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The role of adrenoceptors in the central nervous system in male and female rat sexual behavior

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ABSTRACT

Three different phases can be distinguished in rats' sexual cycle, the introductory (precopulatory), the copulatory and the executive (ejaculatory) phases. In this review, a new analysis of existing pharmacological data is made, both in male and female rats, in which the different aspects of sexual behavior are taken into account. An effort is made to distinguish pharmacological effects on sexual behavior from a possible physiological role of noradrenaline. In addition, new data on the role of α_2 -adrenoceptors on female sexual behavior is presented.

The new analysis suggests that noradrenaline has a stimulatory role on the executive phase of male sexual behavior, while the introductory and copulatory phases remain unaffected. Adrenoceptors play a role in the regulation of sexual behavior in the medial preoptic area and the lateral septum. In female rats, noradrenaline also does not play a vital role in the introductory phase. Only the lordosis behavior of the copulatory phase is sometimes affected by adrenergic agents, but only under a certain hormonal condition. The medial preoptic area, the ventromedial nucleus, the arcuate ventromedial nucleus and median eminence are involved in the regulation of female sexual behavior. The new data suggest that α_2 -adrenoceptors play no major role on any indices of female sexual behavior.

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1. Introduction

This review was written to honor Professor Berend Olivier, an excellent scientist of the field of neuropharmacology in affective disorders. Berend has been interested in many topics in neuroscience, but studies on sexual behavior in rats always took a special place in his career.

During our latest collaboration, we were interested in the role of serotonin (5-HT) 1A receptors in the regulation of sexual behavior and the comparison between male and female rats. At first sight, the existing literature suggests that serotonergic agents have opposite effects on male and female rat sexual behavior. 5-HT_{1A} receptor agonists, for example, facilitate sexual behavior in male rats (Ahlenius et al., 1991; Foreman et al., 1994; Haensel and Slob, 1997; Hillegaart and Ahlenius, 1998; Johansson et al., 1991; Mendelson and Gorzalka, 1986; Schnur et al., 1989), but inhibit female sexual activity (Ahlenius et al., 1986, 1989; Fernandez-Guasti et al., 1987; Kishitake and Yamanouchi, 2003; Mendelson and Gorzalka, 1986). This seems quite conflicting, but it could simply be due to our definitions of different elements of sexual behavior. As explained in our latest reviews (Snoeren et al., 2014a, b),

three different phases can be distinguished in rats' sexual cycle and if the appropriate phases of males and females are properly compared, the role of 5-HT_{1A} receptors in rats is more similar than assumed thus far.

Sexual behavior can be divided into three phases: the introductory (precopulatory), copulatory, and the executive phase (in males ejaculations, in female rats unknown) (Fig. 1). The interplay between males and females starts with behaviors like approaching and sniffing each other's anogenital regions to obtain pheromonal cues of sexual receptivity. This introductory phase is followed by the copulatory phase in which female rats in estrus display a variety of complex solicitations, also called paracopulatory (proceptive) behaviors; e.g. hopping, darting and ear wiggling. The copulatory phase for male rats consists of repeated mounts and intromissions. In response to these copulatory behaviors, the female displays lordosis—or receptive behavior (also part of the copulatory phase)—in which the female arches her back and deflects her tail to one side allowing the male access to her vagina. After a series of mounts and intromissions, ejaculation (the executive phase) is reached, after which a postejaculatory interval (PEI, the resting period preceding the next ejaculation cycle) of about 5 min starts (a longer description can be found in Snoeren et al. (2014a,b)).

Conclusions in research on sexual behavior are often based solely on a part of the elements of the displayed male and female

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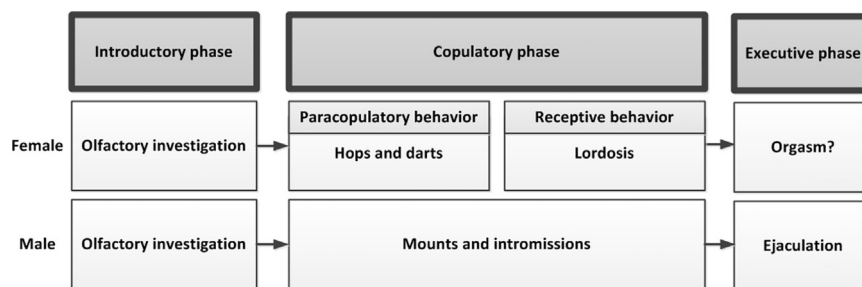


Fig. 1. Hypothesis about the similarities between male and female rat sexual behavior.

sexual behavior. Most often the differentiation in phases is not made. In males, for example, most conclusions in pharmacological research are based on drug effects on ejaculation, while at the same time effects on copulation are omitted. This can result in arbitrary conclusions. To give an example, a drug could decrease the ejaculation latency and meanwhile inhibit the number of mounts and intromissions. The conclusion that the drug facilitates male sexual behavior is therefore not sufficient. A better conclusion would be that the drug facilitates the behavior of the executive phase, while in the meantime it inhibits the behaviors in the copulatory phase. The same drug could, for example, also inhibit paracopulatory behaviors in females, a behavior that is part of the copulatory phase. If the first conclusion in males is maintained, this suggests that the drug has opposite effects on sexual behavior in males and females. However, if the different phases in the sexual cycle are addressed appropriately, it actually indicates that the drug has similar effects in females and in males. The different phases of the sexual cycle (introductory, copulatory and executive phases) can be regulated via different mechanisms and if addressed properly it could mean that the same mechanisms could be involved in males and females.

