitored histone acetylation levels within nuclear extracts in Western Blot assays. Compared to the mock treatment, 10 mM diacetyl significantly increased H3K9 acetylation levels within 2 hours of treatment, whereas the acetylation levels of H3K14 and

H4K5 were not affected (**Figure 2.2A**). This specificity for an increase of the H3K9 mark is consistent with previous observations for β-hydroxybutyrate. Preferable acetylation of H3K9 was also observed previously in HEK293 cells with treatment of the structurally related β-hydroxybutyrate (Shimazu et al., 2013). After 6 hours of treatment, the H3K9 acetylation induced by 10 mM diacetyl was further increased (**Figure 2.2B**). The increase in H3K9 acetylation with diacetyl treatment is dependent both on the duration of exposure and concentration of the odorant.

Organisms are constantly exposed to volatiles commonly found in their food and environment for prolonged periods of time. In order to test the effect of a lower concentration of the volatiles, we selected a 5-day exposure time at a 100-fold lower concentration. When we treated HEK293 cells with this lower dose of diacetyl (100 μM), H3K9 acetylation level increased after 96 hours of exposure and reached significantly higher levels than control after 120 hours (**Figures 2.2C and 2.2D**). These results demonstrate that even prolonged exposure to low levels of diacetyl can greatly impact the epigenetic landscape inside the nucleus. More importantly, a 5-day exposure was sufficient to alter the epigenetic state of nuclei at concentrations that are present in some food sources. Taken together, these results demonstrate that diacetyl can act as an HDAC inhibitor, with the potential of causing broad modulations of gene expression, histone acetylation in cells, and inhibition of purified HDAC enzymes in a dose-dependent manner.

Transcriptional response to odor exposure is conserved in invertebrates and vertebrates

We next performed in vivo experiments to determine whether eukaryotic cells alter gene expression in response to diacetyl exposure, as would be expected with HDAC-inhibition. Epigenetic changes occur slowly over days, and to test its effects on gene expression we used two model systems for eukaryotes: invertebrates (*Drosophila melanogaster)* and vertebrates *(Mus musculus).* We placed *Drosophila* adult males in vials and housed these vials within a closed container exposed to headspace from a 1% diacetyl solution (in paraffin oil) for 5 days, as in a previous long-term odor-exposure study (Sachse et al., 2007) (**Figure 2.3A**). The transcriptome of the primary olfactory organ, the antenna, was compared with that of the control group of age-matched flies that were exposed to the solvent paraffin oil (PO). The antennal transcriptional profile of diacetyl-exposed flies showed substantial changes in gene expression when compared to the solvent control (**Figure 2.3B**). We identified 1234 differentially-expressed genes (DEGs) (false discovery rate, FDR < 0.05) in the antennal transcriptome of diacetyl-exposed flies compared to control animals. Of these, 645 genes were significantly up-regulated ($\log_2$ fold-change > 1; red dots in **Figure 2.3B**) and 589 genes were significantly down-regulated ($\log_2$ fold-change < -1; blue dots in **Figure 2.3B**). A broad range of genes was significantly altered, with several biological process GO terms significantly enriched in the up-regulated gene list including "response to biotic stimulus" ($p < 3x10^{-7}$),"response to bacterium" ($p < 3x10^{-7}$) and "defense response" ($p < 3x10^{-7}$). In the down-regulated gene set the GO term most enriched was "sensory perception of chemical stimulus" ($p< 6x10^{-72}$). The GO molecular functions that were most common in the upregulated sets included enzymes like hydrolases

and oxidoreductases, as well as nucleic acid binding genes (**Figure 2.3C**). Down-regulated genes include receptors, hydrolases and transporters (**Figure 2.3C**).

The first tissue that would have contact with airborne volatiles in terrestrial vertebrates are the airways and lungs. We therefore performed transcriptome analyses on lung tissue of mice exposed to diacetyl headspace at different doses for a period of 5 days, as was done in *Drosophila* (**Figure 2.3D**). The dose of the volatile in the chamber was measured in parallel experiments by tracking volatile loss and airflow and determined to range between a peak 1920 ppm at the end of hour 2, tapering off to 28 ppm by hour 120 (**Figure 2.13B**). Indeed, expression of a substantial number of genes was modulated in the diacetyl-exposed lungs compared to the control. The changes were dose-dependent and more pronounced in mice exposed to headspace from a 1% diacetyl source compared to those exposed similarly to 0.1% (v/v) diacetyl source (**Figure 2.3E, Figure 2.13C**). Among these diverse sets of regulated genes in the lung tissue, a significant overlap was found between 1% (v/v) and 0.1% (v/v) headspace for both up-regulated genes ($p=3x10^{-3}$) and down-regulated genes ($p=6x10^{-3}$, **Figure 2.4F**), further supporting a dose-dependent effect of diacetyl on gene expression in the mouse lung.

The GO enrichment analysis of the lung transcriptome from mice exposed to diacetyl revealed several interesting sets of genes that were significantly altered (**Figure 2.3G and 2.3H**). Among these genes is the SARS-CoV-2 entry receptor ortholog, ACE2. The level of this gene in the lungs of diacetyl exposed mice showed a reduction in expression levels ($\log_2$ fold-change= - 0.62, FDR= $2.02x10^{-5}$). The level of ACE2 in the nasal tissue, lungs and other organs play a critical role in infection by the SARS-CoV-2

virus, suggesting that epigenetic mechanisms may contribute to expression. While we do not know whether expression of ACE2 in humans is regulated similarly, these results highlight the importance of understanding volatile-induced modulation of gene expression in the lungs and other tissues.

HDAC family members are highly conserved across eukaryotes, spanning both animal and insects. Volatile microbial metabolites have been present throughout the evolution of animals, insects, and plants, and have potential as signals for multi-domain communication because they can travel wide ranges; plants detect root infections and time their immune response using volatiles (Effantin et al., 2011), and microbial volatiles elicit olfactory behaviors in insects and nematodes. Our results indicate that a volatile compound, capable of directly inhibiting HDACs and altering acetylation levels, can cause significant changes in gene expression in a variety of organisms following exposure from a distance, through the air.

DEGs overlap those for known HDAC inhibitors and upregulation is partially reversible

One of the hallmarks of epigenetic regulators which makes them attractive candidates for therapeutics is plasticity. Upon removal of the inhibitors, we expect that some of the changes in gene expression are reversible. To test for reversibility, we performed a recovery experiment following diacetyl exposure using the *Drosophila* model. We maintained 5-day diacetyl-exposed flies in clean air for 5 additional days (**Figure 2.4A**). In parallel, we performed age-matched mock experiments with paraffin oil solvent exposure alone. A large number of genes were down-regulated following the recovery in

comparison to the 10-day-old flies in the mock condition (**Figure 2.4B**). Interestingly, there was a significant overlap of these down-regulated genes with the set that was up-regulated in the diacetyl treatment (**Figure 2.4C**). These results suggest that the effects of HDAC inhibitory odorant exposure are not permanent but dynamic, and removal of the odorant leads to subsequent changes in gene expression of the up-regulated set.

Drugs that inhibit HDACs are in various stages of approval as treatments for several diseases. The approved drugs include sodium butyrate and valproic acid. To compare the gene-regulatory effects of these drugs to diacetyl, we performed RNA-seq after raising the flies on food containing sodium butyrate (SB) or valproic acid (VA) (Steffan et al., 2001) and compared gene expression in the antennae of flies raised on untreated food for 5 days. We next compared the up-regulated gene profiles following each treatment to the one induced by exposure to diacetyl. As expected, feeding SB and VA induced significant changes in expression levels of several genes (**Figure 2.4D and 2.4E**). Interestingly we found that 113 of diacetyl up-regulated genes were also up-regulated in either SB, VA or both treatment conditions (**Figure 2.4F**). Pairwise statistical analysis of each gene set revealed a significant overlap of diacetyl-induced genes with SB-induced genes ($p=6x10^{-11}$) and with VA-induced genes ($p=2x10^{-65}$) (**Figure 2.4F**). There was, as expected, also a significant overlap between SB- and VA- induced genes ($p=1x10^{-52}$) (**Figure 2.4F**). This highly significant overlap among up-regulated genes lends further support to our model that diacetyl vapors act as an HDAC inhibitor in vivo. As expected, each of the 3 treatments also modulated a substantial number of unique genes (**Figure 2.4G and 2.4H**), suggesting that differences in oral vs. vapor delivery, molecular structure and activity profile across

the repertoire of HDACs may contribute to differences in gene regulation. These results suggest that some volatile odorants, or the microbes that emit them, may impart therapeutic effects like other HDAC inhibitors from a distance, through the air.

Volatile Diacetyl alters gene expression in the mouse brain

One of the categories of challenging diseases that HDAC inhibitors are being tested for drugs are neurodegenerative diseases (Fischer, 2010) where volatile odorants may provide a new class of inhaled therapeutics. A major design challenge for nervous system drugs is the ability to cross the blood-brain barrier. Due to the volatility and small size of volatile odorants, there is a possibility that they could diffuse through the intranasal route to the brain directly (Chauhan & Chauhan, 2015). We cannot tell *a priori* whether odorants like diacetyl can travel across the nasal membrane to the brain. In order to test whether cells in the brain of mice respond when presented with diacetyl vapors from a distance, we used gene expression as the final readout to measure it. We performed RNA-seq experiments on mice exposed only to aroma of diacetyl in the air for 5 days as before. Littermate controls were exposed in a similar manner to the solvent (PO) in the air. Interestingly, several genes were differentially expressed upon exposure to headspace from 0.1% (v/v) diacetyl passaged through the air in the holding cage where it is further diluted (49 up-regulated, 32 down regulated, $|\log_2$ fold-change$| > 1$, FDR<0.05) or to headspace from 1% (v/v) diacetyl diluted in the holding cage (748 up-regulated, 1031 down regulated, $|\log_2$ fold-change$| > 1$, FDR <0.05) (**Figure 2.5B and 2.5C**). GO analysis of the regulated genes in the exposed mouse brain transcriptome revealed several interesting sets of genes

were significantly altered in each set (**Figure 2.5E**). These results indicate that a volatile odorant like diacetyl is able to reach the brain in mammals, and presumably alter gene expression in neuronal cells. Although the overall DEG sets are different across the lungs and brain, there is a statistically significant overlap, particularly in the 1% exposure, as would be expected from using the same mechanism of action. There is a highly significant overlap ($p=2x10^{-101}$) between genes upregulated in the brain compared with the lungs (248 of 748), as well as for downregulated genes ($p=3x10^{-163}$; 477 of 1031 genes) (**Figure 2.5D**).

Diacetyl prevents proliferation of neuroblastoma cells

Among the significantly down-regulated genes is *MYCN*, which is known to show increased expression and plays a central role in many types of cancers, suggesting that epigenetic regulation may affect tumor cells. Broad-spectrum HDAC inhibitors have been approved by the FDA for treatment of a variety of cancers. To test the exciting possibility that a volatile HDAC inhibitor, which affects gene expression in the brain, would have an effect against cancers as well, we performed a cell-based assay. We picked neuroblastoma as a candidate since it has a strong dependence on *MYCN* and develop from fetal adrenal neuroblasts (Jansky et al., 2021). Several genetic and "omics" studies have identified genes that are upregulated in neuroblastomas, some of which are considered to be key factors (Pugh et al., 2013). We evaluated the DEGs from the diacetyl-exposed mouse brain transcriptome for several of these key genes. Three of the six key genes identified across multiple studies were significantly altered, two of which were significantly downregulated, *MYCN* (P=2.06E-13, FDR=1.76E-12) and *Alk* (P=3.3E-5, FDR=9.48E-5) (**Figure 2.5F**).

An unbiased computational study evaluated omics datasets and identified 4 genes that were the best predictors of clinical outcome (Zhong et al., 2018), all of which are significantly different in the brains of the diacetyl exposed mice, strikingly 3 of which were significantly downregulated, *NCAN (p=1.33E-16, FDR=1.59E-15), STK33 (p=4.6E-7, FDR=1.79E-6)* and *ERCC6L2 (p=4.57E-5, FDR=0.00012)* (**Figure 2.5F**). These findings are extremely provocative, given that the downregulated genes, particularly MYCN play a role in neuroblastomas and in several other cancers.

We tested diacetyl for the ability to inhibit proliferation of a SH-SY5Y neuroblastoma cell line from a metastatic bone tumor. A significant reduction in cell count was seen in diacetyl treatments in the SH-SY5Y cancer cell lines (**Figure 2.5G**). In order to validate the initial result, we retested diacetyl with at two concentrations across 3 different cancer cell lines. Diacetyl showed a significant reduction in cell numbers for the neuroblastoma cell line specifically, and not other cell lines, relative to the control (**Figure 2.5G**). These results demonstrate that the effect is specific to the SH-SY5Y cancer cell line, and unlikely to be caused by a non-specific general toxic effect. It also suggests that the potential epigenetic regulation of cancer promoting genes may be caused by exposure to volatiles like diacetyl in the environment.

In addition to diacetyl, we further assessed ethyl pyruvate and propyl formate against A549, PC3, and SH-SY5Y. A549 showed no significant proliferation for compounds except for 33 μM diacteyl (**Figure 2.10A**). However, it is to be noted in previous **Figure 2.5G**, which assessed A549 at different doses of diacetyl and showed no significant difference, this result may require additional experimental verification. When

assessing PC3, prostate cancer cell line derived from a bone metastasis, we saw no significant difference of proliferation against the compounds, with the exception of 100 μM Diacetyl which significantly inhibited proliferation (**Figure 2.10B and 2.10C**). SH-SY5Y as previously demonstrated to be inhibited by diacetyl was again inhibited by 33 μM Diacetyl, but not against 33 μM ethyl pyruvate or propyl formate (**Figure 2.10D**).

Testing therapeutic effect in neuroblastoma and Huntington's neurodegeneration

Since diacetyl is able to affect changes in a mammalian brain by crossing the blood brain barrier, we wanted to test if it can impart therapeutic effects in disorders of the brain like neurodegeneration for which HDAC inhibitors have been proposed as therapeutics. In order to test diacetyl in the context of neurodegenerative disease, we used the well-established *Drosophila* model of Huntington's disease (HD), which has previously been used to demonstrate the efficacy of sodium butyrate in slowing neurodegeneration (Marsh & Thompson, 2006; Steffan et al., 2001). The human Huntingtin protein with expanded poly-Q repeats is expressed in the neurons of the compound eye in *Drosophila*, causing progressive degeneration of the seven visible photoreceptor rhabdomere cells in each ommatidium (Jackson et al., 1998). We selected this model in particular since polyglutamine disorders are well suited for targeting by inhibitors of HDAC1 and HDAC3 (Thomas, 2014) such as diacetyl (**Figure 2.1B**). Moreover, previous studies have shown that orally administered HDAC inhibitors such as sodium butyrate and SAHA can significantly reduce photoreceptor degeneration in this model (Steffan et al., 2001). When the transgenic flies expressing two copies of the human Huntingtin with poly-Q repeats

(HTTQ120) under control of the eye-specific GMR promoter were raised at 18°C, the number of rhabdomeres in each ommatidium was similar to that normally observed in wild-type flies immediately post-eclosion (day 1, **Figures 2.6A-C**). When these HTTQ120 flies were moved to 25° C following eclosion (**Figure 2.6A**), they showed dramatic degeneration of rhabdomeres over a period of 10 days (**Figures 2.6B, 2.6D-G**). The mean number of rhabdomeres was reduced from 7 to ~1 by day 10. The dose of the volatile in the chamber was measured in parallel experiments by tracking volatile loss and airflow (0.5 L/min) and determined to range from 260-95 ppm, an average of 125 ppm at the end of hour 1, tapering off to 0 ppm by hour 24. The odorant was replaced each day, leading to a dosage profile that would seem like a once-a-day treatment regimen (**Figure 2.13A**).

Remarkably, when the Huntingtin (HTTQ120)-expressing flies were exposed immediately after eclosion to volatile headspace of 1% diacetyl (**Figure 2.6A**), they showed a substantial (~50%) reduction of rhabdomere loss (**Figures 2.6B, 2.6D-G**). The majority of ommatidia retained 6-7 rhabdomeres at day 5 (**Figures 2.6D and 2.6F**). Even after 10 days, the majority of the omamtidia still had 2-3 rhabdomeres left in the odor-exposed flies, while the solvent controls had only ~1-2 rhabdomeres (**Figures 2.6E and 2.6G**). These results demonstrate that exposure to volatile diacetyl in air slows down the photoreceptor degeneration caused in these Huntington's disease model flies. Thus, odorants like diacetyl may have potential as a prophylactic against this neurodegenerative disorder. Therefore, the volatile odorant can both significantly alter gene expression from a distance as well as cause a phenotypic change in the fly with a human disease gene.

Since some of the odorants also inhibit the class II HDAC6's to some extent we wanted to evaluate the contribution of HDAC6 towards protection of rhabdomere degeneration in the Huntingtin (HTTQ120)-expressing fly model. We tested HDAC6 null mutants for effects of diacetyl and propyl formate. When comparing HD flies in the HDAC6 mutant background, we noted an initial decrease in neurodegenration after 5 days, as observed with an increase in average rhabdomeres. This effect however is lost after 10 days of exposure (**Figure 2.7A**). When comparing both strains exposed to diacetyl, we see higher rhabdomere counts after 10 days in both strains, but not at the 5 day the HDAC6 mutants show no significant differences (**Figure 2.7B**). Propyl formate, the most selective of our discovered volatile odors to show HDAC inhibition against purified human HDAC6, we decided to assess this compound against HD wild-type and HD HDAC6 mutant flies. HD wild-type displayed significant higher rhabdomere averages with propyl formate exposure over 5 and 10 day time points, but HD HDAC6 mutants displayed higher rhabdomeres at 10 day time point (**Figure 2.7C**). Interestingly in the HD HDAC6 mutants, propyl formate exposure produced lower rhabdomere counts than control treatment at 5-day timepoint. Considering propyl formate shows more of a specificity to HDAC6 inhibition and weaker inhibition of HDAC1,3, and 4, the potential benefit of the propyl formate may be hindered due to loss of expected target HDAC6. While HDAC6 mutants did display a slower rhabdomere degeneration, it does not play a sole role in rhabdomere degeneration in these fly models.

Discussion

In this study, we discovered that eukaryotic cells have the ability to alter gene expression in response to an odorant, in a manner independent of traditional neuronal activity-induced pathways. Members of a conserved family of HDACs detect the concentration of diacetyl differentially. Diacetyl exposure increased levels of H3K9 acetylation in the nucleus in a dose-dependent manner and leads to changes in gene expression. The odorant diacetyl occurs naturally and is generated from the metabolism of a variety of food components, including triglycerides, sugars and amino acids (Shibamoto, 2014). Moreover, the chemical is produced by the activity of microorganisms such as yeasts and lactic bacteria during fermentation in many foods and beverages (Shibamoto, 2014). Although beyond the scope of this study, the discovery that cells can alter gene expression upon prolonged exposure to a common naturally occurring odorant raises important questions about the potential physiological consequences of the expression changes. Given our repeated exposure to particular flavors and fragrances, the findings outlined here highlight a new consideration for evaluating the safety of certain volatile chemicals that can cross the cell membrane.

In mammals, up-regulation of circulating β-hydroxybutyrate during fasting or calorie restriction induces changes in the expression of a set of genes (Shimazu et al., 2013). The acetylation mark specificity and IC_{50} of β-hydroxybutyrate is similar to that of diacetyl. Any beneficial physiological effects of odor-detection at lower odor concentrations would also be countered by studies of potential risks at higher concentrations. In fact, the deleterious effect of exposure to high levels to diacetyl causing

bronchiolitis obliterans, or “popcorn lung”, and its toxicity in cultured cells is already known (More et al., 2012). Even so it is present in several foods we eat and is on the GRAS (Generally Regarded as Safe) list of Flavor and Extract Manufacturers Association (FEMA) for use as a flavoring ingredient at low concentrations. While the specific mechanism of “popcorn lung” is unknown, it has previously been proposed that carbonyl groups of diacetyl can react to modify amino acid side chains on proteins or generate reactive dicarbonyl and reactive oxygen species, leading to excessive cytokine production and inflammation (Starek-Swiechowicz & Starek, 2014). Our results raise the possibility that the molecular mechanisms underlying this disorder could also be partially attributed to the unusually high HDAC-mediated genetic response to diacetyl by cells in the lungs. Several studies using rodent animal models have shown toxicity of high levels of diacetyl in the respiratory tracts including the nose and lungs (Morgan et al., 2008; Palmer et al., 2011). The toxic effect of higher dosages has been observed for many types of HDAC inhibitors. For example, in one *Drosophila* study, feeding of a high dosage of 4-phenylbutyrate reduces survival rate, while a lower dosage extends longevity (Kang et al., 2002). Another concern is that one of the highest known levels of diacetyl exposure to humans, however, is through smoking cigarettes, where exposure from even a single cigarette (250-361ppm) is high (Pierce et al., 2014; Rigler & Longo, 2010): Salem (128 μg/cigarette), Camel (128.1 μg/cigarette), Carlton (45.6 μg/cigarette) (Pierce et al., 2014). Different types of diets and lifestyle choices have been known to have effects on health and well-being due to differences in balance of different health promoting ingredients, yet little is known about role of such flavors, fragrances and metabolites acting on epigenetic

marks and altering gene expression. Our findings raise the possibility that diacetyl and structurally related odors in the environment may affect gene expression directly through absorption/transport into these cells. In mammals, the epithelium-lined lungs and nasal/oral pathway is directly exposed to odorants presenting an opportunity to affect gene expression and physiology.

