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Sexes on the Brain: Sex as Multiple Biological Variables in the Neuronal Control of Feeding

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Abstract

Neuronal interactions at the level of vagal, homeostatic, and hedonic circuitry work to regulate the neuronal control of feeding. This integrative system appears to vary across sex and gender in the animal and human worlds. Most feeding research investigating these variations across sex and gender focus on how the organizational and activational mechanisms of hormones contribute to these differences. However, in limited studies spanning both the central and peripheral nervous systems, sex differences in feeding have been shown to manifest not just at the level of the hormonal, but also at the chromosomal, epigenetic, cellular, and even circuitry levels to alter food intake. In this review, we provide a brief orientation to the current understanding of how these neuronal systems interact before dissecting selected studies from the recent literature to exemplify how feeding physiology at all levels can be affected by the various components of sex.

Keywords

Feeding; sex; neuronal; hormone; epigenetic; chromosome

1. Introduction

Food and eating play dual roles in global society, providing both biological and cultural capital. Humans eat for more than mere sustenance; food can provide a social back drop and an emotional reprieve, while also producing anxiety over body image. These socioemotional factors can lead to extreme modulations in food intake, including over- and under-eating, resulting in detrimental health outcomes. Increased food intake of calorie-dense foods can

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increase the likelihood to develop obesity and its comorbidities, while binge and under-eating can result in dysmenorrhea, cardiovascular problems, starvation, and even death. Though both obesity and eating disorders may have multifactorial metabolic, psychological, and societal etiologies, the modulation of food intake remains both a symptom of and exacerbating factor in these conditions. Both obesity and eating disorders are also significantly gendered – women are the fastest growing constituent of obese and extremely obese individuals (despite body mass tending to be higher in men than women) [1], and women and girls engage in disordered eating up to three times more than men and boys [2].[2] Thus, sex factors (a set of biological variables typically associated with reproduction) may predispose people of a certain gender (a combination of our social reaction to the phenotypes resulting from those variables and internal identification) to modulate food intake in response to various environmental pressures. Much research investigating sex differences in feeding has focused on hormonal contributions to food intake. However, these studies often result in an incomplete understanding of sex difference etiology. This is most likely because sex is not a simple dichotomy of estrogen vs. testosterone, but a complex and interacting network of related but distinct factors, including not only hormones but also sex chromosomes, parental imprinting, and sex-specific environment, which may interact, counteract, or synergize with one another. An understanding of how, then, specific components of sex shape and act upon feeding circuitry is vital to our understanding of the neuronal control of food intake. In this review, we will first provide a brief overview of the vast overlap in the central nervous system's control of homeostatic and hedonic feeding. We will then explore how sex, sex differences, and the various facets of sex affect all levels of feeding physiology.

2. The Neuronal Circuitry of Feeding – Homeostatic & Hedonic Cooperation

The physiology of feeding is typically construed as a universal homeostatic process, which, due to its vital nature, remains relatively physiologically conserved across the animal kingdom. Across vertebrates, both the hypothalamus and hindbrain prove crucial to the control and regulation of food intake (reviewed in [3,4]). Despite this apparent conservation of structure and function, patterns and uses of food intake vary both across and within species. In a variety of animals, including rodents and humans, homeostatic circuitry is integrated with hedonic, motivational, reward, and higher-order top-down circuitry. This integration lends flexibility to the system yet increases chances for circuitry "malfunction." Most current literature separates this homeostatic and hedonic circuitry. These systems, however, are inextricably intertwined and interdependent [5–7] (Figure 1). For instance, when canonical homeostatic regions are developmentally ablated, hedonic mechanisms can provide compensatory support [8].

[2]These epidemiological surveys do not report how they determine sex or gender. As there are typically no reported physical examinations, karyotypes, or hormone levels, we assume that this is gathered by self-report and therefore it is probable that these studies only consider cis individuals. This is a vast oversight in the field, as the trans population is at an increased risk for eating disorders due to a multiplicity of factors, including a higher incidence of gender dysphoria, body dysmorphia, and varied gender expression [120–122].

The interaction of homeostatic and hedonic circuitry spans across all phases of feeding behavior. The melanocortin system canonically consists of the appetitive agouti-related peptide (AGRP)/neuropeptide Y (NPY) neurons and the satiety-related proopiomelanocortin (POMC) neurons within the arcuate nucleus of the hypothalamus (ARC) along with second order α-melanocyte-stimulating hormone receptor cells in the paraventricular nucleus of the hypothalamus (reviewed in [9]). While this system has been characterized as promoting homeostatic foraging and food seeking [10,11], there is also evidence for AGRP/NPY neuronal recruitment of learning/reward circuitry, as these neurons both induce a negative valence state [12] and promote fearlessness in the face of starvation through projections to the amygdala [13]. In the lateral hypothalamus, GABAergic, orexin, and/or melanin-concentrating hormone neuronal subpopulations involved in homeostatic feeding [14,15] (for review, see [16]) exhibit extensive communication with motivational circuitry (reviewed in [17]). Connections, in some cases bidirectional, with regions including the ventral tegmental area [18], bed nucleus of the stria terminalis [19], nucleus accumbens (both shell and core; reviewed in [6,16]), and hedonic hotspot the parabracheal nucleus [20,21] allow the lateral hypothalamus to integrate homeostatic signals of metabolic need as well as motivational and hedonic cues to promote eating behavior for the duration of a meal. Even regions functioning as homeostatic nodes of satiety, satiation, and meal cessation have significant overlap with stereotypical hedonic circuitry. The nucleus of the solitary tract (NTS) receives a significant amount of vagal afferent synapses to communicate hormonal and mechanosensory markers of satiety to the brain (reviewed in [7]). These signals then integrate with hedonic circuitry on multiple levels. Glucagon-like peptide 1 neurons in the NTS send direct processes to dopaminergic neurons in the ventral tegmental area, which then in turn project to the nucleus accumbens shell [22]. NTS populations expressing norepinephrine and cholecytoskinin recruit the hedonic/homeostatic parabracheal nucleus. From here, calcitonin gene-related peptide neurons promote meal termination by way of projections to the central amygdala and other connections [7,23].

