Pharmacology Biochemistry & Behavior, Vol. 19, pp. 917–919, 1983.

Hypophysectomy Prevents Yawning and Penile Erection but not Hypomotility Induced by Apomorphine

G. SERRA, M. COLLU, S. LODDO, G. CELASCO* AND G. L. GESSA[1]

Institute of Pharmacology, University of Cagliari, Italy
**Parke-Davis Laboratories, Casetenovo, Como, Italy*

Received 22 April 1983

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(6) 917–919, 1983.—A small dose of apomorphine (25 or 50 μg/kg, SC) induced repeated episodes of yawning, penile erection, genital grooming and a decrease in locomotor activity in rats. Hypophysectomy almost completely abolished yawning, penile erection and genital grooming but failed to modify the hypomotility induced by apomorphine. These results suggest that pituitary hormones are directly or indirectly involved in the apomorphine-induced yawning, penile erection and genital grooming but not in the sedative response to this drug.

Pituitary Apomorphine Yawning Penile erection Genital grooming Hypomotility

THE administration of small doses of apomorphine or other dopaminomimetic drugs in rats produces a behavioural syndrome characterized by hypomotility (see [6]), yawning [10, 11, 13, 15], penile erection [1, 8, 11, 13] and genital grooming [11,13].

These effects are considered to be the behavioural consequence of the inhibition of dopaminergic transmission mediated by the stimulation of dopamine (DA) autoreceptors in the CNS. Indeed, doses of DA agonists producing these behavioural effects are within the dose range needed to activate DA autoreceptors, but much lower than those needed to stimulate postsynaptic DA receptors and to produce stereotypy and stimulation of motor activity.

We have recently shown that the inhibition of protein synthesis prevents apomorphine-induced yawning, penile erection and genital grooming, suggesting that the inhibition of DA transmission might result in the release of some newly synthetized peptides [13].

The fact that MSH-producing cells in the intermediate lobe of the pituitary are under the inhibitory control of dopaminergic neurons [9, 12, 14] and that ACTH and MSH share with apomorphine the ability to produce penile erection and yawning (see [3]) suggests that these peptides might be possible candidates for mediating yawning, penile erection and genital grooming induced by low doses of apomorphine.

On the basis of these considerations, we might suggest that inhibition of dopaminergic activity results in the release of ACTH or MSH peptides from pituitary or from peptidergic neurons in the brain.

The present study was carried out to investigate the role of pituitary on the behavioural effects induced by low doses of apomorphine. The present results indicate that hypophysectomy inhibits yawning, penile erection and genital grooming but not the hypomotility induced by small doses of apomorphine.

METHOD

Animals

Male Sprague-Dawley rats, weighing 100±10 g at the time of surgery, were used. The animals were hypophysectomized in the Parke-Davis laboratories (Cosatenovo, Como) with the transauricular technique as described by Falconi and Rossi [7]. Control animals were anesthetized as the hypophysectomized ones, but surgery was simulated. One week after surgery, the animals were transferred to our laboratories, where they were housed 4 per cage at 22°C, humidity 50–60%, with a 12 hr light-dark cycle, until experimentation was begun. The experiments were carried out 3–4 weeks after hypophysectomy between 9.00 and 14.00 in a sound proof room. At the end of the experiments, the hypophysectomized animals were sacrificed and the sella turcica visually inspected to confirm the absence of the pituitary. At this time, hypophysectomized and control rats weighed 92±2 and 183±9 g, respectively.

Drug

Apomorphine·HCl was freshly dissolved in saline and administered subcutaneously in the dorsal part of the neck.

[1]Requests for reprints should be addressed to G. L. Gessa: Institute of Pharmacology, University of Cagliari, Via Porcell, 4, 09100 Cagliari, Italy.

TABLE 1

EFFECT OF HYPOPHYSECTOMY ON APOMORPHINE-INDUCED YAWNING, PENILE ERECTION (PE) AND GENITAL GROOMING

Condition	Mean No. of yawns	No. of rats exhibiting PE†	Mean duration of genital grooming (sec)
Control	10.64 ± 1.49	22/24 (1.60 ± 0.19)	20.0 ± 3.50
Hypophysectomy	1.30 ± 0.35*	2/24 (0.09 ± 0.05)*	1.4 ± 1.01*

Each value represents the mean ± S.E. of 24 animals. Apomorphine (50 μg/kg) was given SC to both control and hypophysectomized rats. Both these groups, when treated with saline, only occasionally showed episodes of yawning, penile erection or genital grooming: yawns=0.33 ± 0.15 and 0.25 ± 0.12; PE=2/24 and 1/24; genital grooming=1.3 ± 0.9 and 0.7 ± 0.6, respectively. The behavioural elements were scored for 25 min starting 5 min after apomorphine injection (see Method). †Mean No. of episodes of PE during the observation period is shown in parentheses. *$p<0.001$, with respect to the control group (Student's t-test).

