

Association of Spontaneous and Dopaminergic-Induced Yawning and Penile Erections in the Rat

B. HOLMGREN,¹ R URBÁ-HOLMGREN, N. TRUCIOS, M. ZERMEÑO
AND J. R. EGUÍBAR

Departamento de Ciencias Fisiológicas, Instituto de Ciencias, Universidad Autónoma de Puebla, Puebla, México.

Received 11 June 1984

HOLMGREN, B., R URBÁ-HOLMGREN, N TRUCIOS, M ZERMEÑO AND J. R. EGUÍBAR *Association of spontaneous and dopaminergic-induced yawning and penile erections in the rat* PHARMACOL BIOCHEM BEHAV 22(1) 31-35, 1985 —In a Sprague-Dawley-derived line of rats, selectively bred to establish a high incidence of spontaneous yawning behavior, the simultaneous and systematic monitoring of yawning and penile erections, during observation periods of one hour, demonstrates a linear correlation between these two behavioral patterns. Dose-effect curves of yawning and penile erections elicited by apomorphine and bromocriptine, and their inhibition by metoclopramide are quite similar. These results strongly suggest that yawning and penile erection are subject to some common regulating and modulating mechanisms, one of which seems to involve dopaminergic pathways

Apomorphine	Bromocriptine	Metoclopramide	Yawning	Penile erection
-------------	---------------	----------------	---------	-----------------

EARLY reports on the stretching and yawning syndrome (SYS) induced in rats by intracisternal injections of ACTH and MSH [10-12] were soon followed by others which described that intraventricular or intracerebral administration of ACTH or MSH also produced signs of sexual excitement (penile erection (for the sake of brevity we will use the expression penile erection to describe a behavioral pattern which, in the rat, may also include genital grooming, pelvic thrusts or ejaculation [7]) and licking of the genitalia in the male, lordotic posture in the female), not only in rodents but also in other mammals [7, 8, 9, 13, 16, 19, 20, 27]. Different pharmacological evidence suggesting an association between yawning and sexual excitement began with work by Baraldi and Benassi-Benelli [3] and Mogilnicka and Klimek [17] demonstrating that systemic administration of apomorphine (APO) and other dopamine (DA) agonists elicits both yawning and penile erections in the rat.

Systematic observation of spontaneous and pharmacologically induced yawning and penile erections in a line of Sprague-Dawley rats selectively bred in our laboratory to establish a high incidence of yawning has led us to suggest that yawning and penile erection are correlated even in the normal spontaneously behaving animal. As reasonable parallelism exists between the elicitation or inhibition of yawning and penile erections by drugs acting through DA pathways, we further suggest that dopaminergic mechanisms operate in the regulation or modulation of these two behavioral patterns.

METHOD

The observations and experiments described in this work have been made in 374 male Sprague-Dawley rats, from the F1 to F6 generations of a line selectively bred to establish high yawning frequency and in 210 randomly bred animals.

Behavioral Observations

Observations were performed in 2-3 months-old male rats, with each animal placed in a transparent glass cylinder (diameter 190 mm, height 100 mm), the floor of which was covered with a sheet of clean filter paper, and the top with a Plexiglas plate, leaving a 1 cm wide segment open for ventilation. The period of observation had a standard duration of 1 hr. All experiments, except those using bromocriptine, were performed between 8 and 10 a.m. Yawns and penile erections were monitored and clocked by two observers sitting on opposite sides of the table on which the animals were placed. Not more than eight rats were observed simultaneously. Dose-effect curves for both yawning and penile erections were traced with two DA agonists: APO and bromocriptine. The effect of metoclopramide, a DA antagonist with relative selectivity for presynaptic autoreceptors [1], was studied on both spontaneous and drug-elicited yawning and penile erections.

