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Review

Male Sexual Behavior and Brain Catecholamine Levels in Middle-Aged Rats

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Abstract

During aging, increased qualitative variations in copulatory behavior are observed in male rats. At the age of 18-19 months, only a small proportion of male rats (16%) still display the complete mating behavior, including mounts, intromissions, and ejaculations, but the rest of these middle-aged animals (84%) fail to exhibit one, two or all of the three behavioral components. With distinct behavioral phenotypes, the middle-aged male rats provide us a useful animal model to investigate the neuroendocrine mechanisms responsible for the age-related reduction in sexual behavior. We have previously elucidated the correlation between the loss of specific copulatory behavioral components and tissue levels of catecholamines in the medial preoptic area (MPOA), nucleus accumbens (NAc) and the bed nucleus of stria terminalis (BNST) of middle-aged male rats. Thus, our findings not only demonstrate that levels of dopamine and norepinephrine in the MPOA, NAc and BNST are critical for eliciting copulatory behavior, but also suggest that these two neurotransmitters play distinct roles in different brain regions to control specific behavioral components in male rats.

Key Words: copulatory behavior, catecholamine, medial preoptic area, nucleus accumbens, the bed nucleus of stria terminalis, middle-aged rats, aging

Introduction

Male sexual behavior that consists of both appetitive and consummatory components is regulated by gonadal steroid hormones secreted from the testes (36). In adult males, lack of testosterone (T) after castration abolishes both sexual drive and copulatory behavior, and the declined sexual ability can be restored by T replacement (34). The dependence of male sexual behavior on T extends to most of the mammalian species studied, including humans (14, 64). Since there are substantial similarities in neuroendocrine functions regulating sexual behavior between humans and rats, the rat has been widely used as the animal model to study the neuroendocrine mechanisms for the control normal male reproductive function, such as mating behavior, and for the dysfunction caused by diseases and aging.

The age-related decline in copulation in male rats has been extensively documented in the literature; most importantly, there is great variation in the copulatory ability among individual aged males (15, 68). During aging, the male rat shows a gradual decline in circulating T levels (45). The decrease in T is noticed in male rats at the age of 13-15 months (26). Although T is essential for eliciting mating behaviors in young male rats, supplement with excessive T to compensate T levels in circulation

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does not prevent the decline in sexual performance of aging male rats (5, 27, 30, 66). Copulatory behavior in aged male monkeys is not correlated with T levels (3, 4), and similar to rats, exogenous T treatment does not restore sexual performance in castrated aged monkeys (52). Thus, these data suggest that deterioration in the central nervous system rather than alterations in peripheral hormonal milieu might be the primary cause of the behavioral deficits in aged animals (44).

Male sexual behavior is mainly governed by a well-organized neural circuit that connects a variety of brain areas, including the medial preoptic area (MPOA), nucleus accumbens (NAc) and the bed nucleus of stria terminalis (BNST), which appear to control different components of mating behaviors. In these brain areas androgen and estrogen receptors are highly expressed (10, 11, 17, 28, 38, 61, 62, 78). In addition, these brain regions are also heavily innervated by the catecholaminergic neurons, including both dopamine (DA) and norepinephrine (NE), which have been demonstrated to be the key neurotransmitters to regulate mating behaviors in male rats (36). Thus, this review will first briefly describe normal copulatory behavior in young adult male rats and the behavioral changes in middle-aged male rats, and then focus primarily on the roles of catecholamines in the MPOA, NAc and BNST in the control of male sexual behavior in middle-aged rats.

Male Rat Copulatory Behavior

The laboratory rat has been long used as an animal model to study the mechanisms that control male sexual behavior. A standard test of mating behavior for rats is conducted under a dim red light during the dark phase of a circadian cycle. A male rat is first placed in a testing chamber, followed by introduction of a steroid-primed female. Soon after the introduction of the female, for example, a normal young male rat often approaches the female and investigates by sniffing the female's mouth and anogenital region, which provides chemosensory cues to arouse the male. The female remains immobile while the male investigates her. Meanwhile, both partners also emit ultrasonic vocalization, which mutually arouse each other (23, 72). Precopulatory behaviors help the male rat collect the information about female's desirability and willingness prior to mate.

