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Review

Sex differences in the neural circuit that mediates female sexual receptivity

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ABSTRACT

Female sexual behavior in rodents, typified by the lordosis posture, is hormone-dependent and sex-specific. Ovarian hormones control this behavior via receptors in the hypothalamic ventromedial nucleus (VMH). This review considers the sex differences in the morphology, neurochemistry and neural circuitry of the VMH to gain insights into the mechanisms that control lordosis. The VMH is larger in males compared with females, due to more synaptic connections. Another sex difference is the responsiveness to estradiol, with males exhibiting muted, and in some cases reverse, effects compared with females. The lack of lordosis in males may be explained by differences in synaptic organization or estrogen responsiveness, or both, in the VMH. However, given that damage to other brain regions unmasks lordosis behavior in males, a male-typical VMH is unlikely the main factor that prevents lordosis. In females, key questions remain regarding the mechanisms whereby ovarian hormones modulate VMH function to promote lordosis.

1. Introduction

The basic pattern of sex differences in mating behavior has been conserved by evolution. As a case in point, in the well-studied insect model system, *Drosophila melanogaster*, females display a receptive posture while approached from behind for insemination by males [70]. This invertebrate model system has proven useful for the dissection of the genetic controls of these behaviors. Such sex-specific mating behaviors also are seen in mammals. The laboratory rat is a widely used, tractable model system for the study of the neural controls that underlie mammalian mating behavior [131]. Rather than direct effects of sex chromosomes on the patterning of brain sex differences, as occurs in insects, abundant evidence suggests that in rodents the presence or absence of gonadal steroids during development exerts epigenetic effects in the brain to specify the adult mating behavior [105]. In particular, the absence of hormone action during development is associated with lordosis behavior in adult female rats.

During the hours just before ovulation, a female rat becomes sexually receptive. At this time, courting males approach the female and attempt to mount her to elicit the receptive stance in females, termed the lordosis reflex. This reflex is gated by the sequential actions of the ovarian hormones estradiol and progesterone. Ovariectomy prevents the display of the lordosis reflex, and this effect is reversed by estradiol and progesterone replacement [18]. The lordosis response is not exhibited by intact males or even by adult castrated males treated with ovarian hormones [137], although there are some illuminating exceptions to this general rule, to be discussed below. Therefore, this behavior has provided a platform to examine the neurological mechanisms underlying a sex-specific mammalian behavior. The goal of this review is to consider what has been learned about sex differences in the neural circuitry that underlies female rat mating behavior.

The hypothalamic ventromedial nucleus (VMH) is a critical site of ovarian hormone action to permit the lordosis response, as detailed below. Axonal projections from the VMH to the periaqueductal gray enable the lordosis reflex by modulating posture-control relays to the reticular formation [34,153]. A few sex differences have been observed in the periaqueductal gray itself [91]. Given that considerably more attention has been focused on sex differences in the VMH than its downstream relays, the present review will attend to the ontogeny of the VMH and the various sex differences that have been observed. I also will consider mechanistic studies that have begun to elucidate the manner in which sex differences are established in the VMH. Lastly, I will discuss how the pattern of sex differences in the VMH may elucidate the neural components that contribute to VMH function.

2. The behavioral significance of the VMH

Numerous lines of evidence support the important role of the VMH in female rat sexual behavior. First, the VMH can retain estradiol and progesterone [132,95], based on its ability to express estrogen and progestin receptors [159,43,16]. The local application of ovarian hormones to the VMH is sufficient for the behavioral effectiveness of these hormones [36,150,138], which further

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implicates steroid receptors in the VMH as a major target in the control of lordosis. Moreover, VMH lesions disrupt sexual behavior in female rats [101,133], as do transections of the axonal projections that arise from the VMH and descend to the midbrain [136]. Conversely, electrical stimulation of the VMH enhances lordosis responses in the VMH [134]. Finally, female sexual behavior induces immediate early gene expression in the rat VMH, indicative of neuronal activation [52,53,135,176,149,139]. These results are consistent with electrophysiological studies that showed that VMH neurons are responsive to flank and VCS stimulation [22]. Thus, the fundamental role of the VMH in the control of reproductive behavior in female rats is well established.

Beyond laboratory rats, the importance of the VMH for female sexual behavior has been documented in a range of other mammals. For example, the VMH contributes to the lordosis response in guinea pigs [64], hamsters [98,161,166], cats [89], and sheep [14]. Studies in reptiles, such as whiptail lizards [82,143], have indicated that this neural mechanism is phylogenetically old. Furthermore, electrophysiological recordings have supported an active role of the VMH in female sexual behavior in non-human primates [4]. Although mice have not been the mainstay for the behavioral neuroscience of female reproductive behavior, transgenic mice have been tremendously informative regarding the role of developmental transcription factors and ovarian hormone receptors in VMH structure and function [109,21,125,15,8]. The similarities and differences between mice and rats make the case for both species providing valuable complementary information [19]. Thus, it remains true that the elucidation of the neural mechanisms within the VMH that mediate female mating behavior in laboratory rats may pertain to diverse vertebrate species.