Drug Administration

The drugs used were the following: apomorphine HCl

¹Requests for reprints should be addressed to Dr B Holmgren, Departamento de Ciencias Fisiológicas, Apartado Postal 406, Puebla, PUE. Mexico

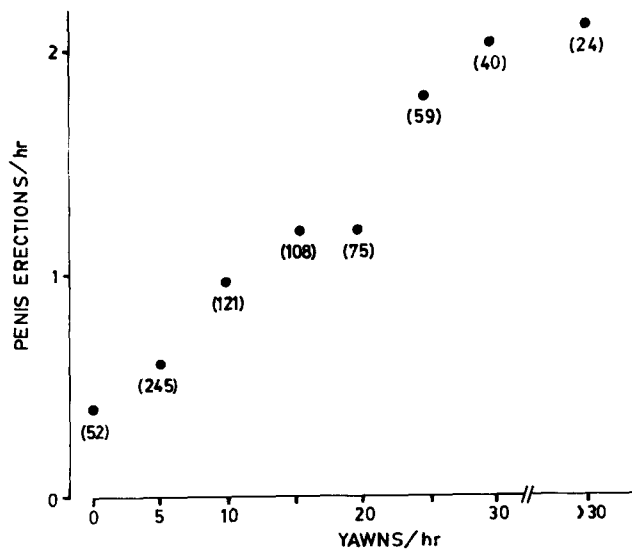


FIG 1 Correlation between spontaneous yawning and penile erections. Abscissa ranges of yawn frequency. Zero corresponds to non-yawning rats, 5 represents range from 1 to 5, 10 from 6 to 10 and so forth. Ordinate average penile erection frequency. Numbers in parenthesis represent N for each range of yawn frequency. $r=0.84$, $p<0.05$.

(Chimimport, Bulgaria), bromocriptine mesylate (Sandoz, S.A. México) and metoclopramide HCl (Lundbeck and Co., Denmark). APO and metoclopramide solutions were freshly prepared in distilled water and properly diluted in saline (0.9% NaCl) to reach a standard injection volume of 0.20 ml/100 g bodyweight. In the case of APO solutions ascorbic acid was added to the distilled water (0.20 mg/ml) to hinder drug oxidation. Bromocriptine was dissolved in tartaric acid (0.20 mM), in a concentration ten times higher than that appropriate for injection, immediately prior to injection it was further diluted with distilled water. Both DA agonists were injected subcutaneously. APO immediately before the observation period; bromocriptine 90 minutes before, because of the longer latency but great persistence of its effects [9]. Metoclopramide was always injected intraperitoneally 15 minutes before the observation period or the injection of a DA agonist. All drug doses are referred to the salt form.

Statistical procedures will be mentioned with the results.

RESULTS

Spontaneous Yawning and Penile Erections

Spontaneous yawning and penile erections are rather infrequent behavioral patterns in Wistar rats [6, 14, 17, 27]; this low frequency has hindered the study of quantitative relations between these two behavioral patterns. In the Sprague-Dawley-derived 'frequent yawning' line of rats, in process of selective breeding in our animal house in Puebla, yawning occurrence in male animals, during standard periods of observation of 1 hour, has increased from 47% in F1 to above 90% from F3 forwards. Average yawning frequency increased from 6 yawns/hr in F2 to 27.4 in F5 and 18.1 yawns/hr in F6. The highest individual figures in male

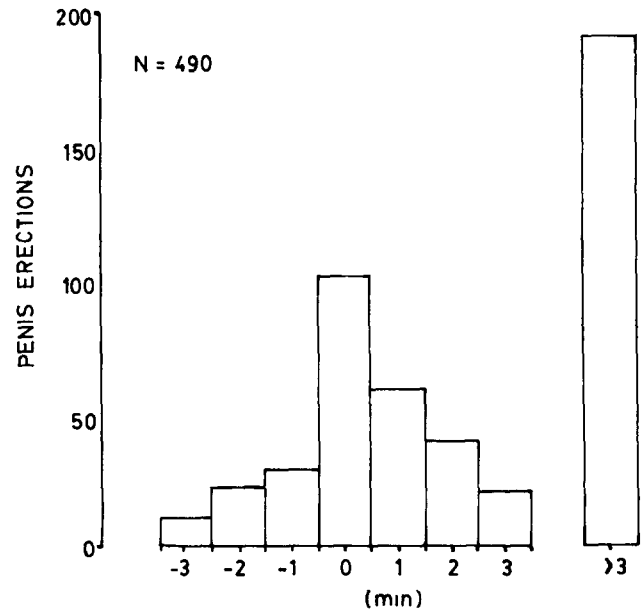


FIG 2 Temporal relations between individual penile erections and nearest yawn. Ordinate number of erections within each range of intervals. Abscissa intervals between yawns and erections. Zero, coincidence of the two behaviors within the same minute. N, total number of erections considered. Other details in the text.