Eukaryotes primarily detect volatile odorants in the environment using olfactory neurons that express a variety of transmembrane receptors, a family of genes that have independently evolved multiple times in different phyla. Examples of these unrelated genes include: the ionotropic 7-transmembrane (TM) odorant receptor *(*Or*)* family, which is insect-specific; 3-TM ionotropic receptors (IRs), which are present across most arthropods; the nematode-divergent 7-TM GPCRs belonging to the *str, sra, srg, srw, srz, srbc, srsx* and *srr* families; the mammalian 7-TM GPCR olfactory receptor (OR) family; and the trace amine-associated receptor (TAAR) family (Benton et al., 2009; Buck & Axel, 1991a; Clyne et al., 1999; Troemel et al., 1995; Vosshall et al., 1999). The activation of these receptors induces neuronal action potentials, and this information is conveyed to higher brain centers where olfactory perception is generated (Knaden & Hansson, 2014). This second response pathway which we have discovered is much slower and has an enzymatic mechanism which draws parallels with the multiple pathways in place to detect light. In the specialized cells of the eye, detection of light occurs via rhodopsins (7-transmembrane GPCRs) and leads to neuronal activity and behavioral responses. However, other cells, including in plants, are also able to respond to changes in light intensity of certain wavelengths using the ancient, conserved cryptochrome proteins that are related to

photolyases (Fogle et al., 2015). This suggests that vital sensory modalities can be detected via multiple pathways. Our observations raise the question whether HDACs represent a conserved detection mechanism for odorants like diacetyl that link odor-detection to a specific gene expression response. HDAC proteins, however, are an ancient family of genes that predate even histones themselves (Gregoretti et al., 2004; Postberg et al., 2010). It is conceivable that odor detection mechanisms that emerged in ancient forms may not have involved specialized transmembrane receptors, or neurons, or resulted in rapid behavioral movements.

Our data suggests that an HDAC inhibitory odorant also affects gene expression in the lungs and brain of mice, including significantly decreasing the expression level of the ACE2 receptor, whose ortholog in humans is the entry receptor for the SARS-CoV-2 virus that causes Covid-19. The applied impact for the future could be far-reaching, as HDACs are known to affect a wide variety of pathways in eukaryotes, and inhibitors are candidates for novel inhaled therapeutics as treatment of many conditions such as Covid-19, cancers, neurodegeneration and a variety of infectious diseases (Cai et al., 2010; Komatsu et al., 2006; Park et al., 2012; Platta et al., 2007; Shankar & Srivastava, 2008; Wang et al., 2012; Wang et al., 2013; Witt & Lindemann, 2009; Yeung et al., 2012).

Our studies also show that one of the volatiles is protective against the neurodegenerative effects of Huntington's disease model and neuroblastoma. Exposure to diacetyl volatiles in the fly model of Huntington's disease reduces cell degeneration, as has been previously observed with orally administered HDAC inhibitors like sodium butyrate and SAHA in this genetic model (Steffan et al., 2001). Previous studies indicate that the

inhibition of HDACs counter the acetyltransferase inhibitory activity of the polyglutamine-domain of the Htt protein which binds to p300, P/CAF and CBP (Steffan et al., 2001).

This newly discovered activity in this class of volatile chemicals will also allow us to understand how their presence in our environment, diet and microbiome shapes the epigenetic landscape in the lungs and affects inflammation and immune responses. Our approach to investigate consequences in model systems allows for a foundation for future research, and also allow identification of key molecular biomarkers that can be associated with observation of epigenetic effects, toxic or not, in individuals. The public health impact of these findings can be far-reaching, both from the perspective of toxicity as well as therapeutics. Investigating the health safety concerns of exposure to such odorants at high doses or prolonged periods is essential to understand potential for damage. Conversely, at non-toxic concentrations HDAC inhibitors can be used for treatment of many debilitating conditions in the lungs such as COPD, inflammation, and Covid-19 infection (Shakespear et al., 2011).

Taken together, our discovery that cells can alter gene expression in response to an odor that acts as an HDAC inhibitor and reprogram gene expression, promises the pursuit of new types of odor-based therapeutics already approved for human consumption as prophylactics for a myriad of diseases. Simultaneously, they raise the concern of a new type of environmental agent which can reprogram gene expression and have widespread effects that are yet unknown.

Materials and Methods

Drosophila Stocks and Manipulations

Fly stocks were maintained on conventional fly food under a 12-hr. light:12 hr. dark cycle at 18°C or 25°C. The fly strain of *w1118* backcrossed 5 times to *Canton-S* (*wCS*) was used in all the *Drosophila* transcriptome experiments. P{GMR-HTT.Q120}2.4 (Bloomington # 8533) were used for neurodegeneration experiments. HDAC6[KO] (Bloomington #51182) were used for producing HDAC6 mutant HD flies used in neurodegeneration experiments. For imaging *Gr63a-Gal4; UAS-mcd8:GFP, Gr21a-Gal4; UAS-mcd8:GFP* stocks were obtained as a kind gift from the Carlson lab, Yale.

Odor exposure experiments for imaging

Newly eclosed male wCS flies were sorted in groups of 30 into vials with standard cornmeal medium. Vials were closed with two overlapping 3''x3'' polypropylene mesh squares and tied with cotton twine. Vials were used within 6 hours. Four vials were placed in a 1000ml Nalgene straight sided jar with a 10ml glass beaker with 10ml of diacetyl 10^{-2} in paraffin oil. Jars were closed for exposure periods ranging from 2-6 days. In recovery experiments, vials were removed from the jars and were placed in a 25°C incubator for the remainder of the recovery period. Flies were anesthetized on ice, sacrificed in ethanol, and then immediately put into 1X phosphate buffered saline with 0.3% triton-x (PTX). Brains or antenna were put in 4% paraformaldehyde in PTX and incubated for 30min while rotating at 25°C. Samples were washed 5 times in PTX, and blocked in 5% natural goat serum in PTX for 1 hr while

rotating at 25°C. Samples were then incubated in primary antibody with 5% goat serum in PTX, mouse-nc82 (1:20) (Development Studies Hybridoma Bank, University of Iowa) and rabbit-antiGFP (1:150) (Invitrogen) in PTX for 48 hours in 4°C while rotating. After washing 5 times in PTX samples were incubated in secondary antibody with 5% goat serum in PTX, rabbit-anti-Alexa488 (1:400) (Invitrogen) and mouse-antiAlexa568 (1:400) (Invirtogen) for 48 hours in 4°C. Samples are washed 5 times in PTX and stored in 70% glycerol in PTX. Images were taken using a Ziess 510 laser scanning confocal microscope, and image analysis was done using Image J software.

QRT-PCR

Drosophila heads (with antenna) were collected on liquid nitrogen and stored at -80°C until processing. 300 heads were collected for each sample, and ground on liquid nitrogen. mRNA was extracted using a PolyATract kit (Promega), and was reverse transcribed using Superscript III (Invitrogen) according to the manufacturer's protocol. The quality of the cDNA was assessed on a 1.5% agarose gel. cDNA was added to individual reactions of SYBR green master mix (BioRad) and run on a BioRad-MyQ thermocycler. The program began with a single cycle for 3-min at 95°C, followed by 40 cycles of 15-sec at 95°C, 30-sec at 58°C and 30-sec at 72°C. Afterward, the PCR products were heated to 95°C for 1-min, and cooled to 55°C for 1-min, to measure the dissociation curves. The efficiency of each primer set was first validated by constructing a standard curve and three 10x serial dilutions of first strand cDNA. For each serial dilution, the CT value was plotted against the log (template dilution) and the slope and r^2

value of each regression line calculated. Expression of each *Or* or *Gr* gene was assessed in triplicate. Dissociation curves were used to assess the purity of the PCR reactions. *Or* and *Gr* transcript levels were normalized by using the transcript levels of *ribosomal protein 49*. Expression levels were calculated using the Pfaffl equation.

In general, primers were designed by using coding sequences close to the 3' end of the gene, and where possible, primers spanned an intron.

Primers:

Gr21a F: CGATCGTCTTTCCGAATCTC

Gr21a R: GGCTCAGATCCACCCATAGA

Gr63a F: AAATGAACTCCGCCTCCTTT

Gr63a R: CGCAATTTCAGAGGCAAACT

RP49 F: CTGCCCACCGGATTCAAG

RP49 R: GTTTCATGCGGCGAGATCG

Or47a F: ATCACAGGCCACATTGAACA

Or47a R: TCCCCGCAGTAGCAGTAGAT

Or88a F: TTAAAGTGGCCTTCCTGGTG

Or88a R: ATGCGGCAATAAAGTTCCAC

Or83b F: TTCTTGGCATTCGCTTTTCT

Or83b R: TCCCTGGATTTGTTTGCTTC

Odor Exposure Protocol for Transcriptome Analysis

Flies were exposed to diacetyl (B85307, Sigma-Aldrich, St. Louis, MO) by placing them in vials in a cylindrical closed container (112 mm diameter x 151 mm height) along with an odor-containing glass vial. The odorant was dissolved in 5 mL paraffin oil at 1% dilution. For a given exposure protocol, two groups of flies were prepared: those exposed to 1% diacetyl headspace and those exposed to paraffin oil headspace alone (control flies). Adult male flies aged 1 d were transferred to fly vials containing fresh medium and put into the container with the odor vial. At the end of the fifth day of exposure, flies were collected, and their antennae were dissected for RNA extraction. All treatments and experiments were performed at room temperature. For the recovery experiment, flies were transferred to a container with a glass vial of paraffin oil after 5 days of diacetyl exposure. At the end of the fifth day of recovery, flies were collected, and their antennae were dissected for total RNA extraction. The second and third antennal segments from 40-60 male flies after treatment were carefully hand-dissected from the head and collected in 1.5 ml microfuge tubes kept cold in liquid nitrogen. Antennae were mechanically crushed with disposable RNAse-free plastic pestles, and total RNA was isolated using a Trizol-based protocol. cDNA libraries were prepared from total RNA using the Illumina TruSeq RNA Sample Preparation Kit (v2) and 50 bps single- and paired-end sequencing was done using the HighSeq2000. Two biological replicates were sequenced for each condition, with an average of 27 million reads / replicate, and with an average of 84% mapped.

Two-month old C57BL/6 male mice (2-3 for each condition in a single cage) were continually exposed to air flowing over headspace of paraffin oil (solvent control), 0.1%,

or 1% diacetyl over a period of 5 days, then euthanized for collecting the lung and brain tissues and processing for mRNA isolation. All protocols for animal use and euthanasia were approved by the Institutional Animal Care and Use Committee (#20150028) and were in accordance with the provisions established by the Animal Welfare Act and the Public Health Services (PHS) Policy. In the transcriptome analysis, two replicates were performed for each condition, with an average of 123,687,411 reads / replicate, with an average of 88% mapped. Multiplexed libraries were made from total RNA input using the Illumina TruSeq RNA sample preparation kit (v2) and 50 bps single-end sequencing was done using the NextSeq500.

Calculation ppm in air based on weight loss of odorant over time

The odor solution in PO in each setup (Drosophila and mouse) was weighed using a sensitive balance. PO is non-volatile and therefore weight loss is attributable to diacetyl volatilization. Volatile Headspace exposure (ppm) is calculated through odor cartridge weight change from pure odor compound volatizing out (Inamdar et al., 2012).

ppm=(10^6 w/MW)/(v/V_m)

Where ppm is the concentration of tested VOC in parts per million (v/v); w is the weight of the tested chemical in grams; MW is the molecular weight of the tested VOC (grams/mole); v is the total volume of the respective exposure chambers; and Vm is the molecular volume under the tested condition.

•V_m=24.45(760/P)((t+273.15)/298.15)

Where 24.45 = gram molecular volume, under standard Lab conditions of 760 mm Hg, 25°C; P = ambient pressure, in mm Hg; and t = ambient temperature, in °C. Odor cartridges, consisting of varying odor volume/volume dilutions, were weighed periodically under standard ambient temperature and pressure. Under these conditions, the pure volatile odor compounds volatize out of the odor cartridge and the evaporation rates were used for our exposure calculations. Based on Ideal Gas Law and experimental conditions, ppm is calculated based on volatized odor compound and experimental chamber volume based on airflow.

HDAC inhibitor Treatment Protocol for Transcriptome Analysis

Sodium butyrate (B5887, Sigma-Aldrich) or valproic acid (P4543, Sigma-Aldrich) were dissolved in normal fly food medium at the final concentration of 10 mM. Three groups of flies were prepared: those treated with one of the HDAC inhibitors and those without HDAC inhibitor treatment (control flies). Adult flies aged 1 d were transferred to fly vials containing medium with or without a HDAC inhibitor. At the end of the fifth day of treatment, flies were collected, and their antennae were dissected for RNA extraction. All treatments and experiments were performed at room temperature. Two biological replicates with 60 flies/replicate were performed for each condition, with an average of 23 million reads / replicate, and with an average of 92% mapped. Multiplexed libraries were made from total RNA input using the Illumina TruSeq RNA sample preparation kit (v2) and 50 bps paired-end sequencing was done using the HighSeq2000.

Bioinformatic analysis of RNA-seq experiments

Reads aligned to the latest release of each of the genomes used (dm6 for the *Drosophila* genome, GRCm38 for the *Mus Musculus* genome) and quantified with kallisto (version 0.43.1) (Bray et al., 2016) Only libraries for which we obtained >75 % alignment were used for downstream analysis. Transcript counts were summarized to gene-level using tximport package (version 1.4.0)(Soneson et al., 2015). For any instances of detected batch effects, we removed unwanted variation using RuvR in the RuvSeq package (version 1.10.0)(Risso et al., 2014). Differentially expressed gene (DEG) analysis was performed with the edgeR package (version 3.18.1)(Robinson et al., 2010) using low count filtering (cpm >0.5) and TMM normalization. Protein classification analysis was performed with PANTHER (version 13.1)(Mi et al., 2017). All significance analyses of gene overlap were done using the GeneOverlap package in R package (version 1.14.0). GO enrichment analysis was performed using clusterProfiler (version 3.6.0)(Yu et al., 2012).

HDAC Activity Assays

HDAC activity of class I HDACs (HDAC1, 2, 3 and 8) was measured with the fluorometric HDAC Activity Assay kit: HDAC1 (10011563, Cayman Chemical, Ann Arbor, MI), HDAC2, HDAC 3, and HDAC 8 (50062, 50073 and 50068, BPS Bioscience, San Diego, CA), according to the manufacturer's instructions. HDAC activity of class II HDACs (HDAC4 and HDAC6) were measured with the fluorometric HDAC Activity Assay kit: HDAC4, HDAC 4 (50064 and 50076, BPS Bioscience, San Diego, CA), according to the manufacturer's instructions. HDAC activity in these 96-well format kits

are directly correlated with fluorescence produced by the enzyme and substrate interaction. Each test compound was tested in duplicates, minimum. Due to interference, concentrations of >30 mM were not used in the IC50 calculation. To account for any potential absorbance or fluorescence contributed by the test chemicals interacting with the assay substrate, all baseline background measurements of test compound + substrate control wells (everything, but no HDAC enzyme) were performed and subtracted against the respective test compound wells. It is fair to note that no significant changes in background fluorescence were seen with tested compounds in comparison to control background fluorescence. In the SOP, this would be just referred to as blanks with only the substrate and solvent without compound or HDAC enzyme. HDAC activity was calculated based on averaged maximum fluorescence from negative control wells and the averaged fluorescence in test compound wells.

$$\frac{Fluorescence_{Negative\ \ control} - Fluorescence_{HDACi}}{Fluorescence_{Negative\ \ control}} x100\%$$

$$= Remaining\ HDAC\ activity\ \%$$

HDAC % inhibition was directly calculated from obtained HDAC activity %.

Cell Culture and Treatment

Human embryonic kidney 293 (HEK293) cells were grown in 100 mm cell culture dishes with Dulbecco's modified Eagle's medium (DMEM) (10-013, Corning, Manassas, VA), supplemented with 10% fetal bovine serum (FBS) (26140-079, Gibco, Carlsbad, CA) at 37°C with 5% CO_2. Cells that were ~80% confluent were treated with freshly prepared

medium supplemented with diacetyl at concentrations indicated. The cells for mock controls were handled in the same manner without adding diacetyl to the medium. In order to prevent diffusion of diacetyl odor from the treatment dishes to the ones of mock control, the cell culture dishes in different conditions were cultured in separate CO_2 incubators.

Cell proliferation assays were performed to assess effects of compounds against cancer cell lines. Cells were maintained in a 37°C incubator with 5% CO2 throughout the whole experiment. Compound stocks are dissolved in 10% DMSO, and final concentrations made fresh in complete media as needed. 10% DMSO solvent is used as control in complete media. Cells were seeded onto 12-well plates and allowed 12-24 hours until treatment to allow cells to adhere to wells. This is followed by minimum 5-day treatment of compounds, changing the media with treatment every 48 hours. Cell lines A549, PC3, and SK-MEL-5 will be seeded at 8000 cells/well, which was determined to provide 80-100% confluency after 6-day growth. SH-SY5Y was seeded at 8000 cells/well and 16,000 cells/well due to their known slower division rate and given at least 10 days for sufficient growth. After allotted growth times, cell counts were performed using the CountessTM automated cell counter. All assays had a minimum of three replicates for all conditions and analyzed through GraphPad Prism One-way ANOVA for significance.

Odor Exposure Protocol for Huntington's Disease Model Flies

Flies were exposed to diacetyl in a cylindrical container (112 mm diameter x 151 mm height). Each container was tightly closed but had 2 holes, one of which connected to

an air suction port, and the other to a vial containing either of 5 mL paraffin oil or 5 mL 1% diacetyl in paraffin oil. A gentle suction was applied to pull the headspace from the odor or paraffin oil vials into the cylindrical structure. pGMR-HTTQ120 flies were maintained at 18°C. Adult flies aged 1 d were transferred to fly vials containing fresh medium and put into the odor-filled container at room temperature. Paraffin oil and 1% diacetyl solution were prepared and replaced every day. At the end of the fifth day of exposure, half of the flies were collected and subjected to pseudopupil analysis as before (Steffan et al., 2001). The remaining flies were transferred to fresh medium and exposed to the odors for an additional 5 days. All treatments and experiments were performed at room temperature. The number of rhabdomeres in each ommatidium was counted using the pseudopupil analysis, and statistical significance was determined by unpaired t test (two-tailed) against PO at each time point.

Preparation of Nuclear Extracts from HEK293 Cells

Nuclear extracts of HEK293 cells were prepared according to a protocol described previously (Andrews & Faller, 1991), with minor modifications. In brief, HEK293 cells were washed twice with cold phosphate-buffered saline (PBS) and lysed with hypotonic buffer (10 mM HEPES-KOH [pH 7.9], 1.5 mM $MgCl_2$, 10 mM KCl, protease inhibitor cocktail (04693159001, Roche, Indianapolis, IN), 1 mM DTT, 1 mM TSA). Following a brief centrifugation, the pellet was resuspended in hypertonic buffer (20 mM HEPES-KOH [pH 7.9], 25% glycerol, 420 mM NaCl 1.5 mM $MgCl_2$, 0.2 mM EDTA, protease inhibitor cocktail, 1 mM DTT, 1 mM TSA). The supernatant was recovered as nuclear extract.

Western Blot Analysis

Proteins in the nuclear extracts (60 µg protein) were separated by SDS–PAGE gels (456-1043, Bio-Rad, Hercules, CA), transferred onto PVDF membranes (162-0174, Bio-Rad), and incubated with anti-histone antibodies: acetylated H3K9 (1/2000: ab4441, abcam, Cambridge, MA), acetylated H3K14 (1/5000: 06-911, EMD Millipore, Billerica, MA), acetylated H4K5 (1/2000: 07-327, EMD Millipore). Bound antibody was detected by horseradish peroxidase-conjugated anti-rabbit secondary antibody (1/20000: 1705046, Bio-Rad) and developed using Clarity™ Western ECL Substrate (1705060, Bio-Rad). Signals were detected and captured by ImageQuant™ LAS 4000 mini (GE healthcare, Pittsburgh, PA), and band intensities were quantified with ImageJ software. H3K9 acetylation intensity in individual lanes was reported relative to the normalized Mock treatment, and calculated using this formula: Relative H3K9ace intensity for each timepoint = (H3K9ace / PCNA) / averaged (Mock H3K9ace / Mock PCNA). Statistical significance was determined by unpaired *t* test (two-tailed) against mock at each time point.

Data availability

All transcriptome data sets in this publication have been deposited in the GEO repository with accession number GSE116502. All other data is presented in the figures, tables and supplementary materials.

