



Spinal proerectile effect of apomorphine in the anesthetized rat

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Considering the presence of dopaminergic receptors in the lumbosacral spinal cord, we tested whether apomorphine could exert a proerectile effect by acting at the spinal level. Intracavernous (ICP) and blood pressures (BP) were measured in anesthetized rats. ICP rises were quantified (duration, percentage of ICPmaximum/meanBP (ICPmax/BP \times 100), area under ICP curve (AUC/BP) and sum of AUC/BP after intravenous (i.v.) and intrathecal (i.t.) injections of apomorphine alone or in presence of i.t. oxytocin (10 ng). Both 10 and 30 μ g i.v. apomorphine dosings elicited erectile events evidenced by ICP rises. Upon the 30 μ g i.v. injection, duration of ICP rises were increased from 25 ± 10 to 69 ± 18 s ($P < 0.001$), ICPmax/BP \times 100 from 21 ± 3 to $50 \pm 14\%$ ($P = 0.001$), AUC/BP from 3 ± 1 to 14 ± 6 s ($P = 0.002$) and sum of AUC/BP from 5 ± 7 to 34 ± 35 s ($P = 0.021$). Upon 30 μ g i.t. injections of apomorphine at the lumbosacral level, the number of ICP rises was increased from 0.2 ± 0.4 to 3.0 ± 1.5 , ICPmax/BP \times 100 from 16 ± 9 to 43 ± 12 and sum of AUC/BP from 1 ± 3 to 31 ± 15 s compared to vehicle injection ($P < 0.05$ for all parameters). Injection of 30 μ g i.v. or i.t. apomorphine non-significantly enhanced the number and amplitude of the ICP rises induced by 10 ng i.t. oxytocin. However, the enhancement of the amplitude of the ICP rises elicited by i.t. oxytocin was more pronounced with i.t. apomorphine than with i.v. apomorphine. These results suggest the existence of a spinal site of action for apomorphine which may (1) participate to generation of erection and (2) exerts a facilitator effect on erection of supraspinal origin. *International Journal of Impotence Research* (2001) 13, 110–115.

Keywords: apomorphine; erection; spinal cord; rat

Introduction

Subcutaneous delivery of apomorphine, a D1/D2 dopamine receptor agonist, induces penile erection in animals and humans.^{1,2} Apomorphine formulated in sub-lingual, slow release tablets has appeared as a promising pharmacological treatment for erectile dysfunction of various origins.^{3,4} The proerectile activity of apomorphine is caused by stimulation of supraspinal central dopaminergic receptors and, in this view, the paraventricular nucleus of the hypothalamus (PVN) has been identified as a key target.^{5,6}

Cytological data suggest that apomorphine may also act at the spinal level. Immunocytochemical studies revealed that dopaminergic (DA) fibers and terminals exist in virtually all laminae throughout the spinal cord.^{7,8} Furthermore, studies using ligand binding techniques have shown the presence of D1 and D2 receptors in the spinal cord.⁹ In male rats, D2

receptors identified with immunocytochemistry and *in situ* hybridization have been located in the parasympathetic nucleus of the lumbosacral spinal cord, which contains the cellular bodies of the proerectile autonomic neurons innervating the penis.^{10,11} D2 receptors have also been found to be particularly abundant in the dorsomedian and the dorsolateral nucleus which innervate bulbospongiosus and ischiocavernosus striated muscles involved in penile rigidity in the rat.¹⁰

The implication of spinal DA receptors in the control of penile erection have been little explored. In conscious rats, reflexive erections are depressed by peripheral injection of the non-specific dopaminergic agonist RDS-127 in normal and spinalized rats, and by intrathecal (i.t.) injection of apomorphine at the lumbosacral level.^{12,13} However, the hypothesis of a spinal site of action for the inducer proerectile effect of apomorphine has never been tested.

The aim of the present study was to assess whether apomorphine could induce erectile events measured by ICP rises of the intracavernous pressure when delivered at the lumbosacral level of the spinal cord in the anesthetized rat. The effects of intravenous (i.v.) and i.t. apomorphine injections

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were also compared in combination with i.t. oxytocin injections, which induce erection by mimicking supraspinal command.¹⁴

Materials and methods

Animal preparation

Sprague-Dawley rats (Charles-River, France), weighing 200–250 g, were used in this study. Rats were anesthetized by intraperitoneal injection of urethane (1.2 g/kg) and placed on a homeothermic blanket to maintain their temperature at 37°C during the experiment. A catheter was inserted into the left carotid artery for blood pressure (BP) monitoring and in the jugular vein for i.v. injections.