In this review, a new analysis of existing pharmacological data and release studies is made, both in males and females, in which the different aspects of sexual behavior are taken into account. An effort is made to distinguish pharmacological effects on sexual behavior from a possible physiological role of noradrenaline.

2. Noradrenaline in the brain

The noradrenaline system consists of different receptor types, including α_1 , α_2 , β adrenoceptors, and noradrenaline transporters. Adrenoceptors are located in the brain, spinal cord and periphery (Frankhuyzen and Mulder, 1982; Nasseri and Minneman, 1987). The receptors are localized both post- and presynaptically, as inhibitory receptors on non-adrenergic neurons (heteroceptors) and on the terminals and dendrites of the noradrenergic neurons themselves (autoreceptors) (Frankhuyzen and Mulder, 1982; Nasseri and Minneman, 1987). The α_2 -adrenoceptors manifest a high level of tonic activity and their blockade markedly accelerates the synthesis and release of noradrenaline in the cortex and elsewhere (Dennis et al., 1987; Kiss et al., 1995; Millan et al., 1994). To the contrary, agonists such as dexmedetomidine result in a decrease in noradrenaline release and synthesis (Gobert et al., 1998; Millan et al., 2000). Approximately 80–90% of the released noradrenaline is taken up again through the neuronal noradrenaline transporters located at the presynaptic cell membrane (Esler et al., 1990; Schroeder and Jordan, 2012). Therefore, noradrenaline transporters play an important role in the homeostasis of the noradrenaline system.

Noradrenaline is widely distributed throughout the central and peripheral nervous system. Practically, all cell bodies of the noradrenaline neurons in the brain are localized in the pons and

the medulla oblongata, as shown by lesions (Anden et al., 1966; Loizou, 1969), pharmacology (Corrodi et al., 1970), and immunohistochemistry (Fuxe et al., 1970) experiments. The noradrenaline pathway can be divided in a ventral and dorsal pathway, in which the dorsal pathway originates from the locus coeruleus (LC) and mainly innervates the neopaleo-, meso-, and achicortex and gives rise to very fine terminal plexi (Blackstad et al., 1967; Fuxe, 1965; Maeda and Shimizu, 1972; Ungerstedt, 1971), whereas the ventral pathway (which originates in the pons and medulla oblongata) mainly innervates the hypothalamus, the preoptic area and the subcortical parts of the limbic system. The ventral pathway gives rise to fairly thick terminal plexa (Fuxe, 1965; Maeda and Shimizu, 1972; Ungerstedt, 1971). A detailed description of the distribution of noradrenaline in the rat brain and especially in the hypothalamus can be found in Olson and Fuxe (1972), Palkovits et al. (1974), and Versteeg et al. (1976).

The involvement of specific brain regions in the different elements of male and female sexual behavior has been reviewed before (Snoeren et al., 2014a,b). There is a clear overlap between these functional brain areas and the existence of noradrenergic innervations and expression of adrenoceptors, for example in the medial preoptic area (MPOA) and the ventromedial nucleus of the hypothalamus (VMN). Lesions of noradrenaline neurons by 5-ADMP disrupt noradrenaline in MPOA and VMN and also disrupt lordosis (Davis et al., 1991). But also the nucleus paragigantocellularis (nPGI) receives a dense noradrenergic innervation from either the lateral tegmental or the locus coeruleus noradrenergic cell groups (Kojima et al., 1985; Lyons et al., 1989; Rajaofetra et al., 1992). Some of the noradrenergic innervation of the spinal cord may also originate from spinal cells and play a role in motor coordination (Kjaerulff and Kiehn, 1997). It is likely that the coordinated, rhythmic contractions of the muscles involved in ejaculation are modulated by noradrenergic pathways acting on the spinal generator to release ejaculation. As suggested in Snoeren et al. (2012), potential candidate areas for the noradrenergic effect on ejaculation, besides a direct effect in the spinal cord, might be the nPGI, LC and the paraventricular nucleus (PVN). α_2 adrenoceptors are widely distributed in the central nervous system (Albures et al., 1993; Wamsley et al., 1992), and the localization of this receptor subtype in these specific brain areas have been confirmed, in addition to noradrenergic connections with other brain areas (Kojima et al., 1985; Lyons et al., 1989; Rajaofetra et al., 1992).

The existence of noradrenergic innervations and expression of adrenoceptors in brain areas that play an important role in sexual behavior confirm the involvement of noradrenaline in sexual behavior. Many pharmacological studies confirm the fact that noradrenaline is involved in male and female sexual behavior. These studies will be discussed in the next sections of this review.

3. Noradrenaline and male rat sexual behavior

A substantial amount of data suggests that blockade of α_2 -adrenoceptors stimulates rat sexual behavior, while stimulation

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