In rats and many rodent species, there are three easily distinguishable components of the male consummatory behavior: mount, intromission, and ejaculation. Moments later after the precopulatory activity, the male attempts to mount the female by lifting his forebody over her hindquarters, clasping her flanks with his forepaws, and beginning a series of rapid, shallow thrusts with his pelvis. The male's penis is at least partially erect during first thrusts. The female remains immobile for the male to initiate a mount and then assumes a rigid lordosis posture in which her back is concave and her tail is deflected.

Intromission, defined as the penis entering the vagina during a mount, is facilitated by the exhibition of lordosis posture. After several mounts and shallow thrusts, a male rat will perform a deep thrust with intromission, followed by a rapid, springing dismount. The male typically grooms his genitalia after an intromission.

After several intromissions, a male rat ejaculates, which is characterized by a deep, long thrust and a slow, relaxed dismount. During ejaculation, the male arches his spine and often lifts his forepaws off the female prior to the withdrawal of his penis. After ejaculation, the male rat grooms himself and becomes sexually quiescent, but sexual activities resume 5-10 min later. This period between an ejaculation and the first intromission after that ejaculation is called the post-ejaculatory interval. Most laboratory male rats can ejaculate 5-8 times during an unlimited-time mating test (1). The mating potential of a male rat is determined by the number of ejaculations during a time-limited behavioral test or by the number of ejaculations prior to his attaining sexual satiety (59). The latencies to show the first mounts, first intromission, and the post-ejaculatory interval are commonly used for evaluating male's sexual motivation (18).

Male Sexual Behavior in Middle-Aged Rats

Larsson first described that sexually experienced rats at the age of 23-25 months showed a decrease in the number of mounts, intromissions, and ejaculations as well as an increase in the latencies for these behaviors compared to young adults (37). In addition, a significant decrease in sexual motivation and erection frequency is also seen in middle-aged rats (27). The changes of these two factors surely affect the overall behavioral performance of copulation in male rats. Davidson and his co-workers conducted a longitudinal study and reported age-related changes in male sexual behavioral patterns (15). Eighty-nine sexually active male rats were exposed to female rats at the age of 3 months and then received copulatory tests every 2 months from 7 to 27 months of age. Among the 39% of rats surviving up to 27 months, 70% failed to mate, but 6% still maintained their behaviors virtually unchanged. The most striking decline in the copulatory performance in male rats occurred from 17 to 19 months of age.

To further understand the individual variation

in the sexual performance that occurred at middle age, we conducted six 30-minute behavioral tests in 197 18- to 19-month-old male rats to thoroughly investigate the decline in sexual behavior at middle age (65). Based on the presence or absence of specific copulatory behavioral components, we classified four groups of middle-aged rats with distinct behavioral phenotypes (68). Among these middle-aged rats, 16% displayed the complete copulatory pattern like young animals, including mounts, intromissions, and ejaculations (Group MIE). About 36% of the animals exhibited mounts and intromissions, but no ejaculation (Group MI). Only 6% of the subjects showed mounts with an absence of intromission or ejaculation (Group M). The majority of these middle-aged male rats (42%) were noncopulators (Group NC), which did not display any copulatory behavior. Although Groups MIE and MI both exhibited intromissions, the former showed greater number and shorter latency of intromission than the latter. Similarly, significant differences in the numbers and latencies of mounts were also observed among three groups displaying mounts (Groups MIE, MI, and M) except the mount latency for Group MI and Group M. Among those showing complete sexual performance, the scores for various parameters of copulatory behavior in Group MIE were significantly lower than those observed in young adults (4-5 months), demonstrating that male copulatory activities in rats decline as age increases. Our results support Davidson's finding that three components of male sexual behavior are differently affected by senility and the ejaculatory reflex disappears first (15).

