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BRIEF COMMUNICATION

Increased Sexual Behavior in Male *Macaca arctoides* Monkeys Produced by Atipamezole, a Selective α_2-Adrenoceptor Antagonist

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LINNANKOSKI, I., M. GRÖNROOS, S. CARLSON AND A. PERTOVAARA. *Increased sexual behavior in male Macaca arctoides monkeys produced by atipamezole, a selective α_2-adrenoceptor antagonist.* PHARMACOL BIOCHEM BEHAV **42**(1) 197–200, 1992.—The effect of a highly selective and potent α_2-adrenoceptor antagonist, atipamezole, on sexual behavior was studied in three stumptail macaques (*Macaca arctoides*). Following IM administration of atipamezole or saline control, the behavior of the male monkey with a female monkey was observed for 30 min. Atipamezole dose dependently (0.01–0.15 or 0.30 mg/kg) produced a significant increase in the number of ejaculations in all three monkeys, including an old one with decreased sexual activity in control conditions. Both ejaculations obtained by copulation and masturbation were increased. It is concluded that atipamezole is effective in increasing sexual behavior in male stumptail monkeys.

Atipamezole α_2-Adrenoceptor antagonist Sexual behavior Monkey

YOHIMBINE, an α_2-adrenoceptor antagonist, has been used for the treatment of impotence in clinical medicine for a number of years. In controlled human studies, the effect of yohimbine has varied depending a.o. on the etiology of the impotence (8,9,14). Concerning the effect of yohimbine on sexual behavior of animals, there are several recent reports indicating that in male rats yohimbine increases sexual activity [(2,10, 11); however, (4)]. Yohimbine also attenuates aging-induced sexual deficiencies in rats (13). However, concerning nonhuman primates a recent study on rhesus (*Macaca mulatta*) males indicated that yohimbine did not have a significant effect on their sexual behavior (1).

Atipamezole is a novel highly selective imidazole-type α_2-adrenoceptor antagonist (5,12,15). The α_2/α_1 selectivity ratio of atipamezole is 200–300 times higher than that of either idazoxan or yohimbine (15). Thus, atipamezole provides a more potent and specific tool for revealing the role of α_2-adrenoceptors in sexual behavior than the previously used α_2-adrenoceptor antagonist. In the current study, we determined the effect of atipamezole on sexual behavior of male stumptail macaques.

METHOD

Three male and one female stumptail macaques (*Macaca arctoides*) were studied in the experiments. The ages of the males were 13, 16, and about 24 years. Two of the males were laboratory born, whereas the oldest male was wild born. The oldest male was captured from the jungle 17 years earlier and, based on the development of his canine teeth, his age at the time of capture was about 7 years. The only female monkey used in the experiments was laboratory born 6 years earlier. She was sexually mature and had a normal hormonal cycle. She had no previous pregnancies, nor were there any signs of pregnancy during the experiments. During the testing period, monkeys were housed individually in stainless steel cages. All

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monkeys were fed commercially available food twice each day and water was always available. The experiment was approved by the Institutional Ethics Committee of the University of Helsinki.

Males were weighed before the first injection of each series of tests. Drug doses were adjusted accordingly when appropriate. Sexual behavior was tested between 11:00 a.m. and 4:00 p.m. The same test cage and testing procedure were used in all experiments. Two experienced observers, one at a time, viewed the animals at a distance of about 0.5 m from the cage. Three other female monkeys, housed individually but with visual contact with the experimental animals, were located in the test room.

During the testing period, the couple being tested was housed in a single cage (0.6 × 0.9 × 1.2 m) with two compartments. Between the sessions and during the first 10 min of each session, a sliding wall made of steel bars separated the male and female in the test cage. The monkeys could see and touch each other through this wall. After IM administration of the studied drug dose/saline control to the male, observation of the sexual behavior began as described below. Ten minutes after drug administration, the sliding wall between the male and female was pulled away and the observation of sexual activity continued for the next 20 min. At the end of the observation period (= 30 min after drug administration), the sliding wall was replaced. Every time a new couple was being tested, the first three sessions were done as above but without drug administrations to allow habituation of the couple to each other. These first three sessions were not included in the results.