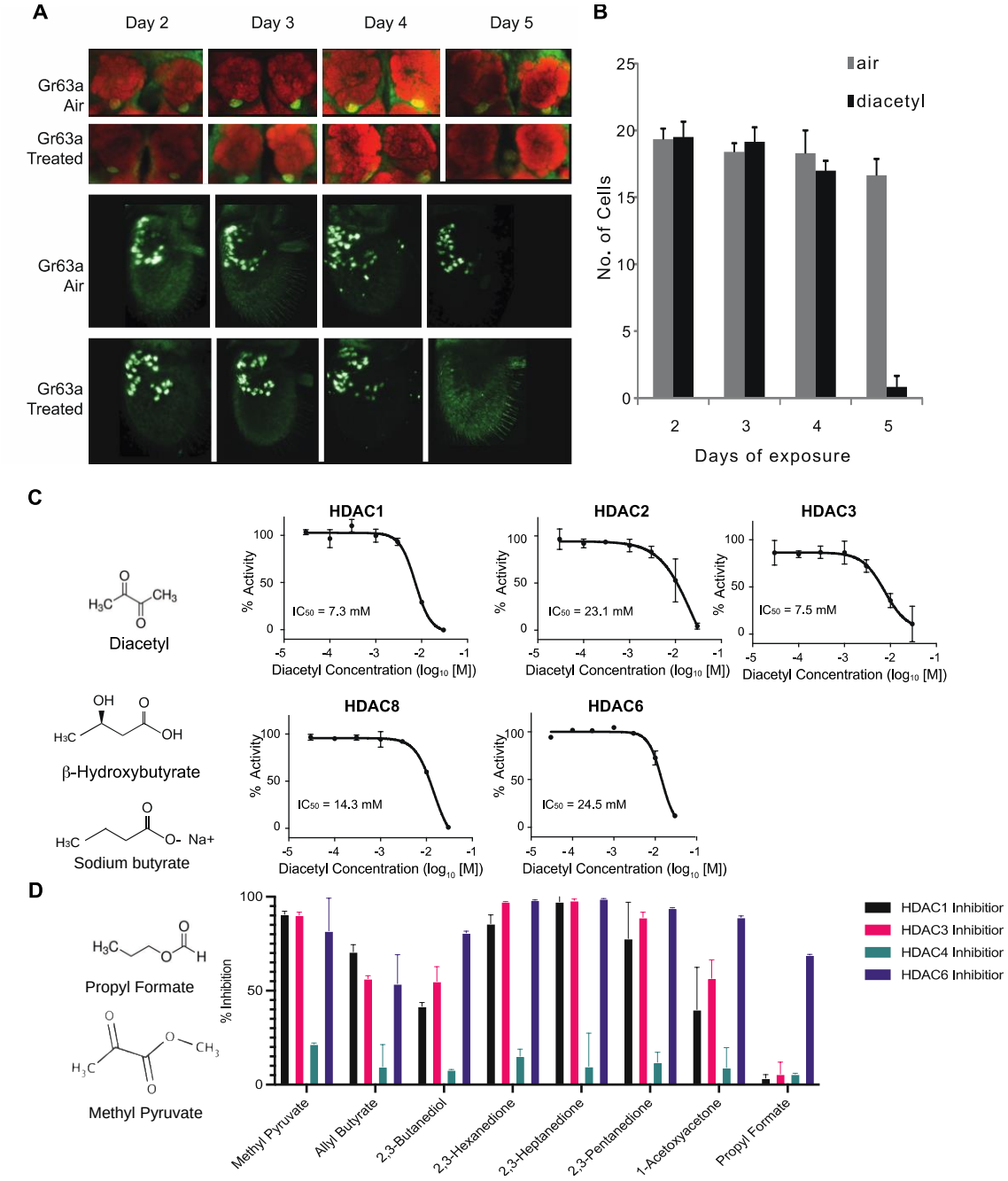

A
Day 2
Day 3
Day 4
Day 5
Gr63a Air
Gr63a Treated
Gr63a Air
Gr63a Treated
B
air
diacetyl
No. of Cells
Days of exposure
C
Diacetyl
β-Hydroxybutyrate
Sodium butyrate
HDAC1
HDAC2
HDAC3
HDAC8
HDAC6
% Activity
IC50 = 7.3 mM
IC50 = 23.1 mM
IC50 = 7.5 mM
IC50 = 14.3 mM
IC50 = 24.5 mM
Diacetyl Concentration (log10 [M])
D
Propyl Formate
Methyl Pyruvate
% Inhibition
HDAC1 Inhibitior
HDAC3 Inhibitior
HDAC4 Inhibitior
HDAC6 Inhibitior
Methyl Pyruvate
Allyl Butyrate
2,3-Butanediol
2,3-Hexanedione
2,3-Heptanedione
2,3-Pentanedione
1-Acetoxyacetone
Propyl Formate

Figure 2.1 Volatiles found in microbes can inhibit HDACs in vitro

(**A**) Antennal and whole mount brain staining of *Gr63a-Gal4* flies. Flies were exposed to diacetyl (headspace from 10^{-2} soln) or air for 2 to 5 days. Brains and antenna were dissected on the indicated days, fixed, and then stained for neuropil marker nc82 (red) and anti-GFP (green). (**B)** Mean of ab1C neurons expressing GFP after indicated days of odor exposure. d4on=2,3-butanedione. n=6, error bars=s.e.m. Schematic chemical structures of diacetyl, β-hydroxybutyrate and Sodium butyrate. **(C)** Dose-activity curves of class I HDACs: HDAC1, HDAC2, HDAC3, HDAC8 and class II HDAC6 treated with various concentrations of diacetyl. Percentage of HDAC activity is relative to the activity of each enzyme without diacetyl. IC50s are indicated in the chart areas. Error bars, S.E.M., n = 4-5. **(D)** Representative structures of odorants that inhibit HDACs, and Average percentage inhibition of class I HDACs: HDAC1, HDAC3 and class II HDAC4, HDAC6 treated with 15mM of indicated volatiles. Error bar= S.D., each tested in duplicate.

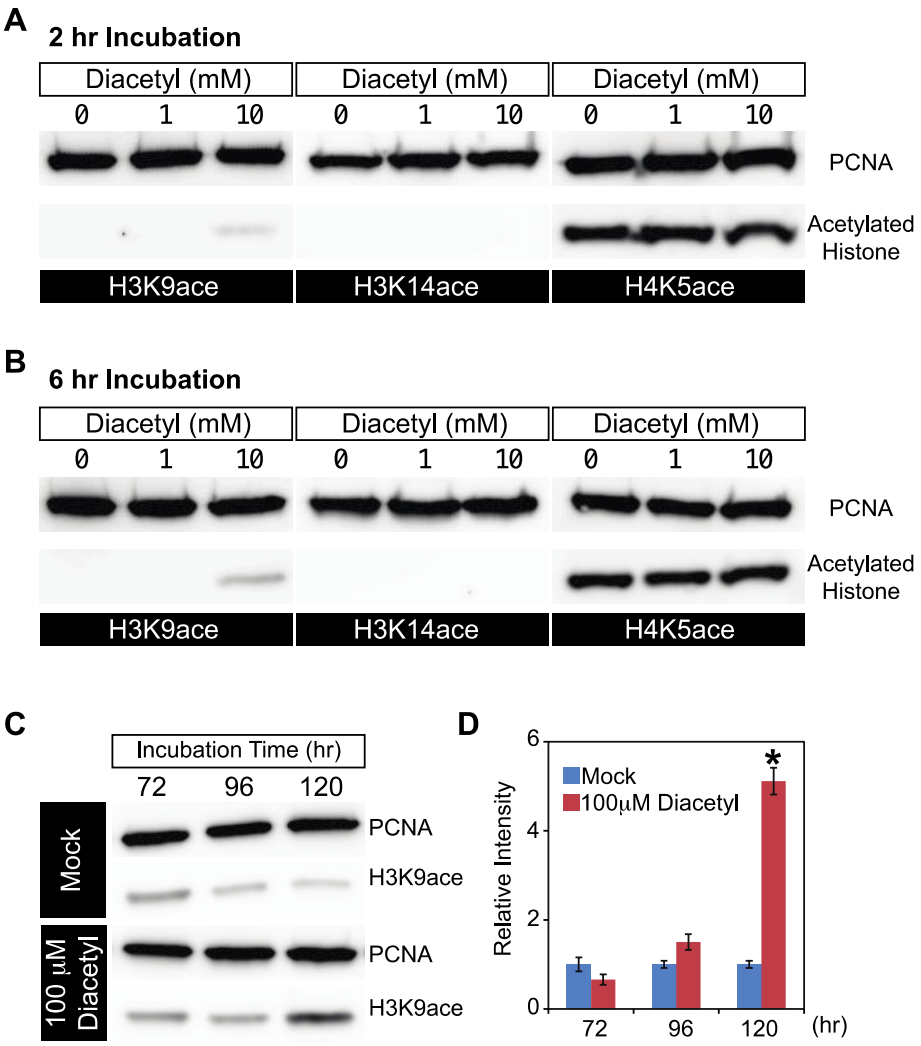


Figure 2.2 Diacetyl increases level of histone acetylation in HEK293 cells (A and B) Representative images from Western blots showing acetylation levels of H3K9 (left), H3K14 (middle) and H4K5 (right) in HEK293 cells after 2 hours **(A)** and 6 hours **(B)** of diacetyl exposure. PCNA (Proliferating cell nuclear antigen) is a 29 kDa nuclear protein used as a loading control for nuclear protein extracts. **(C)** Western blots showing acetylation levels of H3K9 in HEK293 cells treated with 100 µM diacetyl for 72, 96, and120 hours. PCNA is used for a loading control. **(D)** Bar graph showing the relative intensities of acetylated H3K9 in HEK293 cells treated with 100 µM diacetyl for 72 -120 hours. n = 4 samples, * $p < 0.05$, and **** $p < 0.0001$.

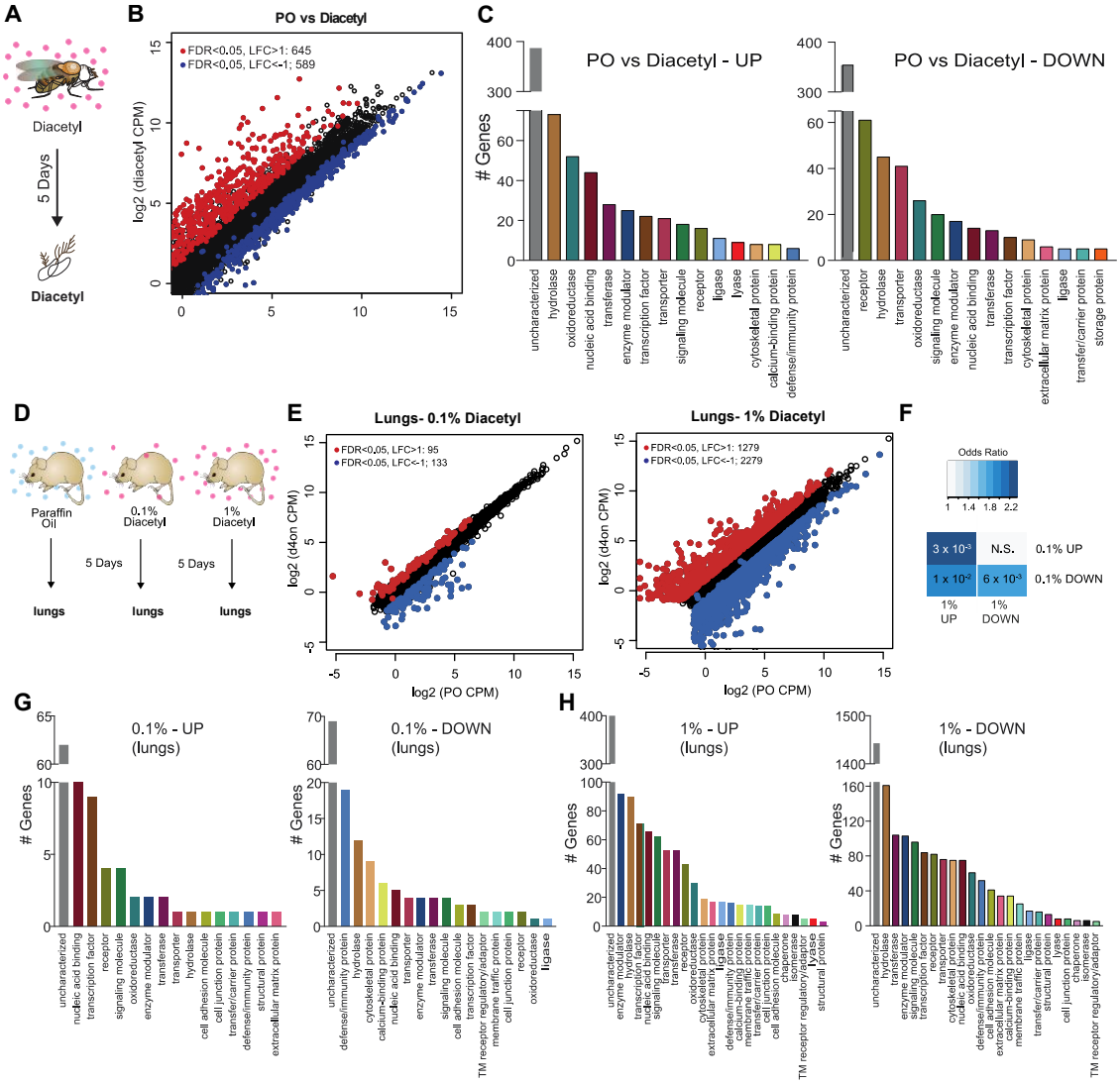

A
Diacetyl
5 Days
Diacetyl
B
PO vs Diacetyl
FDR<0.05, LFC>1: 645
FDR<0.05, LFC<-1; 589
log2 (diacetyl CPM)
log2 (PO CPM)
C
PO vs Diacetyl - UP
PO vs Diacetyl - DOWN
Genes
uncharacterized
hydrolase
oxidoreductase
nucleic acid binding
transferase
enzyme modulator
transcription factor
transporter
signaling molecule
receptor
ligase
lyase
cytoskeletal protein
calcium-binding protein
defense/immunity protein
extracellular matrix protein
transfer/carrier protein
storage protein
D
Paraffin Oil
0.1% Diacetyl
1% Diacetyl
5 Days
5 Days
lungs
lungs
lungs
E
Lungs- 0.1% Diacetyl
Lungs- 1% Diacetyl
FDR<0.05, LFC>1: 95
FDR<0.05, LFC<-1; 133
FDR<0.05, LFC>1: 1279
FDR<0.05, LFC<-1; 2279
log2 (d4on CPM)
log2 (PO CPM)
F
Odds Ratio
1
1.4
1.8
2.2
3 x 10-3
N.S.
0.1% UP
1 x 10-2
6 x 10-3
0.1% DOWN
1% UP
1% DOWN
G
0.1% - UP (lungs)
0.1% - DOWN (lungs)
Genes
H
1% - UP (lungs)
1% - DOWN (lungs)
Genes

Figure 2.3 Remote exposure to HDACi volatile alters gene expression in an invertebrate, and vertebrate.
(**A**) Schematic of odor exposure protocol for transcriptome analysis from the antennae. (**B**) Plot highlighting up- and down-regulated genes in the diacetyl-exposed group. Red and blue dots represent up-regulated genes (false discovery rate (FDR) < 0.05, $\log_2$ fold change (LFC) > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively. (**C**) Bar graphs denoting the protein classification of the genes up- and down-regulated after odor exposure. **(D)** Schematic of diacetyl exposure protocol for transcriptome analysis of mouse lung tissue. **(E)** Plot highlighting up- and down-regulated genes in the diacetyl-exposed groups. Red and blue dots represent up-regulated genes (FDR < 0.05, LFC > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively in lungs. **(F)** Table showing pairwise tests of significance of overlap between gene sets. P-values from Fisher's exact test, colored with associated odds ratio (strength of association). **(G and H)** Bar graphs denoting the protein classification of the genes up- and down-regulated in the lung after exposure to headspace above 0.1% (v/v) **(G)** and 1% (v/v) **(H)** of diacetyl solutions.

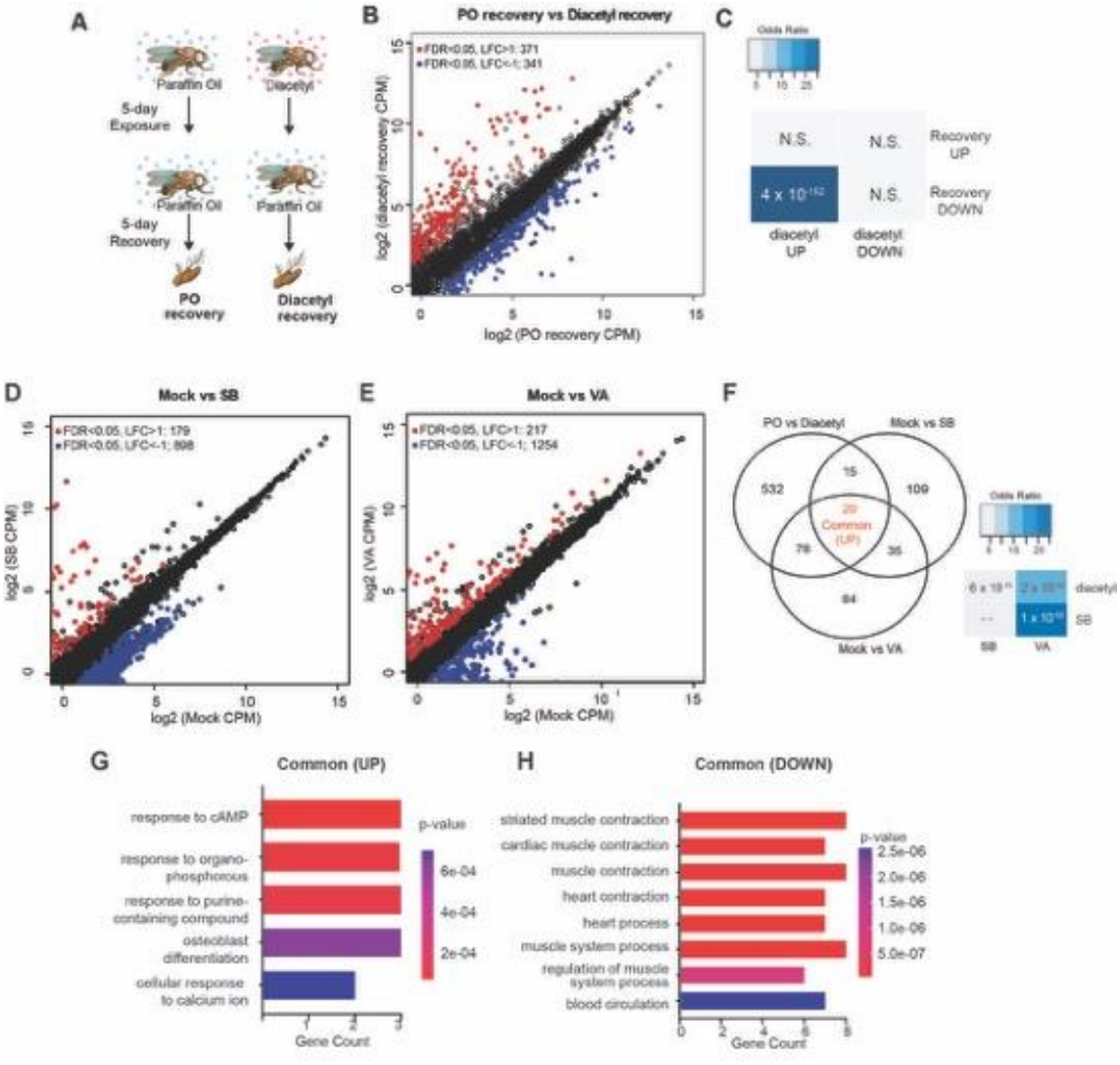

A
Paraffin Oil
Diacetyl
5-day Exposure
Paraffin Oil
Paraffin Oil
5-day Recovery
PO recovery
Diacetyl recovery
B
PO recovery vs Diacetyl recovery
FDR<0.05, LFC>1: 371
FDR<0.05, LFC<-1: 341
log2 (diacetyl recovery CPM)
log2 (PO recovery CPM)
C
Odds Ratio
N.S.
N.S.
Recovery UP
4 x 10-152
N.S.
Recovery DOWN
diacetyl UP
diacetyl DOWN
D
Mock vs SB
FDR<0.05, LFC>1: 179
FDR<0.05, LFC<-1: 898
log2 (SB CPM)
log2 (Mock CPM)
E
Mock vs VA
FDR<0.05, LFC>1: 217
FDR<0.05, LFC<-1: 1254
log2 (VA CPM)
log2 (Mock CPM)
F
PO vs Diacetyl
Mock vs SB
Mock vs VA
532
15
109
20 Common (UP)
78
35
84
Odds Ratio
diacetyl
SB
SB
VA
G
Common (UP)
response to cAMP
response to organo-phosphorous
response to purine-containing compound
osteoblast differentiation
cellular response to calcium ion
p-value
6e-04
4e-04
2e-04
Gene Count
H
Common (DOWN)
striated muscle contraction
cardiac muscle contraction
muscle contraction
heart contraction
heart process
muscle system process
regulation of muscle system process
blood circulation
p-value
2.5e-06
2.0e-06
1.5e-06
1.0e-06
5.0e-07
Gene Count

Figure 2.4 Gene expression changes are partly reversible, and overlaps with known HDACi drugs

(**A**) Schematic of odor exposure and recovery protocol for transcriptome analysis from the antennae. (**B**) Plot highlighting up- and down-regulated genes in the recovery from diacetyl exposure group. Red and blue dots represent up-regulated genes (FDR < 0.05, LFC > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively. (**C**) Table showing pairwise tests of significance of overlap between gene sets. P-values from Fisher's exact test, colored with associated odds ratio (strength of association). (**D** and **E**) Plots showing enrichment of up- and down-regulated genes in sodium butyrate- (**D**) and valproic acid-treated (**E**) groups. Red and blue dots represent up-regulated genes (FDR < 0.05, LFC > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively. (**F**) *Left:* Venn diagrams showing the overlaps of up-regulated genes among diacetyl-, sodium butyrate- and valproic acid-treated groups. *Right:* Table showing pairwise tests of significance of overlap between gene sets. P-values from Fisher's exact test. (**G and H)** GO-enrichment analysis of the common Up-regulated and down-regulated genes across all 3 treatments in (**F**)**.**