As is evident, these canonically homeostatic nodes regularly interact with hedonic, motivational, and learning pathways (Figure 1). Interestingly, it has been hypothesized that dysregulation of homeostatic/hedonic balance promotes disordered eating [24]. And as the propensity for disordered eating in humans is gendered, the effects of sex on both homeostatic and hedonic nodes, and how they interact, must be considered when investigating the neuronal control of feeding.

3. Current Understanding of Neuronal Sex Differences in Feeding

In mice and rats, males consume more food daily than do female conspecifics. Hence, sex differences in feeding have been long appreciated (for review, see [25]). Phenotypic sex is comprised of various factors, including the organizational and activational effects of hormones, chromosome complement and expression, and sex-based experiences [26]. Despite this, the bulk of neuroscience research regarding sex differences in feeding has focused on the effects of sex steroid hormones, namely 17β-estradiol, and its interactions with estrogen receptor subtype α (ERα). A recent review highlighted multiple nodes across homeostatic and hedonic circuitry wherein estradiol acts (typically through ERα [27,28]) to decrease food intake across species [29], though the particular effects and mechanisms of

estradiol varies from species to species. Rats and guinea pigs provide models of feeding that are tightly correlated to estrogen levels. In these organisms, increased levels of endogenous ovarian estrogens decrease food intake: feeding decreases following the high estradiol phase of the estrous cycle [25,30,31] and ovariectomy significantly increases feeding and subsequently body weight [30–33]. This anorexic effect of estradiol appears to be mediated by affecting both the appetitive and meal-cessation stages of feeding. In the melanocortin system, estrogens have been shown to decrease food intake in the ARC [34] through POMC neuron activation via both ERα and the g protein-coupled membrane estrogen receptor (known as GqMER) [35–37], as well as by altering both the effects and expression of NPY and α-melanocyte-stimulating hormone [38,39]. In the brainstem, estradiol has been found to interact with ghrelin (an orexigenic stomach hormone) [32], leptin (a hormone released by adipocytes which can signal adiposity levels to the brain) [38,40], cholecytoskinin [32,41], and glucagon-like peptide 1 [42] signaling in the NTS to promote meal cessation. This modulation of homeostatic feeding by estradiol can act in addition to, in opposition to, or synergistically with estrogenic alteration of hedonic, motivational, and reward circuitry. Endogenous and replacement estradiol has been found to reduce food-motivated reward in the ventral tegmental area [33]. Furthermore, both ERα and estrogen receptor subtype β (ERβ) have been found to be expressed and affect cellular activity in regions such as the bed nucleus of the stria terminalis, amygdala, ventral tegmental area, and nucleus accumbens (reviewed in [43]).

In mice, however, the picture becomes complicated. While some studies have found a typically mild effect of endogenous estrous cycle [44,45], ovarian hormones [27,46,47], and/or estrogen receptor presence [27,48,49] on food intake, others have reported no clear estrogenic effects [31,50,51]. This lack of consensus indicates that caution must be employed when interpreting how the discovered effects of estrogens on feeding and metabolism in one species apply to another. Interestingly, the more robust and consistent phenotype in mice following depletion of estrogen signaling is a sex-specific decrease of energy expenditure [48,49,52]. As weight gain in post-menopausal women also does not result from an increase in food intake and is instead primarily due to a decrease energy expenditure [53], mouse models may be more applicable to humans than other rodents when considering the effects of estrogens on feeding and metabolism.

Limited research has focused on testosterone and androgenic effects on feeding. Castration in adulthood has been shown to decrease food intake, while replacement and/or long- term testosterone treatment increases feeding [47,54,55]. Though the precise mechanisms of these effects remain unknown, the effect of testosterone on male feeding is most probably not due to aromatization and is therefore androgenic in nature [55]. During development, on the other hand, neonatal androgen exposure decreases POMC mRNA content and projections from the ARC [56], indicating that lifetime increase of food intake in males may be partially due to developmental inhibition of the anorexic arm of the melanocortin pathway. Interestingly, the effects of neonatal androgen on feeding patterns may also require further development during puberty, as perinatal testosterone decreased female rats' risk for binge eating only after mid- puberty [57].

This approach to sex, viewing it as a single variable alterable by presence or absence of various steroid hormones and their respective receptors, is useful but incomplete. When applied to feeding, adulthood hormone manipulations alone are insufficient to elucidate the role of sex differences on neuronal physiology. For example, in a recent tracing study, vagal afferents were found to have sex differences both within and beyond simple hormone manipulations (Figure 2). Female and male Wistar rats exhibit variations in both density and localization of heavily myelinated (A) and unmyelinated (C) peripheral fiber innervation into the brainstem, including the NTS [58]. While peri-pubertal ovariectomy decreased and subsequent estradiol replacement increased innervation density in females, the NTS of females in both conditions was still more densely innervated with non-myelinated fibers as compared to males. Furthermore, regardless of hormonal manipulation in females, females and males exhibited a differential pattern of peripheral fiber innervation into the brainstem [58]. Together, these results indicate that vagal- NTS connective anatomy is modulated by sex variables above and beyond that of pubertal and post-pubertal hormone levels. While the organizational effects of the neonatal testosterone surge on this innervation pattern have yet to be explored, some sex differences exist beyond these early-life hormonal influences as well.

In recent work, sex differences in food anticipatory behavior in mice were found to exist independent of various hormonal manipulations [59]. Due to the circadian nature of feeding, scheduled food-restriction can result in increased animal movement in anticipation of food delivery, particularly in males [60,61]. One study searching for the etiology of this sex difference investigated the effects of hormones in adolescence and in early life. Neither peripubertal gonadectomy nor neonatal injections of estradiol, accepted to be the primary neurologically- bioactive compound in rodents during the organizing testosterone surge, increased female food anticipatory activity [59]. However, this study does lie in contrast to earlier work in which early adulthood gonadectomy in males decreased and ovariectomy in females increased food anticipatory activity, abolishing the sex difference [61]. These conflicting results may be due to methodological differences in the timing of female ovariectomy, indicating a possible organizational role for pubertal hormones in addition to other sex factors.