Roles of Catecholamines in the Control of Male Sexual Behavior

An extensive body of research has indicated that catecholamines, both DA and NE, play an important role in the regulation of male sexual behavior. Administration of DA or its agonists facilitate male sexual behavior (34, 35). Lesion of the locus coeruleus, which contains many noradrenergic perikarya, or systemic administration of the NE synthesis inhibitor, diethyl-dithiocarbamate, inhibit male copulation (43). Inhibiting $\alpha 2$ autoreceptors with yohimbine enhances sexual behavior (9, 65) and reverses sexual satiety (56-58). In addition, the stimulatory effect of yohimbine on male mating behavior can be blocked by haloperidol, a DA antagonist (56), suggesting that these two catecholamine neurotransmitters might interact with each other to regulate male sexual behavior. Here, we will review the roles of catecholamines in three different brain areas in the regulation of male copulation: MPOA, NAc and BNST (6, 7, 67). These three brain regions are highly innervated by the dopaminergic and noradrenergic neurons located in the midbrain and brainstem, and they play important, but distinct roles in the regulation of male sexual behavior (24, 69, 77).

Medial Preoptic Area

The MPOA plays a crucial role in the regulation of male copulatory behavior in rats and many other mammals (37). While male rats with MPOA lesions fail to mount females (25, 29), electrical stimulation of the MPOA enhances male copulatory behaviors by reducing the number of mounts and intromissions preceding ejaculation as well as the ejaculation latency (40, 46). In addition, androgen receptor and estrogen receptor are highly expressed in the MPOA, and implantation of T into the MPOA of castrated male rats restores their copulatory behaviors, suggesting that the MPOA might be required for integrating steroid signals for successful copulation (13).

The MPOA receives the dopaminergic and noradrenergic innervations from the periventricular hypothalamic nucleus, midbrain and brainstem, respectively (63). During copulation, extracellular DA levels in the MPOA in male rats increase in response to an estrous female (33). Injection of DA agonists into the MPOA enhances male sexual behavior (32, 41, 60) and genital reflex (48), while treatment of DA antagonists impair not only the genital reflex and copulation but also sexual motivation (49, 51, 71). Similar to DA, injection of NE into the MPOA in male rats increases sexual arousal and copulatory performance, and these stimulatory effects are inhibited by phenoxybenzamine or propranolol, an α- or a β-adrenergic receptor antagonist, respectively (37). Activation of $\alpha 2$ adrenergic autoreceptor by systemically administered clonidine suppresses male copulatory behavior, which is prevented by administration of yohimbine into the MPOA (8). These results indicate that neurotransmission of both DA and NE in the MPOA is important for the control of male sexual behavior.

Nucleus Accumbens

The NAc is principally innervated by dopaminergic neurons of the ventral tegmental area and plays a key role in the control of sexual arousal and motivation rather than the consummatory component of male copulatory activity. Activation of dopaminergic receptors in the NAc enhances sexual motivation and onset of copulation (18, 47). Numerous studies have also indicated that increased sexual motivation and enhanced copulatory behavior in male rats are associated with DA release in the NAc (12,

