Annals of R.S.C.B., ISSN:1583-6258, Vol. 24, Issue 2, 2020, Pages. 2165- 2169
Received 20 October 2020; Accepted 04 December 2020

A Review on The Neural Circuits of Male and Female Sexual Motivation and Behavior, From Initial Sensory Detection of Pheromones

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Abstract:

Gonadal hormones contribute to the sexual differentiation of the brain and behavior throughout the lifespan, from initial neural patterning to "activation" of adult circuits. Sexual behavior is an ideal system in which to investigate the mechanisms underlying hormonal activation of neural circuits. Sexual behavior is hormonally regulated, innate social behavior found across species. Although both sexes seek out and engage in sexual behavior, the specific actions involved in mating are sexually dimorphic. Thus, the neural circuits mediating sexual motivation and behavior in males and females are overlapping yet distinct. Furthermore, sexual behavior is strongly dependent on circulating gonadal hormones in both sexes. There has been significant recent progress on elucidating how gonadal hormones modulate physiological properties within sexual behavior circuits with consequences for behavior. Therefore, in this mini-review, we review the neural circuits of male and female sexual motivation and behavior, from initial sensory detection of pheromones to the extended amygdala and on to medial hypothalamic nuclei and reward systems. We also discuss how gonadal hormones impact the physiology and functioning of each node within these circuits. By better understanding the myriad of ways in which gonadal hormones impact sexual behavior circuits, we can gain a richer and more complete appreciation for the neural substrates of complex behavior.

Keywords: Reproductive Behavior, Gonadal Hormones, Sex Hormones, Activation, Sex Differences

I. Introduction

Gonadal hormones play an essential role in the sexual differentiation of brain and behavior. Perinatal exposure to gonadal hormones guides neuronal growth, death, synaptogenesis, cytoarchitecture, chemoarchitectural, epigenetic modification, and many other brain characteristics to shape or "organize" sexually dimorphic neural circuits. Later exposure to gonadal hormones "activates" these circuits to promote expression of the relevant sex-typical behavior, and it is this deceptively simple concept we seek to spotlight in this mini-review. What does hormonal activation of a circuit mean at a mechanistic level? How is this implemented differently across circuit nodes and what is the consequence for behavior? We focus on sexual behavior as an ideal system in which to ask these questions: the behavior is ethologically relevant across species, easily studied in the laboratory, intensely dictated by hormonal status, and importantly—robustly expressed by both sexes. Therefore, herein we review key components of the neural circuitry underlying male and female sexual behaviors and highlight, whenever possible, recent advances in our understanding of the hormonal regulation of such circuits. We focus on literature from rodent models, due to their notable reliance on hormonal activation for sexual behavior and for the vast wealth of knowledge available from nearly a century of careful experimentation on these genetically tractable models.

II The Hormonal Regulation of Sexual Behavior

Sexual behaviors are often conceptualized into 2 categories: appetitive and consummatory. Appetitive sexual behavior entails actions that increase the likelihood of mating to occur and are thought to reflect sexual motivation. This includes approach, solicitation, or investigation of a potential mate and the exhibition of mate preference, or preference for an intact opposite-sex conspecific over a same-sex or gonadectomized conspecific. These behaviors can be displayed by both sexes with some species-specific differences (ie, specific solicitation behaviors may differ between sexes). On the other hand, consummatory sexual behavior entails the act of mating itself and is highly sexually dimorphic. In male rodents, this includes mounting and intromission, whereas in female rodents it is primarily adoption of the lordosis posture (stationary flexion of the spine and deflection of the tail permitting male intromission). Each of these aspects of sexual behavior is mediated by distinct but frequently overlapping neural substrates, which will be reviewed in the following sections (Fig. 1).

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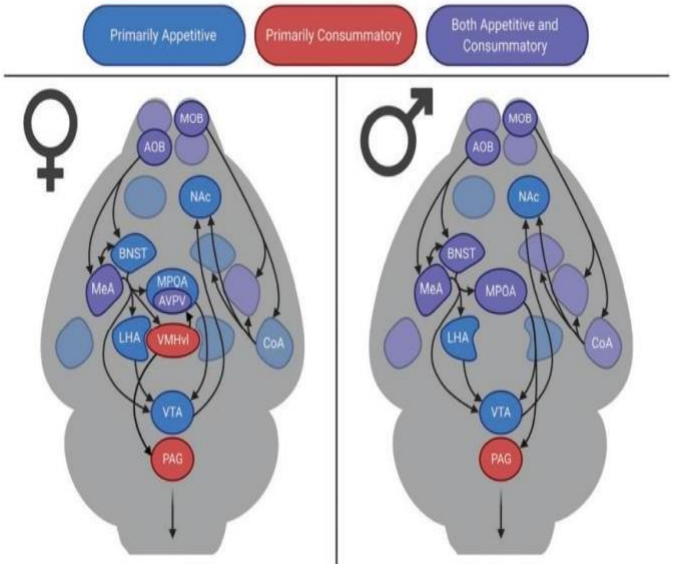