The time of occurrence and duration of the following behaviors were observed: perineal investigation, mounting, masturbation, ejaculation, tieing, grooming, direct aggression toward the female, yawning, self-scratching, and teeth-grinding. In the current report, only the number of ejaculations in each session is given since it gives the most straightforward index of male sexual behavior. For the same reason, ejaculations obtained by copulation and masturbation were pooled in the

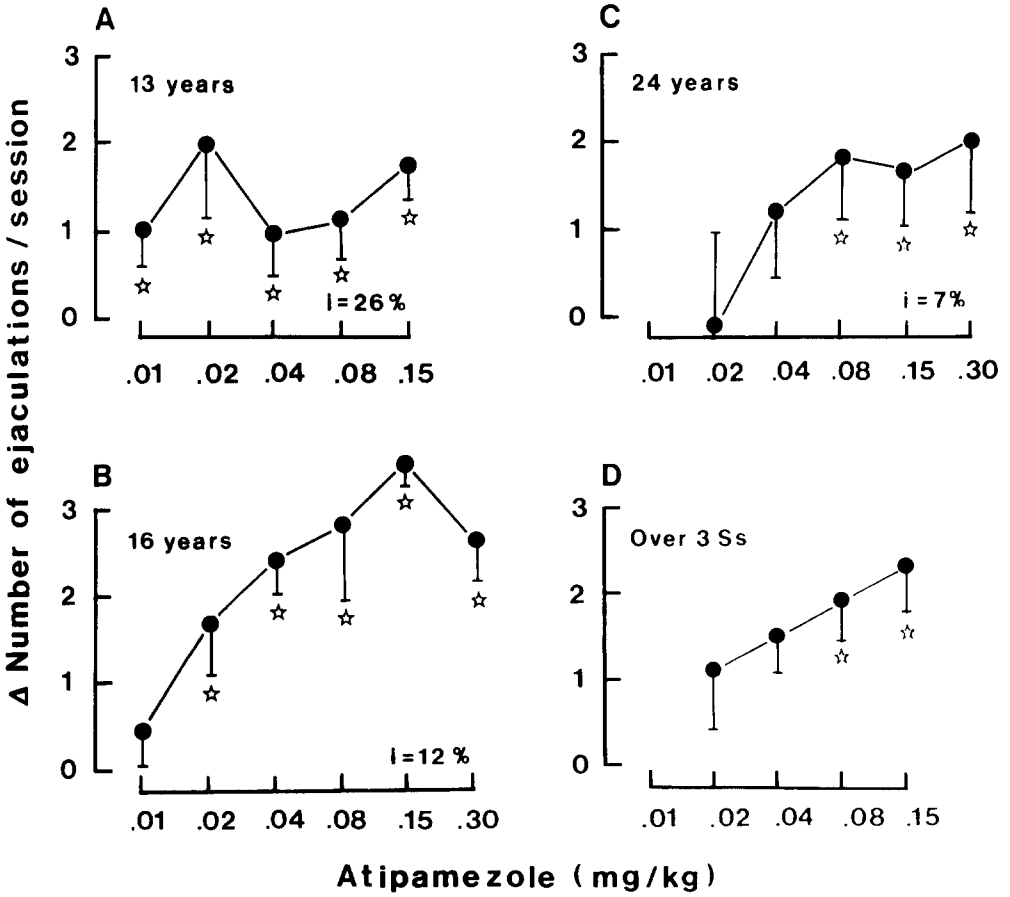

FIG. 1. Increase of the total number of ejaculations (pooled data from ejaculations obtained by copulation and masturbation) produced by atipamezole in three male stumptail macaques. In the ordinate, the difference between the results obtained during the successive atipamezole and saline (control) days (number of ejaculations during the atipamezole day−number of ejaculations during the corresponding saline day). (A–C) Results for individual males. In the upper left corner of each graph is the age of the male and in the lower right corner the incidence of sexual activity in control conditions (the percentage of saline days with any number of ejaculations obtained by copulation or masturbation). (D) Average results over three males. ☆Significant difference ($p < 0.05$, t-test) from the control (saline days). The error bars represent SEM.

