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Short communication

Induction of mating behavior by apomorphine in sexually sated rats

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Abstract

We have tested the hypothesis, suggested by our previous neurochemical studies, that the inhibition of sexual behavior that follows unrestricted mating could be caused by a blockade of dopaminergic transmission. Male rats were allowed to copulate until they reached a satiety criterion. The following day, after verification that they were sexually inactive, the animals were injected with the dopamine agonist, apomorphine, at doses of 80, 200, and 500 μg/kg body weight and their behavior with receptive females was recorded. A bell-shaped dose-response curve was found, with the 200 μg/kg dose having the maximal stimulatory effects on mating. Whereas these findings seem to support the above hypothesis, it should be noted that apomorphine treatments were unable to restore fully the copulatory pattern shown by sexually rested animals. This could be due to several factors including the interference of apomorphine-induced stereotypies, and/or the involvement of additional transmitter systems in the mechanisms of sexual satiety.

Keywords: Sexual satiety; Mating; Apomorphine; Dopamine

1. Introduction

The involvement of dopaminergic mechanisms in the regulation of masculine sexual behavior, as well as other motivational processes, has long been suggested by a wealth of pharmacological studies. Thus, dopamine agonists have generally been found to have stimulatory effects on sexual activity of male mammals whereas dopamine receptor blockers had the opposite effects (see Meisel and Sachs, 1994, for review). The physiological significance of these findings has been emphasized recently by the assessment of neurochemical changes in mating animals. Studies in this and other laboratories using either in vivo voltammetry (Mas et al., 1990) or microdialysis (Fumero et al., 1994; Hull et al., 1992; Mas et al., 1995a; Pfaus et al., 1990; Pleim et al., 1990) have consistently shown mating-related increases in dopamine release and metabolism in forebrain areas known to participate in the expression of sexual behavior, such as the nucleus accumbens (Fumero et al., 1994; Mas et al., 1990; Pfaus et al., 1990; Pleim et al., 1990) and the medial preoptic area (Fumero et al., 1994; Hull et al., 1992; Mas et al., 1995a).

A potentially useful experimental model for assessing the neurochemistry and pharmacology of sexual motivation is the sexually sated state (Mas et al., 1995b), a phenomenon first described by Beach and Jordan (1956). When sexually rested male rats are allowed unrestricted interaction with receptive females they display several bouts of copulatory activity, until they attain a relatively constant number of ejaculations (approximately 7). They then enter into a state of sexual refractoriness, lasting a few days, in which no further mating is elicited even if they are repeatedly exposed to proceptive females. This is followed by a gradual resumption of copulatory activity, usually taking about a week for full recovery. Recent reports have shown that sexual satiety can be influenced by experimental manipulations such as brain lesions (Yells et al., 1992) and systemic treatment with noradrenergic or serotonergic drugs (Rodriguez-Manzo and Fernandez-Guasti, 1994).

Using repeated microdialysis sampling for extended periods, we have documented a sustained increase in dopamine turnover, with no apparent changes in serotonergic activity, in the medial preoptic area during the

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days of sexual inactivity following exhaustion, decreasing to levels closer to those found in the sexually rested state prior to the resumption of mating (Mas et al., 1995a). Whereas these neurochemical findings could reflect increased dopaminergic transmission they are also reminiscent of the effects of dopamine receptor antagonist drugs (see Mas et al., 1995a and references therein). Based on the above pharmacological data we suggested that some endogenous signal impairing dopaminergic transmission in the forebrain could operate during the state of sexual satiety (Mas et al., 1995a, b). The present study tests this hypothesis.

2. Materials and methods

Male sexually experienced Sprague-Dawley rats weighing 250–300 g were used as experimental animals. Stimulus females were brought into behavioral estrus by the s.c. injection of 50 μg of estradiol benzoate and 500 μg of progesterone at, respectively, 48 h and 4 h before being introduced in the male rats' cages. The tests for sexual activity were conducted under a dim red light starting at the beginning of the dark phase of the 12:12 h light:dark cycle.