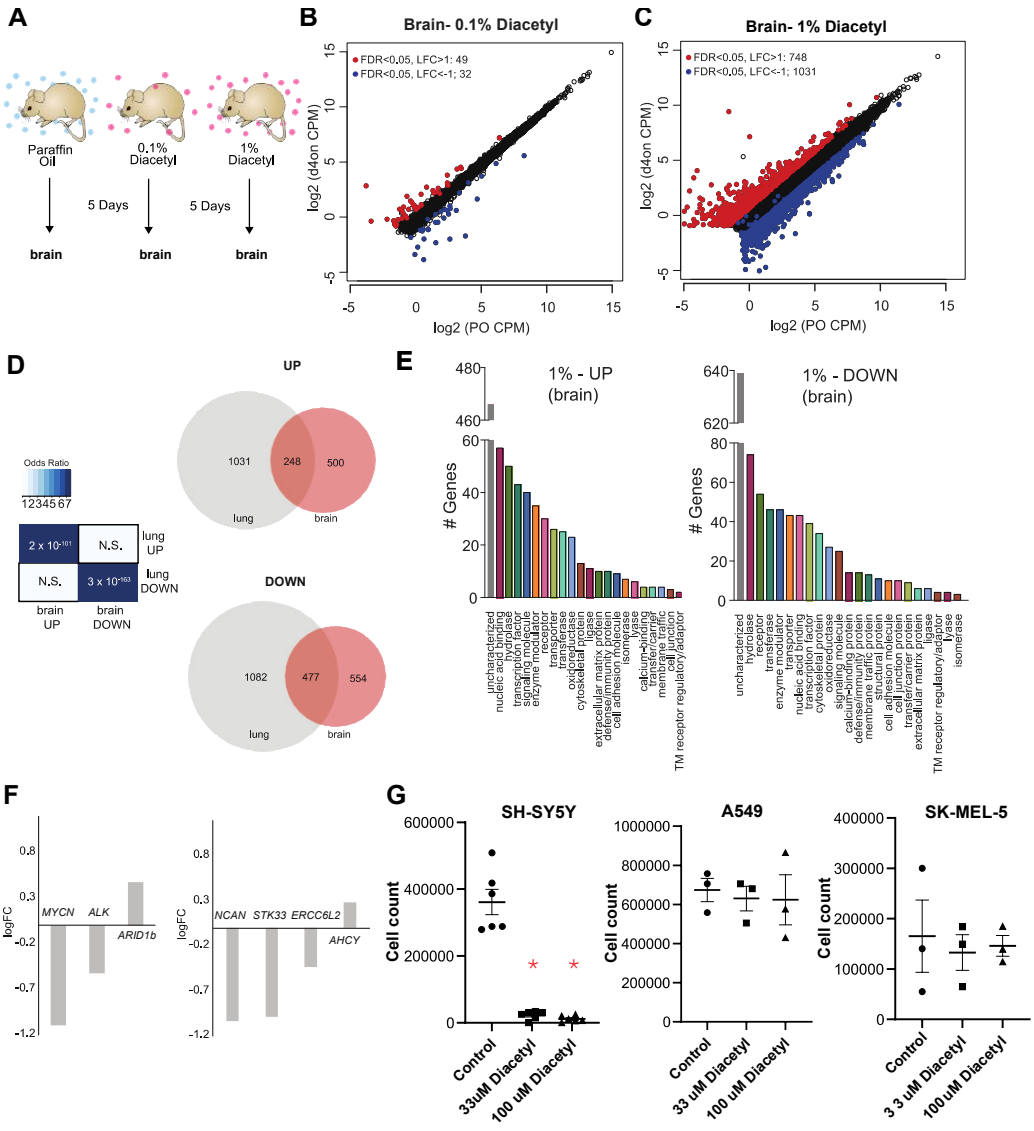


Figure 2.5 Exposure to diacetyl vapor alters gene expression in the mouse brain
(A) Schematic of diacetyl exposure protocol for transcriptome analysis of mouse brain tissues. **(B and C)** Plot showing up- and down-regulated genes in the diacetyl-exposed groups. Red and blue dots represent up-regulated genes (FDR < 0.05, LFC > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively in the brain. **(D)** *Left:* Table showing pairwise tests of significance of overlap between gene sets. P-values from Fisher's exact test. *Right:* Venn diagrams showing the overlaps of DEGs between lung and brain groups. **(E)** Bar graphs denoting the protein classification of the brain genes up- and down-regulated after 1% diacetyl exposure. **(F)** Mean fold change of select neuroblastoma related genes in the brain of mice exposed to diacetyl vapors. **(G)** Cell counts of indicated cancer cell lines in tissue culture treated with solvent control or indicated concentration of diacetyl. N=3-6, p<0.001.

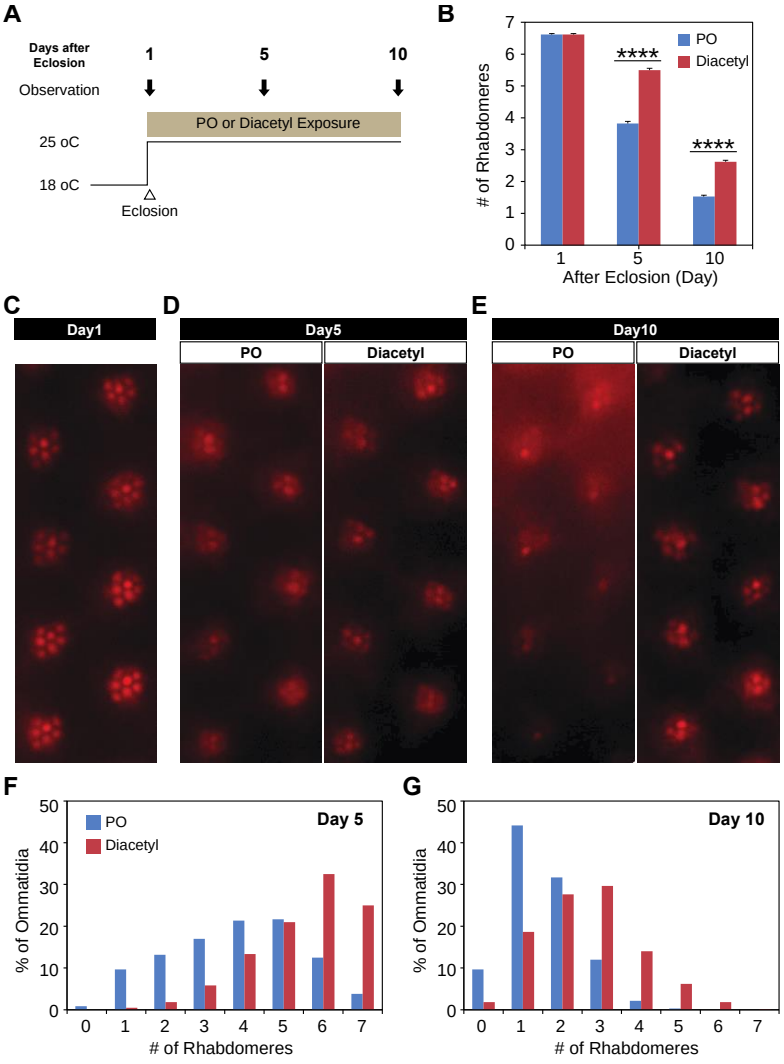


Figure 2.6 Odor exposure slows Huntington's neurodegeneration model in fly eye
(A) Schematic diagram showing temperature of experimental condition and timing of the eye examination in pGMR-HTTQ120 flies. **(B)** Bar graph showing mean number of rhabdomeres in each ommatidium in solvent paraffin oil (PO, blue) and diacetyl-exposed (red) pGMR-HTTQ120 flies at 1, 5, and 10 days after eclosion (AE). n = 600 ommatidia from 15 flies, **** $p < 0.0001$. **(C)** A representative image of ommatidia of pGMR-HTTQ120 flies at 1 day AE. **(D and E)** Representative images of ommatidia of pGMR-HTTQ120 flies exposed to paraffin oil (PO) or diaceyl at 5 **(D)** and 10 **(E)** days AE. **(F and G)** Histogram showing the percent of the ommatidium with a given number of rhabdomeres indicated on the x axis at 5 **(F)** and 10 **(G)** days AE.

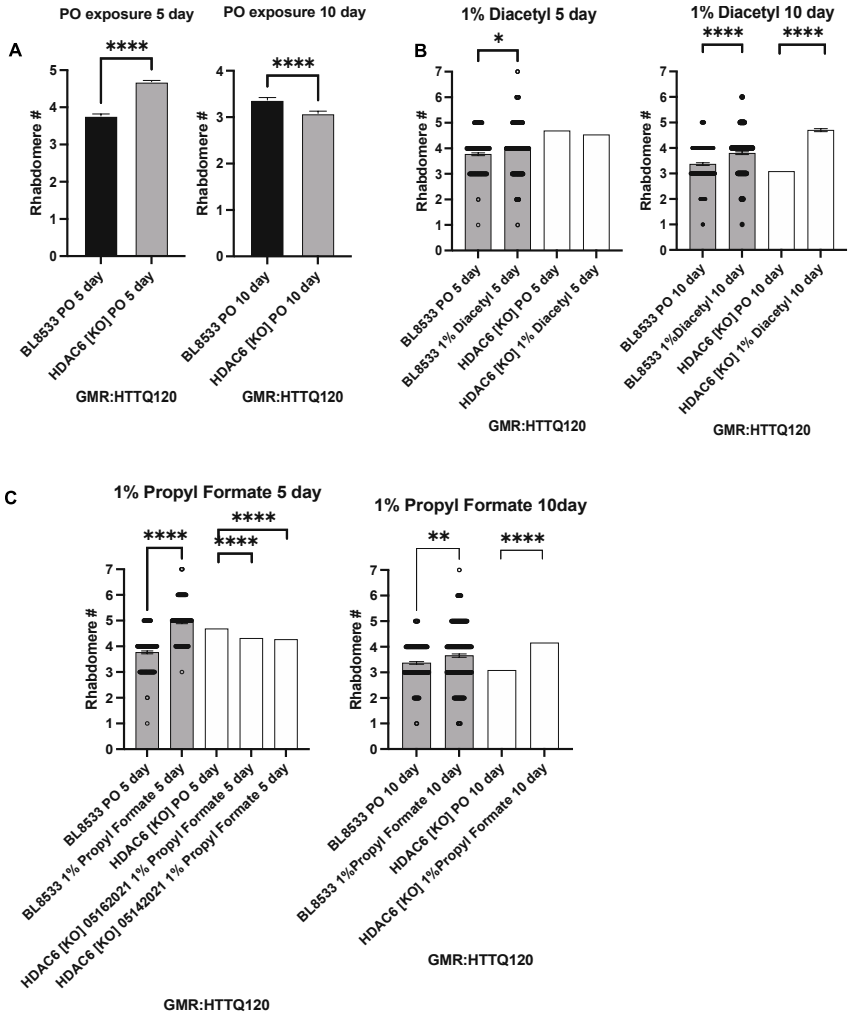


Figure 2.7 Odor exposure slows Huntington's neurodegeneration model in fly eye (diacetyl and propyl formate)

(A) Bar graphs showing mean number of rhabdomeres in each ommatidium of pGMR-HTTQ120 flies vs HDAC6 [KO] pGMR-HTTQ120 flies over the course of 5- and 10-day solvent PO exposure. HDAC6 [KO] pGMR-HTTQ120 flies displayed initial inhibition of rhabdomere degeneration at 5-day mark, but potential detrimental effect after 10 days. **** $p < 0.0001$. **(B)** Bar graph showing mean number of rhabdomeres in each ommatidium after diacetyl-exposure pGMR-HTTQ120 flies at 5 and 10 days after eclosion versus HDAC6[KO] pGMR-HTTQ120 (red). BL8553 1% Diacetyl 5 days, n=340 rhabdmomere from 10 flies. * $p = 0.0136$, **** $p < 0.0001$. **(C)** Bar graph showing mean number of rhabdomeres in each ommatidium after propyl formate-exposure (red) pGMR-HTTQ120 flies at 5 and 10 days after eclosion. ** $p < 0.01$, **** $p < 0.0001$

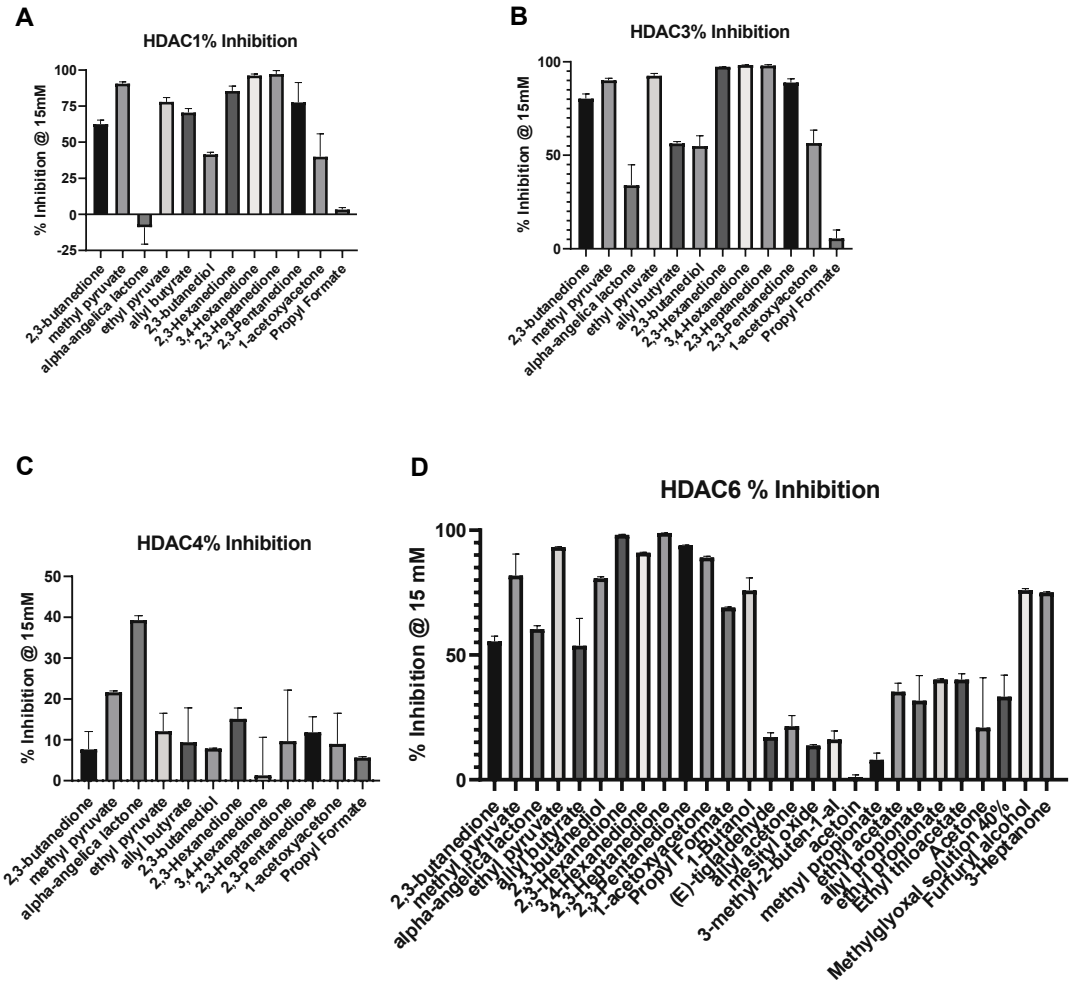


Figure 2.8 Average percent inhibition of all screened odorants for HDAC inhibition **(A-D)** Bar graphs showing average percentages of class I HDACs: HDAC1, HDAC3, and class II HDAC4, HDAC6 treated with 15mM of indicated volatile odor compounds. Error bar=SD, each tested in duplicate.

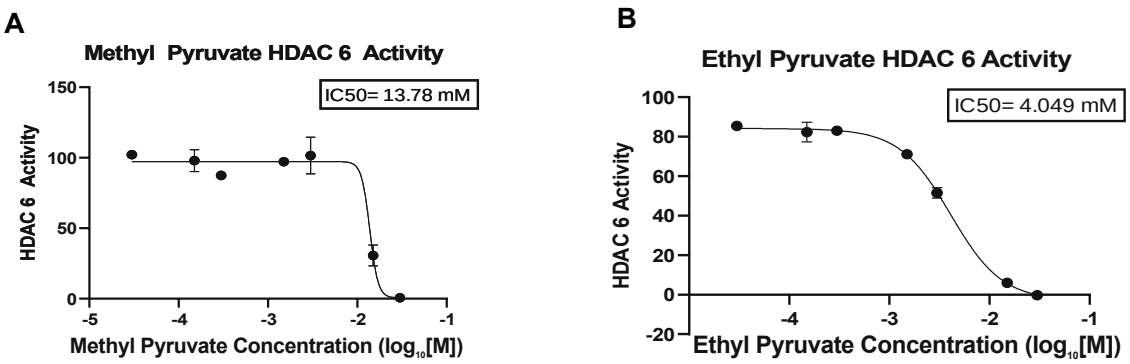


Figure 2.9 Dose-Activity Curves of volatile compounds Methyl Pyruvate and Ethyl Pyruvate against Class II HDAC6

A) Dose–activity curves of class II HDAC6 treated with various concentrations of Methyl Pyruvate. **B)** Dose–activity curves of class II HDAC6 treated with various concentrations of Ethyl Pyruvate. Percentage of HDAC activity is relative to the activity of each enzyme without compound of choice. IC50s are indicated in the chart areas. Error bars = SEM, each tested in duplicate.

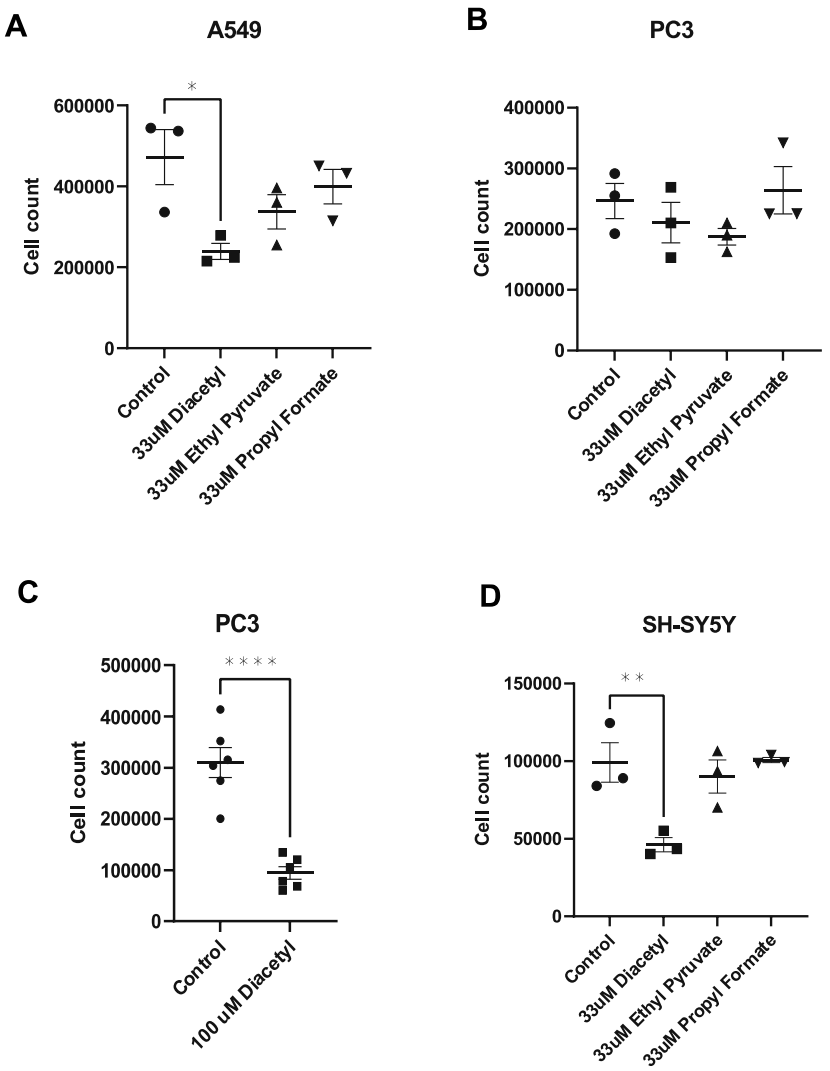


Figure 2.10 Cell culture assay of various human cancer cell lines against several promising volatile HDAC inhibitors

A) A549, lung carcinoma epithelial cells, demonstrated no significance in proliferation against 33.3 µM ethyl pyruvate and propyl formate, except for diacetyl * p=0.0394 **B)** PC3, prostate cancer cell line, showed no significant difference in proliferation against 33.3 µM diacetyl, ethyl pyruvate, and propyl formate. **C)** However, PC3 showed significant inhibition of proliferation against 100 µM diacetyl. **** $p<0.0001$ **D)** SH-SY5Y, neuroblastoma cell line, was significantly inhibited by 33.3 µM diacetyl but not the other tested compounds. ** $p=0.0065$ Cell counts of indicated cancer cell lines in tissue culture treated with solvent control or indicated concentration of diacetyl. n = 3–6.

