Activation with (±)N-n-propyl-nor-apomorphine (NPA) of the male rat copulatory behavior

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Summary. I.p. (±)N-n-propyl-nor-apomorphine HCl (NPA) influences copulatory behavior of vigorous adult male rats in the same ways as apomorphine, i.e., it reduces the latency to ejaculation as well as mount and intromission frequency. Furthermore, NPA administered to impotent male rats restores normal mating behavior in some of them.

We have previously shown that low doses of (±)N-n-propyl-nor-apomorphine HCl (NPA) provoke in rats apomorphine-like behavioral effects such as repeated stretches and yawns (SYS), penile erection (PE) and stereotypes (SB)[1]. However, the brain dopaminergic mechanisms involved exhibit different sensitivity to NPA; the threshold i.p. doses for SYS, PE and SB induction were 0.112, 9.12 and 74.15 $\mu g \cdot kg^{-1}$ of the hydrochloride salt, respectively. Since in our opinion the capability of a drug to evoke PE may be an indicator of its influence on mating behavior, we set out to ascertain how NPA altered some typical expressions of the copulatory behavior in the adult male rat.

Methods and materials. Adult Wistar rats (S. Morini, S. Polo d'Enza, Reggio Emilia, Italy), weighing 250 g at the start of the experiment, were employed. They were maintained in a quiet, climatized (22±1 °C, 60% humidity) room under a reverse light-dark rhythm (12 h of light and 12 h of dark) in a macrolon cage (30×40×20 cm), 5 per cage, with appropriate food (MIL-ratti, S. Morini, S. Polo d'Enza, Reggio Emilia, Italy) and tap water ad libitum. Female rats (initial b.wt, 250 g) of the same strain were used as mating stimulus, their behavioral receptivity being assessed in advance of testing by vaginal smear analysis and by placing them with a sexually experienced nonexperimental 'indicator' male.

Male copulatory behavior was evaluated according to Dewsbury[2], with only minor modifications[3]. In brief, a male rat was put into a glass observation cage (40×60×40 cm) where, 3 min later, a stimulus female rat was introduced, experiments being performed 4 h after the start of the dark period. The behavioral patterns measured were: mount latency (Ml) and frequency (MF), intromission frequency (IF), latency to the first intromission (IL), interval from the first intromission to ejaculation (EL), and the time from ejaculation to the following intromission (post ejaculation interval, PEI). The inter-intromission interval was not considered. Tests were considered finished when IL was > 15 min or EL was > 30 min or PEI was > 15 min.

Among 40 male rats put into experiment, 23 characterized as 'vigorous' and 7 as 'impotent' were used, the remaining 10 being discarded. 'Vigorous' males are those which completely performed at least the last 4 consecutive preliminary mating tests out of the 5 conducted at 6-day intervals. On the other hand, 'impotent' males are those which never initiated any of the 5 preliminary mating tests.

Preliminary mating tests are necessary not only to separate rats with very different natural mating activity, but also to insure a fairly constant behavioral pattern in each individual over long periods of time[4,5], so that copulatory parameters before and after drug administration could be compared in the same animal.

(±)NPA HCl (Sterling-Winthrop Research Institute, Rensselaer, N.Y., USA) was dissolved in sterile water just before its i.p. administration at the constant fluid volume of 1 $ml \cdot kg^{-1}$. NPA doses are given as HCl salt. Mean values obtained before and after NPA administration were compared by means of Student's t-test for paired data[6].

Results. In the first set of experiments, 16 'vigorous' males received a 10 $\mu g \cdot kg^{-1}$ dose of NPA. In the second set 7 'vigorous' males received a 80 $\mu g \cdot kg^{-1}$ dose. All doses were administered i.p. Copulatory test was started 18 min after drug administration. Table 1 shows that a) both doses reduced all the mating behavior parameters, except IL and PEI which increased. However, mean values recorded before and after NPA administration were statistically different ($p < 0.05$) only in the case of IF and EL; b) IF, EL and MF reduction provoked by 80 $\mu g \cdot kg^{-1}$ of NPA was greater than after 10 $\mu g \cdot kg^{-1}$. In the case of MF, reduction caused by 80 $\mu g \cdot kg^{-1}$ of NPA approached, but did not reach the minimum level for statistical significance.

