ELSEVIER

Pharmacology, Biochemistry and Behavior 72 (2002) 717–722

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Modulatory activity of sildenafil on copulatory behaviour of both intact and castrated male rats

A. Ottani, D. Giuliani*, F. Ferrari

Department of Biomedical Sciences, Division of Pharmacology, University of Modena and Reggio Emilia, Via G. Campi 287, I-41100 Modena, Italy

Received 16 October 2001; received in revised form 11 February 2002; accepted 12 February 2002

Abstract

The first experiment of the present study investigates the effects induced by sildenafil (1 or 10 mg/kg po) on the copulatory behaviour of intact male rats, categorized, on the basis of seven consecutive mating pretests, as sluggish or normal ejaculators (SE or NE, respectively). The data obtained show that sildenafil modifies both sexual arousal and the ejaculatory mechanisms of copulation, diminishing ejaculation latency in both categories and increasing copulatory efficacy in SE rats; in addition, it reduced the inter-intromission interval in both SE and NE animals and the post-ejaculatory interval only in SE animals. The second experiment, conducted on rats 3 weeks after their castration, shows that sildenafil alone (1 or 10 mg/kg) did not modify copulatory failure. However, 3 months after castration, and 24 h after the last injection of testosterone (25 μg/kg sc) given twice weekly for 4 weeks, sildenafil (1 or 10 mg/kg) ameliorated rat copulatory performance.

Keywords: Sildenafil; Testosterone; Copulatory behaviour; Dopamine; Castration; Rat

1. Introduction

Animal behavioural studies on sildenafil are scanty, in spite of its popularity in the treatment of human erectile dysfunction (Nurnberg et al., 2000; Zesiewicz et al., 2000). Although sildenafil-induced sexual stimulation has been ascribed to local action (Jeremy et al., 1997; Andersson et al., 1999; Gemalmaz et al., 2001), more recently it has been demonstrated that, in animals, intrathecal injection of the drug produces a physiological profile that is qualitatively similar to that observed clinically after systemic administration (Sato et al., 2001). The erectogenic effect of sildenafil is mediated by a specific increase in cyclic guanosilmonophosphate (cGMP) accumulation, consistent with the known activity of the drug as a potent inhibitor of cGMP phosphodiesterase (Jeremy et al., 1997). This effect may be linked to nitric oxide (NO)-mediated relaxation pathways in the corpus cavernosum (Jeremy et al., 1997; Hedlund et al., 2000), for numerous studies have demonstrated that NO released from peripheral nitrergic nerves plays a prominent role in ensuring corporal smooth muscle relaxation (Cellek et al., 1999). However, NO functions as a diffusible messenger in the CNS as well (Bruhwyler et al., 1993; Krukoff, 1999), and new data indicate that central modulation of the NO/cGMP pathway affects dopamine (DA)-mediated behaviour (Lorrain et al., 1996; Melis et al., 1996; Du and Hull, 1999). The central activity of sildenafil can also be inferred from its ability to modify human memory tasks (Schultheiss et al., 2001) and facilitate long-term retention of an inhibitory avoidance response in mice (Baratti and Boccia, 1999). Since previous studies in our laboratory had demonstrated that sildenafil modifies central DA-mediated behaviour in rats (Ferrari et al., 2002), the first aim of the present work was to assess the influence of the drug on arousal and ejaculation mechanisms of copulatory behaviour, whose modulation by central DA pathways is well established (Melis and Argiolas, 1995). It is also known that testosterone is fundamental for a normal mating pattern, which is totally disrupted by castration and can be restored by the replacement of the hormone (Stone, 1939; Beach and Holz-Tucker, 1949). It has been suggested that testosterone-induced activation is linked to increased synthesis and/or release of DA in the brain (Scaletta and Hull, 1990), and NO could be the bridge between testosterone and DA for copulatory behaviour (Lorrain et al.,

* Corresponding author. Tel.: +39-59-2055374; fax: +39-59-2055376.
E-mail address: giuliani.daniela@unimo.it (D. Giuliani).

0091-3057/02/$ – see front matter
PII: S0091-3057(02)00744-X

1996; Melis et al., 1996; Du and Hull, 1999). By increasing NO levels, sildenafil could affect DA release and, consequently, mating behaviour. As DA agonists facilitate copulation in both intact (Ferrari and Giuliani, 1995) and castrated male rats (Malmnas, 1977; Clark et al., 1982; Scaletta and Hull, 1990), further experiments were performed to find out whether sildenafil might reverse the decline of copulatory behaviour in castrated animals.