The males were placed individually in test cages and a receptive female was introduced and replaced every 30 min. In the first session the animals were allowed to copulate until reaching a criterion of 90 min without further mating. The next day they were tested again for sexual behavior. After a 90-min period in which no mounting of the successively replaced estrus females was displayed the males were considered as sexually refractory and suitable for the pharmacological treatment. Each dose level was given to 8 proven sexually inactive animals. They were injected s.c. with either the dopamine receptor agonist, apomorphine hydrochloride, at doses of 80, 200 and 500 μg/kg body weight or vehicle (0.1% ascorbic acid) and returned to the test cages. These doses are well within the range documented by several laboratories as being stimulatory of sexual behavior in male rats (see Meisel and Sachs, 1994, for references). A new receptive female was introduced 15 min later, and was replaced again periodically until no sexual activity was seen for 90 min.

3. Results

The development of sexual exhaustion took a median number of 7 ejaculations. The post-ejaculatory interval (i.e. time from one ejaculation to the resumption of mating) increased exponentially as the subjects approached exhaustion whereas the number of intromissions preceding each ejaculation (intromission frequency) decreased after the first ejaculatory series. All

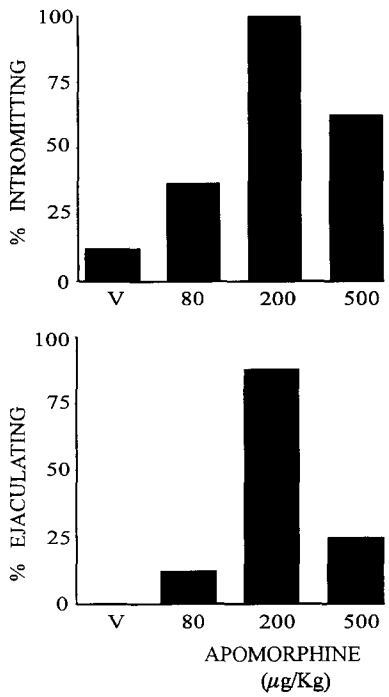

Fig. 1. Effects of different doses of the dopamine agonist, apomorphine, and vehicle (V) on the display of sexual behavior in male rats rendered sexually inactive following unrestricted mating. Significance of the 200 μg/kg-treated group by Fisher's exact probability test: $P < 0.001$ vs. vehicle for both percent intromission and ejaculating; $P < 0.01$ vs. 80 μg/kg and $P < 0.04$ vs. 500 μg/kg for percent ejaculating; $P > 0.02$ vs. 80 μg/kg for percent intromission; 8 animals per group.

these findings are consistent with previous descriptions (e.g. Beach and Jordan, 1956; Mas et al., 1995a; Rodriguez-Manzo and Fernandez-Guasti, 1994; Yells et al., 1992). The next day, a large proportion of these animals (76%) met the sexual exhaustion criterion (i.e. not mating when being exposed for 90 min to estrus females). Accordingly, they were treated with either vehicle or the different apomorphine doses.

Apomorphine injections were able to induce mating activity in these sexually sated animals, showing a bell-shaped dose-response curve (Fig. 1). Clearly, the most effective dose was 200 μg/kg. Thus, all but one of the animals in this group copulated to ejaculation after a median interval from the first intromission (12 min) and intromission frequency (11) fairly similar to those found in baseline mating tests in this and previous studies (e.g. Fumero et al., 1994; Mas et al., 1990). The animal failing to ejaculate showed 23 intromissions. No further mating was observed in most of the subjects after they completed one ejaculatory series. Only two animals in this group resumed mounting (with post-ejaculatory intervals of 10 and 15 min) and one of these ejaculated twice.

Only one rat given the 80 μg/kg dose ejaculated once, after 20 intromissions. Two other animals in this

group showed 2 and 3 intromissions but no ejaculation during the test period. Five animals treated with the 800 μg/kg dose mounted but only two of these ejaculated once (after 19 and 30 intromissions). Those not ejaculating displayed 2–5 intromissions. The low number of animals showing a full pattern of copulatory behavior in the groups other than the 200 μg/kg dose precluded a formal statistical comparison of standard measures of sexual behavior between the different dose levels studied.