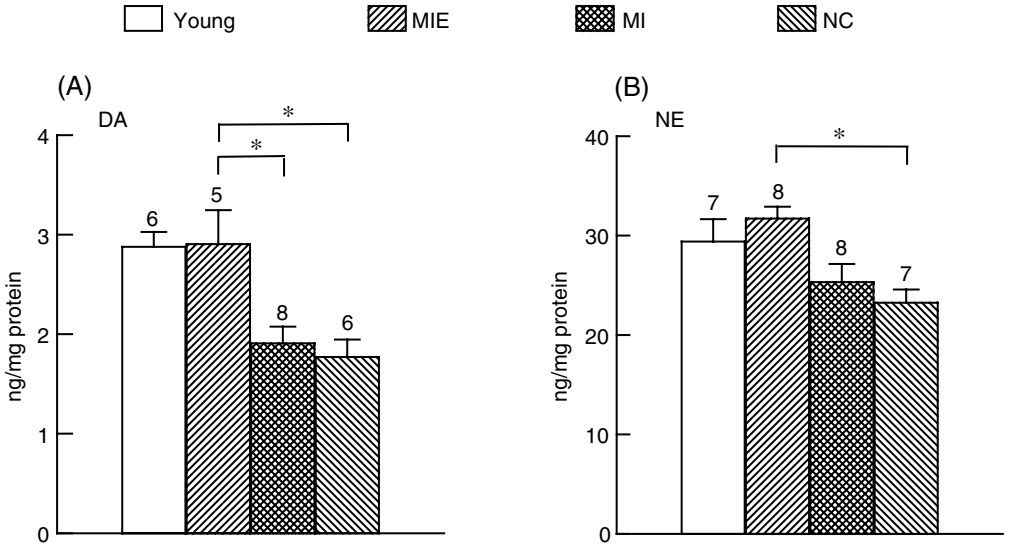

Fig. 1. Tissue levels of DA (A) or NE (B) in the MPOA of young and middle-aged male rats. Each bar represents the means ± SEM. The number at the top of each bar indicates the number of rats used in the group. *$P < 0.05$, significantly different from the MIE group. Data were reproduced from our own publication (6) with permission. MIE = mounts, intromissions, and ejaculations, MI = mounts and intromissions, but no ejaculation; NC = noncopulatory.

20-22, 42, 50, 51, 53, 54, 70).

Bed Nucleus of the Stria Terminalis

The BNST belongs to the limbic system and has reciprocal connections with the MPOA and medial amygdala (2). In rodents, the medial amygdala receives projections from both the main and accessory olfactory bulbs and mediates the female odor-elicited chemoinvestigative behavior and non-contact erection (36). Male rats with the lesion of the BNST show moderate defects in copulation with reduced numbers of intromission and ejaculation as well as increased inter-intromission intervals and post-ejaculatory refractory periods, but display severely impaired non-contact erection (69). In addition, the BNST also contains abundant androgen receptor (17), and implantation of T in the BNST restores mating behaviors in castrated male hamsters (74). This observation suggests that the BNST might not be essential for inducing male sexual behavior, but it indicates that the BNST might be important for integrating both the chemosensory and hormonal signals to activate copulatory behavior and genital reflex in males (73, 75).

Like the NAc, the BNST receives DA innervations from the ventral tegmental area (16, 19), and it also contains dense NE terminals projected from the medullary A1 and A2 regions as well as the locus coeruleus (A6), suggesting that both DA and NE neurotransmission might influence the BNST function (55, 76).

Changes in Catecholamine Levels in Different Brain Areas of Middle-aged Rats

The data above show that DA and NE in these three brain regions play important, but distinct roles in the regulation of male sexual behavior (24, 69). Our earlier observation has characterized different phenotypes of male sexual performance in subpopulations of middle-aged male rats (68). Thus, if DA and NE are involved in the age-related decline in sexual behaviors during aging, we should observe differential changes in DA and/or NE levels in the MPOA, NAc or BNST of middle-aged rats, which correlate with their sexual behaviors. Here we summarize our previous findings in middle-aged rats:

Levels of Dopamine

As shown in Fig. 1A and Fig. 2A, there were no differences in DA tissue levels of the MPOA or NAc observed between MIE rats and young adult rats, but levels of DA in the BNST of MIE rats were significantly lower than those in young controls (Fig. 3A). Although both groups of male rats show complete mating behaviors, the scores for various parameters of copulatory behavior in Group MIE were significantly lower than those observed in young adults. Thus, a decrease in DA in the BNST of MIE rats might suggest that DA transmission is critical for the connection of BNST with other brain region, which is more sensitive to aging. Among three groups of middle-aged rats, different changes in DA levels were

