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A potential aphrodisiac for female macaques

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Abstract

Earlier studies suggest that α_2-adrenoceptor antagonists and dopamine receptor agonists may enhance sexual activity in human and nonhuman male primates. It is not known whether these compounds influence the sexual behavior of female primates. We determined whether the administration of a selective α_2-adrenoceptor antagonist (atipamezole), a dopamine receptor agonist (apomorphine), or their combination to female *Macaca arctoides* (stumptail macaque) monkeys produces changes in sexual behavior of the female with a male. Following the administration of drugs to the female, the behavior of the female with a male stumptail was observed for 30 min. Atipamezole dose dependently (0.03–0.3 mg/kg im) increased short-time mounting behavior of the male and the total number of copulations. Apomorphine alone (0.125–0.25 mg/kg) or in combination with atipamezole had no significant effects on sexual behavior. The result indicates that a selective α_2-adrenoceptor antagonist administered in the female stumptail increases sexual behavior of the male with the female. A plausible explanation for this finding is that a selective α_2-adrenoceptor antagonist increases sexual arousal in female stumptails and this, possibly due to a change in psychosocial behavior of the female, triggers increased sexual activity in males.

Keywords: α_2-Adrenoceptor antagonist; Apomorphine; Atipamezole; Female sexual behavior; *Macaca arctoides*

1. Introduction

Due to a lack of direct assessment methods, the pharmacological modulation of sexual activity of nonhuman primates has been difficult to study in females, whereas many aspects of male sexual behavior, such as erection and mounting, provide direct and prominent measures for determining the efficacy of aphrodisiacs (Linnankoski and Leinonen, 1985; Linnankoski et al., 1995). The sexual behavior of stumptail macaques (*Macaca arctoides*) provides a useful experimental animal model because it resembles human sexual behavior more than that of many other nonhuman primates, as shown for example by the minor influence of season and menstrual cycle on sexual activity (Linnankoski et al., 1981). Although with stumptails, as with humans, the male is the more active partner in sexual behavior, the female is able to trigger the sexual activity of the male by various psychosocial gestures, such as eye contacts or exposure of the perineal region to the male (Linnankoski et al., 1993). Therefore, the observation of the male sexual activity triggered by the female can be used as an indirect measure of female sexual arousal.

α_2-Adrenoceptor antagonists and dopamine agonists have been shown to increase sexual behavior in human males (Lal et al., 1984; Reid et al., 1987; Susset et al., 1989) and nonhuman male primates (Linnankoski et al., 1992; Pomerantz, 1990, 1992). However, it is not known whether these compounds have aphrodisiac properties in nonhuman female primates. We determined the aphrodisiac effects of a selective α_2-adrenoceptor antagonist, atipamezole (Haapalinna et al., 1997; Virtanen et al., 1989), a dopamine agonist, apomorphine, and their combination on the female stumptail by observing its sexual behavior with a male.

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2. Materials and methods

2.1. Experimental animals

The experiments were performed using four female and two male stumptail macaques (*M. arctoides*) that were born in captivity. The age of the females ranged from 12 to 25 years and that of the males from 14 to 23 years. The females were sexually mature and with normal hormonal cycles. The female monkeys' vaginas were swabbed daily for the detection of menstruation. There were no signs of pregnancy during the experiments. The Institutional Ethics Committee accepted the experimental protocol, and the guidelines of European Communities Council Directive of 24 November 1986 (86/609/EEC) were strictly followed.

2.2. Testing procedure

During the testing period, the stumptails were housed individually in stainless-steel cages. They were fed commercially available food twice each day, and water was always available. Females were weighed before the first injection of each series, and doses were adjusted accordingly when appropriate. Sexual behavior was tested between 11.00 and 16.00 h. The same test cage and testing procedure were used in all experiments. One experienced observer, blind to the treatment, viewed the animals at a distance of about 0.5 m from the cage.

During the testing period the couple being tested was housed in a single case (0.6×0.9×1.2 m) with two compartments. During the first 10 min of each session, a sliding wall made of steel bars separated the male and the female in the test cage. The stumptails could see and touch each other through this wall. Between the testing sessions, the female being tested was housed in another room with no visual contact with the male.

After the intramuscular administration of the studied compounds to the female, the observation of sexual behavior began as described subsequently. Ten minutes after the end of drug administration, the sliding wall between the male and the female was pulled away, and the observation of sexual activity continued for the next 20 min. At the end of the observation period, the sliding wall was replaced, and the female was taken to her home cage in another room.

