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From bile acids to melancholia

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In this issue of *Neuron*, Li, Zhang, et al.[1] find that the bile acid receptor TGR5 in the lateral hypothalamus influences neuronal dynamics underlying stress-induced depression-like behaviors. Inhibition of these neurons produces antidepressant-like effects through a circuit that includes hippocampal CA3 and dorsolateral septum, revealing a novel potential therapeutic for depression.

Throughout history, bile acids (BAs), a family of cholesterol-derived steroid acids synthesized in the liver, have intrigued medical scholars. Even modern medicine's father, Hippocrates, postulated their influence on mental well-being, suggesting that imbalances in bodily fluids, or "humors," including bile, phlegm, blood, and black bile, could impact physical and mental health. Hippocrates associated an excess of black bile with melancholia, a feeling of deep sadness and gloom, symptoms resembling modern-day depression. While his understanding was rooted in ancient theories of bodily humors, Hippocrates' observations laid a foundation for understanding the connection between bodily functions and mental states. In modern psychiatry, it is well appreciated that depression is a circuit-based disorder arising from dysfunction in interconnected networks and circuits that generate normal adaptive behaviors. However, there is increasing evidence that bioactive molecules, such as BAs, may contribute to the development of depressive symptoms,[2] with differences in blood BA levels between depressed and healthy individuals being reported.[3] Importantly, there is strong evidence that BAs do not only impact metabolism via peripheral mechanisms but may act centrally via the Takeda G protein-coupled receptor 5 (TGR5). Chronic stress is a significant risk factor for depression, and previous studies in rodents showed a reduction in TGR5 levels in the hippocampus and hypothalamus under chronic stress conditions.[4] Therefore, understanding how TGR5 signaling modulates emotional behavior is crucial for targeting this pathway for potential therapeutics.

The study by Li, Zhang, et al.[1] provides new insight into this process. By investigating how TGR5 influences stress-induced depression-like behaviors in mice, they identify a target in GABAergic neurons in the lateral hypothalamic area (LHA). The study first reveals that TGR5 modulates the excitability of LHA inhibitory (GABAergic) neurons via extracellular signal-regulated kinase (ERK)-dependent potassium channels (Kv4.2). These LHA GABAergic neurons project to the hippocampus, where they target excitatory neurons in dorsal CA3 (dCA3). These dCA3 neurons project to GABAergic cells in the dorsolateral septum (DLS), a brain region implicated in regulating stress responses (Figure 1). The authors go on to show that chronic stress causes downregulation of TGR5 in LHA GABAergic neurons in susceptible mice but not in resilient or control mice. This downregulation produces depression-like effects through increased activity in LHA GABAergic neurons, resulting in enhanced inhibition of dCA3 calcium/calmodulin-dependent protein kinase II (CaMKIIα) neurons that project to DLS GABAergic neurons. Reduced excitation on to DLS GABAergic neurons leads to the disinhibition of various downstream targets, ultimately resulting in depression-like behaviors in stress-susceptible mice. Together, these results provide insights into the complex neural mechanisms underlying depression and suggest potential therapeutic strategies targeting TGR5 and its associated neural circuitry.

The LHA has prominent roles in the regulation of feeding and reward behaviors as well as the control of the hypothalamic-pituitary-adrenal (HPA) axis, adapting an organism to stress. For example, orexinergic LHA neurons receive corticotropin-releasing hormone (CRH) inputs from the paraventricular nucleus of the hypothalamus.[5] Activation of these orexin neurons through their CRH receptors mediates arousal, wakefulness, and motivation due to projections to various brain regions, including corticolimbic, hypothalamic, and peripheral structures. Increased arousal may therefore also result in stress and anxiety and their physiological and behavioral consequences.[6] Future studies testing how downregulation of the TGR5 receptor upon stress exposure influences local LHA circuits will shed further light on the extent of BAs' direct and indirect action on LHA. In addition, as stress-induced increases in corticosterone might partially explain the downregulation of TGR5 in the LHA, independent of BA-driven signaling, future work can dissociate potentially distinct roles for BA and corticosterone in LHA in modulating different stress-induced outcomes.

