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Serotonergic Modulation of Yawning

R. URBA-HOLMGREN, B. HOLMGREN, R. RODRIGUEZ AND R. M. GONZALEZ

Centro Nacional de Investigaciones Cientificas Apartado 6990, La Habana, Cuba

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URBA-HOLMGREN, R. , B. HOLMGREN, R. RODRIGUEZ AND R. M. GONZALEZ. *Serotonergic modulation of yawning.* PHARMAC. BIOCHEM. BEHAV. 11(1) 371–372, 1979.—Yawning induced by intraperitoneal (IP) injection of physostigmine (0.15 $mgKg^{-1}$), in infant or adult rats is potentiated by Lu 10-171 (0.5–10 $mgKg^{-1}$), a selective serotonin uptake inhibiting drug, which, by itself does not induce yawning. This effect is counteracted by metergoline (5-10 $mgKg^{-1}$, IP) which blocks serotonin postsynaptic receptors. It is suggested that serotonin may exert a positivie modulating effect on yawning.

Yawning Serotonin Lu 10-171 Metergoline Physostigmine

YAWNING is a fixed innate motor pattern that has been rather neglected in experimental behavioral studies. Nevertheless, some attention has recently been focussed on its underlying neurotransmitter mechanisms [1, 3, 6, 8]. From results of experiments mainly performed in infant rats, it has been suggested [1, 3, 8] that central cholinergic synapses may play an important role in relation to yawning, since cholinomimetic drugs (physostigmine and pilocarpine) greatly influence its frequency. The responsible receptors seem to be of the muscarinic type, because the yawning-inducing effect of the two above mentioned drugs is blocked by scopolamine [8].

Other experiments performed in adult male albino rats indicate that some dopaminergic (DA) component might be present in yawning. Low doses of systemically injected DA agonists (apomorphine, piribedil, amphetamine, nomifensine and L-DOPA) produce recurrent episodes of yawning [6], responses which are completely inhibited by spiperone.

As yawning seems to be commonly associated with transitional phases in the sleep-waking cycle, particularly with the state of drowsiness preceding or following sleep, and strong evidence links the serotonergic pathways with slow-wave sleep [5,7], it seemed worthwhile to explore the possible participation of serotonergic mechanisms in the induction or modulation of yawning.

METHOD

Most of the experiments to be reported were performed in infant (6–7 day-old) Wistar rats, born in the laboratory, their age being estimated with an approximation of ± 8 hours. All litters were reduced to eight pups 24 to 36 hr after birth. The animals were randomly distributed among experimental and control groups. Yawning was induced by intraperitoneal (IP) injection of physostigmine (BDH) in doses of 0.15 $mgKg^{-1}$. The animals were placed in glass cylinders 18 cm in diameter, the floor of which was covered with filter paper, and were observed during one hour, paying attention only to the number of yawns. Two drugs influencing serotonergic synapses were used: Lu 10-171, 1-(3-dimenthyl-amino) propyl)-1-(p-fluorophenyl)-5-phtalancarbonitrile, (H. Lundbeck and Co.) and metergoline (Farmitalia). Lu 10-171 is a very potent and selective serotonin (5-HT) uptake inhibitor [4]. Some evidence indicates that metergoline blocks selectively central 5-HT receptors [2]. All drugs were dissolved in saline (0.9% NaCl) in such a way that the total volume to be injected was equivalent to 0.01 $mlKg^{-1}$ bodyweight. Controls received IP injections of the same volume of saline.

RESULTS AND DISCUSSION

Infant rats injected with Lu 10-171, in doses ranging from 0.1 to 10 $mgKg^{-1}$, do not exhibit any noteworthy changes in overt behavior. If 40 min later they receive physostigmine (0.15 $mgKg^{-1}$) the latter drug's yawning inducing effect [8] is strongly potentiated, as is illustrated in Fig. 1. The effect is statistically significant with Lu 10-171 doses from 0.5 $mgKg^{-1}$ upwards, reaching a four to eight-fold increase in mean yawning frequency with the higher doses.

Similar results, but at a lower level of basal yawning frequency, were observed in young (45-day-old) male rats, injected with Lu 10-171, in doses of 5 to 10 $mgKg^{-1}$, the results being statistically significant for the latter dose (Mann-Whitney U Test, $p<0.05$).

The potentiating effect of Lu 10-171 on physostigmine induced yawning is counteracted by metergoline (5 $mgKg^{-1}$) when metergoline is injected IP 30 min before receiving Lu 10-171, that is, 70 min before the yawning test with physostigmine (Fig. 2). It may be seen that metergoline also reduces the number of yawns induced by physostigmine in the control group, an effect which even if not statistically significant suggests the existance of a basal serotonergic tone favouring the expression of cholinomimetically induced yawning. This suggestion was strengthened by the results of an experiment with a higher dose of metergoline (10 $mgKg^{-1}$), with which