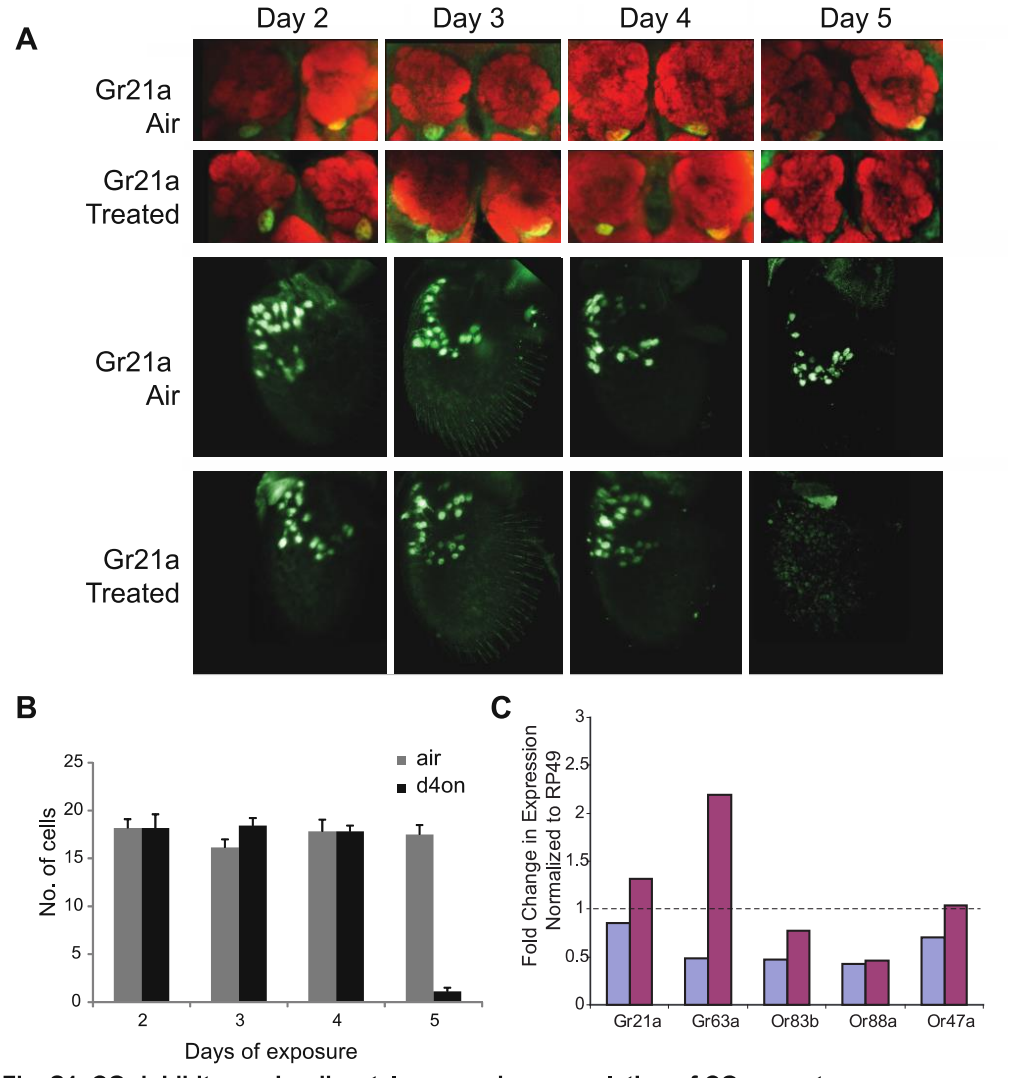


Figure 2.11 CO_2 inhibitory odor diacetyl causes down regulation of CO_2 receptor.

A) Antennal and whole mount brain staining of *Gr21a-Gal4* flies. Flies were exposed to diacetyl (headspace of 10^{-2}) or air for 2 to 5 days (see methods). Brains and antenna were dissected on the indicated days, fixed, and then stained for neuropil marker nc82 (red) and anti-GFP (green). **B)** Mean of ab1C neurons expressing GFP after indicated days of odor exposure. d4on=diacetyl. n=6, error bars=s.e.m. **C)** Flies were exposed to headspace from diacetyl 10^{-2} for 6 days (Day 6 treated, 5 day recovery). Gene expression by QPCR is compared to flies raised in air for the equivalent amount of days. Expression data is based on fold expression normalized to RP49. Fold expression=1 indicated no change in expression. n=2**.**

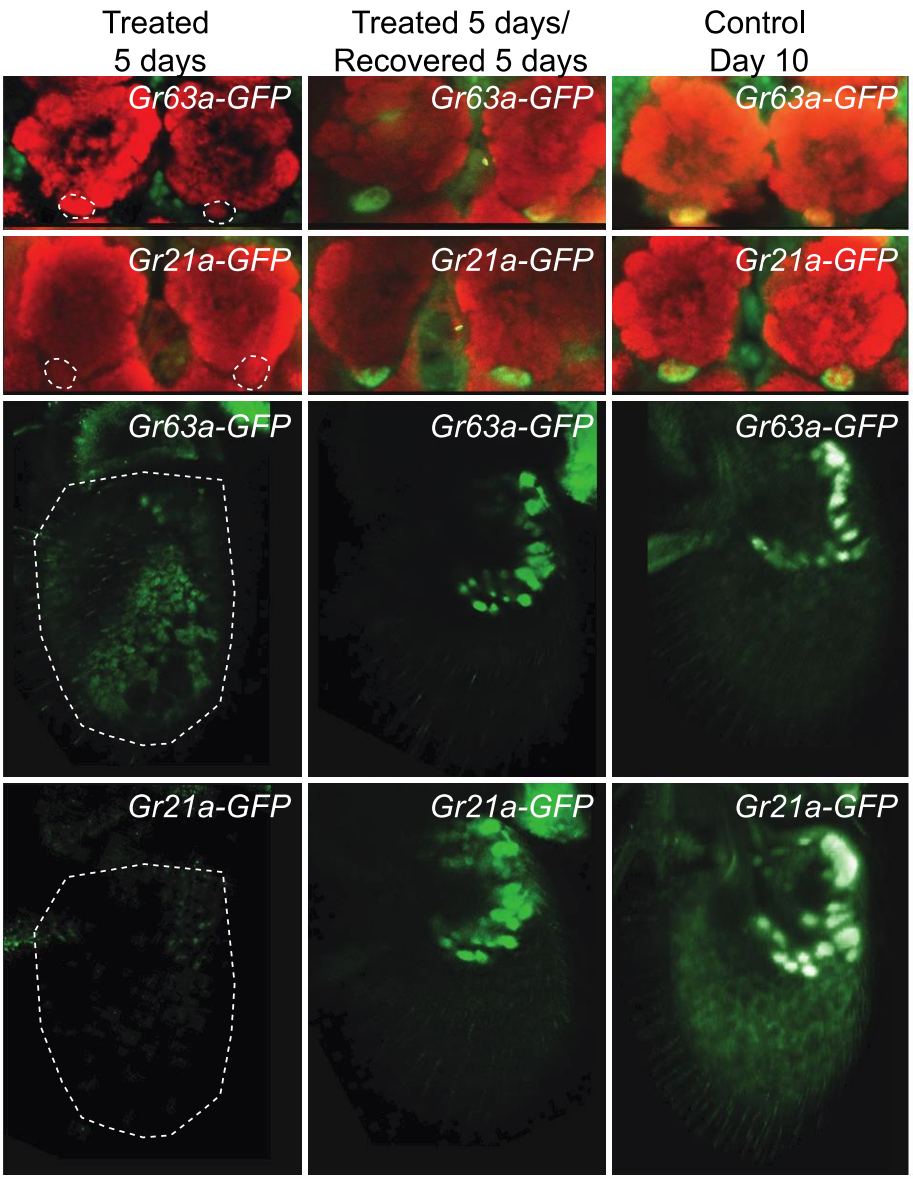


Figure 2.12 Down regulation of the CO2 receptor driver is reversible.

Antennal and whole mount brain staining of Gr63a-Gal4, and Gr21a-Gal4 flies. Flies were exposed to diacetyl 10^{-2} for 5 day (treated 5 days), and allowed to recover in clean air for 5 days (treated 5 days/recovered 5 days), or exposed to air for 10 days (control day 10). Brains and antenna were dissected on the indicated days, fixed, and the stained for neuropil marker nc82 (red) and anti-GFP (green).

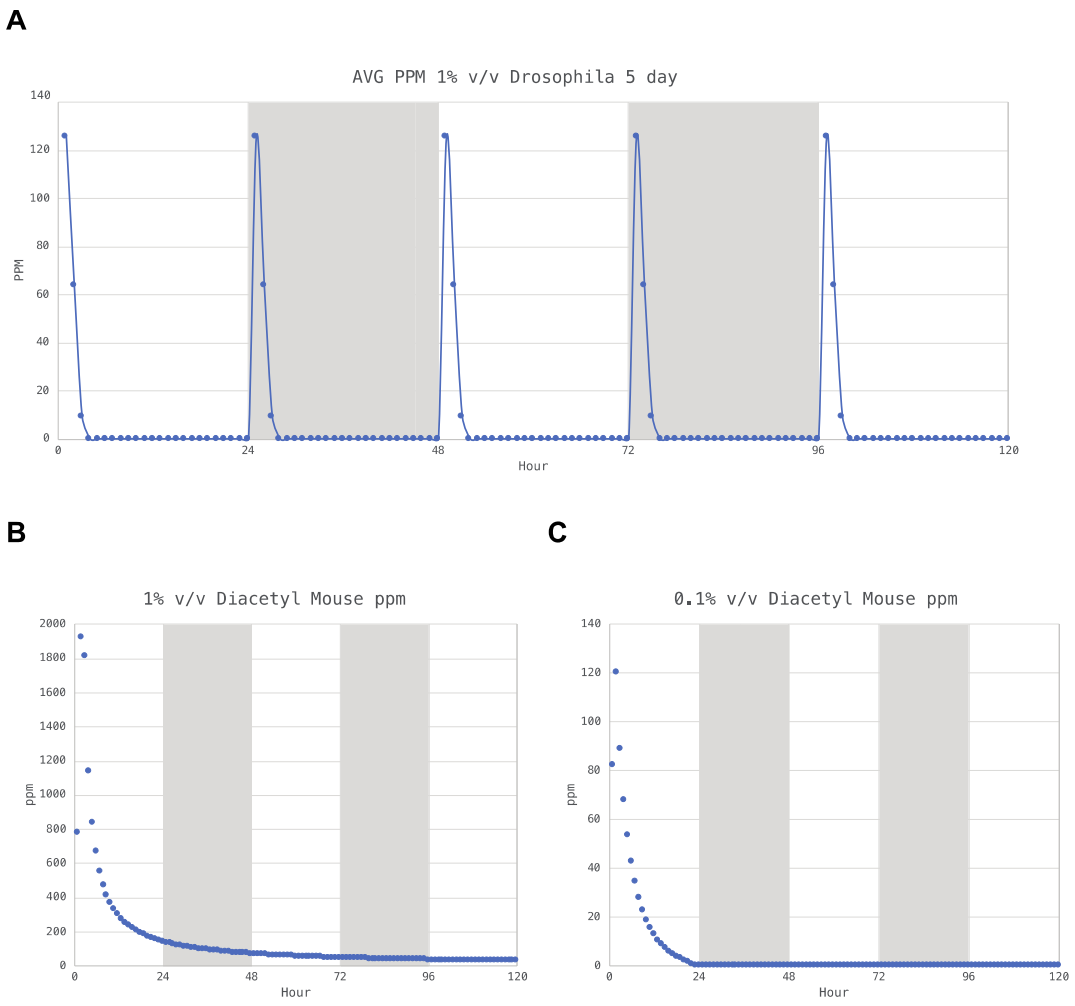


Figure 2.13 Dose of diacteyl in ppm in experimental chambers over time.

Mean concentration of diacetyl in the air in the exposure experimental chambers in ppm calculated based on weight loss of the compound.

#	Common sources of Diacetyl	AVG Diacetyl (ppm)	References
1	Starter Distillates (SDL)in Dairy Product Production	1.2-22,000	Rincon-Delgadillo, M. I., Lopez-Hernandez, A., Wijaya, I., & Rankin, S.A. (2012). Diacetyl levels and volatile profiles of commercial starter distillates and selected dairy foods. *Journal of dairy science*, *95*(3), 1128-1139.
2	Mainstream cigarette smoke	250-361	Pierce, J.S.,et al., *Diacetyl and 2,3-pentanedione exposuresassociated with cigarette smoking: implications for risk assessmentof food and flavoring workers.* Crit RevToxicol, 2014. **44**(5): p. 420-35.
3	Microwave Popcorn Facility	1-57.2	Kanwal, R., et al., *Occupational Lung Disease Risk and Exposureto Butter-Flavoring ChemicalsAfter Implementation of Controls at a Microwave Popcorn Plant.* Public Health Reports, 2011. **126**(4): p. 480-494.
4	Baked goods	44	Hall, R.L. and B.L. Oser, *Recent Progress in Consideration of Flavoring Ingredients under Food Additives Amendment .3. Gras Substances.* Food Technology, 1965. **19**(2p2): p. 151-&.
5	Candy	21-35	Hall, R.L. and B.L. Oser, *Recent Progress in Consideration of Flavoring Ingredients under Food Additives Amendment .3. Gras Substances.* Food Technology, 1965. **19**(2p2): p. 151-&.
6	Gelatins/Puddings	19	Hall, R.L. and B.L. Oser, *Recent Progress in Consideration of Flavoring Ingredients under Food Additives Amendment .3. Gras Substances.* Food Technology, 1965. **19**(2p2): p. 151-&.
7	Unflavored Brewed cup of Coffee	7	Pierce, J.S.,et al., *Characterization of naturally occurring airborne diacetyl concentrations associatedwith the preparation and consumption of unflavored coffee.* Toxicol Rep, 2015. **2**: p. 1200-1208. Yeretzian, C., A. Jordan, and W. Lindinger, *Analysing the headspaceof coffee by proton-transfer-reaction mass-spectrometry.* International Journal of Mass Spectrometry, 2003. **223**(1-3): p. 115-139.

Table 2.1 Concentration of diacetyl in some common sources

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CHAPTER III: A novel class of microbial and plant volatiles that affect plant development, growth and response to abiotic stress by acting as HDAC inhibitors

Abstract

Plants exist in a rich milieu of volatiles in their proximal environment and have been shown to respond physiologically to some of them, yet little is known about how they are detected. We find that plants respond to some volatiles using an atypical detection pathway involving epigenetic changes that causes dramatic changes in gene expression. These VOCs directly inhibit members of the conserved histone deacetylase enzyme family and cause changes in gene expression in roots and shoots. Exposure to such volatiles, at doses as low as ~10ppm, can cause significant changes in developmental programing such as root growth, lateral root initiation, leaf development and flowering timing. In addition, exposure can also impact response to an abiotic stress like freezing by significantly relieving leaf yellowing. Our findings reveal a conserved and slow-acting pathway in plants for responding to volatiles and raises important questions about harnessing epigenetics in agriculture.

Introduction

In plants several important signaling pathways use VOCs, like methyl salicylate, jasmonic acid, and ethylene, which cause a variety of downstream effects including changes in gene expression (Walling, 2000). Plants are known to have systemic responses

to many other volatile chemicals too, which alter growth or immune responses (Lee et al., 2019). Both monocotyledonous and dicotyledonous species with herbivorous insect damage release aboveground VOCs, which alter neighboring plants (Heil & Karban, 2010). Moreover, both intra and interspecies forms of communication via VOCs exist. Plant roots also produce VOCs, as do the plant rhizobiome, and microbes living in the soil (Effmert et al., 2012; Farag et al., 2006; Morcillo et al., 2020; Ortiz-Castro et al., 2009). Interestingly, while it is known that plants can respond to volatile compounds, the mechanisms of detection remain unclear. In this regard, it is particularly important to detect and respond to odorants that can enter cells.

RESULTS

Exposure to diacetyl vapors alters root development and gene expression

In order to study the physiological effects of long-term exposure to microbial volatiles we exposed the model system *Arabidopsis* for 5 days to diacetyl, a volatile made by microbes in the soil associated with roots (Farag et al., 2006; Morcillo et al., 2020; Ryu et al., 2003). The Odor Exposure assay consisted of controlled exposure of volatile HDAC inhibiting compounds to model plant *Arabidopsis* within enclosed aquariums and similar growth conditions. The test compound odor cartridges, consisting of 60 x 15 mm polystyrene Petri dishes containing 2 ml of indicated concentration in Paraffin Oil, were replaced at the 3.5, 5, and 6-day time mark during our 7-day experiment (Fig 1A, left). In separate experiments we also measured the weight loss from the odor cartridges over time and used it to calculate the concentration of diacetyl in the glass chambers in parts per

million (**Fig 3.1A**, **right**). These levels are comparable to sources where measurements have been taken previously.

Root growth was marked during each point and the plates were photographed. The plants were collected after the 7-day exposure, photographed, and the roots were separated. Visible phenotypic differences were seen in the root length and numbers of lateral roots in a dose dependent manner comparison to the control paraffin oil exposed plants (**Fig 3.1B**). In the presence of diacetyl vapors, the primary root length shows a lack of growth with the higher dose showing the most significant loss. Interestingly, the lateral roots show the opposite effect and at the highest dose are nearly 3 times more numerous (**Fig 3.1B**).

In order to understand the molecular changes occurring with the volatile exposure and possibly underlying this developmental phenotype, we took an unbiased approach and performed RNA-Seq analysis of the roots in diacetyl exposed vs control. We found a large number of differentially expressed genes (DEGs) in the roots of the diacetyl vapor exposed *Arabidopsis.* We identified 5197 differentially expressed genes (DEGs) (false discovery rate, FDR < 0.05) in the root transcriptome of diacetyl-exposed seedlings compared to control. Of these, 2625 genes were significantly up-regulated (log_2 fold-change > 1; red dots in **Figure 3.1C**) and 2572 genes were significantly down-regulated (log_2 fold-change < -1; blue dots in **Figure 3.1C**). A broad range of genes was significantly altered, with several biological process GO terms significantly enriched in the up-regulated gene list including “metabolic interconversion enzymes”, “nucleic acid metabolism” and “RNA metabolism”. In the down-regulated gene set the GO term most enriched was “metabolic interconversion enzymes” and “oxidoreductases”.

VOCs inhibit HDAC family members differentially and affect root development

Since diacetyl is known to penetrate eukaryotic cells, a 2-D structural comparison of diacetyl to known bioactive compounds revealed that it is similar to a β-hydroxybutyrate, which is a known inhibitor of histone deacetylase enzymes (HDACs) and is produced by the liver (**Figure 3.1E**) (Shimazu et al., 2013). HDAC inhibitors are known to modulate gene expression broadly by promoting the acetylation of lysine residues on histone tails, thereby promoting accessible chromatin structure. In mammals, β-hydroxybutyrate has been shown to induce changes in the expression of several genes. This suggested a potential mechanism for diacetyl odor exposure to alter gene expression in the roots.

We therefore evaluated diacetyl and 3 structurally related VOCs using the *in vitro* assay kits for measuring activity of four purified HDACs. Of the four VOCs), each has a different functional group, two are natural in origin, previously detected from microbes that are known to be present in soil (Cagan & Zeiger, 1978; Lemfack et al., 2018). Ethyl pyruvate on the other hand, while structurally related, is a potent antimicrobial acting on bacteria and fungi (Debebe et al., 2016). All 4 VOCs inhibited both Class I HDACs (1 and 3) and the Class II HDAC6 with differences in degree (**Figure 3.2A,B**). The α-angelica lactone inhibited Class II HDACs more strongly than Class I. Our findings suggest that these HDAC-inhibitory VOCs could potentially effect gene expression in the roots and therefore affect their development. These findings fit well with a past study using soluble

drugs that showed HDACs function in primary root elongation and root emergence by modulating auxin-mediated development (Nguyen et al., 2013).

In order to directly evaluate whether exposure to vapors of the four HDAC-inhibitory VOCs affect root development, we performed a set of experiments using *A. thaliana* seedlings as before. Solutions for each of the four chemicals on a small petri dish were placed away from the seedlings growing in agar plate and enclosed in glass tank. The Root tips were marked at specified days post treatment start and photographs analyzed. The plants were collected after the 7-day exposure, photographed, and the roots were separated. Detailed measurements were made from the photos using ImageJ and the root length and numbers of lateral roots quantified at day 3.5 and day 7 after start if the treatment (**Figure 3.1B**). In the presence of diacetyl vapors, the primary root length shows a lack of growth with the higher dose showing the most significant loss. Interestingly, the lateral roots show the opposite effect and at the highest dose are nearly 3 times more numerous (**Figure 3.1B**).

Exposure to VOCs alters shoot development and gene expression

The HDACs are also important for gene expression in the shoots as well. And volatiles such as diacetyl are also present in high quantities above soil in ripe fruits, as well as by yeast in over fruits at relatively high levels (1350 ppb in ripe banana) *(*Hughes, 2001*;* Martineau, 1995*;* Nykanen, 1991*;* Shibamoto, 2014*)*. We exposed young plants in pots to vapors of diacetyl from a solution of the same concentration as before and performed an RNASeq analyses. As expected, we found that 321 genes are differentially regulated in the

leaflet of *Arabidopsis thaliana* following exposure to volatile diacetyl for 5 days (FDR<0.05). These DEGs are distributed across multiple chromosome locations and represent genes of diverse molecular functions (**Figure 3.3C**). Taken together, our results indicate that HDACs serve as highly conserved pathways to transduce detection of VOCs like diacetyl, resulting in specific alteration of gene expression in both roots and shoots.

We next counted the number of true leaves in the seedling VOC exposure assay as before, after 7 days of VOC exposure. We saw a variety of phenotypes, with α-angelica lactone and diacetyl showing significant decreases relative to the control paraffin oil (solvent PO) exposed plants (**Figure 3.3C**). Interestingly 3,4-hexanedione showed a significant increase in the number of leaves, while ethyl pyruvate seemed to have no effect (**Figure 3.3C**). These results suggest that the development of leaves in the shoot are also affected by the HDAC inhibitory volatiles, presumably through the influence on gene expression.

Effect of HDAC inhibitors on adult plants: flowering and cold resistance

So far we have seen dramatic effects of VOCs in the seedling stage. The chromatin and HDACs are known to play a role in number of different processes or responses in the adult plants as well. One of the effects we wanted to observe was with flowering timing since the process involves numerous changes in gene expression and therefore potentially susceptible to HDAC inhibitory volatiles. Mutants in HDACs like HDA5 show delayed flowering due to upregulation of flowering repressor genes like *FLC* and *MAF1* (Luo et al., 2015). Conversely, mutants in HDA9 lead to early flowering due to increased

expression of *FLOWERING LOCUS T (FT)* and *AGAMOUS-LIKE 19 (AGL19)* (Kang et al., 2015). We placed 3 weeks old *A. thaliana* plants in the glass chambers and exposed them to the vapors of two of the VOCs, diacetyl and α-angelica lactone volatilizing from 0.1% solutions in the glass chamber.

The plants in the treatments showed a significant and substantial delay in the number of days it took to flower. Exposure to volatiles from α-angelica lactone, which inhibits only Class 2 HDACs strongly, showed approximately a week delay in flowering. Plants exposed to diacetyl, which inhibits both class 1 and class 2 HDACs, showed a 11-day delay in flowering (**Figure 3.4A and 3.4B**). These results indicate that these volatiles can show significant effects on flowering even at minute doses. While the levels were too low to calculate using the weight loss method, we can expect it to be as low as ~10 ppm in the glass chambers (**Figure 3.1B**).

