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Hypophysectomy Prevents ACTH-Induced Yawning and Penile Erection in Rats

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SERRA, G., W. FRATTA, M. COLLU AND G. L. GESSA. *Hypophysectomy prevents ACTH-induced yawning and penile erection in rats.* PHARMACOL BIOCHEM BEHAV **26**(2) 277–279, 1987.—The intracerebroventricular administration of $ACTH_{1-24}$ (3–5 μg/rat) produced a behavioural syndrome characterized by recurrent episodes of penile erection and yawning in rats. Hypophysectomy prevented $ACTH_{1-24}$-induced yawning and penile erection. These results suggest that pituitary has a "trophic" action not only on peripheral target organs but also on structures in brain controlling specific behavioural responses.

Yawning Penile erection ACTH Hypophysectomy

THE administration of ACTH or ACTH-derived neuropeptides into the cerebrospinal fluid (CSF) in mammals induces a behavioural syndrome characterized by recurrent episodes of stretching, yawning and penile erection [3, 4, 6].

A similar behavioural syndrome, though less intense, may be induced by systemic administration of minute doses of apomorphine or other dopamine (DA) receptor agonists [1, 7, 9, 10, 13–17].

We have recently shown that inhibition of protein synthesis [12] or hypophysectomy [11] prevents apomorphine-induced yawning and penile erection and suggested that these behavioural responses might be mediated by the release of ACTH or MSH newly synthetized from pituitary, reaching the brain via a retrograde portal flow [2]. Further support for this hypothesis is provided by the finding that small doses of apomorphine stimulate ACTH release from pituitary [8].

However, an alternative explanation for the suppressant effect of hypophysectomy on yawning and penile erection may be that hypophysectomy modifies the sensitivity of receptors in the CNS to DA and/or ACTH responsible for such behaviours.

To clarify this hypothesis, we investigated whether hypophysectomy would modify yawning and penile erection induced by the administration of $ACTH_{1-24}$ in rats.

The present results indicate that hypophysectomy prevents $ACTH_{1-24}$-induced yawning and penile erection, suggesting that pituitary has a permissive role for the expression of specific behaviours mediated by ACTH and related neuropeptides.

METHOD

Male Sprague-Dawley rats (Charles River, Como) weighing 120±10 g at the time of surgery were used. The animals were hypophysectomized in the Charles River laboratories (Como) with the transauricular technique. Control animals were anesthetized as the hypophysectomized ones, but surgery was simulated. One week after surgery, the animals were transferred to our laboratory, where they were housed 4 per cage at 22°C, humidity 60%, with a 12 hr light/dark cycle. The experiments were carried out 3 weeks after hypophysectomy between 09:00 and 14:00 hr 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 115±10 and 260±20 g, respectively.

Drug Administration

$ACTH_{1-24}$ (Synacthen-Ciba Geigy) was injected intracerebroventricularly (ICV) at the dose of 5 or 3 μg/rat in a volume of 3 μl saline through a C 313 G Guide Cannula aimed at a lateral ventricle. The cannula had been fixed under chloral hydrate anesthesia to the skull with acrylic dental cement and stainless steel screws. The rats were allowed 5–7 days recovery from the surgery before being used for the behavioural test.

Behavioural Observations

Animals were placed immediately after drug injection in individual small perspex observation cages (25×20×25 cm). Starting 5 min after the animals were put into the cage, the number of yawns and penile erections occurring during the following 120 min was scored.

