Neural mechanisms of female sexual behavior in the rat; comparison with male ejaculatory control

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ABSTRACT

The sequential organization of sexual behavior of the female rat is described, eventually leading to the lordotic posture, shown during mating. A complex set of signals: olfactory, cutaneous sensory as well as genitosensory, is guiding the female to this specific posture, eventually. Genitosensory signals converge in the lumbosacral levels of the spinal cord, from where they are dispersed to a series of supraspinal brain areas, in the brainstem, thalamus, hypothalamus and limbic system. The similarity with the neural activation patterns observed in the male rat is remarkable. In a number of brain areas, however: the midbrain periaqueductal gray, the ventrolateral part of the ventromedial hypothalamic nucleus (VMHvl) and the medial preoptic–lateral septum regions, specific male–female differences have been observed. Especially the VMHvl is an intriguing area, as it has been shown that the same neurons may be involved in 'opposite behavior' like aggression and the induction of lordosis.

The motor mechanisms controlling the lordosis posture in the rat as well as in some other mammals are discussed, as well as some aspects of the reward mechanisms contributing to female sex. We conclude that we have collected a great amount of neurophysiological knowledge over the last 20 years, but that the unresolved questions are still numerous. In this field, there is still much to explore.

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1. Introduction

Female sexual behavior in the *Rattus norvegicus* can be observed when the female is in the estrous phase of her cycle, once every 4 or 5 days. It is complex including a variety of specific behavioral elements (Beach, 1976; Madlafousek and Hlinak, 1977; Barnett, 2009). After an 'arousal-phase' which starts with the introduction of another animal (Veening, 1975, 1992; Swanson and Mogenson, 1981; Pfaff, 1999; Swanson, 2003), the sex and the physiological condition of the intruder are determined via increased locomotory activity and (anogenital)-sniffing. If the female is in estrus if an active male partner is involved in the companionship, precopulatory activities will be initiated, consisting of proceptive behavioral elements like hopping, darting and ear-wiggling. These elements not only attract the attention of the male and increase the chances for physical contact, but they are also necessary to prepare the female for the lordosis response, by activating the descending motor systems of the spinal cord directly or indirectly via activation of the semicircular canals of the vestibular system (Grillner et al., 1970; Peterson, 1970; Wilson et al., 1970; Brink et al., 1980). This phase refines the responses of the male partner and

provides the female with the opportunity to pace the number and frequency of the sexual contacts when provided with that opportunity in the testing chamber (Mendelson and Gorzalka, 1987; Mendelson and Pfaus, 1989). Eventually and only when the female is in the appropriate hormonal condition (Pfaff and Sakuma, 1979a,b; Pfaff, 1980), the consummatory/receptive phase starts with the female showing the lordotic posture to allow the successive intromissions and eventually the ejaculation by the male. After ejaculation, the female isolates herself from the male to start her Post-Ejaculatory-Interval (PEI) (Forsberg et al., 1987), when the circumstances allow her. Fig 1 shows the sequential structure of the female sexual activities, parallel to the male performances.

The proceptive phase is extremely variable and strongly dependent on the conditions chosen for the experimental observations (small versus large cages, bilevel chambers) (Veening, 1975; Whitney, 1986; Mendelson and Gorzalka, 1987; Coolen et al., 1996) and on the responses of the male (the frequency of approaching and 'chasing' the female and the number of ejaculations) (Pattij et al., 2005). In the copulatory phase, female behavior of the rat becomes much more reflex-like by the display of the lordotic posture to different degrees. This suggests that the behavior of the female can also be described in terms of the 'Funnel-Model' presented for the male rat (see review in current issue: Veening and Coolen, 2014): after the proper 'level-setting' of the spinal circuitry, the adequate cutaneous stimulation

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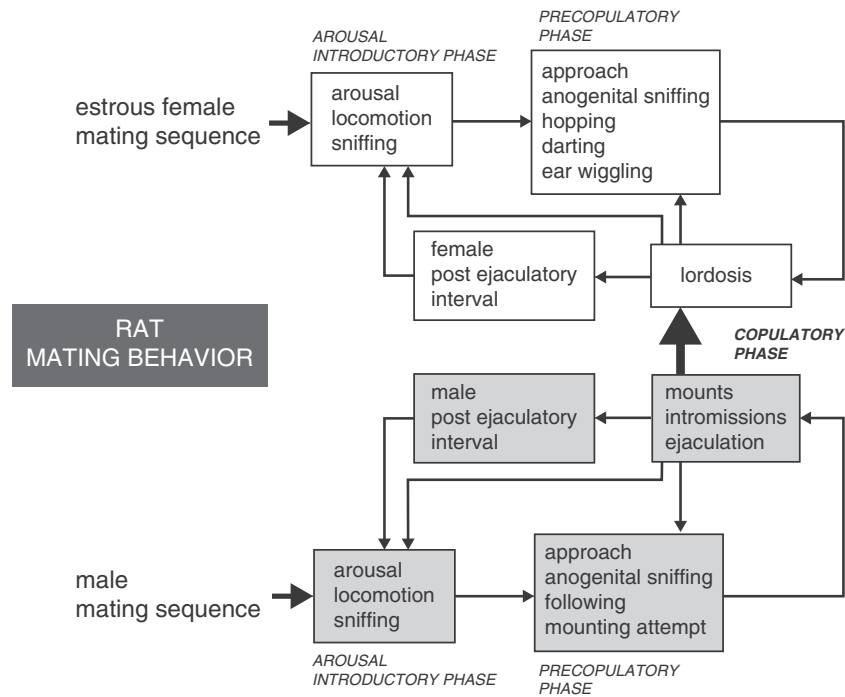E-mail address: j.veening@anat.umcn.nl (J.G. Veening).