Together, these and other studies exemplify how we must cease viewing sex as an all-encompassing heuristic or as a function purely of gonadal hormones and their receptors. In order to fully understand the complexities underlying feeding physiology, we must instead adopt a model of sex as a set of diverse, covarying, but independently acting components [62].

4. Room for Investigation: The Components of Sex as Contributors to Sex Differences in the Neuronal Control of Feeding

The prominence of neuroendocrinological examinations of sex differences in feeding is due to not only the relative ease of hormonal manipulations, but also the historical dominance of the organization/activational paradigm with regards to sexual differentiation. Initially pioneered in the 1950s, this hypothesis hinges on the idea that the neonatal testosterone

surge, primarily through its metabolite estradiol in rodents, “organizes” the male brain by permanently defeminizing and/or masculinizing brain circuitry. Gonadal hormones, elevated during puberty and into adulthood, are then able to reversibly act on, or “activate,” the circuit as hormone levels fluctuate [63]. In the years following its initial introduction, the hypothesis has been amended to include puberty as an organizational event as well [64]. The stand-alone primacy of the organizational/activational hypothesis in forming and creating sex differences in the mammalian brain has been repeatedly challenged [65,66] despite this and other amendments. That is not to say that the effects of sex steroid hormones, particularly the neonatal testosterone surge, on structural differences in neuronal populations [67], cellular expression [68], and epigenetic modulation [69] are not real, varied, and persistent. However, by viewing these effects as absolute, uniform, and all-encompassing, we neglect how other components of sex may interact with these to compensate for or contribute to physiological heterogeneity in the brain [70]. Hence, by viewing sex as a binary of “testosterone or estradiol” instead of a spectrum created by the composition of interrelated parts, we miss how the components of sex work together or separately to affect feeding physiology and dysfunction. In the sections that follow, we will interrogate how other sex components – sex chromosomes, parental imprinting, and environmentally-induced epigenetic modifications – interact with feeding circuitry.

4.1 Sex Chromosome Complement

As has been repeatedly seen across species, sex chromosome complement (e.g. XX, XY, etc. in most mammals, and ZW, ZZ, etc. in birds) can affect both physiology and behavior. This can occur not only through gene expression, but also through epigenetic autosomal regulation by the sex chromosomes [71]. Indeed, sex differences can occur at a cellular level prior to gonadal hormone exposure [72–74]. The difficulty in assessing sex chromosome effects independent of gonadal hormones is that the two are typically linked. The Y chromosome canonically contains *Sry*, the testis-determining gene, which typically results in the development of testes from the bipotential gonad in mammals. The four core genotypes mouse model allows for the dissociation of sex chromosome complement and gonadal type due to the translocation of *Sry* to an autosome, resulting in four offspring of varying sex components: XX+ovaries, XY+ovaries, XX+testes, and XY+testes. The four core genotypes model can thus be used to discover hormonal/gonadal (ovaries vs. testes) or sex chromosome complement (XX vs. XY) contributions to sex differences, as well as the interactions between these factors [75].

The effects of sex chromosome complement can manifest in several ways. In mammals, both gene differences on the X and Y chromosomes (namely the presence of a Y chromosome) and X gene dosage may contribute. Typically, to compensate for a doubling of the X chromosome in XX individuals, one mammalian X chromosome will undergo inactivation by the gene *Xist*. This occurs randomly on an individual cell-by-cell basis, leading to a mosaic organism where some cells have the paternal, and other cells the maternal, X chromosome silenced [26,76]. However, X-inactivation is an incomplete process. Some genes, known as “X escapees,” evade *Xist*-mediated epigenetic inactivation and remain expressed at higher levels in individuals more than one X chromosome [76,77]. Thus, a difference in phenotype between XX and XY mice independent of gonadal hormones could

be explained by either X or Y gene effects. To separate these, the XY* mouse model can be used. This mouse model contains a Y chromosome which has an altered pseudoautosomal region (Y*), resulting in abnormal recombination producing genotypes similar to XO, XX, XY, and XXY [46,78]. Therefore, this model can be used to determine whether effects of sex chromosome complement are due to X effects (due to dosage or imprinting) and/or the presence or absence of the Y chromosome.

Both of these approaches have been applied to feeding and metabolism in a fairly broad capacity. In four core genotypes mice, average body weight was found to result from an interaction between gonadal type and sex chromosome complement [46]. Prior to gonadectomy, mice with testes weighed more than those with ovaries, regardless of sex chromosome complement. XX mice also tended to be heavier than their XY counterparts within testicular and ovarian groups. Following gonadectomy, a strong sex chromosome complement effect emerged, with XX mice gaining weight more rapidly than those with an XY sex chromosome complement (Figure 3A). Interestingly, there also appeared to be an interaction between sex chromosome complement and gonadal status, as XX mice formerly having ovaries gained weight much quicker than XX mice previously having testes. Such a seemingly counteracting nature of typically-paired sex components (XX counteracting ovarian effect, XY counteracting testicular) is not uncommon. Physiological sex differences have been found to both reinforce and counteract others in order to mitigate differences in behavior in various organisms and contexts [65,67,79].