Statistics

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

RESULTS

The results are summarized in the figures. As expected from previous experiments [3,6] the ICV administration of 3 or 5 μg/rat of $ACTH_{1-24}$ induced repeated episodes of yawn-

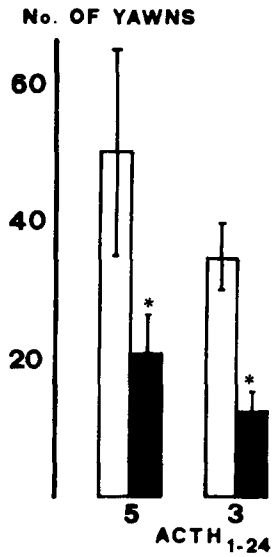

FIG. 1. Hypophysectomy prevents $ACTH_{1-24}$-induced yawning in rats. Each value represents the mean±S.E.M. of 9–10 animals. $ACTH_{1-24}$ (5 or 3 μg/rat) was administered in a lateral ventricle in both control □ and hypophysectomized ■ rats. The behavioural elements were scored for 120 min starting 5 min after drug injection (see the Method section). *$p<0.001$ with respect to the corresponding control group.

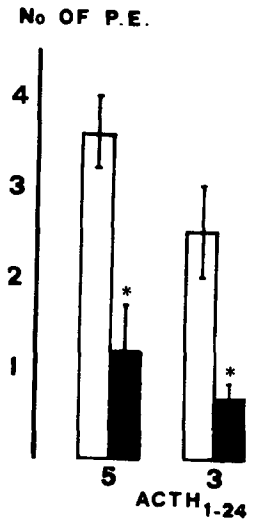

FIG. 2. Hypophysectomy prevents $ACTH_{1-24}$-induced penile erection (P.E.) in rats. Each value represents the mean±S.E.M. of 9–10 animals. $ACTH_{1-24}$ (5 or 3 μg/rat) was administered in a lateral ventricle in both control □ and hypophysectomized ■ rats. The behavioural elements were scored for 120 min starting 5 min after drug injection (see the Method section). *$p<0.001$ with respect to the corresponding control group.

ing and penile erection in intact animals. Both doses of $ACTH_{1-24}$ induced fewer episodes of yawning and penile erection in hypophysectomized than in intact rats.

DISCUSSION

We found that the removal of pituitary, besides preventing apomorphine-induced yawning and penile erection [11], also antagonizes these behavioral responses induced by ACTH suggest that hypophysectomy modifies the sensitivity of receptors to DA and ACTH in the brain mediating yawning and penile erection.

The consequence of hypophysectomy seems to be selective for specific receptors since it causes the loss of apomorphine and ACTH ability in inducing yawning and penile erection, but fails to affect other behavioural responses to apomorphine, such as the hypomotility produced by the minute doses of apomorphine [11], and motor stimulation and stereotypy produced by high doses of the drug (Serra *et al.*, in preparation). Moreover, de Wied's group has shown that hypophysectomy does not prevent the positive effect of ACTH and ACTH-derived peptides on memory and learning in rats [5], suggesting that the central ACTH receptors involved in such response are not modified by hypophysectomy.

Pituitary might control the sensitivity of central DA and ACTH receptors mediating yawning and penile erection directly, via some pituitary hormone, reaching the brain via retrograde portal flow [2], or indirectly, via some pituitary-controlled hormone. Whereas testosterone might have a permissive role in the sexual effect of apomorphine [14] and ACTH [3], the lack of testosterone cannot account for the loss of the yawning response since castration fails to modify such effect elicited by ACTH [3] or apomorphine administration [14].

The present results are of great interest because they suggest that pituitary has a "trophic" action not only on peripheral target organs but also on structures in brain controlling specific behavioural responses.

These results leave unresolved the problem of whether yawning and penile erection induced by apomorphine and other DA-agonists involve the release of ACTH-derived neuropeptides from the pituitary or from central peptidergic neurons. The solution of this problem is hampered by the fact that, unfortunately, no specific antagonists for central receptors to ACTH and ACTH-related peptides are presently available. However we have observed [16] that sulpiride, a specific DA receptor blocker, potently antagonizes apomorphine-induced yawning but fails to affect this behavioural response induce by $ACTH_{1-24}$, suggesting that ACTH-induced yawning involves neither DA receptor activation nor DA release.

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