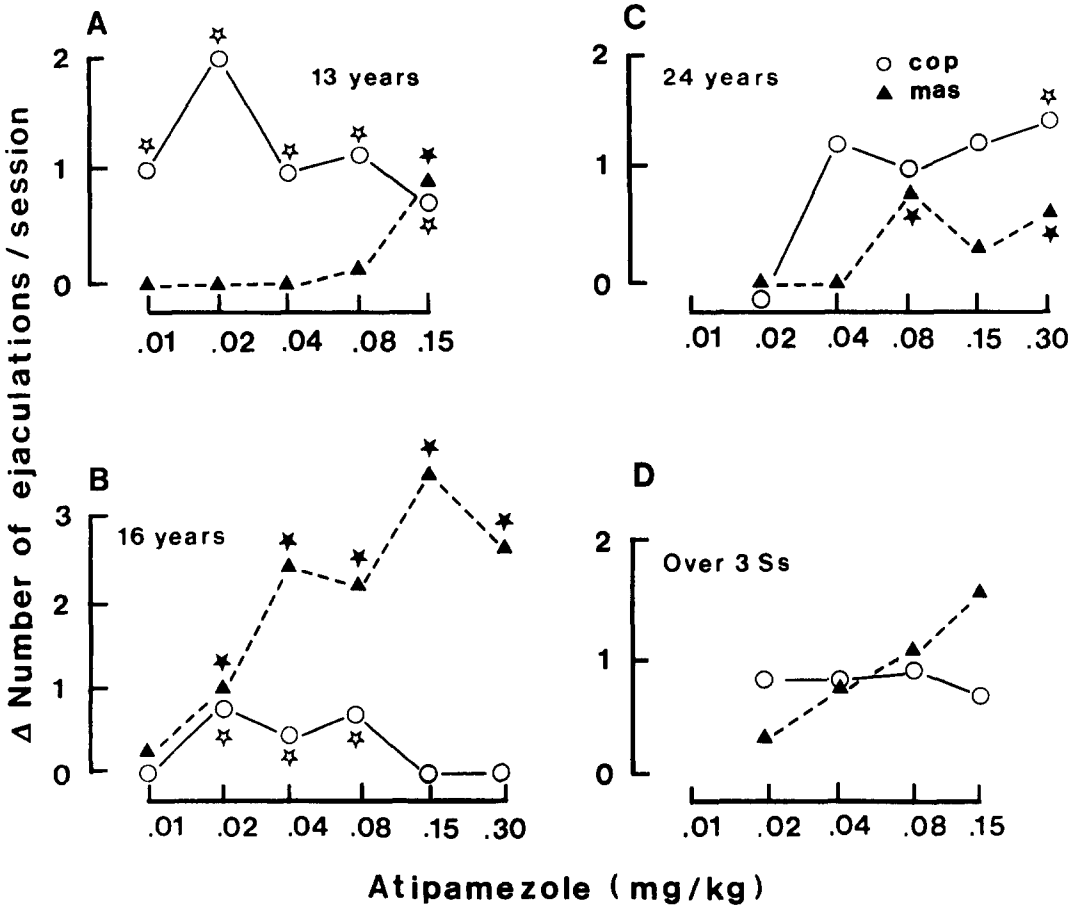

FIG. 2. Effect of atipamezole on the number of ejaculations obtained by (○) copulation vs. (▲) masturbation. For the sake of clarity, error bars are not shown. (A–C) Results for individual males. (D) Results over three males. *Significant difference ($p < 0.05$, t-test) from the control. For further explanations, see Fig. 1.

results. However, ejaculations obtained by masturbation and copulation are also separately reported in the results.

In stumptail macaques, male ejaculation produced by copulation or masturbation can be recognized clearly on the basis of its stereotypic manifestation. This has been described earlier (6,7) and is only briefly described here. Following ejaculation, the male displays momentary rigidity, full body inertia, usually followed by body spasms, a "frowning round-mouthed look," and rhythmic expiration vocalizations. The male remains "tied" to the female for about 20–30 s. After masturbation ejaculation, the male keeps its hand around the penis about 20–30 s.