In the third set of experiments, 7 'impotent' rats were i.p. injected with 10 $\mu g \cdot kg^{-1}$ of NPA and 3 of them became able to perform completely the 'mating' test. Table 2 shows the mean values recorded from these 3 rats. It may be noted that whereas ML and IL were extremely increased in comparison to the same values recorded in 'vigorous'

Table 1. Influence of i.p. (±)N-n-propyl-nor-apomorphine HCl (NPA) on the mating behavior of 'vigorous' male rats

Experiment	Treatment ($\mu g \cdot kg^{-1}$)	ML (sec) (m±SEM)	IL (sec)	MF	IF	EL (sec)	PEI (sec)
1 (16)*	Saline	14.40±4.04	91.19±24.6	10.38±2.0	6.38±0.60	468.31±90.56	318.80±16.4
	NPA, 10	10.30±2.14	145.60±30.37	9.69±1.52	4.25±42**	238.63±33.12	328.88±24.56
2 (7)	Saline	8.00±3.03	123.14±36.26	17.42±0.05	6.85±1.07	456.00±29.0	352.00±31.38
	NPA, 80	6.57±2.49	137.50±71.11	8.28±3.5	3.85±0.59	202.83±58.64**	374.00±38.28

ML, IL, EL: latency to the first mount, the first intromission and the ejaculation, respectively. MF, IF: mount and intromission frequency, respectively. PEI: post-ejaculatory interval. * In brackets the number of rats. ** At least $p < 0.05$ (Student's t-test for paired data).

Table 2. Influence of i.p. (±)N-n-propyl-nor-apomorphine (NPA) on the mating behavior of 'impotent'* male rats

Treatment ($\mu g \cdot kg^{-1}$)	ML (sec) (m±SEM)	IL (sec)	MF	IF	EL (sec)	PEI (sec)
Saline (7)**	–	–	–	–	–	–
NPA, 10 (3)**	315.30±62.48	342.00±160.80	5.67±0.67	4.00±0.58	231.67±66.80	329.60±76.2

* No response in the 4 consecutive preliminary, 6 days spaced, mating tests. ** In brackets the number of rats.

males, the other parameters did not differ in 'impotent' rats in comparison with 'vigorous' NPA-treated rats.

Discussion. It has been shown that apomorphine provokes repeated penile erections in isolated rat[7,8], reduces ejaculation latency and intromission frequency in sexually experienced male rats[9], and restores ejaculation in 'impotent' rats[10], these influences on sexual behavior being antagonized by specific antagonists of brain dopamine receptors such as haloperidol and pimozide.

Generally speaking, NPA has been found to exert the same behavioral effects as apomorphine, being, however, more potent. In particular we have shown that NPA is much more potent than apomorphine as a SYS und PE inducer than as a SB inducer[1]. Accordingly it was suspected that NPA might strongly influence male rat copulatory behavior. Moreover, since it has been suggested that stereotyped movements might disturb copulatory behavior[10], and since it has been demonstrated that apomorphine doses eliciting SB lost the capability of inducing PE, NPA seems more appropriate than apomorphine for affecting male copulatory behavior, because the ratio between PE and SB-evoking doses is greater for NPA than for APO.

The results presented in this paper show that NPA, like apomorphine, affects copulatory behavior of 'vigorous' male rats reducing LE and IF, and restores copulatory behavior in naturally 'impotent' rats. These effects are produced by 10 $\mu g \cdot kg^{-1}$, i.p., a dose which does not provoke SB. On the other hand, increasing NPA dose to 80 $\mu g \cdot kg^{-1}$, NPA influence on copulatory behavior increased, despite the fact that this dose also caused SB (scored 2.5–3 accordingly to Costall et al.[11]). After this dose, however, whereas stereotype movements were easily observed during the latency before the first mount, they were not observed during mating activity.

In conclusion, NPA resembles apomorphine for its influence on male rat copulatory behavior. In particular the capability of NPA in restoring copulatory behavior in 'impotent' male rats must be carefully considered and evaluated also in the perspective of a therapeutic use.