It should be noted that the stimulatory effect of apomorphine treatment on mating behavior in the sexually sated animals was only apparent after a significant time-lag. Thus, in the preceding baseline tests, when these rats were sexually rested and given no treatment, they usually started mating within 2 min after introducing the receptive female. However, their median latencies (min) to the first intromission after receiving the apomorphine doses of 80, 200, and 200 μg/kg were, respectively, 22 ($n = 3$), 27 ($n = 8$), and 42 ($n = 5$).

A likely factor contributing to this phenomenon was the interference of dose-related stereotyped responses shown by the animals given the two higher doses of apomorphine. This included walking slowly along the cage walls while sniffing and gnawing, and paying little attention to the surroundings, including the stimulus female. This behavioral pattern could be noticed for the first 20 min following the injection in the animals given the 200 μg/kg dose and was more intense and longer lasting in those treated with the 500 μg/kg dose, a fact that could account for their lower mating response.

4. Discussion

The present results showed that the pharmacological stimulation of dopamine receptors can induce copulatory activity in male rats with proven sexual refractoriness following unrestricted mating. This should be consistent with the hypothesis of impaired dopaminergic transmission in the mechanism of sexual satiety (Mas et al., 1995a, b), a phenomenon that we have suggested, on pharmacological and neurochemical grounds, could be mediated by the pituitary hormone, prolactin (Gonzalez-Mora et al., 1990; Mas et al., 1995b).

The finding of a bell-shaped dose-response curve is fairly common when assessing the effects of apomorphine and other dopamine receptor agonists on various indices of sexual function (see Meisel and Sachs, 1994, for references). The paradoxical effects of high doses have usually been attributed to the disruption of copulation by concurrent motor stereotypies and/or the recruitment of additional dopamine receptors, perhaps in different locations of the central nervous system, having opposite actions on the sex behavior patterns. The 80-μg/kg dose of apomorphine, which in some studies was able to induce various sexual responses in rested animals, seemed too low for a substantial stimulation of mating in our sexually sated rats. This is reminiscent of a previous report on apomorphine-induced penile erection showing the lack of effect in sexually exhausted rats of a relatively similar dose (60 μg/kg) which was quite effective, however, in either sexually rested animals or when a few intromission had been allowed (Sachs et al., 1994). These data further suggest a reduced sexual responsiveness to apomorphine during sexual satiety.

The fact that the apomorphine-induced restoration of mating behavior was incomplete could be due to several factors. As pointed out above, the side-effects of apomorphine treatment, evidenced by the stereotyped behavior, could disturb the expression of the normal behavioral pattern. The involvement of other transmitter systems in the mechanisms of sexual satiety is also likely. Thus, it has been recently reported (Rodriguez-Manzo and Fernandez-Guasti, 1994) that treatment with the α_2-adrenoceptor antagonist, yohimbine, and the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), stimulated mating in animals that had been exposed for 4 h to receptive females the day before; a procedure that, according to normative data, would be sufficient for rendering them sexually exhausted. Yet, sexual refractoriness was not ascertained in that study as a requirement for the pharmacological challenge, as was done in the experiment described here. This is an important issue, given the finding that almost one fourth of our animals, and one third of those in the Rodriguez-Manzo and Fernandez-Guasti (1994) study, supposedly sexually sated after unrestricted copulation showed various levels of mating activity the following day (i.e. at the time when the pharmacological treatments were scheduled).

It is worth considering that both yohimbine and 8-OH-DPAT have been found to interfere with dopaminergic transmission (e.g. Brannan et al., 1991; Smith and Cutis, 1990), making a possible common mechanism for these pharmacological effects consistent with the present findings. It is also noteworthy that in both the Rodriguez-Manzo and Fernandez-Guasti (1994) report and the present study none of the pharmacological treatments tested was able to fully restore the mating pattern usually found in sexually rested animals, which includes recurring copulation until approximately 7 ejaculations are attained. If the sexual satiety phenomenon is mediated by multiple neurotransmitter systems a combination of different drugs could be necessary for full reversal.

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