This body mass phenotype was propagated, at least partially, by a preceding alteration in food intake. Four weeks following gonadectomy, prior to the divergence of body weights, mice formerly having ovaries consumed more grams of chow during the dark period as compared to mice which had had testes, regardless of sex chromosome complement (Figure 3B). During the inactive daytime period, however, XX mice ingested more grams of chow than XY mice, and XX+ovaries mice tended to have higher food intake than XX+testes mice (though this was not statistically significant, Figure 3B). These joint effects of gonadal hormones and sex chromosome complement on food intake were no longer apparent by 10 months following gonadectomy. And while the XY* mouse model revealed that this effect of sex chromosome complement on body weight was due to X dosage and not Y presence [46] (Figure 3C), it is interesting to note that this is not true of all strains. On another background, *both* X dosage and Y presence contributed to an increase in high fat diet food consumption, with XXY mice consuming almost 4 grams in one 12-hour nighttime period [80]. Thus, sex chromosome complement may have varying effects on alternate genetic backgrounds and when consuming different diets. Importantly, none of these effects were localized to any particular neuronal circuitry, though subsequent investigations revealed that sex chromosome complement and/or gonadal type contribute to various components of meal architecture [47]. It is possible that these effects are due to combined peripheral and central effects, as both gonadal type and sex chromosome complement were found to affect adiposity (and resulting leptin circulation), energy expenditure, muscle activity, and liver function [46,47,80]. Regardless, if we wish to fully understand how the nervous system controls feeding behavior, more research into *where* the effects of sex, including those of sex chromosome complement, manifest within the homeostatic and hedonic feeding circuit must be conducted.

4.2 Parental Imprinting

Closely linked to sex differences due to sex chromosome effects is the possible influence of parent-of-origin genomic imprinting. In this phenomenon, certain genes are subject to epigenetic modulation based on parental inheritance. Such cis epigenetic modulation typically takes the form of silencing through DNA methylation or histone tail modifications to alter the chromatin conformation and thereby decrease transcription. Few genes have been found to be under the control of parent-of-origin effects, though many imprinted genes have been found to be important for hypothalamic development and function [81]. In the human population, parent-of- origin genomic imprinting has been found to be associated with obesity [82]. Quite possibly the most famous imprinting occurs on the 15q11-q13 chromosomal region to produce Prader-Willi Syndrome, which is characterized by both severe hyperphagia and hypothalamic hypogonadism [83]. Interestingly, this syndrome occurs specifically when *paternal* imprinting is evident in this region; maternal imprinting, on the other hand, results in the phenotypically distinct, non- hyperphagic Angelman Syndrome. This phenotypic variance from differential imprinting may be due to the combinatorial effects of differences in methylation site during the imprinting process along with specific parental allelic expression in certain brain regions [83]. Parental imprinting to varying degrees has also been found in specific nodes of the feeding circuit and affiliated nuclei, including the ARC and dorsal raphae nucleus [84]. Given that parental imprinting appears to have such a large effect on hypothalamic development and metabolism (and these effects may be more common than initially believed [85]), this mechanism may also play a role in the development of neuronal feeding circuitry and sex differences within it.

When discussing sex differences due to parental imprinting, it is typically assumed that this phenomenon occurs only on the X chromosome, as mammalian XX individuals alone could be subjected to paternal imprinting, thereby leading to even further modulation of transcript expression aside from random X-inactivation by *Xist* [86]. However, some studies have found that parental imprinting effects can be specifically "targeted" towards one sex or another. In a study of mouse embryonic germ cell lines derived from the genital ridge of four core genotypes mice, sex-specific methylation patterns of a paternally-imprinted gene showed XX-specific demethylation not dependent on gonadal type [87]. Due to lack of quantification, no interactions were evident between sex chromosome complement and gonad type, though the data presented indicate this may be possible. One study demonstrating similar sex-differential parental imprinting in the brain found various loci specifically affiliated with growth and weight exhibiting parent-of-origin imprinting in one sex but not the other (e.g. females showing paternal imprinting of a specific gene while males show no epigenetic regulation) [88]. Together, this evidence suggests that sex-specific parental imprinting may interact with sex chromosome complement or other sex variables to produce, exacerbate, or diminish sex differences in the known nodes of the feeding circuit.

4.3 Environmental effects

Too often, environmental effects on the brain are not taken into consideration when investigating sex differences. This becomes particularly relevant when determining how different treatment of the sexes may result in altered gene expression (through epigenetic mechanisms) or even strengthening/weakening of neuronal connections (through learning) in

a relatively sex- segregated fashion. In human societies, said differential treatment, learning, and expectations constitutes gender socialization, a culturally defined phenomenon based on assumed sex. Such cultures create sex-biased environments that, like other environmental variables, can act on the brain to induce or exacerbate neuronal “sex” differences during both development and adulthood [89]. These gender socialization differences can even register in brain imaging studies. In one small neuroimaging study, women displayed higher activation (as compared to men) in the dorsolateral prefrontal cortex when presented with images of hedonic food following a eucaloric diet and fast [90]. As this region is late to develop in humans and is primarily concerned with executive function and top-down inhibitory control, it is not radical to consider that this difference in brain activation might be largely due to gender socialization instead of purely endogenous differences in neuronal activation. Though the biological underpinnings responsible for societally-induced changes on the brain are difficult to study in the human population, differential sex treatment in early life by rodent dams has provided an interesting model by which to study an environmentally exacerbated (or created) sex difference.

Olfactory cues, such as higher levels of testosterone and/or its metabolites secreted by pup urine, result in rodent dams preferentially licking the anogenital region of male offspring over that of female pups (reviewed in [91]). This differential treatment has been shown to be vital to the development of sex-specific sexual behaviors in both male [92] and female rats [93]. More recent research has revealed that maternal care and grooming results in epigenetic modifications [94] to alter steroid hormone receptor expression [95], including ERα, in various hypothalamic subnuclei [96,97] and other deep-brain regions [98]. Beyond gene expression, such early-life care and exposure has the potential to alter neuronal and dendritic outgrowth [99], activity [97,100], and plasticity [100]. In humans, one might consider such differential treatment by perceived biological sex a construction of gender socialization, whereby infants and children receive differential treatment and have varying expectations placed upon them due to this perception and its interaction with social norms. Thus, it is quite plausible that gendered constructions may alter gene expression through epigenetic means to produce, reinforce, or counteract endogenous biological sex differences [101].