2. Materials and methods

2.1. Animals

The subjects were adult male and female Wistar rats (Harlan Nossan, Udine, Italy) weighing 230–250 g at the outset. They were housed in groups of four, of the same sex, with food and water ad libitum and on a reversed 12 h light cycle, from 7 a.m. to 7 p.m., for at least 2 weeks prior to the start of the experiments.

The regulations in force relating to the care of animals for scientific purposes (CEE Council 86/609; Italian D.L. 27/01/92 No. 116) were strictly complied with.

2.2. Surgery

2.2.1. Ovariectomy

All the females were ovariectomized under ketamine hydrochloride plus xylazine hydrochloride anaesthesia [120 + 2 mg/kg intraperitoneally (ip)] and brought into oestrus with estradiol benzoate [30 μg/rat subcutaneously (sc)], followed 48 h later by progesterone (0.5 mg/rat sc), and used 4–5 h thereafter. Before the copulatory tests, they were screened with sexually experienced males; only those exhibiting good receptivity (solicitation behaviour and lordosis in response to mounting) and no rejection were used.

2.2.2. Castration

Before castration, a group of male rats was trained in seven mating tests by exposing them to oestrous females; only those animals that completed at least the last four training mating tests, were considered of proven copulatory ability and they were castrated; those that never mounted or intromitted or displayed discontinuous activity were discarded. The animals were anaesthetized with ketamine hydrochloride plus xylazine hydrochloride (120 + 2 mg/kg ip). A midsagittal scrotal incision was made, and the testes and surrounding fat were tied off and excised.

2.3. General behavioural procedure

All the experiments were performed between 11 a.m. and 3 p.m. in a sound-attenuated, air-conditioned room (under red light), where the animals were monitored by trained observers unaware of the experimental design, the controls being handled in the same way as the treated animals.

2.4. Evaluation of male sexual behaviour

The male rats were transferred singly to an observation cage (40 × 30 × 34 cm), into which, after a 3-min adaptation period, a receptive female was introduced. Male copulatory behaviour was evaluated as in previous works (Dewsbury, 1972; Giuliani and Ferrari, 1996). The parameters considered were: mount and intromission latencies (ML and IL: the time from the introduction of the female until the first mount and intromission, respectively); mount and intromission frequencies (MF and IF: the number of mounts and intromissions preceding the first ejaculation, respectively); ejaculation latency (EL: the interval between the first intromission and ejaculation); post-ejaculatory interval (PEI: the time between the first ejaculation and the next mount or intromission). After the PEI, the test was considered complete. Tests were discontinued when IL or PEI were >15 min or EL was > 30 min. Only those animals that completed at least the last four training mating tests, out of the seven conducted at 4-day intervals, were considered sexually active; those that never mounted or intromitted during these tests or displayed discontinuous activity were discarded.

2.5. Experimental protocol

2.5.1. Experiment 1. Effect of sildenafil (1 or 10 mg/kg) on copulatory behaviour of intact sexually active male rats

After having verified the consistency of the rats' copulatory pattern in the sixth and seventh tests, the animals were categorized as *sluggish ejaculators* (SE) or *normal ejaculators* (NE), on the basis of the following calculated indexes: copulatory efficacy (CE) as IF/(MF + IF), and inter-intromission interval (III) as EL/IF (Clark et al., 1987). Arbitrarily, rats were considered SE when CE was < 0.5 and III > 35; only those that fulfilled both indexes were admitted to the experiments.

SE ($n = 18$) and NE ($n = 18$) rats were divided into three subgroups ($n = 6$), not statistically different for any of the parameters considered, which were orally (po) treated as follows: (a) saline, (b) sildenafil (1 mg/kg) or (c) sildenafil (10 mg/kg), 50 min before the eighth test.

2.5.2. Experiment 2. Effect of sildenafil (1 or 10 mg/kg) on copulatory behaviour of castrated male rats

Sixty animals, of proven copulatory ability, were castrated and given 1 week to recover.