For i.t. injections, a catheter was inserted through the atlanto-occipital membrane and directed caudally. Correct implantation of the caudal tip of the catheter at the L4-L6 spinal level was checked by complete laminectomy of the spinal cord after the animal was killed. Previous experiments with dyed solutions have demonstrated that in these conditions, the diffusion of the injected solution from the site of injection was restricted to the neighbouring spinal metamers (data not shown).

For intracavernous pressure (ICP) monitoring, the penis was denuded of skin and a 25-gauge needle connected to a catheter was inserted into one corpus cavernosum. Arterial and cavernosal catheters were filled with heparinized saline (25 UI/ml) and connected to pressure transducers (EM 750, Elcomatic, Glasgow, UK). Pressure signals were amplified (Bionic Instruments, Nozay, France), digitized (Labmaster DMA, Scientific solutions, Solon, OH) and converted to millimeters of mercury (mm Hg) after calibration (Axotape V2, Axon Instruments, Foster city, CA). A stimulation of the cavernous nerve (30 s overall duration, 6 V, 10 Hz, 1 ms pulse) was performed at the end of the experiment to elicit an increase of ICP in order to certify the correct implantation of the intracavernosal catheter.¹⁵

Experimental protocol

Drugs were purchased from Sigma (Saint-Quentin-Fallavier, France). Apomorphine was prepared in saline supplemented with 0.05% ascorbic acid. Oxytocin (1 ng/μl) was prepared in saline. Accordingly, vehicle refers to saline with ascorbic acid or saline. Experimental groups were constituted of 10 rats.

The beginning of each experiment consisted in 15 min recording in basal condition, after which the first drug injection (i.t. and/or i.v.) was performed.

Rats in which diastolic blood pressure was inferior to 40 mm Hg during this time were excluded.

To study the effects of apomorphine injected i.v., two groups of rats received vehicle and 15 min later, either 10 μg (equivalent to 40–50 μg/kg) or 30 μg (120–150 μg/kg) i.v. apomorphine. The spinal effects of apomorphine were analysed in another group, in which cumulative injections (15 min delay between each) consisted in vehicle, 3, 10, 30 and 100 μg of apomorphine (10 μl for each injection, each followed by a flush of 10 μl saline) were performed every 15 min. Recording of ICP and BP lasted 15 min after the last injection.

Combination of i.t. apomorphine and i.t. oxytocin was studied in three groups. Ten ng of oxytocin were injected i.t., immediately followed by 10 μg or 30 μg of apomorphine or the same volume of vehicle (10 μl saline).¹⁴ In two other groups, the 10 ng i.t. injection of oxytocin was immediately followed by i.v. delivery of 30 μg apomorphine or by the corresponding volume of vehicle (20 μl). In presence of oxytocin, recording of ICP and BP lasted 30 min after the last injection.

Quantification of ICP rises

BP and ICP tracings were analysed retrospectively using software designed in our laboratory. Only ICP rises with a maximal value superior to the sum of the average +3 standard deviation of the ICP recorded during 15 min before the injection of drug or vehicle were quantified. ICPmax/BP × 100 corresponded to the percentage of the ratio: maximal value reached by ICP during the rise (mmHg)/mean BP (mmHg) for the duration of the ICP rise. The area under the curve of ICP rise divided by the mean BP, termed AUC/BP (s) and the sum of the AUC/BP (s) of all the ICP rises, which represents an index of overall erectile activity, were also calculated for each rat (see Figure 1 for illustration). All parameters were averaged per rat, except the sum of

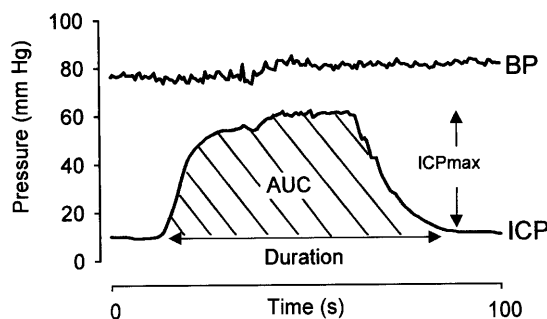


Figure 1 Representation of the parameters measured for each ICP rise. AUC: area under the ICP curve. ICPmax: maximal value reached by ICP during the ICP rise.