This work also describes a novel pathway through which stress may impact dynamics in the hippocampus by demonstrating that stress-induced changes in LHA GABAergic activity directly influence dCA3 activity. This builds upon the well-described HPA feedback loop, where corticosterone release due to repeated exposure to stress produces structural and functional

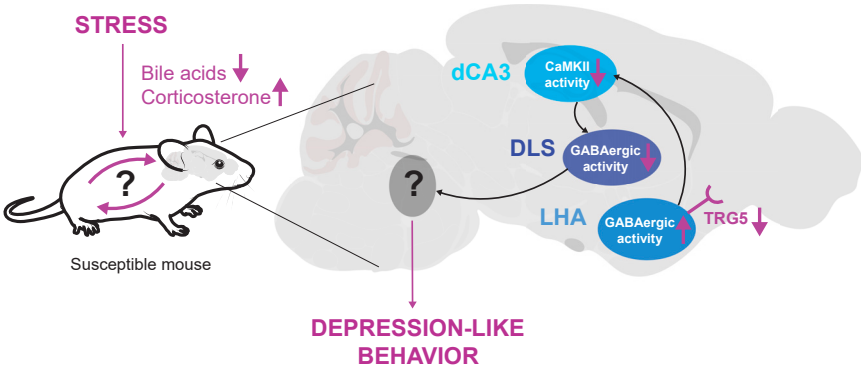

Figure 1. Modulation of stress-induced depression-like behaviors via bile acid receptors in the lateral hypothalamic area

Stress exposure leads to decreased levels of peripheral BA and increased corticosterone release. Either or both of these signals then lead to a downregulation of the BA receptor TGR5 in LHA GABAergic neurons in stress-susceptible mice. This downregulation produces depression-like effects by increased activity in LHA GABAergic neurons, resulting in enhanced inhibition of dCA3 CaMKIIα neurons that project to DLS GABAergic neurons. This inhibition ultimately causes activation of DLS GABAergic neurons, leading to disinhibition of various downstream targets that remain unknown, resulting in depression-like behaviors in stress-susceptible mice. Further, another interesting open question is the mechanism of how peripherally produced BAs exert their central effects. Potential mechanisms include transport via the bloodstream and crossing the blood-brain barrier or neural signaling via neuropod cells synapsing onto the vagus nerve.

remodeling of dCA3.[7] In addition, this work further elucidates the role of hippocampal projections in DLS, which have been well studied for their role in context-reward associations and conditioned fear behaviors.[8] Future work will elucidate pathways downstream of DLS GABAergic neurons that mediate the stress-induced depression-like behaviors. One possibility is modulation of the periaqueductal gray, which receives projections from LHA GABAergic neurons and is implicated in affective behavioral output.[4] Confirming that this projection also mediates the protective effects of TGR5 LHA activation on depression-like behaviors remains subject to future studies.

A growing body of research suggests that the gut-brain axis has a prominent impact on mood and anxiety, and there is growing interest in deciphering the underlying mechanisms. Gut microbiota contribute to BA metabolism, but the mechanism of how peripheral BAs exert their central effects remains elusive. Recent studies suggest that a subset of blood BAs can cross the blood-brain barrier.[9] It is also possible that peripheral BAs activate the recently described neuropod cells, a subset of enteroendocrine cells in the gut that synapse onto the vagus nerve,[10] thereby directly transmitting neural signals from the gut to the brain.

The study by Li, Zhang, et al.[1] has promising translational potential, as peripheral BAs may serve as a novel biomarker for psychiatric diseases. Recent studies have found that blood BA profiles are altered in patients suffering from major depressive disorder or anxiety.[3] One compelling finding by Li, Zhang, et al.[1] is that brief inhibition of TGR5-expressing GABAergic cells in the LHA for 3 consecutive days decreased depression-like behaviors for weeks, revealing the therapeutic potential for targeting these cells and suggesting that a short-term intervention may have long-term effects on mood and well-being. Alternatively, nutritional control of systemic BA levels (e.g., intake of apple vinegar) may be a more natural way of enhancing the protective effects of LHA TGR5 activation. It is important to note that BAs are a heterogeneous group of molecules, and depression and anxiety disorders have been linked with either an increase or decrease in certain types of BAs.[3] Therefore, a carefully titrated and individualized treatment approach would be necessary to reach a balanced BA profile, which may be most helpful in treating patients suffering from depression or anxiety disorders.