All the animals were subjected to two successive weekly mating tests; only those rats ($n = 23$) that never displayed mounts or intromissions, were randomly divided into three groups and, 1 week later, were treated with saline ($n = 9$), sildenafil 1 ($n = 9$) or 10 mg/kg ($n = 5$), 50 min before the third copulatory test. The remaining animals ($n = 37$) were subjected to further weekly mating tests for 1 month, to verify the complete disappearance of copulatory ability. Seven rats that still displayed mounting behaviour were discarded. The tests were then suspended and the rats

subcutaneously (sc) treated with testosterone propionate (25 μg/kg), twice weekly for 4 weeks. Twenty-four hours after the last hormone injection, the animals were randomly divided into three groups ($n = 10$), which were treated with saline, sildenafil 1 or 10 mg/kg, 50 min before a mating test. Thereafter, all treatments were discontinued and, 4 days later, the same groups were subjected to the final test.

2.6. Drugs and treatments

Sildenafil (Viagra, PFIZER) was used. The substance was freshly dissolved in saline at a concentration that allowed the administration of 1 ml/kg by oral gavage (po).

2.7. Statistical evaluation

Data for the parameters of sexual behaviour are the means ± S.E.M of the values recorded in the animals in the seventh test and compared with those obtained in the same animals in the eighth test, after treatment.

Data were analysed using ANOVA followed by Student–Newman–Keul's test, Student's *t* test for paired data, Kruskal–Wallis followed by Mann–Whitney *U* test or Wilcoxon test, where appropriate, with the level of significance set at $P < .05$.

3. Results

3.1. Experiment 1. Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of intact sexually active male rats

Fig. 1 shows that, in the eighth test, saline-treated SE rats behaved as in the seventh test for CE, III, EL and PEI, thus differing from those that had received sildenafil at 1 or 10 mg/kg. A significant effect was detected by ANOVA for EL