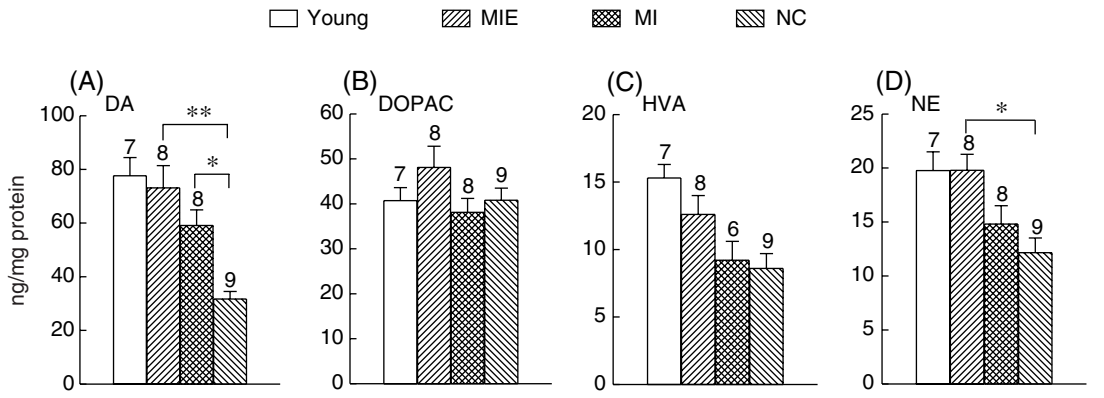

Fig. 2. Tissue levels of DA (A), DOPAC (B), HVA (C), and NE (D) in the NAc of young and middle-aged male rats. Each bar represents the means ± SEM. The number at the top of each bar indicates the number of rats used in the group. *$P < 0.05$ and **$P < 0.01$, significantly different from the NC group. Data were reproduced from our own publication (67) with permission. MIE = mounts, intromissions, and ejaculations, MI = mounts and intromissions, but no ejaculation; NC = noncopulatory.

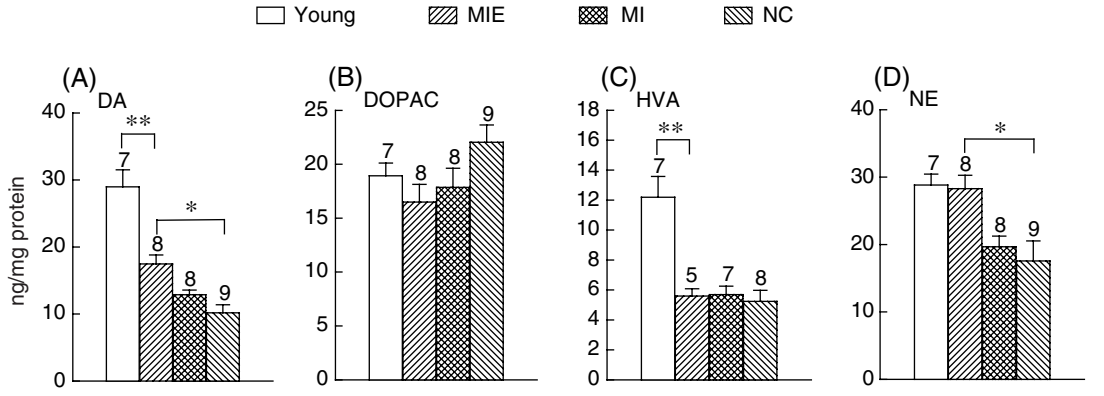

Fig. 3. Tissue levels of DA (A), DOPAC (B), HVA (C), and NE (D) in the BNST of young and middle-aged male rats. Each bar represents the means ± SEM. The number at the top of each bar indicates the number of rats used in the group. *$P < 0.05$ and **$P < 0.01$, significantly different from the MIE group. Data were reproduced from our own publication (7) with permission. MIE = mounts, intromissions, and ejaculations, MI = mounts and intromissions, but no ejaculation; NC = noncopulatory.

observed in the MPOA, NAc and BNST. In the MPOA, DA tissue levels in the MI and NC groups were significantly lower than those in the MIE group, whereas NAc DA tissue levels in NC rats were significantly lower than those in both MIE and MI rats (Fig. 1A and Fig. 2A). Interestingly, DA tissue levels in the BNST were only markedly different between Groups of MIE and NC (Fig. 3A). These observations indicate that DA in the MPOA and BNST might be involved in the control of ejaculation, but DA in the NAc might be important for mounting or sexual motivation, which support the different roles of these brain regions in male sexual behaviors.