HDACs have also been implicated in responses to a number of abiotic stresses like temperature, drought, salt, etc in a variety of ways *(*Luo et al., 2017*)*. One of the phenotypes that can be rapidly tested in a laboratory is tolerance to cold temperatures in *Arabidopsis*. HD2C has been shown to lower expression of *COR* genes under warm temperatures by hypoacetylation of their promoters, and is degraded under cold stress leading to hyperacetylation of H3 in COR and expression (Park et al., 2018). In order to test whether HDAC-inhibitory volatiles we discovered can affect cold-tolerance, we set up an experiment where we cold-acclimatized the plants for 7 days at 4 °C, and then transferred them to respective odor exposure chambers in a freezing chamber and gradually dropped to -10°C, and then covered with ice and placed in the dark for 24 hours at 4 °C and then

transferred under the light at 23 °C as done before (Park et al., 2018). The yellowing of leaves was determined after 5 days and the controls ~30% of the leaves turned yellow-brown in the classic cold response previously documented. In the case of the exposure to diacetyl vapors, the plants showed a significantly lower number of yellow leaves (~20%) suggesting that the HDAC inhibitory volatiles had some degree of protection (**Figure 3.4C and 3.4D**).

Discussion

Volatile microbial metabolites have been present throughout the evolution of plants (McFall-Ngai et al., 2013) and are potential signals for multi-domain communication because they can travel wide ranges. Plants are known to sense microbial metabolites from root infections and control timing of their immune response (Effantin et al., 2011) and microbial volatiles also elicit olfactory behaviors in insects and nematodes (Fischer et al., 2017; Meisel & Kim, 2014), and other bacteria (Audrain et al., 2015; Kim et al., 2013). Our observations that some VOCs can alter gene expression, and development and response raise the question whether HDACs represent a conserved detection mechanism for odorants like diacetyl that link odor-detection to a specific gene expression response. Eukaryotes in particular have evolved very diverse trans-membrane odor receptor families, but several several, like plants, even lack neurons. HDAC proteins, however, are an ancient family of genes that predate even histones themselves (Gregoretti et al., 2004; Leipe & Landsman, 1997; Postberg et al., 2010). It is conceivable that VOC detection mechanisms that emerged in ancient forms may not have involved specialized transmembrane receptors,

or neurons, or resulted in rapid behavioral movements. Alterations in gene expression, however, could be a signaling mechanism indicating the presence of select environmental chemicals.

Our data also show that this unusual class of VOCs that can directly enter cells and alter the epigenetic landscape to bring about changes in gene expression. The VOCs act as inhibitors of histone deacetylases (HDACs), a class of enzymes that plays a crucial role in regulating chromatin. This study has enormous significance for understanding a new mechanism for regulation of gene expression via volatile chemicals, and the consequences of exposure to environmental volatiles that possess such gene-regulatory properties. The HDAC family members are highly conserved across eukaryotes, spanning both animal and plant kingdoms.

In histone tails, lysine acetylation (ac) and methylation, are amongst the two key post translational modifications that play key roles in regulating gene expression, and involve a complex programming (Berger, 2002) of temporal sequences and combinatorial spatial patterns that regulate chromatin state (Kouzarides, 2007), such as open, closed, poised (Elgin & Grewal, 2003). Such epigenetic changes significantly influence gene expression, enabling transcriptional plasticity, in response to environmental exposure to certain odorants. Epigenetic regulation also leads to a certain programmed chromatin state that is transmitted through cell division thus exerting a longer-term influence (Calvanese et al., 2009; Rando & Chang, 2012). In this paper we identify gene-modulation caused by modification of the balance of lysine acetylation via HDACs in the plant, caused by volatiles known to be emitted by commensal microbes or ripening fruits, which leads to profound

changes in gene expression, development and physiology (Graff & Tsai, 2013; Shahbazian & Grunstein, 2007). While soluble metabolites form microbiomes have been very well studied, this novel form of volatile-based communication, or environmental sensing, from a distance via chromatin has not been largely overlooked be a major new form of influence of "nurture" on the epigenome. These findings also open the door to developing volatile small molecules as tools in agriculture to improve plant structures, or change timing of processes, or response to abiotic stresses. These molecules are effective in minute quantities and are extremely affordable if applications were to be developed in the future.

Materials and Methods

Arabidopsis thaliana experimental exposure

The Odor Exposure assay consists of controlled exposure of volatile odor compounds to model plant Arabidopsis within enclosed aquariums and similar growth conditions (23°C with a 12-hour light/dark cycle). The test compound odor cartridges, consisting of (60 x 15 mm) polystyrene Petri dishes containing 2 ml of 1% v/v in paraffin oil (PO), were replaced at the 3.5, 5, and 6-day time mark during the 7-day experiment. Root growth was marked during each time point and the plates were imaged. The plants are to be collected after the 7-day exposure, photographed, and the leaves/roots carefully dissected separated, flash frozen in liquid nitrogen, and preserved for future sequencing. Root growth is measured using ImageJ.

Odor exposure for RNA-seq

A. thaliana plants (Col-0) that had been transplanted at day 7 to soil were placed in the experimental room for 2 days to acclimate (23°C with a 12-hour light/dark cycle). A single potted plant was placed in a 4-liter clear glass jar, with openings attached to a vacuum to allow for air exchange. A small beaker containing 1ml of 1% diacetyl in PO or PO alone were placed inside the jar. Plants were watered at 2.5 days. After 5 days, individual leaflets were dissected, and flash frozen in liquid nitrogen.

A. thaliana plants (Col-0) were grown in an Agar medium were synchronized to germinate using pre-treatment in cold. Exposure experiments were started using plants the plates when they were 11 days old and placed in a 10-gallon glass aquarium as a chamber along with a petri dish containing 1 ml of chemical dissolved in PO or PO alone were placed at the other side of the container. After the desired exposure, the roots were separated, and a Trizol-based RNA isolation was carried out as above. Two biological replicates were performed for each condition, with an average of 68,355,820 reads / replicate, with an average of 95% mapped. Multiplexed libraries were made from total RNA input using the Illumina TruSeq RNA sample preparation kit (v2) and 50 bps single-end sequencing was done using the NextSeq500.

Flowering assay

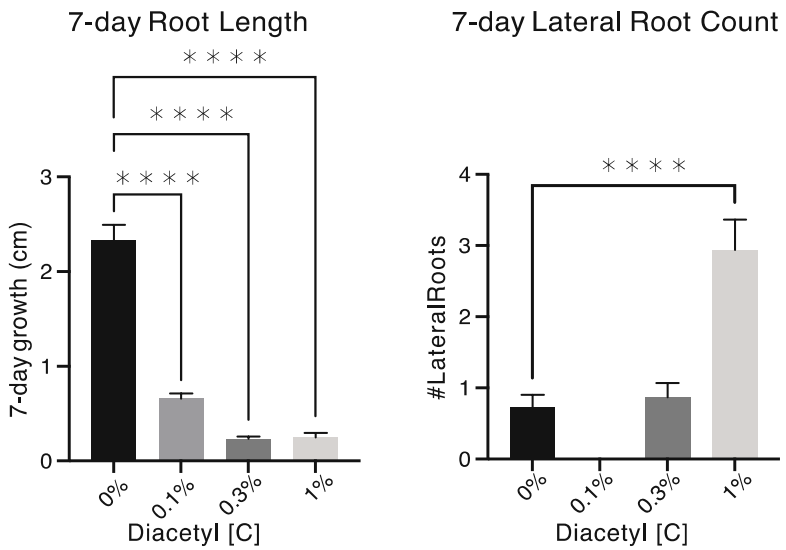
Twenty seven day old *A. thaliana* plants (Col-0), that had been transplanted at day 7 to soil, were placed in 10-gallon glass aquarium as chamber along with a petridish containing 2 ml of chemical dissolved in PO or PO alone were placed at the other side of

the container. Plants were exposed to odors until all plants began to flower, with odor cartridges being replaced daily. Signs of flower buds opening were counted as plant flowering. One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism 9.

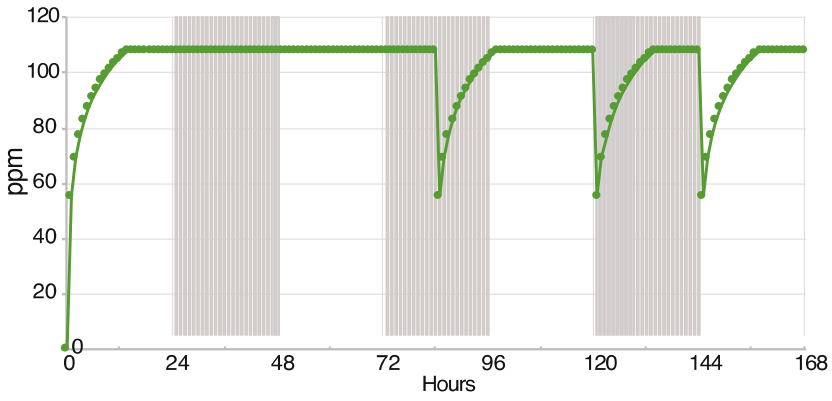
Cold tolerance assay

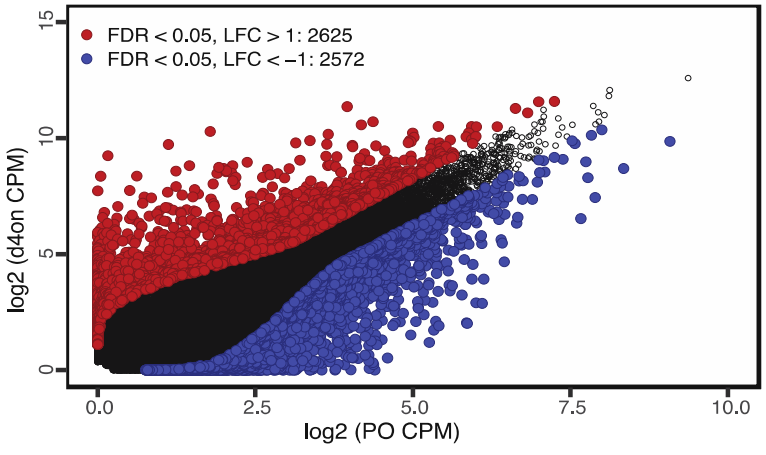
Twenty six day old *A. thaliana* plants (Col-0), that had been transplanted at day 7 to soil, were cold-acclimatized the plants for 7 days at 4 °C, and then transferred to respective odor exposure chambers with a petridish containing 2 ml of chemical dissolved in PO or PO alone in a freezing chamber in which temperatures went down every 2 °C for 0.5 h and maintained for 1 h, and it dropped up to -10 °C . Afterwards, the plants were covered with ice and placed in the dark for 24 hours at 4 °C and then transferred under the light at 23 °C. The survival rate was determined after 5 days. The percentage of the yellow-brown leaves to the total number of leaves were compared in test vs control (solvent) exposed. One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism 9.

A


7-day Root Length
7-day growth (cm)
Diacetyl [C]
0%
0.1%
0.3%
1%
7-day Lateral Root Count
#LateralRoots
Diacetyl [C]

B


ppm
Hours
dark
PPM


FDR < 0.05, LFC > 1: 2625
FDR < 0.05, LFC < −1: 2572
log2 (d4on CPM)
log2 (PO CPM)

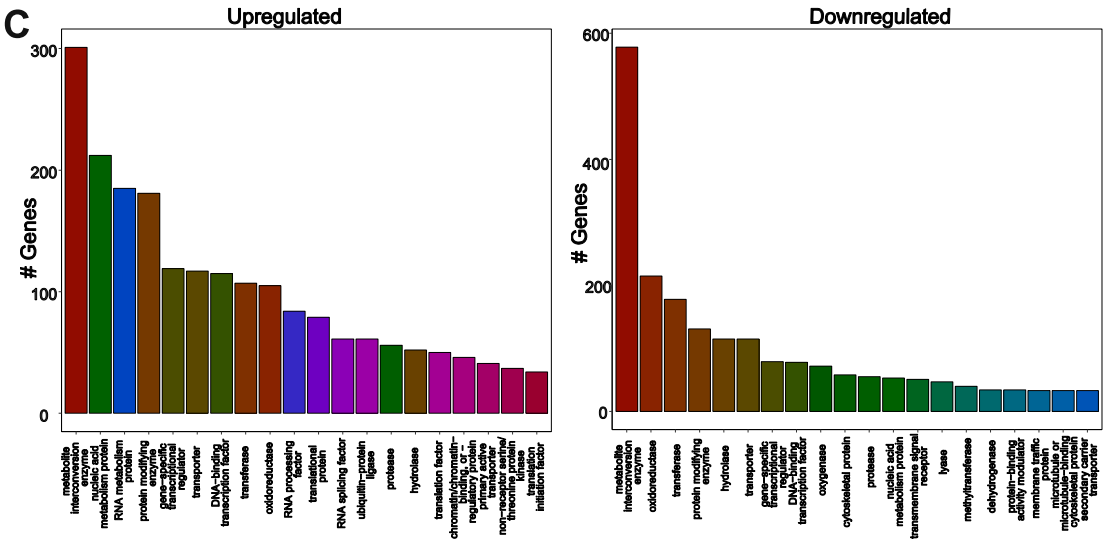


Figure 3.1 Roots respond to a volatile diacetyl emitted by microbes
A. Photograph of the odor exposure setup for *Arabidopsis thaliana* seedlings, and the mean PPM dose of diacetyl based on weight loss measurements. **B.** Mean root length and mean number of lateral roots after odorant exposure from the headspace of solutions at indicated concentrations. **C.** Transcriptome comparison of *Arabidopsis thaliana* roots exposed to diacetyl vapors for 7 days from the headspace of the 1% (v/v) dose. Plot highlighting up- and down-regulated genes in the diacetyl-exposed group. Red and blue dots represent up-regulated genes (false discovery rate (FDR) < 0.05, $\log_2$ fold change (LFC) > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively. **C**. Bar graphs denoting the protein classification of the genes up- and down-regulated after odor exposure.

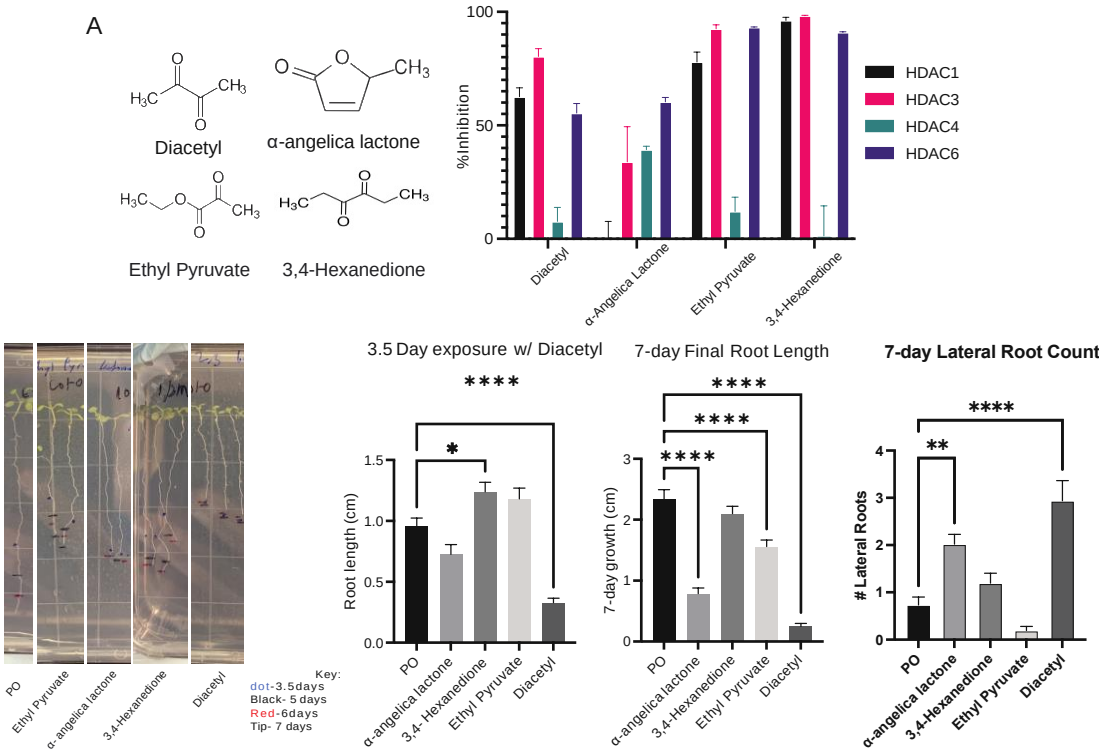


Figure 3.2 Related odorants differentially inhibit HDACs and alter root development
A. Structures. **B**. In vitro assays with purified human Class I and II HDACs. Mean % inhibition to 15mM of each volatile compound is shown. N=3, error bars=std. deviation. **C**. Representative photographs of the seedlings with colored marks indicating length of primary roots at time points after start of the volatile treatment. **D**. Mean root length. **E**. Counts of lateral root outgrowths. N ≥49 One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism. 3.5 Day * p-value=0.0239, **** p-value<0.0001

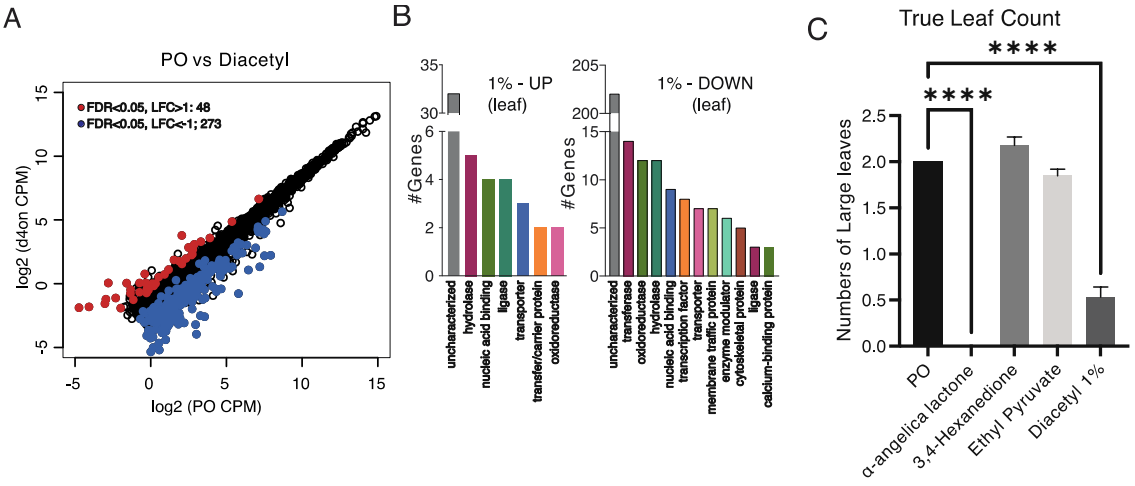


Figure 3.3 Leaves respond to the HDAC-inhibitory volatile compounds
A. Schematic of diacetyl exposure protocol for transcriptome analysis of Arabidopsis leaflets. **B**. Plot highlighting up- and down-regulated genes in the diacetyl-exposed group. Red and blue dots represent up-regulated genes (false discovery rate (FDR) < 0.05, $\log_2$ fold change (LFC) > 1) and down-regulated genes (FDR < 0.05, LFC < 1), respectively. **C**. Bar graphs denoting the protein classification of the genes up- and down-regulated after odor exposure. **D.** Bar graphs denoting the mean count of true leaves in the seedlings at day 7 after exposure to volatiles of the indicated VOCs from the headspace of 1% solution in paraffin oil (PO). Error bars=s.e.m. One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism. N ≥45 . **** p-value<0.0001.