TABLE 2

LACK OF EFFECT OF HYPOPHYSECTOMY ON APOMORPHINE-INDUCED HYPOMOTILITY IN RATS

	Motility counts (for 10 min) after:			
Condition	Saline	(%)	Apomorphine	(%)
Control	900 ± 67	(100 ± 7.4)	536 ± 43*	(59.5 ± 4.7)
Hypophysectomy	787 ± 99	(87.4 ± 11)	461 ± 65*	(51.2 ± 7.2)

Each value represents the mean ± S.E. of 10 animals. Percentages refer to saline-treated control animals. Apomorphine (25 μg/kg SC) or saline was given 10 min before the test. Motility was measured for 10 min as described in the Method section. *$p<0.01$ versus the respective group treated with saline (Student's t-test).

Behavioural Observations

(a) Apomorphine-induced yawning, penile erection and genital grooming. These behavioural effects elicited by a small dose (50 μg/kg SC) of apomorphine were observed by placing the animals individually in small perspex observation cages (25×20×25 cm), immediately after drug injection. Starting 5 min after the animal was put into the cage, the following behavioural elements, occurring during 25 min, were scored: (1) number of yawns; (2) number of penile erections and (3) duration (sec) of genital grooming.

(b) Apomorphine-induced hypomotility. Motor activity was measured by placing the animals individually in motility cages (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm). Each cage had 40 photoconductive sensors placed in the floor area (21×23 cm) at a distance of 4 cm; they were lit uniformly by an incandescent lamp mounted 60 cm above the sensors. Motor activity was defined as the number of interruptions of a beam. The animals were injected with saline or apomorphine and, 10 min after injection, they were placed in the motility cages and motor activity was measured for 10 min.

Statistics

The statistical significance of the results was evaluated using the two-tailed Student's t-test.

RESULTS

Hypophysectomy and Apomorphine-Induced Yawning, Penile Erection and Genital Grooming (Table 1)

As expected from previous experiments [13], the administration of 50 μg/kg SC of apomorphine induced the appearance of repeated episodes of yawning, penile erection and genital grooming in control rats. Hypophysectomy almost completely prevented yawning, penile erection and genital grooming induced by apomorphine.

Hypophysectomy and Apomorphine-Induced Hypomotility (Table 2)

In hypophysectomized rats, spontaneous motor activity, although showing a tendency to decrease, was not significantly lower than in control animals receiving saline. The administration of 25 μg/kg SC of apomorphine decreased locomotor activity by about 50% in both control and hypophysectomized animals.

DISCUSSION

The present findings indicate that hypophysectomy abolishes some behavioural effects of small doses of apomorphine, namely yawning, penile erection and genital

grooming, but fails to prevent apomorphine-induced hypomotility.

Since, at the time of the experiments, there was a significant difference in body weight between control and hypophysectomized animals, the possible influence of the debilitating effect of hypophysectomy in the inhibition of apomorphine-induced yawning, penile erection and genital grooming cannot be entirely excluded. However, an unspecific effect is unlikely since hypophysectomy specifically antagonizes some apomorphine effects but does not influence apomorphine-induced hypomotility.

These results support the hypothesis that the former behavioural effects of apomorphine are mediated by some pituitary hormones [13]. These hormones might be identified with ACTH and MSH peptides, since they are the only ones capable of producing yawning and penile erection [3]. Moreover, MSH-producing cells in the pars intermedia of the pituitary are under the inhibitory control of dopaminergic neurons originating from the arcuate nucleus in the hypothalamus [9, 12, 14]. In might be suggested that stimulation of DA autoreceptors present on these neurons [5] results in the removal of the inhibitory control of DA on MSH release. MSH released from pituitary might reach the target areas in the brain via a retrograde portal flow [4].

An alternative interpretation of our results might be that the lack of some pituitary hormone alters the sensitivity of DA receptors responsible for yawning, penile erection and genital grooming, but not those responsible for the reduction of motor activity.

Finally, the suppressant effect of hypophysectomy on apomorphine-induced yawning, penile erection and genital grooming might be indirect, secondary to the involution of the gonads or adrenals. In fact, it has been reported that castration reduces apomorphine-induced yawning [2].

The fact that apomorphine-induced hypomotility is not altered by hypophysectomy suggests that, contrary to that observed for the other behavioural responses, pituitary peptides are neither directly nor indirectly involved in the sedative effect of the drug.