This potentiation of sex differences via differential treatment of offspring by sex retains the possibility of intersection with the feeding pathways. Much of the research concerning differential epigenetic modification following maternal licking or treatment has investigated the modulation of steroid hormone receptors. However, low maternal grooming has also been found to significantly decrease offspring body weight [99], indicating possible long-term modulation of feeding and/or other metabolic circuitry. Furthermore, there have been ample studies investigating how epigenetic modification, such as DNA methylation, histone modification, and micro-RNAs, alter feeding through the expression of key genes regulating feeding, including POMC and NPY (for review, see [69]). It is therefore not unlikely that sex-specific environmental impacts, exemplified by maternal anogenital licking in rodents and gendered expectations in humans, may also result in epigenetic modifications on the feeding circuit. Thus, the role of differential environment due to perceived sex should not be ignored as a potential source of sex and gender differences in future study of rodents and humans, respectively.

5. Bringing It All Together: How Sex Variables Can Alter Feeding Circuits

5.1 Cellular Effects

Effects of the components of sex can manifest individually and together to result in divergent and/or convergent neuronal activity. Altering cellular activity may result in both divergent and/or convergent behavioral outputs. In one vein, sex differences may result in differential activation of the same neuronal population. In a study demonstrating that female rats consume more palatable food than males, post-mortem analysis demonstrated increased presence of the immediate early gene *Fos*, a marker of neuronal activation, in the nucleus accumbens of females as compared to males [102]. This indicates that differential activation of this region by the same stimulus might result in altering behavioral output as it relates to food intake. Interestingly, this *Fos* difference was only evident when specifically quantifying the nucleus accumbens shell, designated as a “hedonic hotspot” in the hedonic feeding literature [21,102]. While this difference in hedonic activation has not been attributed to any of the aforementioned components of sex in isolation or combination, this region expresses ERα, ERβ, and the androgen receptor [103]. How sex components like gonadal hormones result in differential activation in this case is not known. One mechanism of action could be similar to that examined in serotonin neurons in the dorsal raphae nucleus. Here, estradiol was found to activate neurons through the inhibition inward-rectifying of small conductance calcium-activated potassium (SK) current in an ERα-dependent fashion, and this activation was associated with a suppression of ovariectomy-induced binge eating [104]. In this study, the existence of a similar mechanism in males was not explored, nor were the possible genetic, etc. etiologies investigated for differences in dorsal raphae nucleus organization that may lead to hormonally-dependent binge eating pathology in females [105]. Indeed, evidence from outside the feeding circuitry indicates that equivalent cell populations in females and males contribute to similar but distinct outputs. Aromatase neurons in the medial amygdala have been shown to mediate aggression in both females and males. However, the behavioral manifestation of maternal and intermale aggression, respectively, are distinct in form and function [106]. What, if any, component(s) of sex contribute to and set up this difference in aromatase neuron function (whether by differential gene expression, axonal projection, or something of the like) has yet to be determined.

In the periphery, sex differences in vagal nerve activity, particularly as it relates to heart rate and overall vagal tone, have become apparent. Not only have baseline sex/gender[3] differences in human vagal tone during sleep been reported [107], but these differences persist in the context of disease, where depressed women exhibit greater cardiac vagal control than depressed men [108]. Interestingly, the reports of this simple human sex/gender difference in vagal reactivity are muddled. The same physiology may have different behavioral consequences within the context of assigned sex. Vagal reactivity as measured by respiratory sinus arrhythmia was negatively associated with maternal assessments of irritability & oppositional nature in boys but was positively associated with such in girls [109]. Given the evidence of vagal innervation into regions of central feeding circuitry [58],

[3]Here, we are using the combined term “sex/gender” as in [123] because, in the context of human studies, the endogenous effects of sex variables and the exogenous effects of gender socialization are inextricably linked and arguably unable to be dissociated.

it is plausible that this vagal reactivity and context-/sex-dependency may also affect gut-brain communication as it relates to ingestion feedback [110,111]. A few human studies have suggested this may be the case, namely those indicating that infant diet and early life exposures differentially affect children of differing assigned sex [112,113]. However, little basic research investigating the mechanisms and factors by which these apparent effects of sex manifest has been conducted.

5.2 Anatomical Effects

The components of sex can also affect anatomical morphology and connectivity within neurological feeding pathways. As previously stated, neonatal testosterone was found to decrease POMC projections from the ARC and result in a masculinization of food intake [56]. Interestingly, this projection pattern, while mimicking that of control males, does not fully explain sex differences in adulthood feeding, as this masculinization of food intake did not quite reach the level of male controls. These results may be confounded by the effects of treatment on peripheral energy processing, as neonatal testosterone failed to defeminize/masculinize leptin signaling and white adipose tissue storage in any discernable pattern [56]. Nonetheless, this study makes apparent that neonatal testosterone's "masculinization" of POMC projections from the arcuate is merely *one* factor in how the components of sex alter the neurological control of feeding.

In the human brain, a similar pattern emerges. The use of brain imaging technologies has allowed for investigations into the living human brain. And while sex/gender differences unveiled in these studies may be somewhat inconclusive depending on their interpretations, careful analysis and conservative extrapolations of the data can allow for a deeper understanding of human physiology. In a diffusion tensor imaging study, women (pre-menopausal, apparently naturally-cycling, and scanned during the approximated menstrual follicular phase) exhibited higher connectivity between nodes associated with reward circuitry as compared to men (age-matched and presumably cis) [114]. While the specific pattern of connectivity strength did interact with body mass index, the overall sex/gender difference in connectivity strength remained within reward circuitry nodes. Even understanding the limited extrapolations brain structure can convey to function [67], this evidence is nonetheless intriguing given the hypothesis that disordered eating, a woman/girl-skewed trait, potentially results from an imbalance of homeostatic and motivational/reward circuitry [6,24]. And while this imaging study excluded individuals with diagnosed eating disorders, the underlying circuitry differences may result in a biological predisposition to extreme feeding modulation in certain contexts (though whether this apparent connectivity difference is endogenous, the result of gender socialization, or both remains to be explored).