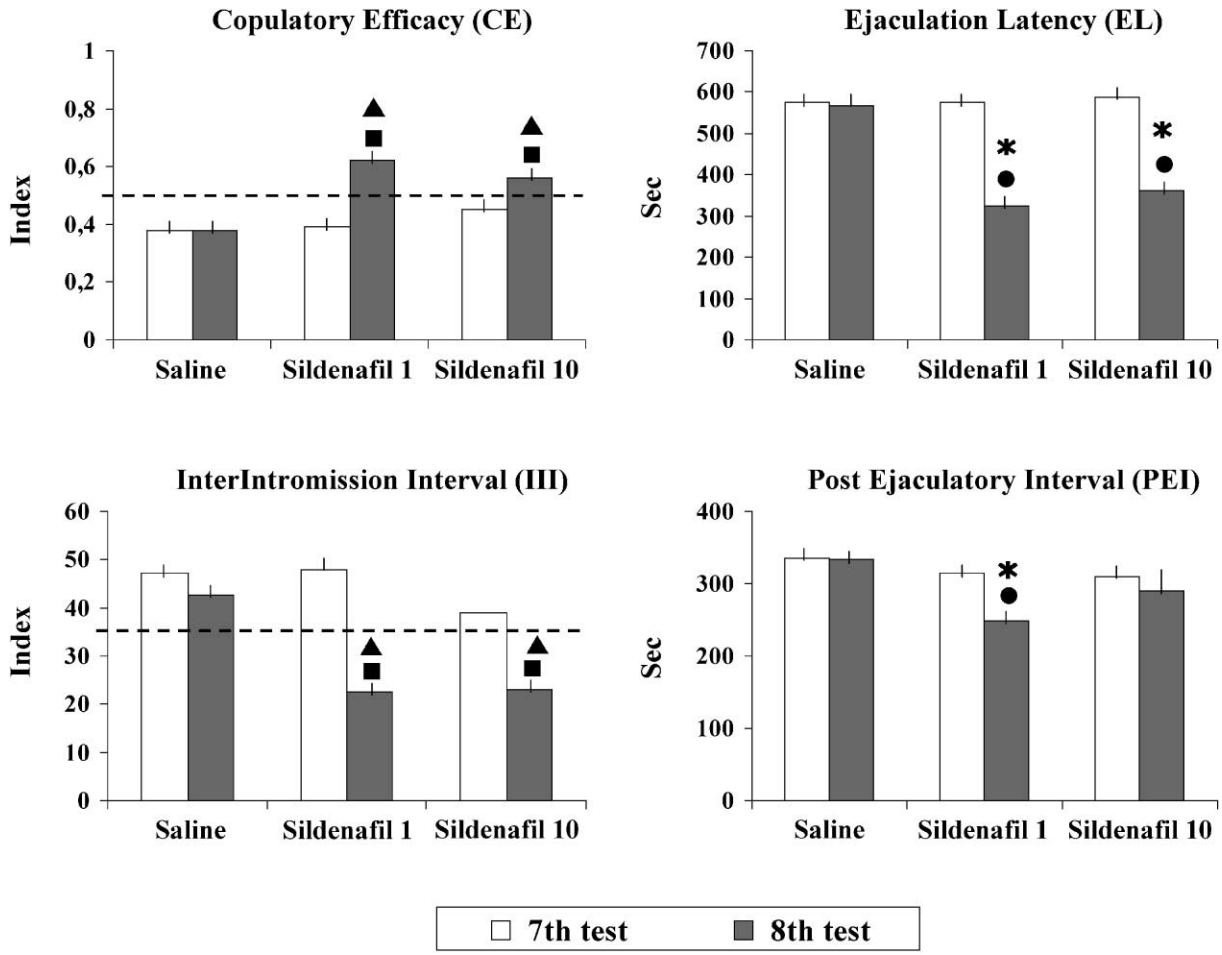

Fig. 1. Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of intact sluggish ejaculator (SE) male rats. Saline or sildenafil (1 or 10 mg/kg) were orally administered 50 min before the eighth test. Each value is the mean ± S.E.M. of the data for each treatment group. The hatched lines show the values arbitrarily fixed to categorize sluggish or normal ejaculators. Significantly different from the same animals in the seventh test: ▲ (Wilcoxon test) or * (Student's *t* test for paired data). Significantly different from saline in the same test: ● (ANOVA followed by Student–Newman–Keul's test) or ■ (Kruskal–Wallis followed by Mann–Whitney *U* test).