AUC/BP, and then per treatment. Rats who did not display any ICP rise (non-responding rats) during the recording were attributed the value 0 for the sum of AUC/BP and number of ICP rises. For non-responding rats, ICPmax/BP \times 100 and AUC/BP were considered as missing data for the statistical analysis.

Depending on the experiments, ICPmax/BP \times 100 and AUC/BP were compared using *t*-test or one way ANOVA followed by multiple comparisons *vs* control group. The corresponding tests with repeated measures were used to compare the number of ICP rises and sum of AUC/BP when successive injections were performed in the same rat. All tests were conducted using SigmaStat[®] software, version 2.03 (SPSS, Erkrath, Germany). Differences were considered significant when $P < 0.05$.

Results

It is noteworthy that ICP rises were observed after vehicle injection, either i.t. or i.v. Such ICP rises are often referred as 'spontaneous ICP rises', because they reflect the erectile activity observed in anesthetized rats in any recording conditions and are not related to saline or saline with ascorbic acid i.t. or i.v. injections.

Apomorphine i.v. did not significantly increase the number of ICP rises compared to previous vehicle injections in the same rats (from 0.8 ± 0.8 to 1.5 ± 1.0 for 10 μ g; from 1.4 ± 1.7 to 2.4 ± 2.0 for 30 μ g). Conversely, the shape of the ICP rises after i.v. delivery of apomorphine was significantly different compared to the ones observed after vehicle injection. Analysis with *t*-test revealed that the mean duration of the ICP rises (10 μ g, $P = 0.006$; 30 μ g, $P < 0.001$) and mean ICPmax/BP \times 100 (10 μ g, $P = 0.027$; 30 μ g, $P = 0.001$) were significantly increased by i.v. apomorphine (Figure 2A and B) when compared to vehicle injection. The increase of the ICPmax/BP \times 100 (135%) and duration (178%) were more important for the 30 μ g dosing than for the 10 μ g dosing (Figure 2A and B). These augmentations are reflected in an increase of the mean AUC/BP of the ICP rises for both doses, which was only significant for the 30 μ g apomorphine injection (440% of the value of the control group, $P = 0.002$, *t*-test, Figure 2C). The sum of AUC/BP was significantly increased by the i.v. injection of apomorphine at the 10 μ g and 30 μ g dosing compared to the vehicle i.v. injection ($P = 0.026$ and $P = 0.023$ respectively, paired *t*-test, Figure 2D).

On average, only 0.2 ± 0.4 ICP rises were observed after i.t. injections of vehicle. In contrast, apomorphine delivered i.t. at the lumbosacral level elicited the occurrence of ICP rises (3.0 ± 1.5 ICP rises after the 30 μ g apomorphine injection; see Figure 3 for an example of original recording). The number of ICP