ACKNOWLEDGEMENTS

We would like to thank Parke-Davis Laboratories for the kind supply of hypophysectomized rats and Mr. Franco Putzolu and Mr. Antonio Boi for their technical assistance. This study was supported by CNR grants CT. 820218756 and CT. 820107683 and a grant from the Italian Ministry of Public Education.

REFERENCES

1. Benassi-Benelli, A., F. Ferrari and B. Pellegrini-Quarantotti. Penile erection induced by apomorphine and N-n-propyl-norapomorphine in rats. *Arch Int Pharmacodyn Ther* **241:** 128–134, 1979.
2. Berendsen, H. H. G. and V. J. Nickolson. Androgenic influences on apomorphine-induces yawning in rats. *Behav Neurol Biol* **33:** 123–128, 1981.
3. Bertolini, A. and G. L. Gessa, Behavioural effects of ACTH and MSH peptides. *J Endocrinol Invest* **4:** 241–251, 1981.
4. Blume, R. B. H., A. Hamilton, P. Monica and R. Peterson. Adrenocorticotropic hormone may be transported directly from the pituitary to the brain. *Science* **210:** 541–543, 1980.
5. Demarest, K. T. and K. E. Moore. Comparison of dopamine synthesis regulation in the terminals of nigrostriatal, mesolimbic, tuberoinfundibular and tuberohypophyseal neurons. *J Neural Tran* **46:** 263–277, 1979.
6. Di Chiara, G., G. U. Corsini, G. P. Mereu, A. Tissari and G. L. Gessa. Self-inhibitory dopamine receptors: their role in the biochemical and behavioural effects of low doses of apomorphine, In: *Advances in Biochemical Psychopharmacology*, edited by P. J. Roberts *et al.* New York: Raven Press, 1978, pp. 275–292.
7. Falconi, G. and G. L. Rossi. Transauricular hypophysectomy in rats and mice. *Endocrinology* **74:** 301–303, 1964.
8. Gessa, G. L., A. Benassi-Benelli, P. Falaschi and F. Ferrari. Role of dopamine in erection and ejaculation mechanisms. In: *Endocrinology 1980*, edited by I. A. Cummings *et al.* Melbourne: Proc. Australian Acad. Sci., 1980, pp. 619–621.
9. Jackson, S., J. Hope, F. Estivariz and P. J. Lowry. Nature and control of peptide release from the pars intermedia. In: *Peptides of the Pars Intermedia*. London: Pitman Med., 1981, pp. 141–162.
10. Mogilnicka, E. and V. Klimek. Drugs affecting dopamine neurons and yawning behaviour. *Pharmacol Biochem Behav* **7:** 303–305, 1977.
11. Nickolson, V. J. and H. H. G. Berendsen. Effects of the potential neuroleptic peptide des-tyrosine^1-γ-endorphin and haloperidol on apomorphine-induced behavioral syndromes in rats and mice. *Life Sci* **27:** 1377–1385, 1980.
12. de Rotte, A. A., T. B. Van Wimersma Greidanus, J. M. Van Ree, E. A. D. Andringa-Bakker and D. de Wied. The influence of β-LPH fragments on α-MSH release: the involvement of a dopaminergic system. *Life Sci* **29:** 825–832, 1981.
13. Serra, G., W. Fratta, M. Collu, L. Napoli-Farris and G. L. Gessa. Cycloheximide prevents apomorphine-induced yawning, penile erection and genital grooming in rats. *Eur J Pharmacol* **86:** 279–284, 1983.
14. Tilders, F. and P. Smelik. Direct neural control of MSH secretion in mammals: the involvement of dopaminergic tuberohypophyseal neurons. In: *Melanocyte-stimulating Hormone: Control Chemistry and Effects*, edited by F. J. H. Tilders *et al.* Basel: Karger 1977, pp. 80–93.
15. Yamada, K. and T. Furukawa. Direct evidence for involvement of dopaminergic inhibition and cholinergic activation in yawning. *Psychopharmacology (Berlin)* **67:** 39–43, 1980.
13. Serra, G., W. Fratta, M. Collu, L. Napoli-Farris and G. L. Gessa. Cycloheximide prevents apomorphine-induced yawning, penile erection and genital grooming in rats. *Eur J Pharmacol* **86:** 279–284, 1983.
14. Tilders, F. and P. Smelik. Direct neural control of MSH secretion in mammas: the involvement of dopaminergic tuberohypophyseal neurons. In: *Melanocyte-stimulating Hormone: Control Chemistry Effects*, edited by F. J. H. Tilders *et al.* Basel: karger, 1977, pp. 80–93
15 Yamada, K. and T. Furukawa. Direct evidence for involvement of dopaminergic inhibition and cholinergic activation in yawning. *Psychopharmacology (Berlin)* **67:** 39–43, 1980.