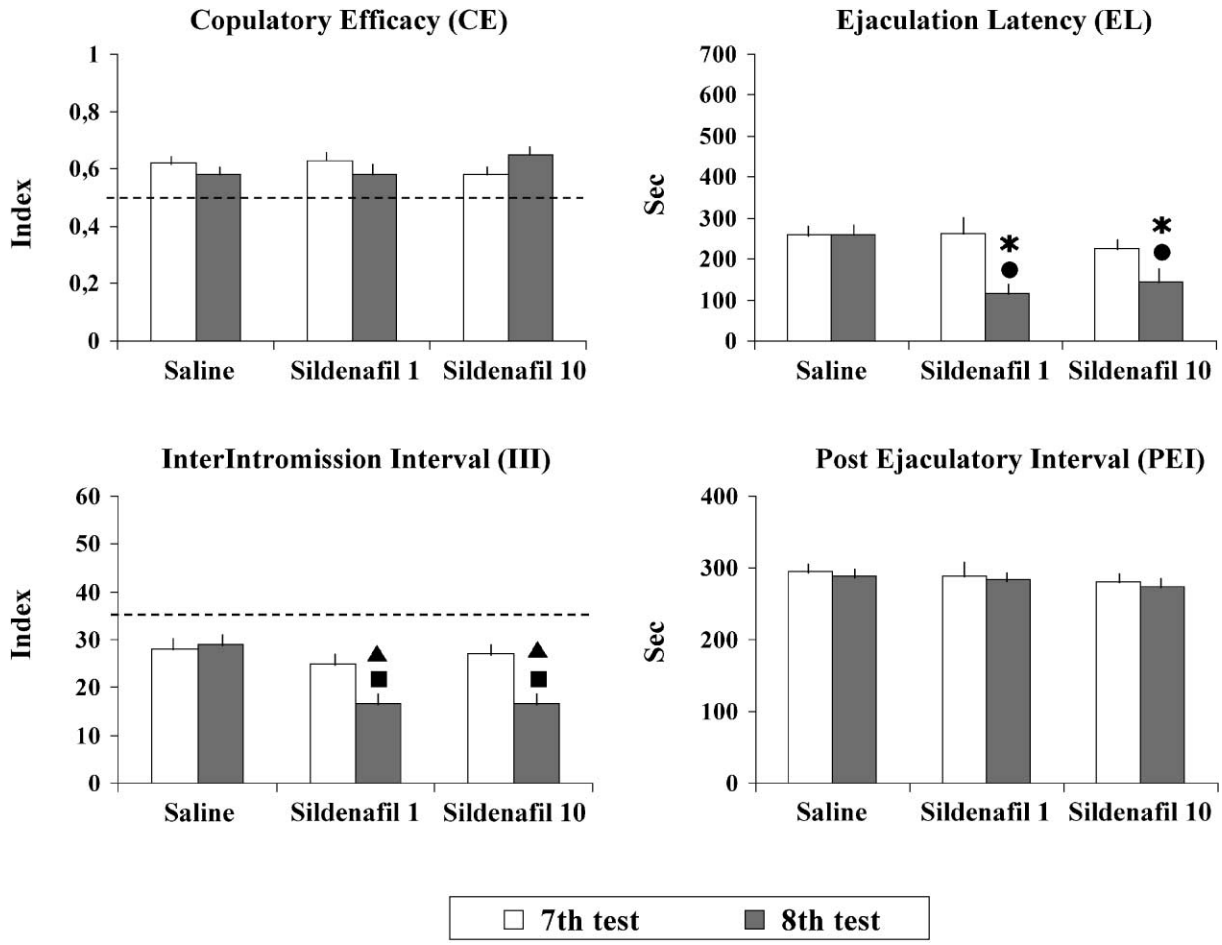

Fig. 2. Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of intact normal ejaculator (NE) male rats. Saline or sildenafil (1 or 10 mg/kg) were orally administered 50 min before the eight test. Each value is the mean ± S.E.M. of the data for each treatment group. The hatched lines show the values arbitrarily fixed to categorize sluggish or normal ejaculators. Significantly different from the same animals in the seventh test: ▲ (Wilcoxon test) or * (Student's *t* test for paired data). Significantly different from saline in the same test: ● (ANOVA followed by Student–Newman–Keul's test) or ■ (Kruskal–Wallis followed by Mann–Whitney *U* test).

[$F(2,15) = 8.68$, $P = .003$] and PEI [$F(2,15) = 8.7$, $P = .003$], and by Kruskal–Wallis for CE ($H = 11.1$, $P = .004$) and III ($H = 9.3$, $P = .01$) in the three treatment groups. Sildenafil (1 or 10 mg/kg) potently modified the copulatory performance of SE rats, significantly diminishing EL ($t = 6.7$, $P = .001$; $t = 54$, $P = .000$, respectively), and III ($W = 21$, for both), and increasing CE ($W = 21$ for both); PEI was reduced only by the lowest dose ($t = 4.9$, $P = .004$).

Table 1
Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of castrated male rats

Treatment (mg/kg)	M	I	E	PEI
Saline	0/9	0/9	0/9	0/9
Sildenafil 1	3/9	2/9	1/9	0/9
Sildenafil 10	1/5	1/5	0/5	0/5

M = mounts, I = intromissions, E = ejaculation and PEI = post-ejaculatory interval. The test was performed 3 weeks after castration, on animals that had not exhibited M or I in two previous mating tests. Saline or sildenafil (1 or 10 mg/kg) were orally given 50 min before the test. Data are presented as number of animals displaying the behaviour observed.

Table 2
Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of castrated male rats chronically treated with testosterone

Treatment (mg/kg)	MF (n°)	IF (n°)	EL (s)	PEI (s)
Saline (8/10)	25.2 ± 3.3	11.5 ± 0.9	482 ± 76	372 ± 6
Sildenafil 1 (10/10)	11.4 ± 2.5*	11.4 ± 0.3	247 ± 16.5#	315 ± 14*
Sildenafil 10 (8/10)	18.2 ± 3	13.2 ± 2.2	409 ± 62	339 ± 14

MF = mount frequency, IF = intromission frequency, EL = ejaculation latency, PEI = post-ejaculatory interval. Testosterone (25 μg/kg sc) was administered twice weekly for 4 weeks; saline or sildenafil (1 or 10 mg/kg) were orally given 50 min before the test, 24 h after testosterone. For details, see Materials and Methods. The number of copulating animals is in brackets. Each number is the mean ± S.E.M. of the values recorded in the rats displaying the phenomenon. * Significantly different from saline or # significantly different from the other treatment groups (ANOVA followed by Student–Newman–Keul's test).