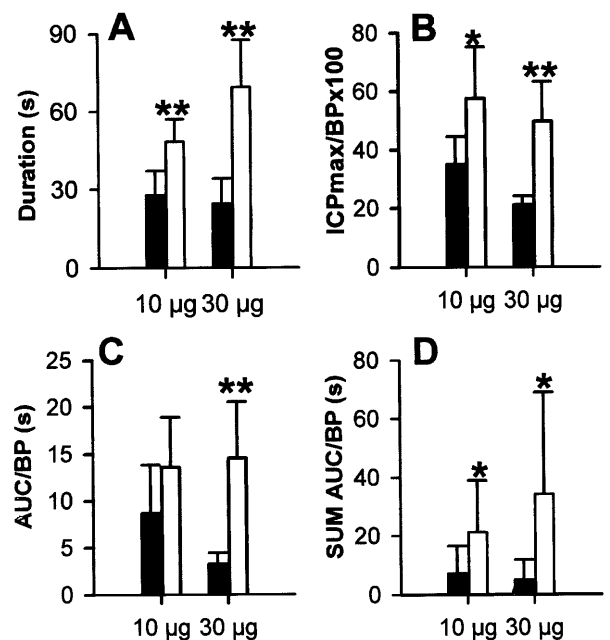


Figure 2 Effects of intravenous injection of apomorphine on ICP rises. Two groups of 10 anesthetized rats are considered. Each group was injected i.v. with vehicle and, after 15 min, either 10 μ g or 30 μ g apomorphine. BP and ICP were monitored for 15 min after each injection. The number of rats displaying at least one ICP rise before and after apomorphine injection were 6 and 8 (10 μ g group), 5 and 7 (30 μ g group). Among the different parameters considered, the duration (A), ICPmax/BP \times 100 (B) and sum of AUC/BP (D) of the ICP rises were significantly increased by apomorphine injection at both doses (open bars) compared to vehicle (filled bars). The AUC/BP (C) was significantly increased with 30 μ g apomorphine, but not with 10 μ g. * $P < 0.05$; ** $P < 0.01$; data in A, B and C compared with *t*-test; data in D with paired *t*-test. Values presented correspond to means \pm s.d.

rises followed a bell-shaped curve upon the cumulative i.t. injections of increasing doses apomorphine (Figure 4A). The number of ICP rises was significantly increased after the 30 μ g injection compared to the vehicle injection (one way ANOVA with repeated measures, $[F(9, 4) = 5.72, P = 0.001]$; Dunnett's test versus vehicle injection $P < 0.05$, Figure 4A). The mean ICPmax/BP \times 100 of the ICP rises was significantly increased after the 10 μ g and 30 μ g injection of apomorphine i.t. compared to the vehicle injection (One way ANOVA, $[F(4, 23) = 4.28, P = 0.01]$; Dunnett's test versus vehicle injection, $P < 0.05$ for both; Figure 4B). The mean AUC/BP of the ICP rises was increased upon the cumulative i.t. injections of apomorphine but this was not significant (One way ANOVA, $[F(4, 23) = 1.26, P = 0.31]$, not shown). One way ANOVA with repeated measures showed a significant effect of the cumulative i.t. injections of increasing doses of apomorphine on the sum of AUC/BP $[F(9, 4) = 6.24, P < 0.001]$. Further analysis with Dunnett's test revealed a significant increase of the sum of AUC/BP for the 10 μ g and 30 μ g dosing of apomor-

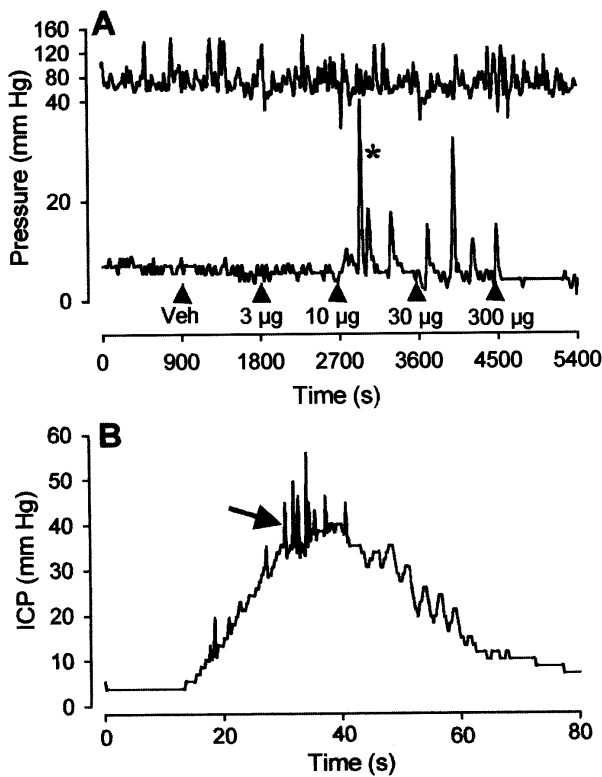


Figure 3 Examples of ICP and BP recordings obtained in anesthetized rats after cumulative injections of vehicle, 3, 10, 30 and 100 µg apomorphine at the lumbosacral level (each injection is indicated by an arrowhead, (A). A magnification of the ICP rise induced by i.t. apomorphine and marked by an asterisk in A is shown in B. Sharp and brief increases of ICP (arrow) superimposed to the ICP rise, with short duration, were systematically recorded upon apomorphine i.t. or i.v. injections (B).

phine compared to vehicle injection ($P < 0.05$, Figure 4C). Duration of ICP rises remained unaffected (not shown).