Levels of Dopamine Metabolites

Besides the synthesis and release, DA transmission is also tightly regulated by the rate of metabolism. Two main DA metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were also measured to indicate DA function (7, 66). No significant differences in tissue levels of DOPAC and HVA were found in the NAc or BNST among MIE, MI and NC groups. These data might suggest that the activities of two main metabolic enzymes for DA, such as monoamine oxidase and catechol-O-methyltransferase in these three brain regions remain unchanged during aging. In the NAc, an age-related decrease in HVA was observed. After normalizing to DA levels, the ratios of the DOPAC/DA in the NAc and BNST as well as the ratio of [DOPAC + HVA]/DA in the NAc, but not the HVA/DA ratios, were higher in NC rats than in MIE and MI rats, suggesting that lower DA levels found in NC rats might result from diminished synthesis of DA rather than increased metabolism or turnover of DA (Tables 1 and 2).

Table 1. DOPAC/DA, HVA/DA and DOPAC plus HVA/DA ratios in the nucleus accumbens of young and middle-aged male rats

Group	DOPAC/DA ratio	HVA/DA ratio	[DOPAC + HVA]/DA ratio
Young	0.56 ± 0.07	0.21 ± 0.02	0.77 ± 0.09
MIE	0.73 ± 0.11**	0.19 ± 0.03	0.92 ± 0.13**
MI	0.70 ± 0.09**	0.18 ± 0.02	0.82 ± 0.11**
NC	1.36 ± 0.12	0.27 ± 0.01	1.62 ± 0.12

All values are expressed as the means ± SEM.
**$P < 0.01$, significantly different from the NC group.
Data were reproduced from our own publication (67) with permission.
MIE = mounts, intromissions, and ejaculations; MI = mounts and intromissions, but no ejaculation; NC = noncopulatory.

Table 2. DOPAC/DA, HVA/DA, and [DOPAC + HVA]/DA ratios in the bed nucleus of the stria terminalis of young and middle-aged male rats

Group	DOPAC/DA ratio	HVA/DA ratio	[DOPAC + HVA]/DA ratio
Young	0.68 ± 0.05	0.45 ± 0.07	1.13 ± 0.11
MIE	0.97 ± 0.10**	0.31 ± 0.04	1.16 ± 0.11
MI	1.43 ± 0.16*	0.44 ± 0.04	1.81 ± 0.17
NC	2.56 ± 0.42	0.56 ± 0.08	1.62 ± 0.12

All values are expressed as the means ± SEM.
*$P < 0.05$ and **$P < 0.01$, significantly different from the NC group.
Data were reproduced from our own publication (7) with permission. MIE = mounts, intromissions, and ejaculations; MI = mounts and intromissions, but no ejaculation; NC = noncopulatory.

Levels of Norepinephrine

In contrast to DA, no age-related changes in tissue levels of NE were found in the MPOA (Fig. 1B), NAc (Fig. 2D), or BNST (Fig. 3D). Decreased NE levels between the NC and MIE rats were consistently observed in the MPOA, NAc, and BNST. Correlated to the sexual behavioral performance of MIE and NC rats, we speculate that NE transmission in these three brain regions might involve in the regulation of mount, intromission, and ejaculation as well as motivation. With the lack of alteration in specific brain areas, our results suggest that NE might play a modulatory role in regulating the function of the MPOA, NAc, and BNST in the control of mating behaviors.

Conclusion

Significant variations in copulatory performance are observed in middle-aged male rats (18-19 months). Most of these rats (42%) are noncopulators; however, some 16% subjects still display the complete copulatory pattern, including mounts, intromissions and ejaculations. Thus, middle-aged rats are suitable as animal model to investigate age-related decline in male sexual behavior. We have used this animal model to explore the correlation between copulatory behavior and catecholamine levels in the MPOA, NAc and BNST in middle-aged male rats. In the support of our hypothesis, our results show that declined male sexual performance is correlated with differentially diminished levels of DA in the MPOA, NAc and BNST. For example, loss of ejaculation appears be associated with critical DA tissue levels in the MPOA, and levels of DA and NE in the NAc and BNST as well as NE tissue levels in the MPOA might be more critical for mounting behaviors. In summary, correlation of DA and NE levels in the MPOA, NAc and BNST with behavioral phenotypes in middle-aged rats supports the hypothesis that catecholamines in different brain regions play important, but distinct roles in the control of male sexual behavior and may be responsible for the age-related decline in behaviors.

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