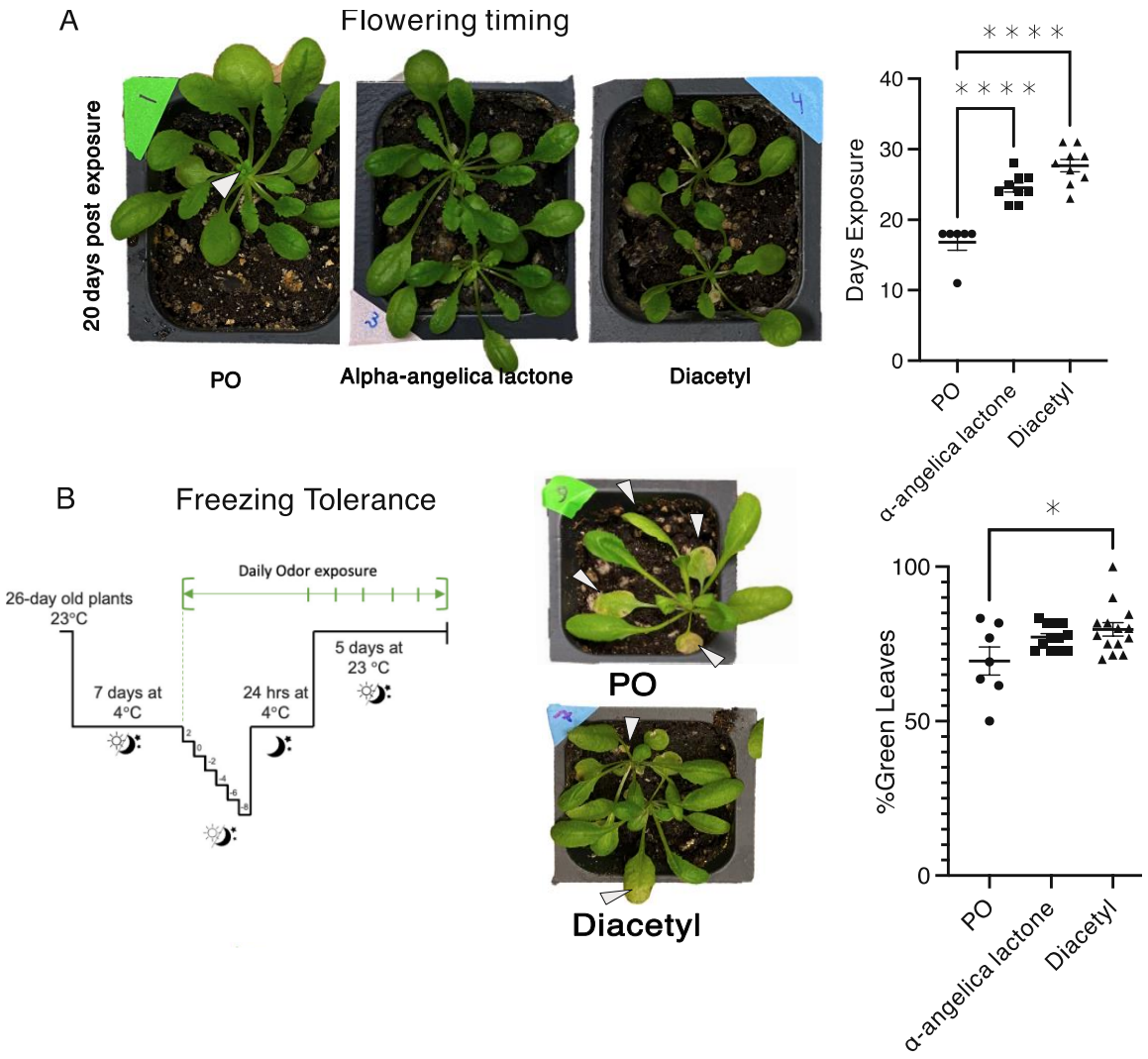

A
Flowering timing
20 days post exposure
PO
Alpha-angelica lactone
Diacetyl
Days Exposure
40
30
20
10
0
PO
α-angelica lactone
Diacetyl
B
Freezing Tolerance
Daily Odor exposure
26-day old plants
23°C
7 days at
4°C
24 hrs at
4°C
5 days at
23 °C
PO
Diacetyl
%Green Leaves
100
50
0
PO
α-angelica lactone
Diacetyl
C
HDAC-based epigenetic
modification and gene expression
Odors
HDAC

Figure 3.4 Volatiles alter flowering times and improve response to freezing

A. Representative images of *Arabidopsis thaliana* plants at different stages of beginning to flower, and the mean number of days to start flowering when exposed to vapors from headspace of indicated compounds at 0.1%. One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism. N ≥6 . **** p-value<0.0001. D. Error bars=s.e.m.
B. Representative images of *Arabidopsis thaliana* plants after cold treatment, and the mean number of days to start flowering when exposed to vapors from headspace of indicated compounds at 0.1%. One-way analysis of Variance (ANOVA) between groups was performed for plant exposure quantitative data using Graph Pad Prism. N ≥7. *=p-value=0.0346.
C. Model for volatile odorants affecting HDACs and gene expression in roots and shoots of plants.

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Chapter IV: Analysis of the mosquito CO_2-sensing cpA sensillum in detecting human odorants and the role of Gr and Ir receptors for their function

Introduction:

Mosquitoes rely on their olfaction system to seek out food sources, potential mates, and suitable egg-laying sites. Several mosquitoes have evolved specifically towards seeking out humans as a blood source, necessary for their egg production. Vector-borne diseases, resulting from an infection transmitted to humans and other animals by blood feeding insects, account for more than 700,000 deaths annually worldwide. Among known disease vectors, *Aedes Aegypti* mosquitoes are known for contributing to the spread of arboviruses, dengue, zika, yellow fever, and chikungunya (WHO, 2020). *Anopheles* mosquitoes are known for vectoring malaria-causing *Plasmodium* parasite responsible for over 400,000 deaths yearly (WHO, 2020). The *Culex* mosquitoes are known for transmitting West Nile Virus and Japanese encephalitis (WHO, 2020). There is great need to understand how such mosquitoes seek out humans using their olfactory system, to develop preventative methods in hiding prey cues.

Female mosquitoes seek out hosts through both chemical and physical cues released via breath and skin. Physical cues include vision, heat, and humidity. Chemical cues include CO_2 exhalation, body odors, and even tastants (Raji & DeGennaro, 2017). In particular, CO_2produced by human breath is highly volatile and travel long distances while some skin odors are considered more short range host cues (Coutinho-Abreu et al., 2022). It is believed the CO_2 emission is what largely draws mosquitoes to zoning in on prey and

the complex cocktail of body odors determines further attraction (Gillies, 1980; Takken & Knols, 2010). Although CO_2 and heat are generic stimuli indicating viable warm-blooded animals, skin odor provides distinguishing information to indicate if their prey is human.

Detection of specific body odorants by Mosquitoes (Acetophenone and Dimethyl Sulfide)

When it comes to mosquito-human targeting it is important to note that based on different body odor profiles, some people are more prone to being "Mosquito magnets" than others. This explains why some people get bitten by mosquitoes more than others. For example, it has been noted differing carboxylic acid levels produced on the skin contribute towards differential mosquito attraction in humans (De Obaldia et al., 2022; Smallegange et al., 2009; Smallegange et al., 2005). While there is currently no single molecule emitted by humans to sufficiently explain mosquito attractiveness, blends of odorants are thought to be more potent depending on concentrations of specific molecules. Bodily emitted volatile odors are key cues that promote attraction and feeding responses from host-seeking mosquitoes.

Even certain diseases can also make a significant impact on body odors which contribute towards targeting response. Arboviruses have a complex life cycle consisting of arthropod vectors (e.g. mosquitoes) and vertebrate hosts (e.g. humans). *Aedes* mosquitoes preferred to seek and feed on mice infected by dengue and Zika viruses (Zhang et al., 2022). Flavivirus infection (e.g. Zika & dengue) increases the production of acetophenone body odor by promoting the skin bacteria that produces this volatile metabolite and further attracts infected hosts to *Aedes* mosquitoes (Zhang et al., 2022). Acetophenone is even

known to activate *Anopheles gambiae* olfactory sensory neurons in the antennae and maxillary palps however whether this leads to attraction is not known (Lu et al., 2007; Qiu et al., 2006). The mechanism behind the viral infection and increased metabolite emission is due to viral suppression of RELMα (essential antimicrobial protein on skin) leading to expansion of acetophenone-producing commensal bacterial (Zhang et al., 2022). Luckily, dietary administration of isotretinoin to flavivirus-infected hosts rescues RELMα skin expression. This increase in acetophenone in body odor increases mosquito attraction to those infected, demonstrating the impact acetophenone plays in prey detection.

Female *Ae. aegypti* mosquitoes have been shown to be attracted to different combinations of L-(+)-lactic acid with specific ketones, sulfides, and/or chloroalkanes, indicating that such odorants can be used to replace CO_2 as an attractant (Bernier et al., 2015; Coutinho-Abreu et al., 2022). Sulfide compounds, products commonly, but not limited to the skin microbiome, have been identified to display attraction to mosquitoes especially in congruence with other skin volatiles such as L-Lactic acid (Allan et al., 2006; Coutinho-Abreu et al., 2022). While CO_2 is thought to be the main trigger for mosquito attraction alongside other attractive odors, dimethyl sulfide, and a few other alternatives function as similar catalysts to enhance mosquito attraction. Dimethyl sulfide for instance is found as a component in human respiration and shown to act similarly to CO_2 as a catalyst (Conkle et al., 1975; Coutinho-Abreu et al., 2022).

There is a need to further evaluate the role the CO_2-receptor neuron has in detecting human associated odors: acetophenone and dimethyl sulfide.

Detection of acetophenone by the mosquito CO_2 neuron

To detect a wide variety of volatile compounds, insect olfactory system uses a diverse family of olfactory receptors: Odorant Receptors (*Ors*), Ionotropic Receptors (*Irs*), and Gustatory Receptors (*Gr*) (Pask & Ray, 2016). In mosquitoes the 3 main appendages contributing to olfaction include the antenna, proboscis, and the maxillary palp which all harbor ORN-containing sensilla (Kwon et al., 2006; Pitts et al., 2004). These sensilla are perforated, facilitating the entrance for volatile molecules. Once the molecules enter, they make their way to their respective receptors, allowing them to convert the chemical signal into an electrical one that is conveyed along their respective neuronal paths to the brain and interpreted (Pask & Ray, 2016). In *Aedes* mosquitoes, these sensilla on the maxillary palp are known as capitate pegs (cp) and each capitate peg sensillum houses 3 sensory neurons. The neurons were traditionally named according to the spike sizes observed via single-sensillum recordings: cpA neuron has the largest spikes, cpB medium, and cpC the smallest (de Bruyne et al., 1999). This organization of maxillary palp with multiple capitate peg sensilla, each containing 3 neurons, is conserved across different mosquito species (McIver, 1982).

In *Aedes*, *Anopheles*, and *Culex* mosquitoes, the cpA function is conserved in detecting CO_2 (Grant et al., 1995; Kellogg, 1970; Lu et al., 2007; Syed & Leal, 2007). Additionally, these Gr-expressing cpA neurons on the maxillary palp are known to detect additional compounds, including known skin odorants (Lu et al., 2007; Tauxe et al., 2013; Turner et al., 2011; Turner & Ray, 2009). When comparing *A. aegypti* and *A. gambiae* cpA responses to a panel of odorants they both displayed highly similar responses (Tauxe et al.,

2013). The cpB and cpC neurons express Orco and a tuning OR (AgOr8 and AgOr28, respectfully) (Lu et al., 2007). This would suggest that within the maxillary palp, only the Gustatory receptors (GRs) and Odorant receptors (ORs) participate in odor detection along with their respective co-receptors. Ionotropic Receptors (IRs) and their respective coreceptors canonically should not play a role in mosquito maxillary palp odor detection.

However, recent work suggests that previous olfaction system organization system may not be so conservative as previously thought. In *Ae. aegypti* the organizational principal unconventionally consists of many neurons co-expressing multiple chemosensory receptor genes (Herre et al., 2022). Using CRISPR-Cas9-based genetic knock-in strategy they were able to label molecularly distinct populations of olfactory sensory neurons. *Orco*, *Ir25a*, *Ir8a*, and *Ir76b* co-receptor driver lines demonstrated overlapping projection in glomeruli and coexpression of coreceptors in antenna and maxillary palp olfactory sensory neurons (Herre et al., 2022). Almost half of *Orco* cells express *Ir25a* and vice versa in the mosquito olfactory system antenna. In maxillary palp, there was no overlap in expression of *Orco* and *Gr3*, but *Ir25a* was expressed in all *Orco* and all *Gr3* cells. This chemosensory receptor co-expression may explain the robust mosquito attraction to humans via highly excessive detection system for different human cues.

It has been demonstrated that CO_2-receptor neuron agonists are largely conserved between flies and mosquitoes, repelling and attracting, respectively (Tauxe et al., 2013). Several known CO_2 receptor neuron inhibitors have been identified and shown to reduce mosquito landings on arm-in-cage mesh and CO_2-baited traps (Tauxe et al., 2013). Ultra-prolonged CO_2 receptor activation via 2,3-butanedione, was even found to produce a

disruption in behavioral response to CO_2 in *A. gambiae*, *A. aegypti*, and *C. quinqufasciatus* (Turner et al., 2011). This ultra-prolonged CO_2 receptor activation significantly inhibited female *Aedes* mosquitoes in wind tunnels to move toward CO_2 sources, effectively masking the source (Turner et al., 2011). Drosophila CO_2-receptor proteins (Gr21a and Gr63a) are well conserved in insects, including mosquitoes which express homologs via three 7-TM subunits (Gr1, Gr2, and *Gr3*) in the CO_2-sensitive cpA neurons found on the maxillary palp (Kumar et al., 2020). However, mosquitoes display a switched behavioral response to *Drosophila* in which activation of cpA neurons by CO_2 and other odorants cause attraction (Takken & Knols, 2010; Tauxe et al., 2013; Turner et al., 2011).

Considering the canonical "one-receptor-to-one-neuron-to-one glomerulus" idea of insect olfaction, that only one chemosensory receptor gene family per olfactory neuron, recent studies have illuminated that this is not always the case. Recent work demonstrates there is extensive overlap in *Drosophila melanogaster* of in expression of different co-receptors, with *Ir25a* being broadly expressed in 88% of all olfactory sensory neuron classes and is co-expressed in 82% of Orco+ neuron classes, including all neuron classes in maxillary palp (Task et al., 2022). Co-expression of chemoreceptors in model organism, *Drosophila melanogaster*, olfactory neurons have been shown to be prevalent. Co-receptors are expected to solely interact with their respective receptor gene family (*Orco* with Ors and *Ir8*, *Ir25a*, *Ir76b* with Irs). Interestingly enough *Ir25a* mutants demonstrated significant increased/decreased responses to certain known odor stimulants in maxillary palp basiconic sensilla that express Ors (Task et al., 2022). This suggests that multiple chemoreceptor gene families could be involved in the signaling or development of a given

OSN class. In the *Aedes aegypti* mosquito, the chemosensory sensilla on the maxillary palps also proved to co-express IRs with ORs or GRs (Herre et al., 2022). Using single-sensillum recordings, recent works showed this coexpression of Ir coreceptors allowed for individual neurons, cpB, to respond to both OR and IR ligands.

ORs require the presence of Orco (Odorant co-receptor) in order to fasciliate the binding of volatile compounds to the respective ORs. Irs function similarly to Ors in which ligand-binding IRs require one or more IR co-receptors *Ir8*, *Ir25a*, and/or *Ir76b* to form a functional unit, making an odor-responsive ion channel. It has been shown *Ir25a* and *Ir8* are required for odorant-evoked responses to several coeloconic ORNs and *Ir76b* is broadly expressed in coeloconic sensilla. Without these coreceptors present to complete the functional units, the ORs and IRs fail to function properly.

In mosquitoes, chemosensory co-receptors *Ir8*, *Ir25a*, and *Ir76b* were shown to be important in human scent detection, with mutants lacking any of these being severely impaired. However, mutants were still able to differentiate highly attractive scent profile people over less attractive people (De Obaldia et al., 2022). Recent discovery of extensive co-expression of ORs and IRs in single olfactory sensory neurons may explain how single loss-of-function mutations in either OR co-receptor (*Orco*) or one of the three IR co-receptors (*Ir8*a, *Ir76b*, and *Ir25a*) still maintain human attraction (Herre et al., 2022; Raji et al., 2019; Task et al., 2022). Mutants lacking *Ir8*a, *Ir76b*, and *Ir25a* retained preferences to attractive "mosquito magnets" human skin odor, albeit reduced (Raji et al., 2019). While neither OR nor the IR pathway is solely required for discriminating differing body odor profiles, mutating the IR pathway produced significantly stronger effects on overall

mosquito-human attraction than the OR pathway. We find that *Ae. Aegypti* is unconventionally co-expressing multiple chemosensory receptors within olfactory sensory neurons in the maxillary palp.

In the maxillary palp the sensilla containing three chemosensory neurons cpA, cpB, and cpC, coordinated coexpression of chemosensory receptors were previously noted via use of RNA *in situ* hybridization with respective probes for *Orco*, *Ir25a*, *Ir8a*, *Ir76b*, and *Gr3* (Herre et al., 2022). These three cell types were found to project to three glomeruli in the antennal lobe and through the use of GF2 and Split-QG2 driver lines examined that Glomerulus 1 (the largest of the 3 glomerulus) received input from Gr3 and Ir25a expressing sensory afferents. Glomerulus 2 and Glomerulus 3 received input from *Orco-*,*Ir25a-*, and *Ir76b*-expressing neurons. This suggests that the cpA, cpB, and cpB neuron cells express multiple co-receptors, spanning Ir-Or and Ir-Gr classes. In the maxillary palp's three OSNs they all demonstrated co-expression of co-receptor Ir25a. In regards to cpB (Or8-expressing cells), and cpC(Or49-expressing cells) these also often co-expressed co-receptor Ir76b, with a bias towards cpB (Herre et al., 2022).

Considering the mosquito maxillary palp houses the CO_2 receptor, consisting of three subunits (Gr1, Gr2, and Gr3) in the cpA neuron, it is important to recognize the potential impact these findings suggest. Interestingly enough, while the CO_2 receptor is from the gustatory receptor family, it can also detect additional compounds, including many found in human skin odors (Lu et al., 2007; Tauxe et al., 2013; Turner et al., 2011; Turner & Ray, 2009). Known human skin odors that activate cpA include pyridine, cyclohexanone, butanone, etc with known cpA inhibitor including isobutyric acid (Kumar

et al., 2020; Lu et al., 2007; Tauxe et al., 2013; Turner et al., 2011; Turner & Ray, 2009). Via the use of empty neuron system used to decode Ors of mosquitoes in *Drosophila*, the Gr1, Gr2, and Gr3 subunits were evaluated in order to assess how these subunits contribute to cpA odor response (Carey et al., 2010; Hallem & Carlson, 2006). Gr1 seems responsible in modulating sensitivity of the cpA neuron (increasing sensitivity to CO_2 but decreasing sensitivity to pyridine) and the Gr2 and Gr3 units are required for CO_2 and odor response (Kumar et al., 2020). This publication suggests that of the three subunits of CO_2 receptor complex needed for detecting different ligands, Gr2 and Gr3 are required for functionality. While use of model organism Drosophila is an important initial assessment of the CO_2 receptor, assessing mosquitoes directly would be most valuable.

Through incorporating *Aedes aegypti* coreceptor mutants for *Gr3*, *Ir76b*, and *Ir25a* we can assess how the maxillary palp CO_2 receptor neurons rely on these co-receptors to known and novel ligands. In this study, we used *in vivo* extracellular electrophysiology to examine odorant responses of maxillary palp sensilla of female mosquitoes in which multiple receptors responding to different chemosensory stimuli are co-expressed. Focusing solely on cpA neuron response we can assess how Grs and Irs coreceptor expression contribute to odorant response.

Results

Analysis of Ir25a, Ir76b, and Gr3 mutants Odor Panel Response

In order to understand the contributions of the *Gr3*, *Ir76b* and *Ir25a* co-receptors that are likely expressed in the cpA neurons according to recent studies, we evaluated the

responses to a variety of structurally diverse ligands in a set of mutants. For our work we used the of *Ae. Aegypti* wild-type Liverpool, *Gr3* mutants, Heteroallelic *Ir76b*$^{32/61}$ and *Ir25a*$^{BamHI/19}$ null mutants. We created odor panel consisting of known cpA activators, inhibitors, and compounds of interest found in human odors. 1% CO_2 was used as means of characterizing for cpA neurons. To verify *Gr3* mutants cpA recordings, known cpB activator 1-octen-3-ol at 10^{-6} dilution, such as published in (Lu et al., 2007; McMeniman et al., 2014), was used.

Initially we compared how the mutants would differ in responding to known cpA activator, CO_2 (**Figure 4.1A**), or baseline room air blown through PO (**Figure 4.1B**), our solvent of choice for odorants. Only *Gr3* mutants displayed complete loss of sensitivity compared to wild-type in response to these compounds. Representative sample traces for CO_2 response are shown demonstrating only Gr3 mutants lost odor detection response (**Figure 4.1C**).

Ir76b$^{32/61}$ null mutant were assessed compared to wild-type mosquitoes against known activators (**Figure 4.2A**) and know inhibitors (**Figure 4.2C**). No significant difference was seen with *Ir76b* mutants compared to wild-type in regard to these select compounds. Only *Gr3* mutant again demonstrated complete loss of function in odor detection. Sample traces of these strains response to cpA activator 1% v/v pyridine are seen (**Figure 4.2B**) showing *Gr3* mutants loss of response. In **Figure 4.2D** we representative sample traces of response to 3% NH_3 demonstrating *Gr3* mutants loss of response to Ammonia. These results suggest that at least with these classes of chemicals the Ir76b co-receptor does not play a role.

Conversely, when we assess *Ir25a*$^{BamHI/19}$ null mutants against the same activators (**Figure 4.3A**) and inhibitors (**Figure 4.3C**) we see some significant changes in sensitivity to propyl acetate and spermidine. *Gr3* mutants demonstrated complete loss of function in odor detection. Representative traces show increased response in *Ir25a* mutants to propyl acetate (**Figure 4.3B**). This suggests that the loss of coexpression of *Ir25a* coreceptor increases sensitivity to the ester, propyl acetate in maxillary palp. In regards with known cpA inhibitors, *Ir25a* mutants demonstrated significant increased sensitivity to inhibition by 1% v/v spermidine, a polyamine, compared to wild-type (**Figure 4.3C**). Representative sample traces show *Ir25a* mutants response to spermidine alongside wild-type (**Figure 4.3D**).

Comparing wild-type against *Ir76b*, *Ir25a*, and *Gr3* mutants we sought to understand the respective contributions of co-receptors cpA response to human odorants discovered as ligands: acetophenone and dimethyl sulfide (DMS). *Gr3* was only compared at 1% v/v acetophenone and DMS due to complete lack of response. *Ir25a* mutants demonstrated significant increased sensitivity to acetophenone at all tested doses: 0.33, 1, and 3.33 % v/v (**Figure 4.4A**). At 1% v/v acetophenone, *Gr3* mutant demonstrated complete loss of function in odor detection, while *Ir76b* mutants showed no significant difference in various doses compared to wild-type (**Figure 4.4B**). Similarly, *Ir25a* mutants displayed increased sensitivity, but only from 1% and 3.33% v/v Dimethyl sulfide. *Gr3* mutants displayed complete loss of response to DMS at 1% v/v. These results suggest Gustatory Receptors are fundamentally required for diverse odor detection seen against our

odor panel. The coexpression of *Ir25a* coreceptors seem to play a modulatory role in odor detection sensitivity of select cpA ligands.