Intrathecal injection of 10 ng oxytocin alone consistently elicited the occurrence of ICP rises (overall 17 rats out of 20 displayed more than six ICP rises with ICPmax/BP $\times 100$ greater than 40% during the 30 min post-injection period, Table 1). The combination of i.t. or i.v. injections of apomorphine with i.t. injections of oxytocin did not induce significant variations of the number and shape of the

Table 1 Values (mean \pm s.d.) of the parameters characterizing ICP rises after combined treatment with oxytocin (i.t., 10 ng) and either apomorphine (i.v. or i.t.) or the corresponding volume of vehicle in independent group of 10 rats

Treatment	Number of peaks	Duration (s)	ICPmax/BP $\times 100$	AUC/BP (s)	Sum (AUC/BP) (s)
10 ng i.t. oxytocin +					
Veh, i.t. (n=9)	6.0 \pm 4.4	56 \pm 21	42 \pm 18	14 \pm 7	85 \pm 56
10 µg apo., i.t. (n=10)	4.0 \pm 3.3	87 \pm 49	65 \pm 27	40 \pm 41	186 \pm 255
30 µg apo., i.t. (n=10)	6.6 \pm 3.3	73 \pm 35	79 \pm 46	33 \pm 42	149 \pm 69
Veh, i.v. (n=8)	6.4 \pm 4.0	55 \pm 14	55 \pm 22	21 \pm 10	112 \pm 78
30 µg apo., i.v. (n=9)	3.8 \pm 2.5	67 \pm 22	75 \pm 41	27 \pm 17	97 \pm 72

The number in brackets represents the number of rats which display at least one ICP rise. One way ANOVA (apomorphine i.t. injections) or *t*-test (apomorphine i.v. injections) did not reveal significant statistical effect of apomorphine injections, despite a strong tendency of 30 µg i.t. apomorphine to enhance the ICP rises induced by 10 ng i.t. oxytocin.

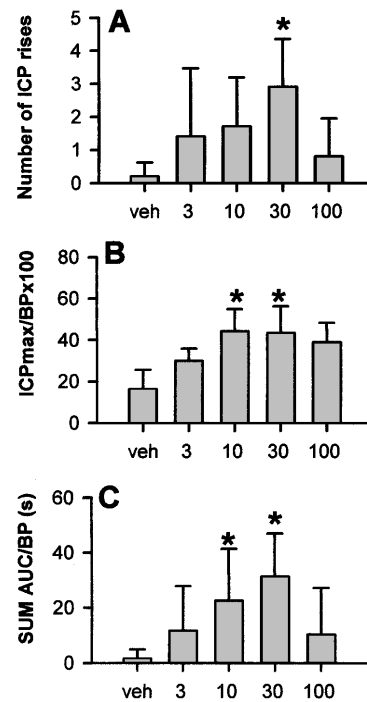


Figure 4 Effect of intrathecal injection of increasing cumulative doses of apomorphine on ICP. One group of 10 anesthetized rats is considered. After vehicle injection, increasing doses of apomorphine were delivered every 15 min at the lumbosacral level. The number of rats displaying at least one erectile event were 2, 5, 8, 9 and 4 respectively for the successive injections. The number of ICP rises (A), ICPmax/BP $\times 100$ (B) and the sum of AUC/BP (C) were significantly increased at some points by the cumulative injection of apomorphine. $*P < 0.05$; Dunnett's method was used after one way ANOVA with repeated measures (A and C); or after one way ANOVA (B). Values presented correspond to means \pm s.d.

ICP rises induced by oxytocin alone (Table 1). However, i.t. injection of 30 µg apomorphine and 10 ng oxytocin increased ICPmax/BP $\times 100$, AUC/BP and sum of AUC/BP by 88%, 136% and 75%, respectively compared to the injection of oxytocin alone (Table 1). In comparison, injection of 30 µg apomorphine i.v. and 10 ng oxytocin i.t. increased ICPmax/BP $\times 100$ and AUC/BP by 36% and 29%, and decreased the sum of AUC/BP by 14%, compared to the injection of oxytocin alone (Table 1).

Lastly, examination of the ICP recordings showed that upon apomorphine i.v. or i.t. injections, brief and sharp repeated increases of the ICP were superimposed to the ICP rises (Figure 3B). Such brief increases of the ICP were not present during the 'spontaneous' ICP rises which occurred upon vehicle injection.