Importantly, it is currently difficult to dissociate the relative contributions of the endogenous components of sex from the exogenous effects of gender on the brain. Endogenously, the organizational and activational effects of sex hormones may indeed contribute, but not fully explain, sex and gender differences in feeding circuitry to differentially promote disordered eating. In a study using 2D:4D digit ratio as a proxy for neonatal testosterone levels [115] along with salivary estradiol levels, researchers found that inferred lower neonatal testosterone and higher circulating adult estradiol levels independently correlated with

disordered eating as defined by the Minnesota Eating Behaviors Survey (MEBS) [116]. However, inferred neonatal testosterone and adult estradiol accounted for only ~5% and 6–11% of the population variability in survey score, respectively, suggesting that other factors are needed to explain the sex difference. Indeed, some portion of these sex differences may be due to sex chromosome complement. Moving back to mice, intact XX animals of either gonadal type show increased food-reinforced habit formation than XY counterparts [117], indicating that sex differences in hedonic/motivational feeding circuitry is probably due to a combination of at least gonadal hormone and sex chromosome complement effect.

6. Conclusions

The contributions of sex differences are multifaceted and varied in any context, including the neuronal control of food intake. Instead of providing a complete account of all studies that report a sex difference, we have chosen a few examples to illustrate how the components of sex can act individually or in combination to affect behavioral output. Sex can modulate many facets of neuronal feeding circuits, from individual cells to circuitry connections, in the homoeostatic and hedonic nodes, and at all stages of feeding. It is vitally important to remember that effects of one component of sex (e.g. gonadal hormones in adulthood) do not exist in isolation. Both synergism [79] and compensation from other sex components can further differentiate or mitigate resulting behavioral output, respectively [65,89]. Not only this, but the degree of “masculinization” or “feminization” may differ from tissue to tissue and brain region to brain region. Such heterogeneity may result from the effects of differing sex components, context, and environment [70,118]. Thus, it is more useful to view both central and peripheral neuronal controls of feeding as being possibly differentially influenced by orthogonal individual components of sex [119].

When we take this view, it is not surprising that sex differences remain apparent in vagal innervation following both pre-pubertal ovariectomy and after subsequent estradiol replacement [58] as previously referenced. While the effects of neonatal testosterone surge should undoubtedly be explored, so too should the effects of sex chromosome complement, parental imprinting, early life experience, and other environmental impacts. This would allow for a more complete understanding of how these factors manifest in an alteration of peripheral-to-central circuitry and potentially change responsiveness to gustatory and/or ingestion cues. Hence, future research investigating sex differences in feeding must pay heed to how *all* the varying components of sex intersect to modulate and shape cells and circuitry in the hypothalamus, brainstem, periphery, and beyond. This approach will improve our understanding of how sex (and even gender) factors modulate food intake to predispose people of certain genders to modulate food intake to the degree of under- or over-nutrition. We believe that this multifaceted approach is crucial for a fundamental understanding of feeding physiology.

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List of Abbreviations:

1

AGRP	agouti-related neuropeptide
AMY	amygdala
ARC	arcuate nucleus of the hypothalamus
BNST	bed nucleus of the stria terminalis
CCK	cholecystokinin
CGRP	Calcitonin gene-related peptide
ERα	estrogen receptor subtype α
ERβ	estrogen receptor subtype β
GLP-1	glucagon-like peptide-1
LH	lateral hypothalamus
MCH	melanin-concentrating hormone
NAc	nucleus accumbens
NE	norepinephrine
NPY	neuropeptide Y
NTS	nucleus of the solitary tract
PBN	parabrachial nucleus
POMC	proopiomelanocortin
PVN	paraventricular nucleus of the hypothalamus
VTA	ventral tegmental area

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Highlights

- Research on sex differences in feeding has largely been limited to gonadal hormones
- We review how the different components of sex and/or gender may modulate feeding
- The components of sex can modulate homeostatic and hedonic feeding nodes
- Chromosomal, epigenetic, & environmental sex/gender contributions are understudied