NE rats treated with saline or sildenafil displayed a different mating performance as regards EL [$F(2,15) = 10.8$, $P = .001$] and III ($H = 7.2$, $P = .027$) (Fig. 2). When the data for the various parameters in the seventh test were compared with those for the same animals in the eighth test, it was seen that sildenafil at 1 or 10 mg/kg significantly reduced EL ($t = 3.9$, $P = .01$; $t = 6.2$, $P = .002$, respectively) and III ($W = 21$, for both); PEI and CE were unaffected.

Since ML and IL were unaffected by the treatments, the data regarding these parameters are not reported.

3.2. Experiment 2. Effect of sildenafil (1 or 10 mg/kg) on the copulatory behaviour of castrated males

Table 1 shows that, when sildenafil (1 or 10 mg/kg) was administered to castrated male rats whose copulatory ability had completely disappeared, it did not significantly modify the behavioural pattern, although a certain stimulant effect was observed for all the parameters considered, apart from PEI.

When the drug (1 or 10 mg/kg) was given to castrated animals, 24 h after the last injection of chronic testosterone (25 μg/kg), the lower dose significantly diminished MF [$F(2,23) = 5.8$, $P = .009$], EL [$F(2,23) = 5.4$, $P = .01$] and PEI [$F(2,23) = 5.5$, $P = .001$] (Table 2); CE was increased by both doses ($H = 9.64$, $P = .008$) while III was reduced only by sildenafil at 1 mg/kg ($H = 9.3$, $P = .01$) (Fig. 3). Sildenafil-induced effects completely disappeared 4 days later (Fig. 3).

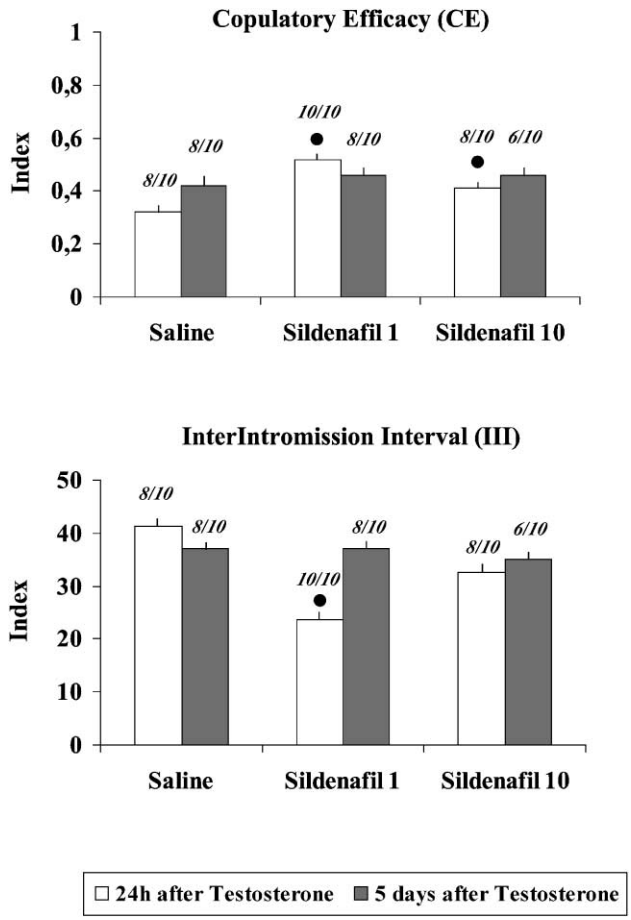

Fig. 3. Effect of sildenafil (1 or 10 mg/kg) on the indexes of copulatory behaviour of castrated male rats chronically treated with testosterone. Saline or sildenafil (1 or 10 mg/kg) were orally administered 50 min before the test. Each histogram is the mean ± S.E.M. of the values recorded in rats displaying the phenomenon (number in brackets). ● Significantly different from saline group in the same day (Kruskal–Wallis followed by Mann–Whitney *U* test).

4. Discussion

The results obtained in Experiment 1 clearly show that, in the intact animals categorized as SE and NE, sildenafil exerted sexual stimulation involving both ejaculation and arousal, two essential aspects of copulatory behaviour that may be independently modulated by pharmacological agents (Beach, 1956; Clark et al., 1987; Hull et al., 1986). Assuming that ML, IL, PEI and III reflect arousal/motivation (Beach, 1956; Clark et al., 1987; Everitt, 1999), in spite of the unchanged ML and IL (probably due to the extremely low values in all the animals at the seventh test), PEI and III were strongly affected in SE rats, and III was reduced in NE, too. These data would suggest that the drug acts in a different manner on appetitive features, depending on the animal's sexual profile.