Discussion

In these experiments in anesthetized rats, few ICP rises were observed after i.t. or i.v. vehicle injections. Apomorphine delivered i.v. at the dosing of 10 and 30 μg (final dosing 40–50 and 120–150 $\mu\text{g}/\text{kg}$ body weight) increased the occurrence of ICP rises compared to vehicle injection, and analysis of the tracings revealed a significant increase of the amplitude and duration of ICP rises for both dosings. This result is in agreement with the well-known central inducer effect of apomorphine originally described in the freely moving rat on the basis of behavioural responses and confirmed later through recording of the intracavernous pressure.^{1,16} Such proerectile inducer activity has been explained through a specific activation of neurons in the PVN by apomorphine.^{5,6} However, the existence of dopaminergic projections from the A11 cell group to the spinal cord as well as an intrinsic dopaminergic innervation within the spinal cord raises the possibility of an additional direct action of apomorphine at this level.^{17,18}

To investigate this statement, we directly delivered apomorphine at the spinal lumbosacral level with an intrathecal catheter, ie in the vicinity of the proerectile sacral parasympathetic nucleus. In preliminary experiments, we failed to modify the occurrence of ICP rises with i.t. injection of apomorphine in the range of 0.1 to 1 μg (not shown). Eventually, the number of the ICP rises and their amplitude measured by $\text{ICP}_{\text{max}}/\text{BP} \times 100$ was significantly increased after the i.t. injection of 30 μg apomorphine compared to an injection of vehicle. This strongly suggests that apomorphine exerts a spinal proerectile effect on the sacral parasympathetic nucleus, in accordance with the cytological data reporting a prominent expression of D2 receptors in neurons of the sacral parasympathetic area.^{9,10}

The small, sharp increases of the ICP superimposed to the ICP rises (Figure 3A) observed after apomorphine injection are likely due to contractions of the ischiocavernosus muscles.¹⁹ In physiological conditions, such contractions, which are only effective after engorgement by blood of the penis, enhances penile rigidity to allow efficient intromission. It is tempting to link the putative activity of the ischiocavernosus muscle observed after apomorphine i.v. or i.t. injections to the particular abun-

dance of D2 receptors in the spinal motor nucleus of the ischiocavernosus muscles.¹⁰ Thus, apomorphine may act at the spinal level on both autonomic (the SPN) and somatic (the spinal motor nucleus innervating the ischiocavernosus muscles) proerectile efferent pathways.

However, similar doses of i.t. apomorphine to the ones that elicit ICP rises in our model were shown to depress reflexive erections induced by retraction of the preputial sheath in the conscious rat.¹³ This suggests that apomorphine delivered at the lumbosacral level inhibits the afferent peripheral proerectile input during reflexive erections. An effect of apomorphine on the sensitive afferents is supported by the presence of D2 receptors in the dorsal horn at the thoracolumbar level.¹⁰ Whether apomorphine also inhibits the afferent input in the anesthetized rat, in addition to its proerectile effect on the efferent limb, remains a question to be answered.

We hypothesized that apomorphine at the spinal level could amplify proerectile inputs from supraspinal origin. In anesthetized rats, i.t. injections of oxytocin at the level of the sacral parasympathetic nucleus triggers the occurrence of erectile events and such injections likely mimic the physiological release of oxytocin through the paraventriculospinal pathway.^{20,21} We combined i.t. oxytocin delivery with apomorphine treatment. In this condition, the enhancement of the amplitude of oxytocin-induced ICP rises was much more pronounced when apomorphine was delivered i.t. at the lumbosacral level than when apomorphine was i.v. injected, although these differences were not significant. The faint increase of the oxytocin-induced ICP rises after i.v. apomorphine suggests that the end result of i.v. apomorphine is the release of oxytocin at the parasympathetic level.^{20,21} Systemic apomorphine could not generate further pro-erectile effect, as exogenous i.t. oxytocin would already mimic the full activation of the pro-erectile descending pathway usually activated after i.v. apomorphine at the PVN level. On the other hand, apomorphine exogenously delivered at the lumbosacral level tends to trigger additional proerectile outputs to the ones generated by oxytocin. This suggests the existence of an intraspinal dopaminergic proerectile pathway which would not be activated after i.v. apomorphine delivery.

Taken together, our data suggest that apomorphine is involved in a multistep central control of penile erection including supraspinal and spinal sites of action. The physiological basis of the proerectile effects of apomorphine at the level of the sacral parasympathetic nucleus could be represented by the activation of the hypothalamospinal dopaminergic pathway.¹⁷ This dopaminergic pathway, possibly proerectile, deserves further investigation. Oxytocinergic and dopaminergic descending pathways may participate to the co-ordination of the somatic and autonomic component of the

erectile response, in order to generate a fully adapted erectile response.