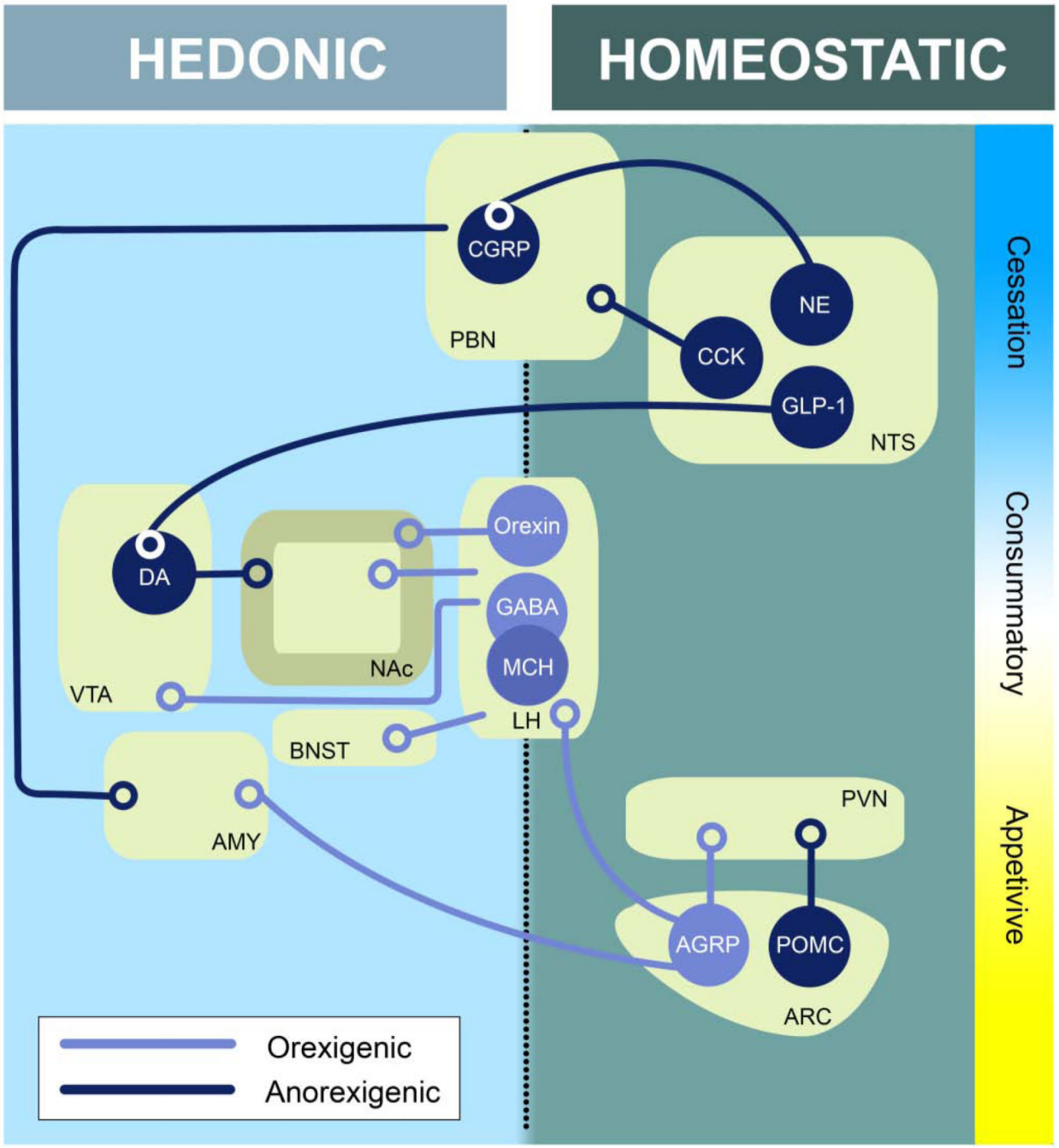

Figure 1: Circuit diagram of homeostatic/hedonic interaction between feeding nodes in the brain.

This non-exhaustive figure provides a rough overview of the large degree of overlap and communication between canonically hedonic and homeostatic feeding nodes across the appetitive, consummatory, and cessation stages of feeding. Processes do not denote excitation/inhibition, merely recruitment. Light blue lines denote typically orexigenic pathways, dark blue typically anorexigenic. Terminal peripheral outputs not depicted. AGRP: agouti-related peptide; AMY: amygdala; BNST: bed nucleus of the stria terminalis; ARC: arcuate nucleus of the hypothalamus; CCK: cholecytoskinin; CGRP: calcitonin gene-

related peptide; DA: dopamine; GLP-1: Glucagon-like peptide 1; LH: lateral hypothalamus; MCH: melanin- concentrating hormone; NAc: nucleus accumbens; NE: norepinephrine; NTS: nucleus of the solitary tract; PBN: parabrachial nucleus; POMC: proopiomelanocortin; PVN: paraventricular nucleus of the hypothalamus; VTA: ventral tegmental area