2.3. Behavioral parameters

The occurrence and duration of the following parameters were observed: presentation, perineal investigation, mounting, masturbation, ejaculation, tying, male and female grooming, eye contact, yawning, self-scratching, direct male aggression towards the female, and teeth grinding (Linnankoski et al., 1981). Ejaculations obtained by copulation and masturbation were pooled in final results. A single mount leading to ejaculation was counted as ejaculation. A single mount not leading to ejaculation was counted as a short-term mount. If the interval between mounts was >30 s, the mount was considered to be separate. In *M. arctoides*, male ejaculation reached in copulation or masturbation can be recognized clearly on the basis of its stereotypic manifestations, as described in detail elsewhere (Linnankoski et al., 1981).

2.4. Drugs

Atipamezole, a selective $\forall_2$-adrenoceptor antagonist (Haapalinna et al., 1997; Virtanen et al., 1989), was obtained from OrionPharma (Turku, Finland) and apomorphine, a dopamine receptor agonist, from Sigma (St. Louis, MO). Physiological saline was used as control. The doses of atipamezole and apomorphine were selected on the basis of previous publications indicating that atipamezole increased sexual activity of male stumptails at doses of 0.03–0.3 mg/kg (Linnankoski et al., 1992) and that apomorphine modulated sexual behavior of rhesus males at doses of 0.125–0.25 mg/kg (Pomerantz, 1990, 1992). The drugs were dissolved in physiological saline to get a volume of 0.5 ml. The experiments were performed once every other day, 3 days/week. In each female, the effect of atipamezole alone (0.03 and 0.3 mg/kg and saline control) was tested during the first 2 weeks. The effect of apomorphine alone (0.125 and 0.25 mg/kg and saline control) was tested during the next 2 weeks. The combination of a low dose of atipamezole (0.03 mg/kg) with a low dose of apomorphine (0.125 mg/kg), a high dose of atipamezole (0.3 mg/kg) with a high dose of apomorphine (0.25 mg/kg), or saline control (two saline injections) was studied during the last two weeks. Due to the difference in their pharmacokinetic properties, atipamezole (or its saline control) was always administered 10 min prior to the testing session and apomorphine (or its saline control) 20 min before the testing session, both when these compounds were given alone or in combination. The order of testing the various doses of drugs and saline control was randomized within each 2-week testing period. Each dose or dose combination was tested twice, and the average result of these two sessions was used in final calculations. The experiments were performed in a blinded fashion.

2.5. Statistics

The statistical evaluation of the data was performed using one-way analysis of variance with repeated measures, followed by Tukey-Kramer test. The effect of each compound was assessed separately. $P<.05$ was considered to represent a significant difference.

3. Results

Following the administration of atipamezole in the female macaques, the total number of copulations of the male with the female was increased [$F(2,11)=5.00$, $P=.05$;

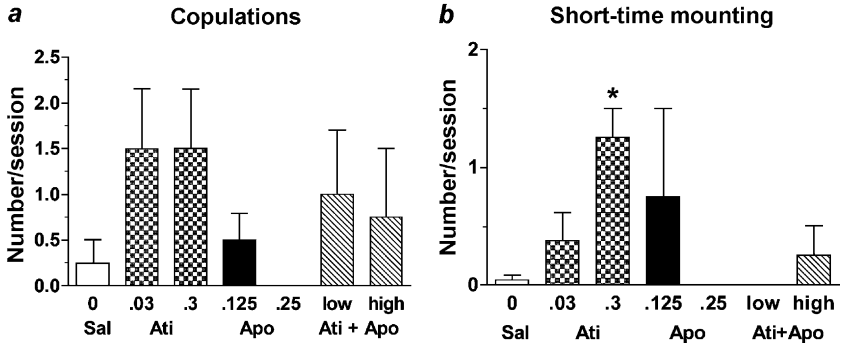

Fig. 1. Effects by blinded, randomized administrations of atipamezole (Ati), apomorphine (Apo) or their combination (Ati+Apo) to the female stumptail on the sexual behavior of the male with the female. (a) Total number of copulations. (b) Short-time mountings. The error bars represent S.E.M. (n=4). *P<.05 (Tukey's test; reference: the Saline condition=Sal). The doses of atipamezole and apomorphine alone are shown below the bars, in mg/kg. Ati+Apo$_{low}$=atipamezole 0.03 mg/kg+apomorphine 0.125 mg/kg; Ati+Apo$_{high}$=atipamezole 0.3 mg/kg+apomorphine 0.25 mg/kg.