rats in each generation have been the following: F2—37; F3—50, F4—55, F5—77, and F6—68 yawns/hr. If average penile erection frequency is plotted against average yawning frequency, as in Fig. 1, it may be seen that penile erections increase linearly from around 0.4 erections/hr in the group of non-yawning rats, to about 2 erections/hr in the group that had an average yawning frequency within a range from 26 to 30 yawns/hr. While in the group of rats with a yawning frequency from 6 to 10 yawns/hr penile erections were observed in only 56% of the animals, in the group exhibiting 26 to 30 yawns/hr the occurrence of erections of the penis reached 85%, during one hour of observation.

As some anecdotal descriptions in the literature on the association of yawning and penile erection could convey the idea of some synchronization between these behavioral items, we have studied time relations between a great number of erections ($n=490$) and individual yawns immediately preceding or following the former behavioral pattern. According to the results illustrated in Fig. 2 in only 20% of the cases did erections and yawns coincide within the same one minute interval.

Association of Pharmacologically-Elicited Yawning and Penile Erections

When these behavioral patterns are induced by DA agonists, apomorphine or bromocriptine, in male rats not exhibiting frequent spontaneous yawning, the dose-effect curves for both behaviors are quite similar (Figs 3 and 4), with an inverted U shape. For the low APO doses that induce yawning the latent period of the effect is very short, around 5 minutes, and its duration is around 45 minutes. Higher doses, from 0.25 mg/kg⁻¹ upwards, produce an initial

TABLE 1
ANTAGONISM OF METOCLOPRAMIDE ON APOMORPHINE AND BROMOCRIPTINE
INDUCED YAWNING AND PENILE ERECTIONS

	Maximal % reduction in frequency		Metoclopramide A50 values (mgkg ⁻¹)	
	Yawning	P erections	Yawning	P erections
APOMORPHINE (0.05 mgkg ⁻¹)	55*	52*	0.34	0.30
BROMOCRIPTINE (10 mgkg ⁻¹)	50*	48*	0.37	0.28

Maximal effects of metoclopramide were obtained with 0.75 mgkg⁻¹ injected intraperitoneally 15 min before the DA agonists. Control rats received injections of the vehicle. The rats were observed during 1 hr. N=12. A50 values were calculated from metoclopramide dose-effect curves traced with 0.3, 0.5, and 0.75 mgkg⁻¹. **p*<0.05 (Mann-Whitney U Test, two tails)

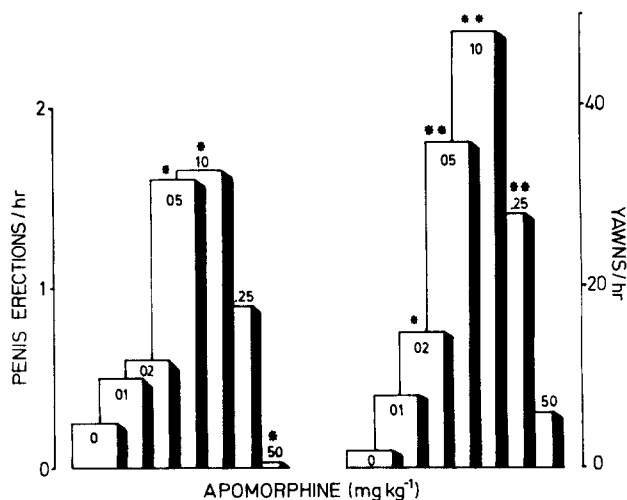


FIG 3 Apomorphine effects on both yawning and penile erections. Ordinate erections (left) or yawns (right) observed during 1 hr. Abscissa apomorphine doses indicated in each bar. N=12 rats in each group. **p*<0.05 and ***p*<0.01 (Wilcoxon and Wilcoxon Test [24]).