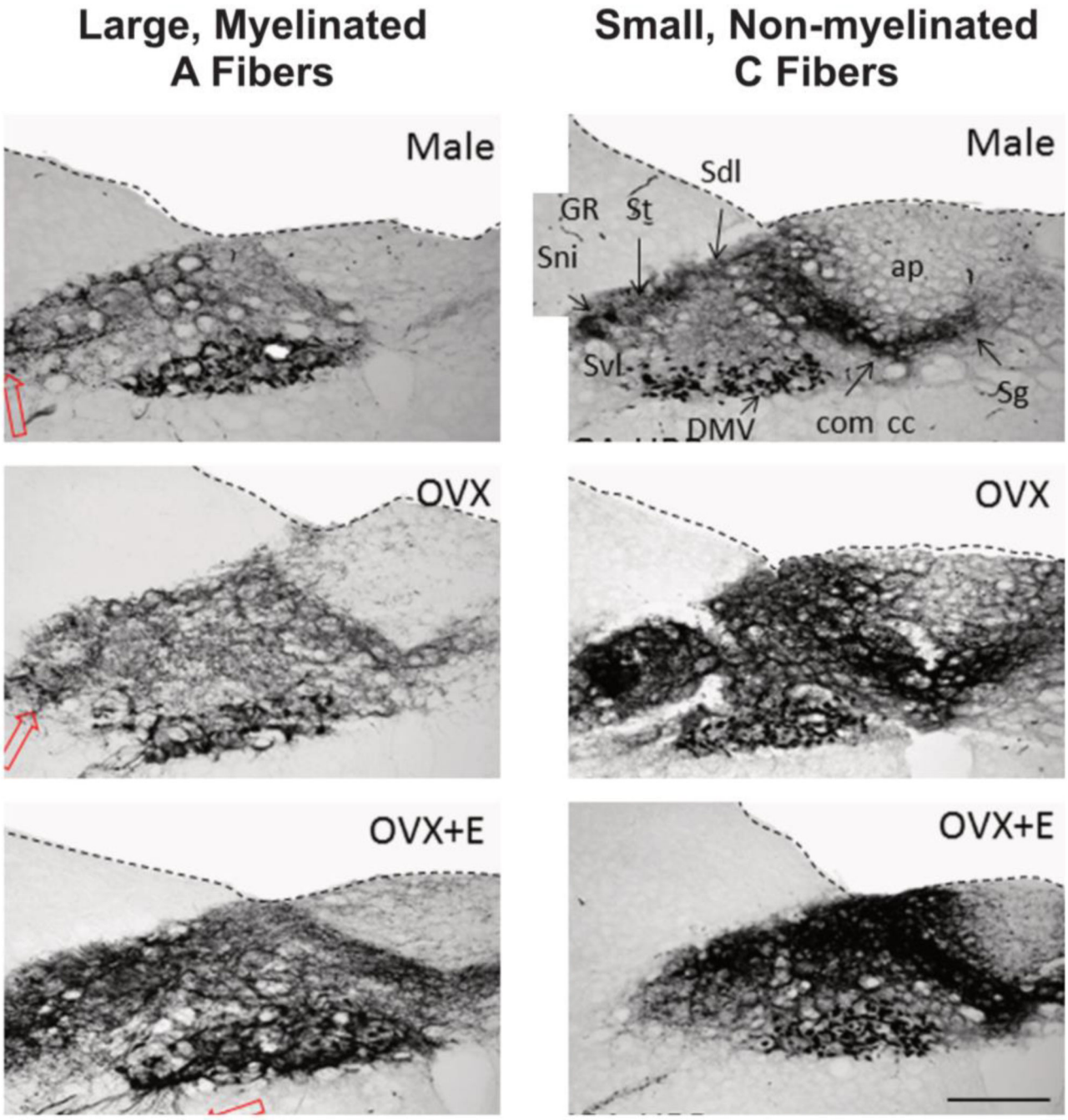

Figure 2: Sex difference in vagal fiber innervation of NTS is not fully explained by adult circulating ovarian hormone presence.

Adapted figure from [58] showing innervation densities and patterns in the NTS. Innervation density is affected by estradiol in females, but innervation pattern of both myelinated and non-myelinated fibers into the NTS remains distinct in female and male animals despite female hormone manipulation. E: estradiol; OVX: ovariectomy

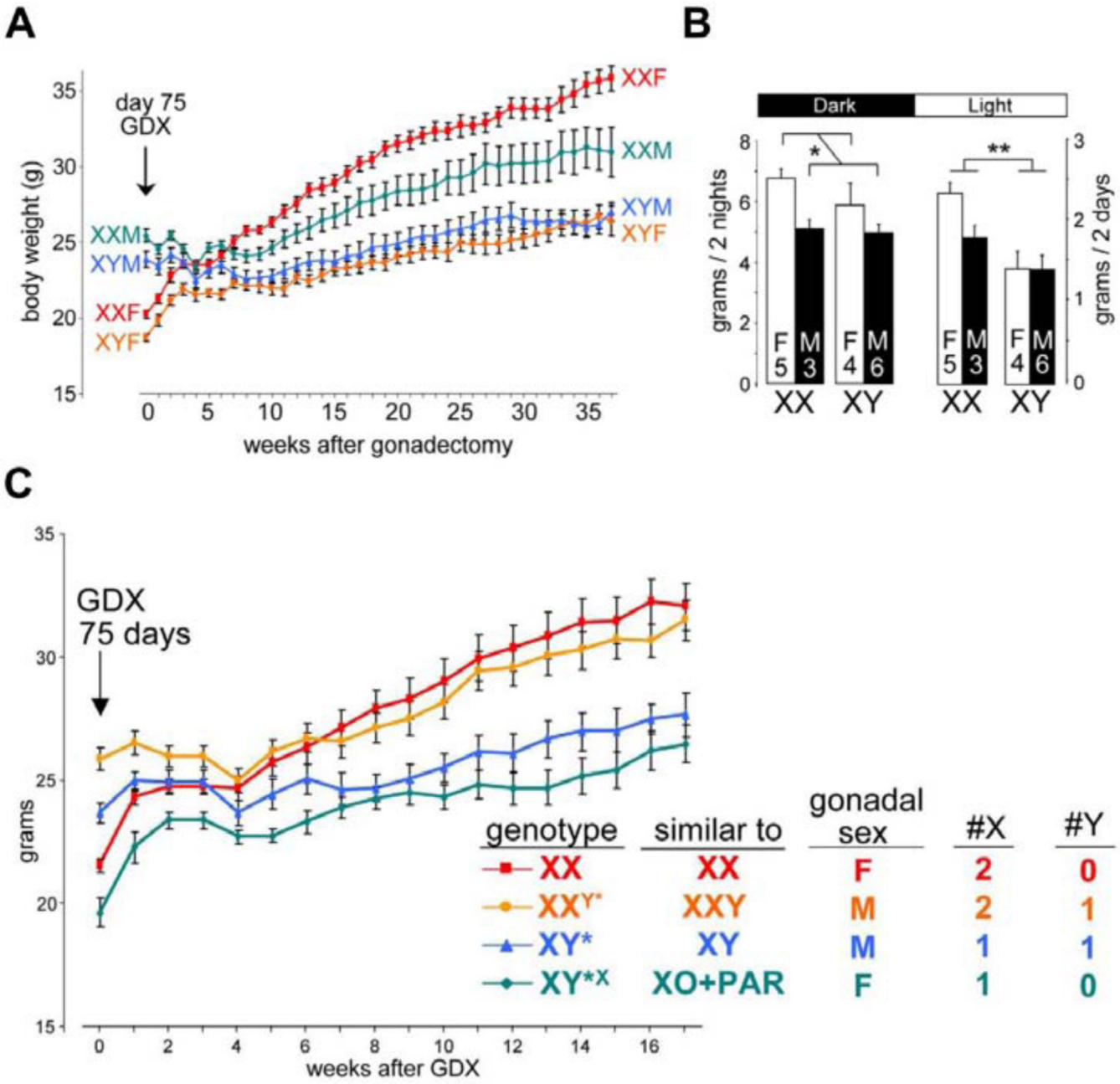

Figure 3: Effect of sex chromosomes on body weight and food intake.

Adapted from [46]. (**A**) Experiments in four core genotypes model demonstrate that body weight is primarily driven by gonadal type prior to gonadectomy (GDX), after which the effect of sex chromosome complement (and interactions with previous hormonal state) are revealed. (**B**) This effect on body weight is contributed to by chromosomal effect (particularly X dosage as revealed by the XY* model, **C**) on daytime food intake.