Discussion

Evolutionary studies have suggested *Ir25a* being the most ancient of insect chemoreceptors, explaining their broad expression (Croset et al., 2010). In *Drosophila melanogaster*, *Ir25a* is required in detecting acids, amines, humidity, cooling and temperature-synchronized circadian clock oscillation (Abuin et al., 2011; Benton et al., 2009; Budelli et al., 2019; Chen et al., 2015; Enjin et al., 2016; Knecht et al., 2017). In *Ir25a* mutant mosquitos, the loss of this coreceptor results in loss of response to heat (Morita et al., 2023). Unlike *Gr3*, *Ir25a* and *Ir76b* are sensory-associated gene expression not regulated in female *Ae. aegypti* maxillay palps in response to blood feeding (Hill et al., 2019). Male and Female *Ae. aegypti* showed similar coexpression and projection patterns for *Ir25a* (Herre et al., 2022). In the antenna of Anthropophilic *Anophelese coluzzi*, no significant difference of expression of *Ir25a* in females and males unlike many other IRs, including Ir8a and Ir76b (Athrey et al., 2020).

In this work we conclude that the *Ae. Aegypti* CO_2 cpA neuron detects other known volatiles including noted human odor attractants, acetophenone and dimethyl sulfide (Bernier et al., 2000; Bernier et al., 2003; Tauxe, 2014; Verhulst, 2010; Zhang et al., 2022). We further evaluated cpA's responses to structurally diverse ligands requiring CO_2 receptor encoded by *Gr3*. The Glomerulus 1, which is the largest glomerulus in the antennal lobe, receives input from *Gr3*-and *Ir25a*-expressing sensory afferents (Herre et

al., 2022). Glomerulus 2 and Glomerulus 3 receives input from *Orco-*, *Ir25a*, and *Ir76b*-expressing neurons (Herre et al., 2022).

From our results we can clearly see that for tested odorants, *Gr3* seemed to be the only one required for detection and inhibition of maxillary palp cpA. *Ir76b* coreceptor did not seem to participate in odor detection, at least not from our selected odor panel. However, *Ir25a* mutants displayed significant increase of response of select odors, suggesting *Ir25a*'s role in modulating response to select ligands. These results suggest loss of IR co-receptor *Ir25a* contributed to an increased sensitivity to ester, cpA activator propyl acetate and polyamine, cpA inhibitor spermidine. Regarding acetophenone and dimethyl sulfide, the *Ir25a* null mutants displayed increased sensitivity to both compounds. These results contradict the idea that different odor detecting pathways can independently detect different ligands. It suggests in CO_2-detecting neurons, Gr receptors are in fact primarily responsible for wide structural array of ligands detected via mosquito maxillary palp. Co-expression of different co-receptors in maxillary palp of *Aedes* mosquito (ref?) may explain how mutants in *Ir25a* co-receptor may demonstrate altered cpA responses primarily mediated by Gr receptors.

Materials and Methods

Insects

All mosquito strains were kindly gifted by Dr. Leslie B. Vosshall's Lab (De Obaldia et al., 2022; McMeniman et al., 2014).

- Wild-type Liverpool (LVP) mosquitoes
- *Gr3*$^{4/4}$ mutants
- *Ir25a*$^{19/19}$ males and *Ir25a*$^{BamHI/-QF2}$ virgin females were used to produce Heteroallelic and null *Ir25a*$^{BamHI/19}$ mutants.
- *Ir76b*$^{32/32}$ males and *Ir76b*$^{61/-QF2}$ virgin females were used to produce Heteroallelic and null *Ir76b*$^{32/61}$ mutants.

Electrophysiology

We used single sensillum recording to measure odorant responses of the OSNs found in maxillary palp capitate-peg sensilla (Tauxe et al., 2013). The use of in-vivo extracellular electrophysiology enables the simultaneous recordings of A, B, and C cells in response to odorant stimuli. The diameter of the cell types directly correlates with their respective spike amplitude, with the largest A cell (responds to CO_2) producing the largest spike amplitude. Adult female *Ae. Aegypti* were tested 3-10 days after emergence. Insects were restrained and saline-filled glass micropipette electrodes were inserted into the test sensillum (recording electrode) and the compound eye (reference electrode). Signals were amplified 1000x, band-pass filtered, and digitized to record action potentials of the neurons in the test sensillum.

Chemicals were purchased from Sigma-Aldrich at the highest available purity, typically >98%. Odor cartridges were made using pasteur pipette attached to a 1ml pipet tip, and 50 ul of the odorant solutions in respective concentrations and solvents were added to a filter paper. Stimuli were presented in roughly the same order across replicates; each cartridge was used for ≤ 3 stimuli. A constant 5 ml/s stream of carbon filtered room air was

switched from a blank cartridge to the odor cartridge using a Syntech CS-55 to present odor stimuli. The resulting airflow was delivered into a glass tube with constant, humidified airstream (10 ml/s) which was centered on and approximately 1 cm from the insect head. CO_2 stimuli was pulsed using a MINJ-D microinjector (Tritech Research) to deliver controlled pulses from pressured cylinders of 1% CO_2 in air into the carrier airstream, resulting in the indicated final concentration of gas at the insect head.

The cp sensillum of *Ae. Aegypti*, isolated action potentials from the individual neurons can be distinguished based by relative magnitude, with cpA producing the largest action potentials and responsive to CO_2. *Ae. Aegypti* cpA ΔA spike response was calculated by counting the response spikes (1 second window following response) and subtracting baseline activity (1 second prior stimulus). In cases of calculating pure odor response, we would subtract average PO response from measured average odor response spikes.

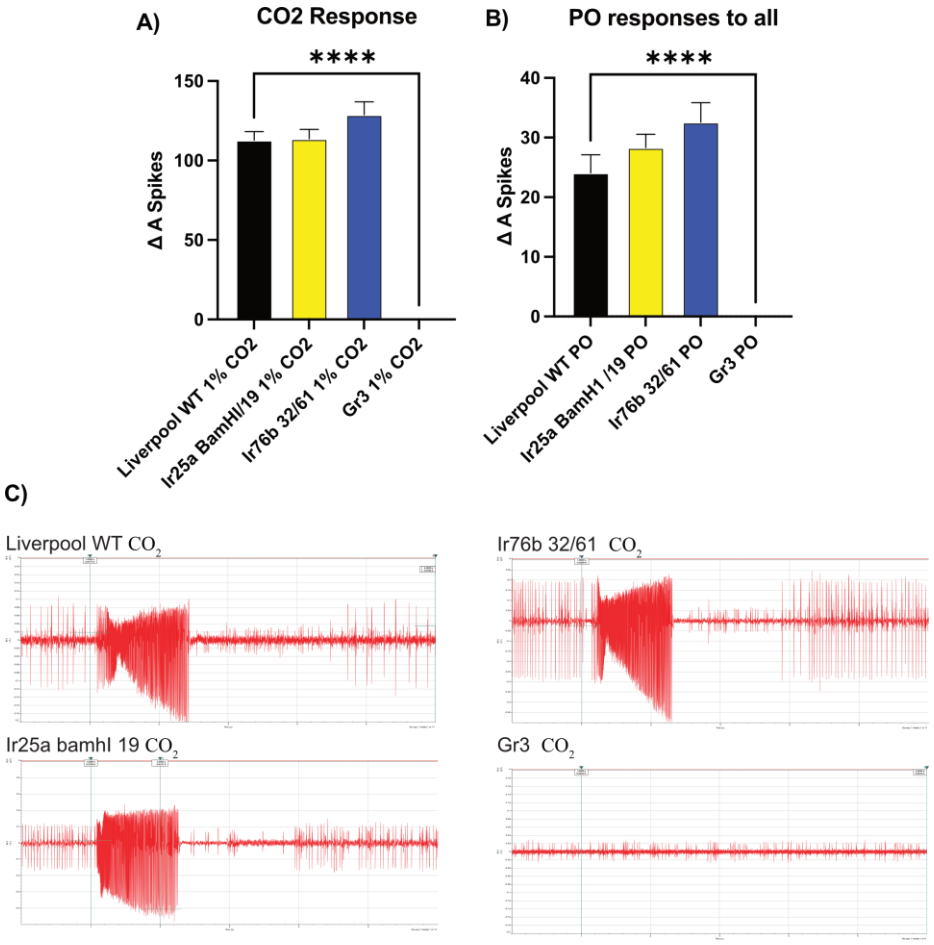


Figure 4.1 Single-sensillum recordings of the capitate peg sensillum in all female *Aedes aegypti* strains

A) CO_2 mean changes in the cpA-neurons action potential frequencies/sec. B) PO mean changes in the cpA-neurons action potential frequencies/sec. C) Sample representative traces for each strain type to CO_2. For wild-type, 9 female mosquitoes were recorded from with n = 24 sensilla recorded. Number of sensilla recorded per mosquito ≤4 and the data is presented as mean ± s.e.m. *Ir25a*$^{BamHI/19}$ null mutants were assessed against this same panel. For *Ir25a* mutants, 8 mosquitoes were recorded with n=16 sensilla. Number of sensilla recorded per mosquito ≤4. Data are presented as mean ± s.e.m. For Heteroallelic *Ir76b*$^{32/61}$, 6 mosquitoes were recorded with n=14 sensilla. Number of sensilla recorded per mosquito ≤4. Data is presented as mean ± s.e.m. For *Gr3*, 3 mosquitoes were recorded with n=7 sensilla. Number of sensilla recorded per mosquito ≤3. Data are presented as mean ± s.e.m. One-way ANOVA **** $p < 0.0001$.

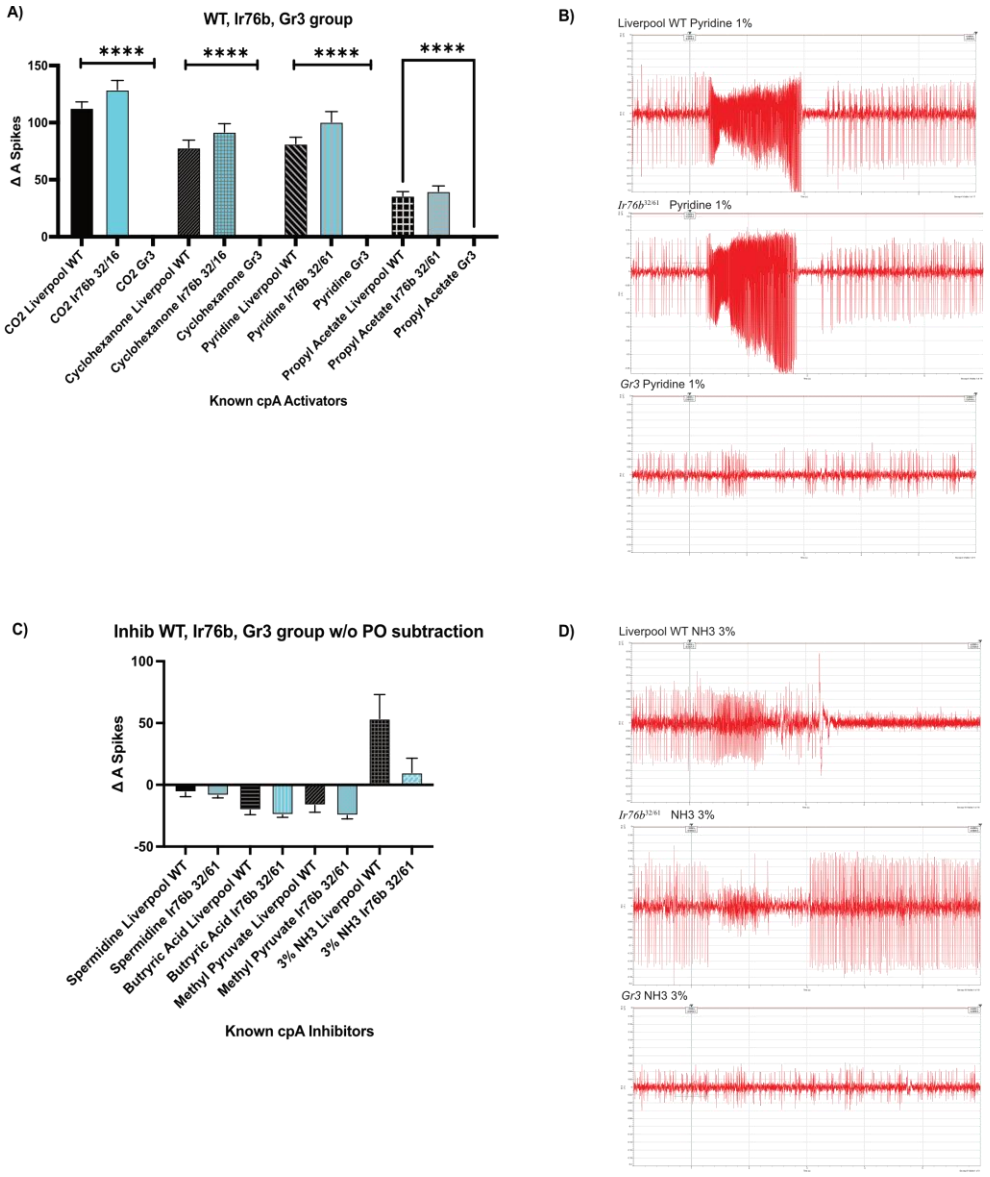


Figure 4.2 Single-sensillum recordings of the capitate peg sensillum in WT, Ir76b mutant, and Gr3 mutants female *Aedes aegypti*

A) Mean changes in the cpA-neurons action potential frequencies/sec to known cpA activators B) Sample representative traces for each strain type to activator pyridine. C) Mean changes in the cpA-neurons action potential frequencies/sec to known cpA inhibitors activators D) Sample representative traces for each strain type to 3% NH_3.

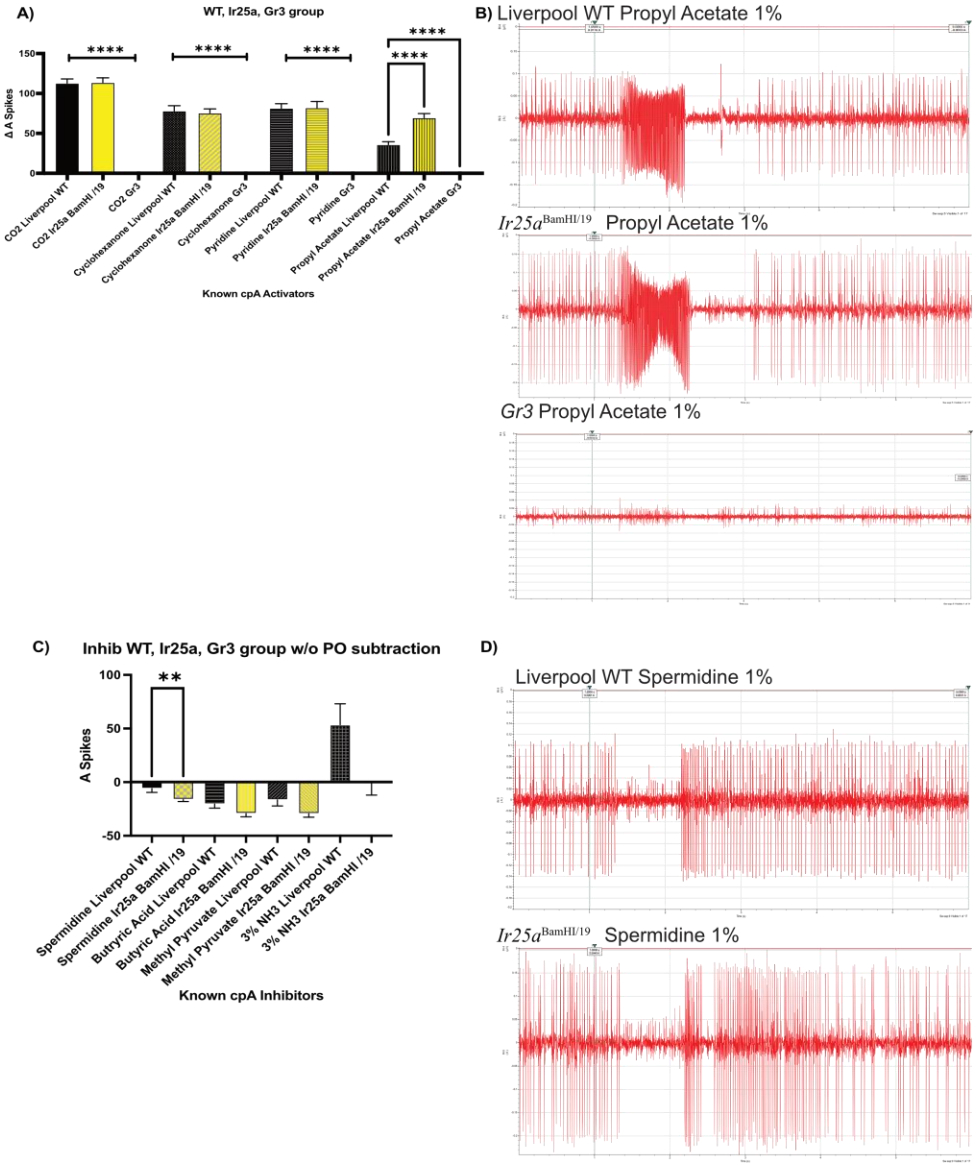


Figure 4.3 Single-sensillum recordings of the capitate peg sensillum in WT, Ir25a, and Gr3 mutant female *Aedes aegypti*

A) Mean changes in the cpA-neurons action potential frequencies/sec to known cpA activators B) Sample representative traces for each strain type to activator propyl acetate. C) Mean changes in the cpA-neurons action potential frequencies/sec to known cpA inhibitors D) Sample representative traces for each strain type to known inhibitor spermidine. One-way ANOVA **** $p < 0.0001$. Unpaired t-test (two-tailed) ** $p=0.0085$.

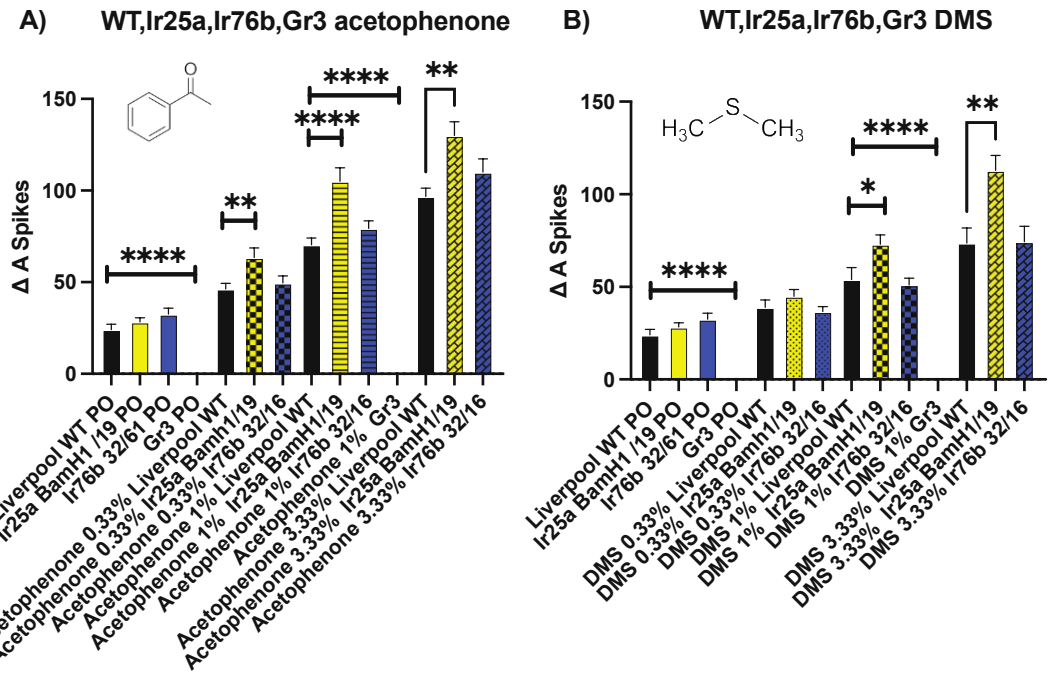


Figure 4.4 Single-sensillum recordings of the capitate peg sensillum in WT, Ir25a, Ir76b, and Gr3 mutant female Aedes aegypti against Acetophenone and DMS

A) Mean changes in the cpA-neurons action potential frequencies/sec to varying concentrations of Acetophenone One-way ANOVA ** p=0.0088 and ** p=0.0010, respectively. **** p<0.0001 B) Mean changes in the cpA-neurons action potential frequencies/sec to varying concentrations of DMS. One-way ANOVA *p=0.0135, **p=0.0014, ****p<0.0001

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CHAPTER V: Conclusion

The culmination of this research underscores the significant role that some volatile organic compounds (VOCs) play in shaping the physiology and gene expression of eukaryotes, including animals, plants, and even disease vectors like mosquitoes. The findings highlight the complex interactions between organisms and their environment, particularly how varying exposure to microbial or environmental volatiles can influence biological processes across different species.

In animals, the work with *Drosophila melanogaster* and subsequent studies in mice and human cells demonstrate that long-term exposure to volatiles such as diacetyl can lead to wide-ranging changes in gene expression and histone modification. These changes not only affect the olfactory system but also have broader implications for brain function and disease progression, suggesting that VOCs could have therapeutic potential(Haga-Yamanaka et al., 2024).

In plants, the study reveals that similar volatile compounds can epigenetically influence key developmental processes and stress responses. The discovery that both plants and animals share conserved pathways for responding to environmental volatiles emphasizes the universal importance of these compounds in eukaryotic biology.

Finally, the research into *Aedes aegypti* olfaction provides critical insights into how disease vectors detect and respond to human-relevant odors. Understanding the olfactory mechanisms of these insects opens up new avenues for controlling their behavior and potentially reducing the spread of diseases.

Overall, this body of work highlights the profound and often underappreciated impact of environmental volatiles on eukaryotic organisms, with implications for health, agriculture, and disease control. It calls for a deeper exploration of how these ubiquitous compounds shape the biological world around us.

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