Atipamezole was obtained from the Farmos Group, Ltd., Orion Pharmaceuticals Inc. (Turku, Finland). Experiments were performed once a day 7 days a week. Atipamezole was given every other day and saline control during the other days. The preliminary results in one monkey indicated no difference in the effect of atipamezole whether it was given every third or other day. Atipamezole doses varied from 0.01–0.3 mg/kg (dissolved in saline to get a volume of about 0.1–0.6 ml). Each dose was tested 5–15 times in each monkey. Taking into account the saline days, the testing of one dose in one monkey took from 10 days to 1 month. The order of testing each dose was the following: male A (age, 13 years)—0.15, 0.08, 0.04, 0.01, and 0.02 mg/kg; male B (age, 16 years)—0.3, 0.15, 0.04, 0.02, 0.01, and 0.08 mg/kg; male C (age, 24 years)—0.3, 0.15, 0.04, 0.08, and 0.02 mg/kg. The difference in the number of ejaculations obtained at a given atipamezole dose and the corresponding saline control days was used as an index of the effect of atipamezole on sexual behavior, that is, the number of ejaculations during each atipamezole day was compared with the number of ejaculations during the preceding saline day. This is how the possible variation in the baseline sexual activity (represented by ejaculations during saline days) could be minimized. The incidence of ejaculations (the percentage of saline days with one or more ejaculations) during saline days was used as an index of baseline sexual activity of each male. One way analysis of variance (ANOVA) and Student's t-test were used in statistical evaluation of the data. $p < 0.05$ was considered a significant difference.

RESULTS

In the saline (control) conditions, the incidence of sexual activity (percentage of sessions with ejaculations produced by copulation and/or masturbation) in the three male monkeys

were 5, 12, and 26%. The oldest male had the lowest and the youngest male the highest incidence of sexual activity in control (saline) conditions.

Atipamezole increased the total number of ejaculations in a dose-dependent way in all three male monkeys (for each individual: $p < 0.05$, ANOVA; Figs. 1A–C). The lowest effective dose of atipamezole varied from 0.01–0.08 mg/kg depending on the individual; the younger the male, the lower the lowest effective dose. The average atipamezole-induced increase in the total number of ejaculations (pooled data of ejaculations obtained by copulation and masturbation) over the three males also was dose-dependent and significant ($p < 0.05$, ANOVA; Fig. 1D). Figure 2 shows that both the number of ejaculations obtained by copulation and by masturbation increased following administration of atipamezole, although there were individual differences in the sexual preferences (copulation vs. masturbation). The drug effect was significant on both the masturbation and copulation produced ejaculations in each individual ($p < 0.05$, ANOVA). About 50% of the atipamezole-induced increase in ejaculations obtained by masturbation took place during the first 10 min following drug administration, when the male did not have access to the female.

DISCUSSION

The main finding of this study was that atipamezole increased sexual behavior (number of ejaculations/session) in male stumptail macaques. The effect was dose dependent and no marked side effects were observed. The doses of atipamezole used in this study produced no significant cardiovascular or other side effects, except increased arousal, in a previous human study (5). It is significant also that the oldest monkey, with a sluggish sexual activity in control conditions, had its sexual behavior increased following atipamezole.

The current results are in agreement with some previous studies that indicated yohimbine, another α_2-adrenoceptor antagonist, is effective in increasing sexual behavior in humans (8,14) and rats (2,10,11,13). However, yohimbine has not proved effective in all human patient groups (9), nor was it effective in increasing the sexual activity of male rhesus monkeys (1). The difference in the effects of yohimbine and atipamezole on sexual behavior in male monkeys may be due to the difference of the selectivity and potency of these two α_2-adrenoceptor antagonists, atipamezole being 200–300 times more selective than yohimbine (15). Also, species differences between the rhesus and stumptail macaques are a possible explanation for the discrepant results. Since atipamezole can be applied to human subjects at the currently used doses (5), further studies are needed to find if atipamezole also increases sexual activity in humans as effectively as it does in stumptail macaques. Also, it remains to be studied whether the atipamezole-induced increase of sexual behavior was due to a specific mechanism related to α_2-adrenoceptors or to an unspecific arousal effect, which also might increase sexual activity as proposed earlier (3).

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