The differential activity of sildenafil in SE and NE rats also emerges from its influence on the consummatory aspects of mating, for it diminished EL in both animal categories, while increasing CE only in SE rats. The ability to lower the ejaculatory threshold is typically shared by all DA agonists, regardless of the specific DA receptor subtype involved (Ferrari and Giuliani, 1996). While, in animals, the relationship between brain DA activity and DA agonist-induced "ejaculation praecox" has been verified (Ferrari and Giuliani, 1994), it is still far from clear whether DA agonists may influence arousal mechanisms (Melis and Argiolas, 1995). Interestingly, it has been reported that centrally injected apomorphine, in sexually active rats, facilitates ejaculation mechanisms, rather than sexual arousal, thus differing from D-amphetamine, which is thought to act by releasing DA from nerve endings and which significantly decreases ML and IL (Hull et al., 1986). This finding points to endogenous DA as a fundamental mediator of arousal, and justifies the differential effects exerted by sildenafil on SE and NE rats, where different DA levels and/or DA receptor sensitivity might exist (Ferrari and Giuliani, 1996; Giuliani and Ferrari, 1996). Examination of the data obtained in castrated animals confirms the sexual stimulant activity of sildenafil, particularly at 1 mg/kg. In rats, whose copulation had completely ceased, sildenafil exhibited only slight facilitative effects; in hormone-treated animals, however, it potently boosted the partial restoration of the mating pattern induced by testosterone alone, when given at a subactive dose. In fact, while the

copulatory parameters of the males treated with saline reflected a sluggish-like profile [on the basis both of the results obtained in previous works and of the level of copulatory indexes established in Experiment 1], the behavioural pattern reverted to normal after sildenafil. This potentiation of testosterone activity was confirmed by the results obtained 5 days later, when sildenafil-induced effects disappeared. In conclusion, the present study demonstrates a remarkable effect of sildenafil on rat copulatory behaviour and would suggest that the drug acts not only peripherally, as traditionally thought, but also centrally. However, since the peripheral activity on penile erection should modify the sensory input to spinal cord and brain, and influences copulatory parameters accordingly (Contreras and Agmo, 1993), further experiments are being carried out to substantiate sildenafil central effects.

Acknowledgments

This work was supported by grants from Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

References

Andersson KE, Gemalmaz H, Waldeck K, Chapman TN, Tuttle JB, Steers WD. The effect of sildenafil on apomorphine-evoked increases in intracavernous pressure in the awake rat. J Urol 1999;161(5):1707–12.

Baratti CM, Boccia MM. Effects of sildenafil on long-term retention of an inhibitory avoidance response in mice. Behav Pharmacol 1999;10(8):731–7.

Beach FA. Characteristics of masculine "sex drive". In: Jones MR, editor. Nebraska symposium on motivation. 1956;1–32.

Beach FA, Holz-Tucker AM. Effects of different concentrations of androgen upon sexual behavior in castrated male rats. J Comp Physiol Psychol 1949;42:433–53.

Bruhwyler J, Chleide E, Liegeois JF, Carreer F. Nitric oxide: a new messenger in the brain. Neurosci Biobehav Rev 1993;17:373–84.

Cellek S, Rodrigo J, Lobos E, Fernandez P, Serrano J, Moncada S. Selective nitrergic neurodegeneration in diabetes mellitus — a nitric oxide-dependent phenomenon. Br J Pharmacol 1999;128:1804–12.

Clark JT, Smith ER, Stefanick ML, Arneric SP, Long JP, Davidson JM. Effects of a novel dopamine-receptor agonist RDS-127 (2-*N N*-D-*n*-propylamino-4,7-dimethoxyindane), on hormone levels and sexual behavior in the male rat. Physiol Behav 1982;29:1–6.

Clark JT, Karla SP, Karla PS. Effects of a selective alpha$_1$ adrenoceptor agonist, methoxamine, on sexual behavior and penile reflexes. Physiol Behav 1987;40:747–53.

Contreras JL, Agmo A. Sensory control of the male rat's copulatory thrusting patterns. Behav Neural Biol 1993;60:234–40.