With regard to the human VMH, neuroanatomical studies suggest a similar organization compared with other species, including its cytoarchitecture, source of afferents, and the peptide content of its afferents [117,55,162,97,164]. In addition, the human VMH expresses estrogen, androgen and oxytocin receptors [112,51], as seen in other species, and a variety of sex differences have been reported in the human VMH [79]. A functional imaging study suggested that a sex-specific activation of the ventromedial hypothalamic area occurs in humans after exposure to putative pheromones [154]. These findings suggest that many aspects of the human VMH have been conserved, and that it is not only sexually dimorphic, but it may processes sexually relevant information.

Interestingly, the VMH has been implicated in both male and female mating behavior [176,71,72], although the role of the VMH in male mating behavior is in need of further study. In this regard, it is important to remember that while females experience cyclic variations in gonadal hormones, the levels in males remain steady across days. A better understanding of VMH neural circuitry will provide a better explanation the neural basis of sex-specific, hormone-gated behaviors. Next, I will consider the ontological events that establish the VMH as a first step towards explaining the sex differences in the structure and function of the VMH.

3. General features of the VMH

3.1. Development of the VMH

The VMH is defined as an elliptical condensation of neurons surrounded by a cell-poor fiber-rich zone in the caudal, mediobasal hypothalamus. This basic structure is apparent before birth in rats. As with other hypothalamic cell groups, VMH development begins with neurogenesis in the proliferative zone of the third ventricle. In the case of the VMH, neurons are born around embryological day 10 (E10; as reviewed by McClellen et al. [108]). Terminally mitotic cells migrate ventrolaterally along the processes of radial glia and then differentiate into neurons. A discernable cytoarchitectonic VMH is visible between E18 and E19 in rats [168]. Axonal projections then are established and synaptic inputs are arranged. The surrounding neuropil that makes the VMH so conspicuous histologically includes dendrites extending from VMH neurons, and these dendrites provide a receptive zone for axons arising from other brain regions [113].

An array of transcription factors contributes to the ontogeny of hypothalamic neurons during brain development. For example, Islet-1 is a marker for the developing hypothalamus [37]. Nkx2.1 has a narrower role, establishing the medial basal hypothalamus [84]. More restricted still, the normal development of the VMH depends on the expression of a transcription factor known as SF-1, officially designated NR5A1, encoded by the *FTZ-F1* gene, with a rat homolog identified as Ad4BP [74,76,148]. This protein is a member of the orphan nuclear receptor superfamily, and within the brain it is uniquely expressed in the VMH [148]. When the expression of SF-1 is disrupted, a striking malformation of the VMH occurs, with various cell types inappropriately positioned within or outside the nucleus [77,94,158]. When SF-1 is selectively disrupted in the brain, the resulting malformation of the VMH is associated with impaired lordosis behavior [83].

In sum, the VMH develops as a typical hypothalamic nucleus, although it is unique in its expression and developmental regulation by SF-1, which contributes to the spatial organization of VMH neurons. With the importance of the developmental positioning of VMH neurons in mind, it becomes clear that another key feature of VMH function would be the chemical phenotypes of its neurons. As discussed below, several important phenotypic markers have emerged for VMH neurons, although our understanding is not yet complete.

3.2. Cytoarchitecture of the VMH

The VMH has been parceled into two hemi-ovals, the dorsomedial (DM-VMH) and the ventrolateral (VL-VMH), with a narrow cell-poor central region between them [113,25,29,49,173]. The DM-VMH and the VL-VMH differ in their patterns of gene expression, as summarized in Table 1. Soma size in the VL-VMH is larger than soma size in the DM-VMH and the central region [96]. Analyses of the subdivision-specific afferents and projection targets also indicate unique patterns of connectivity for these subdivisions [29]. The surrounding shell, also referred to as the fiber plexus, the neuropil, or the lateral rim, contains axonal processes from other brain regions containing neurotransmitters and modulators, including norepinephrine, serotonin, gonadotropin releasing hormone, and oxytocin [110,155,165]. There also are sparse neurons found in the shell [114].

VMH neurons maintain a simple dendritic tree, with the following characteristics: a single very long primary dendrite, a few much shorter primary dendrites, and a few secondary dendrites [26]. The long primary dendrite may be uniquely positioned to contact afferents terminating in the fiber plexus surrounding the VMH. The length of these long primary dendrites are regulated by a variety of physiological conditions [66,67,54,86], thus potentially titrating VMH sensitivity to extranuclear inputs. The short primary dendrites, in contrast, may be situated to receive input from local interneurons. In this way, individual VMH neurons can integrate local computations with afferent inputs arriving from other brain regions.

At the ultrastructural level, both excitatory and inhibitory synaptic contacts exist in the VMH, with approximately half of these remaining after deafferentation of the VMH [123]. About one third of the synapses are axospinous and appear to be exclusively excitatory based on their ultrastructure. A relatively small portion,