Figure 1: Neural circuits of male and female sexual behavior. Regions are color-coded based on major contributions to either appetitive or consummatory aspects of sexual behavior

Sexual behavior in both sexes is strongly regulated by circulating concentrations of gonadal steroid hormones, including androgens (testosterone), estrogens (estradiol), and progesterone. In rodents, this hormonal regulation is perhaps most obvious in females across the 4- to 5-day estrous cycle (Fig. 2). Estradiol concentrations are low during diestrus but build to a peak by the afternoon of proestrus, which, in conjunction with a daily circadian signal, triggersovulation. This is quickly followed by a sharp peak in progesterone produced by the corpus luteum, which declines by the following morning. The sequential rise in estrogen followed by progesterone primes the female brain and physiology for sexual motivation and behavior ("in heat" or in estrus). Outside of these models, window, female mice, rats, and hamsters will notbe receptive toward a male and will actively reject mating attempts. Consequently, by co-opting the neuroendocrine signals of ovulation to regulate sexual behavior, the female conserves energetic resources by only mating when maximally fertile. Importantly, this is distinct from old-world primates. For females of these species, including women, sexual behavior is expressed across the ovulatory cycle and the influence of gonadal hormones on sexual behavioris comparatively subtle.

Male sexual behavior is also dependent on sufficient basal circulating gonadal hormones, primarily testosterone and its metabolites. Many of the activational effects of testosterone on male sexual behavior in rodents can be attributed to its conversion into estradiol by the enzyme aromatase, which is highly expressed along with sexual behavior circuits. However, for the full and complete expression of male sexual behavior in the laboratory both androgen and estrogen receptor signaling is required for discussion of species differences). Typical laboratory modelsdo not exhibit hormonal cycles that greatly impact male sexual behavior, but many other species do display seasonal cycles of reproductive activity, with commensurate changes to neuroendocrine, behavioral, and sensory systems. Furthermore, social experience (eg, social dominance, stress) can modify the hormonal milieu, even within laboratory models. Exposureto a potential mate or to a social challenge elicits an acute and transient increase in testosterone above basal levels in males across species. Such socially induced testosterone pulses have been hypothesized to modify future behavior in several ways, including by promoting territory formation, promoting future winning (ie, the winner effect), modifying social vigilance, reducing anxiety, and potentially facilitating responses to the social situation through rapid, nongenomic actions. Thus, adults of both sexes can experience fluctuations in gonadal hormones that may impact brain and behavior.

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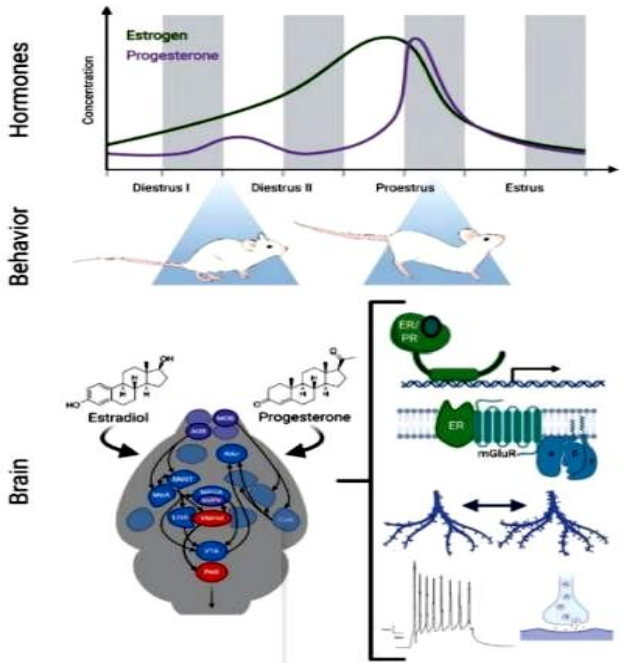

Figure 2: Hormonal control of female sexual behavior.

The sequential rise in estrogen followed by progesterone across the estrous cycle (top) causes female rodents to be sexually receptive near ovulation (middle). This is mediated by an array of neurophysiological changes to the brain induced by hormonal signaling (bottom). Gonadal steroid hormones signal both through nuclear receptors and membrane-bound receptors (bottom right). This signaling regulates gene expression, structural remodeling, neuronal activity, and changes in synaptic properties in a region-specific manner.