Fig. 1a]. In addition, atipamezole dose dependently (0.03–0.3 mg/kg im) increased the short-time mounting behavior of the male during the 30-min observation period following injections [F(2,11)=7.55, P<.03; Fig. 1b]. The atipamezole-induced increase in sexual behavior was independent of the menstrual cycle because menstruation occurred at an equal frequency in different drug conditions. Apomorphine alone (0.125–0.25 mg/kg) or in combination with atipamezole had

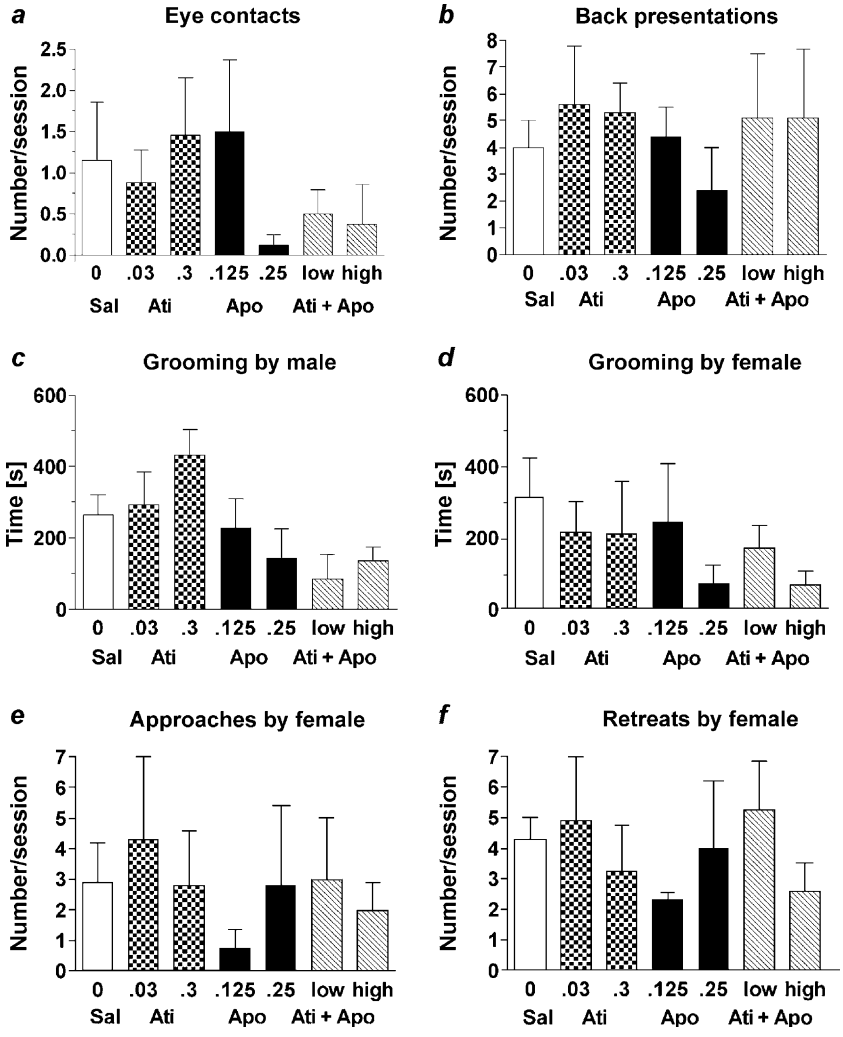

Fig. 2. Psychosocial behavior following administration of drugs into the female. (a) Eye contacts between the female and male; (b) presentations to the male by female; (c) grooming of the female by male; (d) grooming of the male by female; (e) approaches toward the male by female; and (f) retreats from the male by female. For other explanations, see the legend for Fig. 1.

no significant effects on the number of short-time mountings or copulations. The effect of atipamezole, apomorphine, or their combination was not significant on the other behavioral parameters studied (number of eye contacts, presentations, grooming, approaches and retreats; Fig. 2).

4. Discussion

The results indicate that a selective α_2-adrenoceptor antagonist atipamezole, which stimulates central noradrenergic activity (Haapalinna et al., 1997), increases not only male (Linnankoski et al., 1992) but also female sexual behavior in stumptails, whereas a dopamine agonist, apomorphine, at a dose effective in rhesus males (Pomerantz, 1990, 1992), was ineffective in female stumptails. The results provide the first evidence about the possible aphrodisiac effects of α_2-adrenoceptor antagonists in female monkeys. This finding suggests that atipamezole increases sexual arousal in the female and this, possibly due to a change in the psychosocial behavior of the female, triggers increased sexual activity of the male. The present study design also provides an experimental model for studying the pharmacological modulation of female sexual behavior in nonhuman primates. Because no single psychosocial gesture of the female was significantly associated with the atipamezole-induced increase of copulatory and short-time mounting activity, the females may have signalled about their increased sexual desire to the males by a varying combination of psychosocial gestures. Alternatively, the critical psychosocial signal may have been too subtle to be detected by a human observer. Particularly, potential olfactory cues might not be detected by a human observer. A drug-induced increase of attractiveness as a contributing factor cannot be excluded, although we are not aware of any potential mechanisms that could produce a change in the attractiveness of females following the administration of atipamezole.