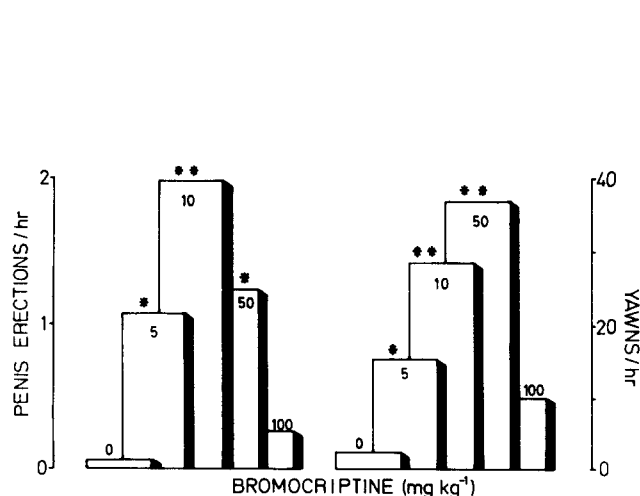


FIG 4 Bromocriptine effects on both yawning and penile erection. Ordinate as in Fig. 3. Abscissa bromocriptine doses indicated in each bar. N=12 animals in each group. **p*<0.05, ***p*<0.01 (Wilcoxon and Wilcoxon Test [24]).

depression of yawning [23], and perhaps also of erection of the penis, which explains the falling phase of APO's dose-effect curves (Fig. 3). Such an explanation is not valid for bromocriptine's dose-effect curve, because the observations were performed 90 minutes after its injection, and during a period of very stable effects, which may persist for several hours.

The antagonistic effects of metoclopramide on penile erections and yawning induced by standard doses of APO (0.05 mgkg⁻¹) or bromocriptine (10 mgkg⁻¹) are also quite similar, maximal and statistically significant reductions in the frequency of both behavioral patterns to about half of their control values being obtained with the same dose of metoclopramide (0.75 mgkg⁻¹), whatever the DA agonist used to elicit them. No significant differences were observed in the slopes of the metoclopramide dose-effect lines traced

for yawning and penile erection with 0.3, 0.5 and 0.75 mgkg⁻¹, nor in the respective A50 values (Table 1)

DISCUSSION

A strict correlation between spontaneous yawning and penile erections was certainly difficult to establish in Wistar rats, because of the low frequency of these behavioral patterns. In that strain of rats spontaneous yawning has, according to different authors [6, 14, 17, 27] average frequencies within a range from 0.1 to 2 yawns/hr. For penis erection, an occurrence of 30% and an average frequency of 0.3 erections/hr were reported by Bertolini *et al.* [6], from experiments in which the animals were observed during two hours. Their data show a yawning occurrence of the order of 60%, with an average frequency of 1.5 yawns/hr. The progress

made in our laboratory, in the selective breeding of a 'frequent yawning' line of Sprague-Dawley rats has allowed us to demonstrate that penile erection frequency increased linearly from around 0.4 erections/hr in the group of non-yawning rats, to 2 erections/hr in the group that had an average spontaneous frequency within a range from 26 to 30 yawns/hr. This correlation suggests that some common underlying factors may participate in the regulation of these two behavioral patterns. For Bertolini *et al* [7], when both behavioral patterns "occur under physiological conditions, they might be elicited by an endogenous peptide closely related to CRF," and containing "the peptide sequence required for eliciting stretching, yawning and sexual stimulation."

The very similar dose-effect curves obtained by us for yawning and penile erection, when elicited with two DA agonists (APO and bromocriptine) (Figs 3 and 4) and their equivalent depression in frequency by the selective presynaptic DA antagonist, metoclopramide (Table 1) strongly suggest that penile erection and yawning are both under dopaminergic control. In relation to yawning, which is also elicited in rats by cholinomimetic drugs, physostigmine or pilocarpine [22,26], a hypothetical model of its central control mechanism has been proposed [14, 23, 26], which includes a dopaminergic inhibitory-cholinergic excitatory link. Low doses of APO or other dopaminergic agonists, by activating presynaptic DA autoreceptors would inhibit DA release and thus disinhibit the cholinergic neurones exciting yawning. Wood *et al* [25] have proposed that septal-hippocampal cholinergic neurones are involved in the specific SYS elicited by intraventricular injection of MSH or ACTH. It is therefore tempting to suggest, as Yamada and Furukawa implicitly do [27], that the dopaminergic-cholinergic link in yawning might involve the DA pathway ascending from the A10 mesencephalic cell group to the limbic region and the septal-hippocampal cholinergic neurones. It seems interesting to recall that Passouant *et al* [18] had observed yawning in cats during the post-discharge period following electrical stimulation of the hippocampus.