Dewsbury DA. Effects of tetrabenazine on the copulatory behavior of male rats. Eur J Pharmacol 1972;17:221–6.

Du J, Hull EM. Effects of testosterone on neuronal nitric oxide synthase and tyrosine hydroxylase. Brain Res 1999;31:90–8.

Everitt BJ. Sexual motivation: a neural and behavioural analysis of the mechanisms underlying appetitive and copulatory responses of male rats. Neurosci Biobehav Rev 1999;14:217–32.

Ferrari F, Giuliani D. The selective D_2 dopamine receptor antagonist eticlopride counteracts the ejaculatio praecox induced by the selective D_2 dopamine agonist SND 919 in the rat. Life Sci 1994;55:1155–62.

Ferrari F, Giuliani D. Sexual attraction and copulation in male rats: effects of the dopamine agonist SND 919. Pharmacol Biochem Behav 1995;50:29–34.

Ferrari F, Giuliani D. Behavioral effects induced by the dopamine D_3 agonist 7-OH-DPAT in sexually-active and -inactive male rats. Neuropharmacology 1996;35:279–84.

Ferrari F, Ottani A, Giuliani D. Influence of sildenafil on central dopamine-mediated behaviour in male rats. Life Sci 2002;70:1501–8.

Gemalmaz H, Waldeck K, Chapman TN, Tuttle JB, Steers WD, Andersson KE. In vivo and in vitro investigation of the effects of sildenafil on rat cavernous smooth muscle. J Urol 2001;165(3):1010–4.

Giuliani D, Ferrari F. Differential behavioral response to dopamine D_2 agonists by sexually naive, sexually active and sexually inactive male rats. Behav Neurosci 1996;110:802–8.

Hedlund F, Ny L, Alm P, Andersson KE. Cholinergic nerves in human corpus cavernosum and spongiosum contain nitric oxide synthase and heme oxygenase. J Urol 2000;164(3):868–75.

Hull EM, Britan D, Pehek EA, Warner RK, Band LC, Holmes GM. Dopaminergic control of male sexual behavior in rats: effects of an intracerebrally infused agonist. Brain Res 1986;370:73–81.

Jeremy JY, Ballard SA, Naylor AM, Miller MAW, Angelini GD. Effects of sildenafil, a type-5 cGMP phosphodiesterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro. Br J Urol 1997;79(6):958–63.

Krukoff TL. Central actions of nitric-oxide in regulation of autonomic function. Brain Res Rev 1999;30:52–65.

Lorrain DS, Matuszewich L, Howard RV, Du J, Hull EM. Nitric oxide promotes medial preoptic dopamine release during male rat copulation. NeuroReport 1996;8:31–4.

Malmnas CO. Dopaminergic reversal of the decline after castration of rat copulatory behaviour. Endocrinology 1977;73:187–8.

Melis MR, Argiolas A. Dopamine and sexual behaviour. Neurosci Biobehav Rev 1995;19:19–28.

Melis MR, Succu S, Argiolas A. Dopamine agonists increase nitric oxide production in the paraventricular nucleus of the hypothalamus: correlation with penile erection and yawning. Eur J Neurosci 1996;8(10):2056–63.

Nurnberg HG, Hensley PL, Lauriello J. Sildenafil in the treatment of sexual dysfunction induced by selective serotonin reuptake inhibitors. CNS Drugs 2000;13(5):321–35.

Sato Y, Zhao W, Christ GJ. Central modulation of the NO/cGMP pathway affects the MPOA-induced intracavernous pressure response. Am J Physiol: Regul, Integr Comp Physiol 2001;281:R269–78.

Scaletta LD, Hull EM. Systemic or intracranial apomorphine increases copulation in long-term castrated male rats. Pharmacol Biochem Behav 1990;37:471–5.

Schultheiss D, Muller SV, Nager W, Stief CG, Schlote N, Jonas U, Asvestis C, Johannes S, Munte TF. Central effects of sildenafil (Viagra) on auditory selective attention and verbal recognition memory in humans: a study with event-related brain potentials. World J Urol 2001;19(1):46–50.

Stone CP. Copulatory activity in adult male rats following castration and injection of testosterone propionate. Endocrinology 1939;24:165–74.

Zesiewicz TA, Helal M, Hauser RA. Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. Mov Disord 2000;15(2):305–8.