Together, these results shed light on the critical role of a previously unknown modulator, the BA receptor TGR5, on specific neural circuit mechanisms involved in the regulation of stress-induced depression and emphasize the tight connection between the body and brain in mood disorders. Thus, we should not always set aside seemingly outdated hypotheses by our predecessors, as, by connecting bile and mood, Hippocrates might have been on to something all along.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Turning down the body heat: A novel mechanism for TRPV1 antagonist-induced hyperthermia

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While effective analgesics, TRPV1 antagonists can dangerously alter thermoregulation. In this issue of *Neuron*, Huang et al.[1] demonstrate that interaction with the S4-S5 linker of TRPV1 determines whether an antagonist affects core body temperature, with promising implications for analgesic development.

The promiscuous nociceptor transient receptor potential vanilloid 1 (TRPV1) has been a hotly pursued target for analgesic discovery for over two decades. TRPV1, a non-selective ion channel expressed primarily in nociceptive sensory neurons, is activated by numerous noxious stimuli, including heat and chemicals (vanilloids, protons), and is instrumental in numerous pathological pain conditions.[2] While TRPV1 antagonists have shown promise as potential therapeutic analgesics, to date, no TRPV1 antagonists have been approved for use in humans. One factor hindering these efforts is that many TRPV1 antagonists that target its vanilloid binding domain alter core body temperature (CBT), with some producing hyperthermia and others paradoxically evoking hypothermia similar to TRPV1 agonists such as capsaicin and resiniferatoxin.[2–6] In a thorough and compelling new study, Huang and colleagues[1] provide novel insights into the mechanisms underlying TRPV1 antagonist-driven changes in CBT, which could provide a path forward for the development of TRPV1-targeted analgesics free of effects on CBT.

The exact methods by which TRPV1 ligands alter CBT are unknown, though multiple hypotheses have been put forward. One proposition is that ligand-induced effects on TRPV1 receptors expressed in the hypothalamic preoptic area, a region responsible for thermoregulation, drive changes in CBT. This hypothesis is supported by the fact that infusion of capsaicin directly into the brain was capable of eliciting changes in CBT.[6] Others have postulated that since vascular TRPV1 receptors can influence vascular tone (i.e., vasoconstriction and vasodilation) in the periphery, specific activation or inhibition of the channel in these locales could regulate heat loss and, thus, CBT.[7] However, a recent study demonstrated that selective ablation of peripheral TRPV1$^+$ sensory neurons, but not TRPV1$^+$ vascular smooth muscle cells, eliminated TRPV1 ligand-induced effects on CBT, suggesting that TRPV1 ligand-driven changes in CBT are dependent on TRPV1 expressed in peripheral sensory neurons.[8] In line with this theory, proton-mediated modulation of tonic TRPV1 activity in the trunk, rather than TRPV1's innate thermosensing capacity, has been proposed to underlie TRPV1-dependent thermoregulatory effects. Various studies have shown that the TRPV1 modality an antagonist targets determines whether it elicits hyperthermia or hypothermia or has no effect on thermoregulation. In particular, hyperthermia has been correlated with the ability of TRPV1 antagonists to block proton activation, mode-selective antagonists that have no effect on proton activation do not induce changes in CBT, and antagonists that potentiate proton activation induce hypothermia.[5,9] It is theorized that tonic activation of TRPV1 in the viscera by protons inhibits "cold defenses" such as skin vasoconstriction and thermogenesis. Antagonist-induced blockade of proton activation would therefore disinhibit these autonomic responses, resulting in hyperthermia.[5,6,9,10]

In this insightful study, Huang et al. call into question the hypothesis that activation of TRPV1 by protons mediates the channel's effects on CBT and instead propose an alternative theory wherein the manner in which an antagonist interacts