With respect to genital function, consistent results from MacLean and coworkers (as reviewed by MacLean [16]) showed that electrical stimulation of several sites in the limbic areas, leading to the buildup of high-voltage potentials or afterdischarges in the hippocampus, are generally accom-

panied by penile erection. In later experiments done with Kinnard, MacLean [16] found that depositing α -MSH or $^{1-24}\beta$ -ACTH in solid form in the septo-preoptic region of the squirrel monkey resulted in recurrent episodes of stretching, yawning, scratching of the body and full penile erections which, in about three hours, could reach a frequency of twice per minute.

The reviewed evidence points strongly to the existence of some common regulating or modulating elements interrelating, under certain physiological or experimental circumstances two behavioral patterns as different as yawning and penile erection. The complex neural circuitry interconnecting the different structures of the limbic brain may offer neuroanatomical sites for this interaction. Common modulating influences seem also important. Hormones such as testosterone [4, 8, 15, 19], or a particular polypeptide sequence contained in α -MSH and β -ACTH [7,13] facilitate both yawning and penile erection. Tonic changes in neurotransmitter influences, as exerted by the ascending mesolimbic pathway [27] or other DA pathways, may inhibit or disinhibit these behavioral patterns.

The most recent report by Serra *et al* [21] that hypophysectomy in rats prevents yawning and penile erections induced by apomorphine is quite a strong argument in favor of their hypothesis that both behavioral effects are mediated by pituitary hormones. They suggest that activation of DA autoreceptors in the hypothalamo-hypophyseal DA neurones by low doses of apomorphine might remove an inhibitory control on MSH release, the hormone reaching target areas in the brain by retrograde portal flow. This hypothesis appears very attractive because it offers a unifying explanation of the elicitation of yawning and penile erections by so different substances as the common polypeptide sequence contained in α -MSH and β -ACTH, and DA agonists.

ACKNOWLEDGEMENTS

These studies have been supported by the grant PCCBBNA-001922, from the Consejo Nacional de Investigación Científica y Tecnológica (CONACYT), México, D.F. We wish to thank Lundbeck and Co., Denmark, and Sandoz, S.A., México, for their gifts of metoclopramide and bromocriptine, respectively. We also wish to express our sincere thanks to Dr. Carlos Beyer and Lowell Roberts Ph.D. for their important suggestions and help in the preparation of the final version of this manuscript.

REFERENCES

- 1 Alander, T., N.-E. Andén and M. Grabowska-Andén. Metoclopramide and sulpiride as selective blocking agents for pre- and post-synaptic dopamine receptors. *Naunyn-Schmiedeberg's Arch Pharmacol* 312: 145-150, 1980.
- 2 Baldwyn, D.M., C.K. Haun and C.H. Sawyer. Effects of intraventricular infusions of ACTH¹⁻¹⁰ on LH release, ovulation and behavior in the rabbit. *Brain Res* 80: 291-301, 1974.
- 3 Baraldi, M. and A. Benassi-Benelli. Apomorphine-induced penile erection in adult rats. *Riv Farm Ter* 6: 771-772, 1975.
- 4 Berendsen, H.H.G. and V.J. Nickolson. Androgenic influences on apomorphine-induced yawning in rats. *Behav Neural Biol* 33: 123-128, 1981.
- 5 Bertolini, A. and M. Baraldi. Anabolic steroids: Permissive agents of ACTH-induced penile erection in rats. *Life Sci* 17: 263-266, 1976.
- 6 Bertolini, A., S. Genedani and M. Castelli. Behavioral effects of naloxone in rats. *Experientia* 34: 771-772, 1978.
- 7 Bertolini, A., G.L. Gessa and W. Ferrari. Penile erection and ejaculation: A central effect of ACTH-like peptides in mammals. In *Sexual Behavior: Pharmacology and Biochemistry*, edited by M. Sandler and G.L. Gessa. New York: Raven Press, 1975, pp. 247-257.
- 8 Bertolini, A., G.L. Gessa, W. Vergoni and W. Ferrari. Induction of sexual excitement with intraventricular ACTH: permissive role of testosterone in the male rabbit. *Life Sci* 7: 1203-1206, 1968.
- 9 Corrodi, H., K. Fuxe, T. Hokfelt, P. Lidbrink and U. Ungerstedt. Effect of ergot drugs on central catecholamine neurons: evidence for a stimulation of central dopamine neurons. *J Pharm Pharmacol* 25: 409-412, 1973.
- 10 Ferrari, W., G.L. Gessa and L. Vargu. Behavioral effects induced by intracisternally injected ACTH and MSH. *Ann NY Acad Sci* 104: 330-345, 1963.