Fig. 1. Mating behavior of the male and female rat.

leads to an 'inevitable' lordosis response. In 1977 Madlafousek and Hlinak studied the sequential organization of sexual behavior in the female laboratory rat in detail, while Pfaus et al. performed an extensive correlational and factor analysis of female sexual behavior in the rat, including the effects of ovarian hormones, expectancy and estrous termination (Pfaus et al., 1999, 2000).

2. The neural basis of female sexual behavior in the rat

2.1. Neural connections

The 'peripheral' innervation of the female reproductive organs has attracted the attention of many investigators. The innervation of the uterus and cervix has been studied by ablation studies as well as by immunocytochemistry, to show the particular involvement of specific peripheral nerves and autonomic plexuses as well as of specific neuropeptides like galanin and calcitonin-gene-related peptide (CGRP) and estrogen-receptors (Inyama et al., 1986; Kumazawa, 1986; Nance et al., 1988; Berkley et al., 1990; Ortega-Villalobos et al., 1990; Papka et al., 1991, 1998, 1999a,b; Houdeau et al., 1995, 1998a,b, 2002; Collins et al., 1999). These studies showed not only remarkable details (for instance that the innervation of the upper and lower (cervical) parts of the uterus is rather different) but also impressive peripheral plasticity (when non-pregnant females are compared with pregnant or parturient animals) (Nance et al., 1988; Berkley et al., 1990; Houdeau et al., 1995, 1998b; Wiesel et al., 2004; Puder and Papka, 2005).

In addition to these 'peripheral studies', many investigators examined the central distribution of the neural connections of the female genital tract (Ortega-Villalobos et al., 1990; Marson, 1995; Gerendai et al., 1998; Papka et al., 1998, 2006; Collins et al., 1999; Lee and Erskine, 2000; Puder and Papka, 2001, 2005; Wiesel et al., 2004; Marson and Murphy, 2006; Gelez et al., 2010). From these studies we conclude that at the *spinal level*, the segments L5 to S1 are most strongly related to the female genital tract, followed by the adjoining segments T12 to L5 and S2 to S4. In the *lower brainstem*, the nucleus paragigantocellularis (nPGi), caudal raphe nuclei, the A5 region and Barrington's nucleus are

involved in the innervation of the clitoris (Marson, 1995; Marson and Murphy, 2006). Concerning the ovaries and the upper and lower (cervical) parts of the uterus, additional brainstem areas have been found to be involved, like the dorsal vagal complex, the locus coeruleus, the gigantocellular nucleus, the A1 and A7 groups and the Kölliker–Fuse nucleus (Ortega-Villalobos et al., 1990; Gerendai et al., 1998; Papka et al., 1998, 1999b; Lee and Erskine, 2000; Wiesel et al., 2004). At the *mesencephalic level*, the caudal ventrolateral part of the periaqueductal gray region (PAGcvl) is strongly involved in the innervation of the female sexual organs (Marson, 1995; Gerendai et al., 1998; Wiesel et al., 2004; Marson and Murphy, 2006) but a more ventrolaterally located relay station has been described as well (Carrer, 1978). The PAG receives direct sensory input from a distinct group of neurons in the dorsal horn of the lumbosacral cord. This cell group overlaps with the location of pelvic and pudendal nerve afferents, which convey information from the perineum, vagina and cervix to the central nervous system (Sakuma and Pfaff, 1980a; Van der Horst and Holstege, 1998). In addition, the PAG is connected to several other brain areas involved in female sexual behavior (Sakuma and Pfaff, 1980a; Beitz et al., 1983; Akaishi et al., 1988).

At the *diencephalic level*, the parvocellular part of the subparafascicular nucleus (SPFp) functions as an important relay center for the sex-related stimuli ascending from the lumbosacral spinal cord (Coolen et al., 1996, 2003b, 2004; Veening and Coolen, 1998; Truitt and Coolen, 2002; Truitt et al., 2003) and brainstem (Yasui et al., 1990). In addition, the ventromedial hypothalamic nucleus (VMH) is involved in the estrogenic induction of lordosis (Mathews and Edwards, 1977b) while the paraventricular hypothalamic nucleus (PVH), the ventromedial hypothalamic nucleus, especially its ventrolateral part (VMHvl) and the medial preoptic nucleus (MPN) show descending relations with the lumbosacral spinal cord and the genital organs (Marson, 1995; Papka et al., 1998; Wiesel et al., 2004; Marson and Murphy, 2006; Gelez et al., 2010). The MPN, VMH, PAG and the nPGi are interconnected by additional projections to the ventromedial medulla (Marson and Murphy, 2006), suggesting an extensive network control of the female organs. In a viral retrograde tracing study of the