1 A. Benassi-Benelli and F. Ferrari, Riv. Farmac. Ter., in press (1979).
2 D.A. Dewsbury, Eur. J. Pharmac. *17*, 221 (1972).
3 P. Södersten, D.A. Damassa and E.R. Smith, Horm. Behav. *8*, 320 (1977).
4 D.A. Dewsbury, in: Sexual Behavior: Pharmacology and Biochemistry, p. 169. Ed. M. Sandler and G.L. Gessa. Raven Press, New York 1975.
5 G. Bignami, Psychopharmacologia *10*, 44 (1966).
6 L. Cavalli-Sforza, Analisi Statistica per Medici e Biologi. Ed. Boringhieri. Torino 1976.
7 M. Baraldi and A. Benassi-Benelli, Riv. Farmac. Ter. *6*, 147 (1975).
8 M. Baraldi and A. Benassi-Benelli, Riv. Farmac. Ter. *6*, 361 (1975).
9 E. Paglietti, B. Pellegrini Quarantotti, G.P. Mereu, M. Petta, A. Bonanni and G.L. Gessa, Riv. Farmac. Ter. *8*, 281 (1977).
10 A. Tagliamonte, W. Fratta, M. Del Fiacco and G.L. Gessa, Riv. Farmac. Ter. *4*, 177 (1973).
11 B. Costall, R. Naylor and T. Wright, Arzneimittel-Forsch. *22*, 1178 (1972).

Baroreceptor and sympathetic responses to acebutolol, a β_1-adrenoceptor-blocking agent, in rabbits

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Summary. Baroreceptor activity was increased after i.v. infusion of acebutolol in rabbits with an intact circulation, and in rabbits with a total cardiopulmonary by-pass. In rabbits with an intact circulation, renal nerve activity was reduced.

We have previously studied the responses in rabbits to i.v. infusion of β_1- β_2-adrenoceptor-blocking agents (propranolol, pindolol, timolol). We observed a reduction in renal nerve activity[2–4]; aortic blood pressure and peripheral resistance were reduced and baroreceptor activity was increased in rabbits with intact circulation[4], as well as in rabbits with total cardiopulmonary by-pass[3]. These results suggested a direct vascular action of the 3 drugs.

The purpose of the present work was to compare the effects of a β_1-adrenoceptor-blocking agent (acebutolol) to those of β_1- β_2-adrenoceptor-blocking drugs.

Methods. All methodological details were similar to those already described[3,4]. 15 experiments were performed in New Zealand white rabbits anaesthetized with i.v. urethane. Aortic blood pressure was measured by means of a catheter introduced via the transfemoral artery and connected to a pressure transducer. Aortic blood flow was measured by meaos of an electromagnetic probe inserted around the abdominal aorta. A total cardiopulmooary bypass (TCB) was created in 5 animals. After thoracotomy, the blood from the right atrium was passed through a bubble oxygenator, rewarmed and reinjected into the ascending aorta by means of a pulsatile pump oqerating at a constant frequency. Arterial flow was measured by means of an electromagnetic flowmeter inserted in series between the pulsatile pump and the arterial cannula. Peripheral resistance was calculated by dividing the mean aortic pressure by the mean aortic blood flow.

Baroreceptor activity was recorded from the whole aortic nerve by means of platinum electrodes. After amplification, the nerve activity was counted over a 2-min period with the aid of a digital counter and expressed in counts/sec as a percentage of the activity recorded before the introduction of the drug. The relationship between nerve activity and blood pressure was determined during a control period by bleeding (up to −20 mm Hg), each animal serving as its own control. After reinfusion of the blood, the drug was infused. The activity of the nerve was compared at the same pressure level before aod during infusion of the drug. Efferent sympathetic activity from a left renal-nerve bundle was recorded, counted and expressed as described for aortic nerve activity.

Acebutolol, dissolved in 0.9% saline, was infused into the right jugular vein (3 mg/kg/h in animals with intact circulation) or into the oxygenator (5 mg/kg/h in animals with TCB). The values were expressed as mean ± SEM and the data were compared by means of the analysis of variance.

Results. Peak effects of acebutolol on haemodynamic variables and nervous activities were obtained when the in-