- 11 Gessa, G L , M. Pisano, L Vargiu, F Grabai and W Ferrari Stretching and yawning movements after intracerebral injection of ACTH *Rev Can Biol* 26: 229-236, 1967
- 12 Gessa, G L., L Vargiu and W Ferrari Stretchings and yawnings induced by adrenocorticotrophic hormone *Nature* 211: 426-427, 1966
- 13 Gispen, W H , V M Wiegant, H M Greven and D DeWied The induction of excessive grooming in the rat by intraventricular application of peptides derived from ACTH Structure-activity studies *Life Sci* 12: 645-652, 1975
- 14 Holmgren, B and R Urbá-Holmgren Interaction of cholinergic and dopaminergic influences on yawning behavior *Acta Neurobiol Exp (Warsz)* 40: 633-642, 1980
- 15 Holmgren, B , R Urbá-Holmgren, M Aguiar and R Rodríguez Sex hormone influences on yawning behavior *Acta Neurobiol Exp (Warsz)* 40: 515-519, 1980
- 16 MacLean, P D Brain mechanisms of primal sexual functions and related behavior In *Sexual Behavior Pharmacology and Biochemistry*, edited by M Sandler and G L Gessa New York Raven Press, 1975, pp 1-11
- 17 Mogilnicka, E and V Klimek Drugs affecting dopamine neurons and yawning behavior *Pharmacol Biochem Behav* 7: 303-305, 1977
- 18 Passouant, P , T Passouant-Fontaine and J Cadilhac Hippocampe et comportement Les modifications du comportement chez les chats après stimulation de l'hippocampe *Rev Neurol (Paris)* 94: 292-295, 1956
- 19 Rodríguez-Sierra, J F , E Terasawa, D A Goldfoot and D DeWied Testosterone potentiation of the effectiveness of ACTH¹⁻²⁴ on induction of the stretch yawning syndrome (SYS) in male guinea pigs *Horm Behav* 15: 77-85, 1981
- 20 Sawyer, C H., D Baldwyn and C. H. Haun Effects of intraventricular injections of corticotropins on hypothalamopituitary ovarian function and behavior in the female rabbit. In: *Sexual Behavior Pharmacology and Biochemistry*, edited by M Sandler and G. L Gessa New York: Raven Press, 1975, pp 259-268
- 21 Serra, G , M Collu, S Loddo, G Celasco and G L Gessa. Hypophysectomy prevents yawning and penile erection, but not hypomotility induced by apomorphine *Pharmacol Biochem Behav* 19: 917-919, 1983
- 22 Urbá-Holmgren, R , R M González and B Holmgren. Is yawning a cholinergic response? *Nature* 267: 261-262, 1977
- 23 Urbá-Holmgren, R , B Holmgren and J Anías Pre- and post-synaptic dopaminergic receptors involved in apomorphine-induced yawning *Acta Neurobiol Exp (Warsz)* 42: 115-125, 1982
- 24 Wilcoxon, F and R A Wilcox *Some Rapid Approximate Statistical Procedures* Pearl River, New York Lederle Laboratories, 1964, p 11
- 25 Wood, P L , D L Cheney and E Costa Modulation of the turnover rate of hippocampal acetylcholine by neuropeptides Possible site of action of α -melanocyte-stimulating hormone, adrenocorticotrophic hormone and somatostatin. *J Pharmacol Exp Ther* 209: 97-103, 1979
- 26 Yamada, K and T Furukawa Direct evidence for involvement of dopaminergic inhibition and cholinergic activation in yawning *Psychopharmacology (Berlin)* 67: 39-43, 1980
- 27 Yamada, K and T Furukawa The yawning elicited by α -melanocyte stimulating hormone involves serotonergic-dopaminergic-cholinergic link in rats *Naunyn Schmiedebergs Arch Pharmacol* 316: 155-160, 1981