III. The Main and Accessory Olfactory Systems

Animals rely on pheromone signaling to communicate social information essential for reproductive behavior. These chemosignals are detected by the complementary but distinct main and accessory olfactory systems (MOS, AOS). Within the MOS, sensory neurons in the main olfactory epithelium (MOE) detect volatile odorants and relay this information to the main olfactory bulb. Accordingly, the MOS is thought to be particularly important for initial approach behavior and inherent social attraction based on volatile cues. On the other hand, within the AOS, sensory neurons of the vomeronasal organ (VNO) detect pheromones transmitted through close contact with a conspecific. This information is then conveyed to the accessory olfactory bulb, which sends projections to the extended amygdala that are considered particularly important for pheromonal elicitation of reproductive behavior and neuroendocrine responses. Although these 2 systems are anatomically distinct and respond to different classes of pheromones, information from the MOS also reaches the extended amygdala through the cortical amygdala and a minor but direct projection from the main olfactory bulb.

Both the MOS and AOS are essential for the complete and appropriate display of sexual behavior. Male and female pheromones elicit distinct sex-specific patterns of activation within both systems. Lesions or genetic disruption of either the MOE or VNO disrupt sociosexual behavior in both sexes. For example, genetic mutation of the ion channel TrpC2 abolishes pheromone signal transduction in the VNO. $TrpC2^{-/-}$ mice inappropriately mount same- and opposite-sex conspecifics at high levels, despite $TrpC2^{-/-}$ mice, or even animals with complete VNO lesions, retaining the ability to discriminate male versus female odorants through the MOS. Thus, the AOS is considered particularly important for regulating the expression of specific social behaviors toward the appropriate target (eg, to mate or to attack).

Recent work has shed light on how fluctuations in sex hormones across the estrous cycle shape sensory processing in the AOS. Estradiol regulates the expression of ion channels within the VNO and rapidly modifies vomeronasal sensory neuron (VSN) responses to pheromones. Furthermore, Dey et al reported that moderate concentrations of progesterone (approximately that of diestrus, ~13 ng/mL) act to silence VSNs. Intriguingly, progesterone-mediated silencing was seen in VSNs sensitive to male pheromones but not VSNs that were sensitive to predator odor, revealing hormonal modulation specifically of socially relevant sensory input. However, this study did not test the

effect of progesterone at high concentrations seen during late proestrus (~50 ng/ mL), so whether the peri-ovulatory progesterone surge might counterintuitively inhibit pheromone-sensing VSNs or whether this effect is dose-dependent remains to be tested. Regardless, changing concentrations of circulating estrogen and progesterone across the estrous cycle can clearly modulate the female's earliest sensory detection of male cues. In males, testosterone has been shown to increase activation of both the AOS and MOS in response to female pheromones, although there is little data available on theunderlying molecular mechanisms mediating this effect.

IV. The Extended Amygdala

The medial amygdala (MeA) is a major target of the AOS and minor target of the MOS that has been strongly implicated in mediating sexual behavior. In particular, the posterodorsal subdivision of the MeA (MeApd) expresses a high density of sex hormone receptors and is

well accepted to be activated during mating or by exposure to opposite-sex pheromones. Indeed, recent work has demonstrated that neurons of the MeA differentially encode male versus female cues, and that this separable encoding is shaped by experience. The MeApd appears to regulate aspects of both mate preference and consummatory sexual behavior. Lesions of the MeApd disrupt mate preference in both sexes. MeApd lesions also disrupt sexualbehavior in males. In females, MeA lesion or MeA chemo-inhibition reduces but does not eliminate lordosis behavior, and MeA lesions do not impact the number of mounts or intromissions received in a mating assay. These data indicate that the MeA promotes lordosis responses but is not essential for its expression.

V. Conclusion

Although for ease of explanation we have presented the above discussion as a forward flow ofinformation from olfactory systems to the extended amygdala to the medial hypothalamus andreward systems, the reality is not so straightforward. All the regions discussed above, and several others, send projections to each other, allowing for the possibility of feedback and crosstalk amongst systems. Furthermore, most of these regions have been implicated in the control of multiple social behaviors beyond sexual behavior, including territorial aggression, parental behavior, or maternal aggression. Indeed, based on neuroanatomical interconnections, strong steroid hormone receptor expression, and overlapping patterns of activation across social behaviors, the existence of a "social behavior network" was proposed. This network is highly conserved across taxa, providing a useful framework for comparative analysis. This perspective has also proven useful for conceptualizing the hormonal regulation of social behavior circuits. Through this lens, gonadal hormones act to tune connections and activity patterns across the social behavior network and thus shift the likelihood of a particular social response. Indeed, as discussed above, gonadal hormones regulate a myriad of structural, electrophysiological, and genetic elements which converge to augment or attenuate circuit activity and behavioral output. Recent and continued development of increasingly powerful tools is enabling unprecedented dissection of neuronal subcircuits with genetic precision. Withthis enhanced understanding of the neural circuits of behavior, we have a stronger foundation from which to probe the hormonal regulation of complex behavior.

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