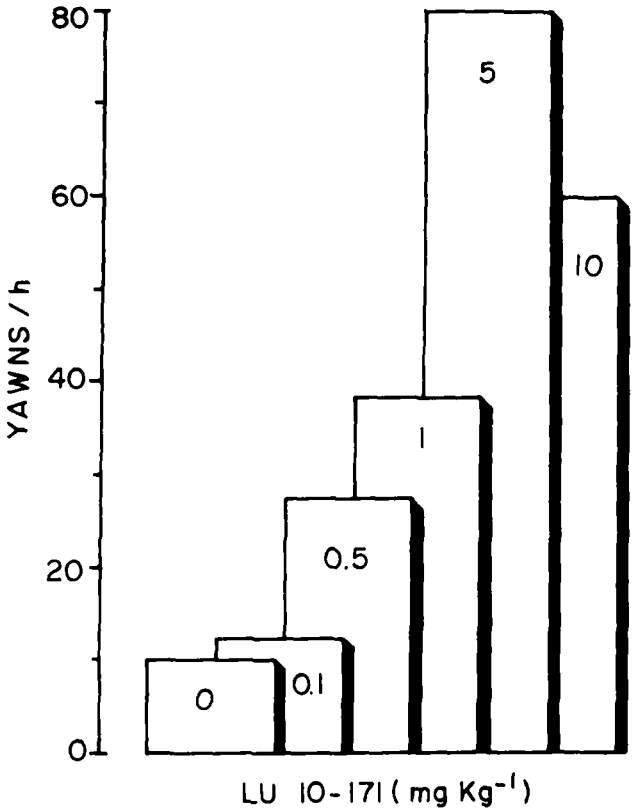

FIG. 1. Dose-effect graph of the potentiating action of Lu 10-171 on physostigmine-induced yawning. Each group consisted of 10–12 six to seven-day-old rats. The columns represent the mean number of yawns during 1 hr after IP injection of physostigmine (0.15 $mgKg^{-1}$). All doses of Lu 10-171 (except 0.1 $mgKg^{-1}$) produced significant effects when compared with the controls (0), as follows: 0.5 and 1 $mgKg^{-1}$), $p<0.05$; 5 and 10 $mgKg^{-1}$, $p<0.001$ (Mann-Whitney U Test). Other details in the text.

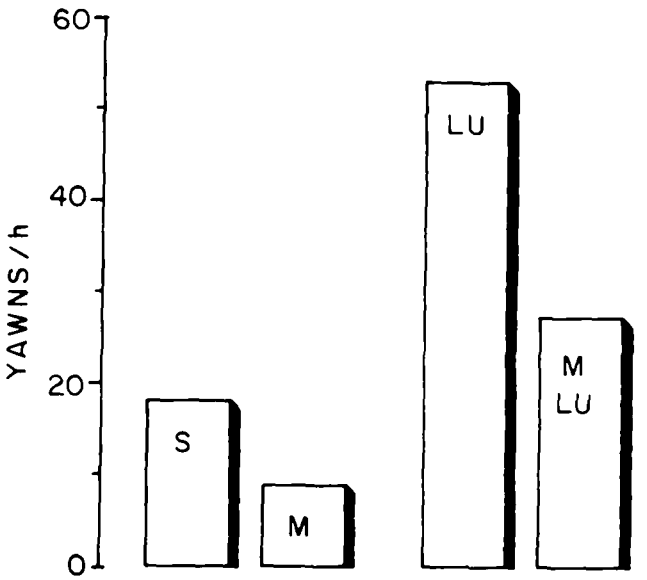

FIG. 2. Blocking effect of metergoline on the yawning potentiating action of Lu 10-171. Yawning induction as in Fig. 1. N = 10–12 in each group. Rats pretreated as follows: S, received saline both at 70 and 40 min before physostigmine: M, were injected with saline and metergoline (5 $mgKg^{-1}$) at the above indicated times: LU, received saline and Lu 10-171 (1 $mgKg^{-1}$) and M-LU were injected with metergoline and Lu 10-171 at the doses and times already indicated. Differences are statistically significant between S and LU at the level of $p<0.01$, and between LU and M-LU at the level of $p<0.05$ (Mann-Whitney U Test). Even if of the order of 50%, the reduction in yawning produced by metergoline, in the absence of LU 10-171 (S against M), is NS.

the mean yawning level after physostigmine was decreased to only 3 yawns/hour, that is, to 20 percent of the original level, a result which is highly significant ($p<0.001$, Mann-Whitney U test).

As Lu 10-171 is a very selective inhibitor of the 5-HT reuptake mechanisms, practically devoid of inhibitory effects on NA reuptake or on monoamine oxidase, and has only very weak anticholinergic and antihistaminergic properties [4], its potentiating effect on physostigmine-induced yawning may reasonably be ascribed to an increase of serotonin in central nervous system synapses somehow related to the cholinosensitive structures responsible for yawning. The effect of serotonin at this level seems to be only positively modulatory, because no yawning has been observed by the administration of Lu 10-171 alone. This interpretation is supported by the blocking effect of metergoline, both on the yawning-potentiating effect of Lu 10-171 and on the yawning-inducing effect of physostigmine, metergoline being a quite selective blocking agent of serotonin receptors [2].

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REFERENCES

1. Cowan, A. Cholinergic link in yawning. *Nature* **271**: 187–188, 1978.
2. Fuxe, K., L. Agnati and B. Everitt. Effects of methergoline on central monoamine neurons. Evidence for a selective blockade of central 5-HT receptors. *Neurosci. Lett* **1**: 283–290, 1975.
3. Holmgren, B. and R. Urbá-Holmgren. Ontogeny of two cholinergically mediated central effects: stereotyped yawning and potentiation of head-shaking. *Acta Neurobiol. Exp.* **38**: 11–23, 1978.
4. Hyttel, J. Neurochemical characterization of a new potent and selective serotonin uptake inhibitor: Lu 10-171. *Psychopharmacology* **51**: 225–233, 1977.
5. Jouvet, M. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. *Ergebn. Physiol.* **64**: 166–307, 1972.
6. Mogilnicka, E. and V. Klimek. Drugs affecting dopamine neurons and yawning behavior. *Pharmac. Biochem. Behav.* **7**: 303–305, 1977.
7. Morgane, P. J. and W. C. Stern. Relationship of sleep to neuroanatomical circuits, biochemistry, and behavior. *Ann. N. Y. Acad. Sci.* **193**: 95–111, 1972.
8. Urbá-Holmgren, R., R. M. González and B. Holmgren. Is yawning a cholinergic response? *Nature 267*: 261–262, 1977.