4.1. Influence of α_2-AR antagonists on female sexual behavior

α_2-adrenoceptor antagonists have been effective in increasing the sexual activity of males in rodents (Clark et al., 1984) and humans (for a review, see Tam et al., 2001). However, in rhesus males, an α_2-adrenoceptor antagonist yohimbine was without effect on sexual activity (Chambers and Phoenix, 1989), unlike atipamezole in male stumptails (Linnankoski et al., 1992). In human females, yohimbine, together with L-arginine glutamate, increased sexual arousal, although the sexually arousing effect of yohimbine alone was short of significance (Meston and Worcel, 2002). In addition, another study in human females reported that yohimbine alone failed to improve sexual desire (Piletz et al., 1998). However, it should be noted that the doses of yohimbine in these studies in human females were low (approximately 0.1 mg/kg) compared with the dose of atipamezole in the present study in nonhuman female primates (up to 0.3 mg/kg). Moreover, atipamezole is more potent and selective as an α_2-adrenoceptor antagonist than yohimbine is (Haapalinna et al., 1997). Clonidine, an α_2-adrenoceptor agonist, decreased the sexual arousal of females in rats (Meston et al., 1996) and humans (Meston et al., 1997), which is in line with the proposal that α_2-adrenoceptor antagonists have aphrodisiac properties in females. It remains to be studied whether the aphrodisiac effect of an α_2-adrenoceptor antagonist could be explained by a specific mechanism or by an unspecific arousal effect that might also increase sexual activity (Crowley et al., 1973). Previous studies in human females have shown that sympathetic nervous system activity increases during sexual activity (Exton et al., 1999). In addition, the stimulation of sympathetic nervous system activity by adrenaline (Meston and Heiman, 1998) or physical exercise (Meston and Gorzalka, 1995) increases female sexual arousal, as measured by vaginal pulse amplitude. These findings in human females suggest that the central increase of noradrenergic activity by atipamezole (Haapalinna et al., 1997) and the consequent unspecific arousal effect may be underlying the increased sexual arousal of female stumptails in the present study. On the other hand, a lack of a significant effect on other behavioral parameters supports the hypothesis that a general increase in activity alone may not explain the increase in sexual behavior following the administration of atipamezole, but, at least partly, the aphrodisiac effect is due to a more specific action of atipamezole on circuitries controlling sexual activity.

4.2. Apomorphine and sexual behavior

It has been reported that apomorphine, a dopamine receptor agonist, increases sexual activity in human males (for a review, see Heaton, 2000) and male rhesus monkeys (Pomerantz, 1990, 1992), although, at least in one study, apomorphine had no significant effect on sexual behavior in rhesus males (Chambers and Phoenix, 1989). In female rats, drugs modifying dopaminergic transmission had no significant effect on sexual behavior (Ellingsen and Ågmo, 2004). In the present study, apomorphine, alone or in combination with atipamezole, did not induce any significant change in the sexual behavior of the male with the female following administration to female stumptails. Because the effect of apomorphine on female sexual behavior was, to a large extent, assessed indirectly by observing male behavior, the present study may have failed to reveal minor effects of the drug. However, the significant effect of atipamezole alone indicates that the present experimental design is able to detect drug-induced changes in sexual behavior, if the effect is strong enough. Thus, it can be concluded that apomorphine, alone or in combination with atipamezole, has weaker effects on the sexual arousal of female stumptails than does atipamezole alone. Furthermore, it should be noted that apomorphine has some well-known side effects,

such as nausea (Heaton, 2000), that are more difficult to assess in animals than in humans. Therefore, we cannot exclude the possibility that some side effects, which we failed to detect, may have counteracted a potential aphrodisiac influence of apomorphine.

4.3. Potential implications

Atipamezole, at the dose range used in the present study, produced no major cardiovascular or other side effects in previous human experiments (Karhuvaara et al., 1990). This finding, together with its significant effect on sexual behavior in female stumptails, suggests that atipamezole is a potential clinically applicable aphrodisiac also for human females.

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