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References

- 1 Benassi-Benelli A, Ferrari F, Quarantotti BP. Penile erection induced by apomorphine and N-n-propyl-norapomorphine in rats. *Arch Int Pharmacodyn Ther* 1979; **242**: 241–247.
- 2 Danjou P et al. Assessment of erectogenic properties of apomorphine and yohimbine in man. *Br J Clin Pharmacol* 1988; **26**: 733–739.
- 3 Padma-Nathan H et al. Efficacy and safety of apomorphine sl vs placebo for male erectile dysfunction. *J Urol* 1999; **241S**: 159.
- 4 Lewis R, Agre K, Fromm S, Ruff D. Efficacy of apomorphine sl vs placebo for erectile dysfunction in patients with hypertension. *J Urol* 1999; **161S**: 214.
- 5 Melis MR, Argiolas A, Gessa GL. Apomorphine-induced penile erection and yawning: site of action in brain. *Brain Res* 1987; **415**: 98–104.
- 6 Chen KK, Chan JY, Chang LS. Dopaminergic neurotransmission at the paraventricular nucleus of hypothalamus in central regulation of penile erection in the rat. *J Urol* 1999; **162**: 237–242.
- 7 Ridet JL et al. Spinal dopaminergic system of the rat: light and electron microscopic study using an antiserum against dopamine, with particular emphasis on synaptic incidence. *Brain Res* 1992; **598**: 233–241.
- 8 Holstege JC et al. Distribution of dopamine immunoreactivity in the rat, cat and monkey spinal cord. *J Comp Neurol* 1996; **376**: 631–652.
- 9 Dubois A, Savasta M, Curet O, Scatton B. Autoradiographic distribution of the D1 agonist [3H]SKF 38393, in the rat brain and spinal cord. Comparison with the distribution of D2 dopamine receptors. *Neuroscience* 1986; **19**: 125–137.
- 10 Van Dijken H, Dijk J, Voom P, Holstege JC. Localization of dopamine D2 receptor in rat spinal cord identified with immunocytochemistry and *in situ* hybridization. *Eur J Neurosci* 1996; **8**: 621–628.
- 11 Giuliano F, Rampin O. Central neural regulation of penile erection. *Neurosci Biobehav Reviews* 2000; **24**: 517–533.
- 12 Stefanick ML, Smith ER, Clark JT, Davidson JM. Effects of a potent dopamine receptor agonist, RDS-127, on penile reflexes and seminal emission in intact and spinally transected rats. *Physiol Behav* 1982; **29**: 973–978.
- 13 Pehek EA, Thompson JT, Hull EM. The effects of intrathecal administration of the dopamine agonist apomorphine on penile reflexes and copulation in the male rat. *Psychopharmacology (Berl)* 1989; **99**: 304–308.
- 14 Giuliano F et al. Evidence for oxytocin regulation of penile erection at the spinal cord level in the rat. *J Urol* 1997; **157S**: 359.
- 15 Giuliano F, Bernabe J, Jardin A, Rousseau JP. Antierectile role of the sympathetic nervous system in rats. *J Urol* 1993; **150**: 519–524.
- 16 Bernabe J, Rampin O, Sachs BD, Giuliano F. Intracavernous pressure during erection in rats: an integrative approach based on telemetric recording. *Am J Physiol* 1999; **276**: R441–R449.
- 17 Skagerberg G, Lindvall O. Organization of diencephalic dopamine neurones projecting to the spinal cord in the rat. *Brain Res* 1985; **342**: 340–351.
- 18 Commissiong JW, Galli CL, Neff NH. Differentiation of dopaminergic and noradrenergic neurons in rat spinal cord. *J Neurochem* 1978; **30**: 1095–1099.
- 19 Giuliano F, Rampin O, Bernabe J, Rousseau JP. Neural control of penile erection in the rat. *J Auton Nerv Syst* 1995; **55**: 36–44.
- 20 Argiolas A, Melis MR. Neuromodulation of penile erection: an overview of the role of neurotransmitters and neuropeptides. *Progress in Neurobiology (Oxford)* 1995; **47**: 235–255.
- 21 Veronneau-Longueville F et al. Oxytocinergic innervation of autonomic nuclei controlling penile erection in the rat. *Neuroscience* 1999; **93**: 1437–1444.