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Hippocampal Oxytocin Mediates Apomorphine-Induced Penile Erection and Yawning

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MELIS, M. R., R. STANCAMPIANO AND A. ARGIOLAS. *Hippocampal oxytocin mediates apomorphine-induced penile erection and yawning.* PHARMACOL BIOCHEM BEHAV **42**(1) 61-66, 1992. – Repeated episodes of penile erection and yawning can be induced in male rats either by low doses of the dopaminergic agonist apomorphine or by oxytocin given systematically or into a lateral ventricle (ICV), respectively, or after microinjection of the two substances directly in the paraventricular nucleus (PVN) of the hypothalamus. These behavioral responses are prevented in a dose-dependent manner by the ICV administration of the potent oxytocin antagonist $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin. In contrast, the PVN injection of $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin (1-30 ng), while effective in preventing oxytocin effect, was unable to prevent apomorphine response. On the other hand, apomorphine-, but not oxytocin-induced penile erection and yawning was prevented by electrolytic lesion of the medial septum (MS). Such a lesion decreased oxytocin content by about 45% in the hippocampus. The above results suggest that the hypothalamic-hippocampal oxytocinergic pathway mediates apomorphine-induced penile erection and yawning and that oxytocin is involved at different levels in the CNS for the control of these behavioral responses.

Apomorphine Oxytocin Penile erection Yawning Rat

PENILE erection and yawning are two different behavioral patterns that often occur concomitantly under physiological and experimental conditions (12). While the importance of penile erection in reproduction of mammals does not need to be stressed, it is pertinent to recall that yawning, alone or associated with stretching, is considered an ancestral vestige surviving throughout evolution that subserves the purpose of arousal [see (4)]. Several lines of experimental evidence suggest that a central dopamine–oxytocin link plays a key role in the expression of such symptomatology. Accordingly, both apomorphine and oxytocin induce penile erection and yawning when unilaterally injected in the paraventricular nucleus (PVN) of the hypothalamus (19,20); lesions of the PVN abolish apomorphine and oxytocin responses (2); dopamine receptor blockers prevent apomorphine but not oxytocin effects (1); nonapeptide oxytocin antagonists prevent apomorphine-induced penile erection and yawning (21); finally, apomorphine increases oxytocin content in brain, as well as in plasma (22). The above results support the hypothesis that apomorphine and dopaminergic agonists induce penile erection and yawning by releasing oxytocin in the CNS by acting in the PVN. In this regard, it is pertinent to recall that the PVN contains not only the majority of the cell bodies of those oxytocinergic neurons, which project to extrahypothalamic brain areas, that is, septum, hippocampus, olfactory bulb, brain stem, pons, medulla and spinal cord (5,6,28), but also dopaminergic neurons, located in the proximity of oxytocinergic cell bodies, that belong to the incertohypothalamic dopaminergic system [see (7,8,15)].

Recently, it has been shown that septohippocampal lesions prevent apomorphine-induced penile erection and yawning (18). Taken together with the finding showing that oxytocin induces penile erection and yawning when bilaterally injected into the CA1 field of the hippocampus (19), this raises the possibility that the oxytocinergic pathways activated by apomorphine and that mediate penile erection and yawning are those projecting to the septum and hippocampus. To verify such a hypothesis, we studied: 1) the effect of a potent oxytocin nonapeptide antagonist injected into the PVN on apomorphine- and oxytocin-induced penile erection and yawning; 2) the effect of oxytocin and apomorphine microinjected in the medial septum (MS) on these behavioral responses; and 3) the effect of electrolytic lesions of the MS on oxytocin-induced penile erection and yawning, as well as on oxytocin concentration in the hippocampus.

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METHOD

Animals

Male Sprague-Dawley rats (200–250 g, Morini, Bologna, Italy) were used in all experiments. Rats were caged in groups of four to six at 24°C, humidity 60%, with water and standard laboratory food available ad lib.

Electrolytic Lesions of the MS

For electrolytic lesion of the MS, rats were anesthetized with chloral hydrate and positioned in a stereotaxic apparatus (David Kopf Instruments, USA). Following exposure of the skull, a small hole was drilled using a dental burr at the MS coordinates (2.0 mm anterior to bregma along the midline) (25). The 0.2-mm diameter tip of a tungsten electrode was lowered to a depth of 6.0 mm into the brain. A current of 2 mA was passed for 30 s using a Grass DC constant-current lesion maker (Grass Medical Instruments, Quincy, MA). In control animals (sham-lesion), the electrode was lowered into the brain at the MS coordinates for 30 s but no current was passed. After the electrode was removed, chronic guide cannulas for ICV or PVN injections were implanted as described below. Experiments were performed 5 days later.

ICV and PVN Injections

Stainless steel guide cannulas (22 ga) aimed at one lateral ventricle (ICV) or unilaterally at the PVN or centrally at the MS or bilaterally at the hippocampus (CA1 field) were also stereotaxically implanted under chloral hydrate anaesthesia 5 days before experiments (coordinates: lateral ventricle, 1 mm anterior to bregma, 1.5 mm lateral to midline, and 2 mm ventral to dura; PVN, 0.2 mm anterior to bregma, 0.4 mm lateral to midline, and 2 mm ventral to dura; MS, 2.0 mm anterior to bregma, along the midline, and 2.0 mm ventral to dura; hippocampal CA1 field, 3.0 mm posterior to bregma, ±1.8 mm lateral to midline, and 2.0 mm ventral to dura) (25). Animals were allowed 5 days to recover from surgery; each rat was used only once. Saline (5 μl in 15 s) or oxytocin dissolved in saline was injected ICV via an internal cannula (28 ga) that extended 2 mm below the tip of the guide cannula and connected by polyethylene tubing to a 10-μl Hamilton syringe driven by a micrometric screw. For PVN, hippocampal, or MS microinjections, saline, apomorphine, oxytocin, and the oxytocin antagonist $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin dissolved in saline (0.3 μl in 2 min) were injected in the PVN by means of an internal cannula (28 ga) that extended 5.3 mm for the PVN, 1.0 mm for the hippocampus, and 4.0 mm for the MS, respectively, below the tip of the guide cannula and connected to a 10-μl Hamilton syringe driven by a Stoelting microinfusion pump. After PVN, hippocampal, or MS injections, the tip of the cannula was left in the injection site for 30 s to allow the spread of the injected solution.

Systemic Treatments

Apomorphine-HCl was dissolved in saline and injected SC in a volume of 0.2 ml/200 g body weight. Controls received the same volume of SC saline.

Behavioral Studies

In experiments in which the oxytocin antagonist was given in the PVN, apomorphine or oxytocin was given 5 min later. Soon after oxytocin or apomorphine, animals were placed individually into Plexiglas cages (30 × 30 × 30 cm) and observed for 60 min, during which penile erection and yawning episodes were counted. At the end of the experiments, animals were killed by decapitation and brains were removed and visually inspected to ascertain the correct position of the cannula tip into the lateral ventricle. In experiments in which MS lesion, PVN, MS, or hippocampal microinjections were performed, at the end of the experiments animals were killed by decapitation and brains removed and stored in saline containing 2% formaldehyde for 12–15 days. To localize the extension of the lesion and injection site, 50-μm transverse brain sections were prepared by means of a freezing microtome, stained with Neutral Red, and inspected on a phase contrast microscope. While the MS lesion was easily recognized, the injection site was localized by following the internal cannula tract through a series of brain sections. Only those animals found to have the lesion localized in the MS and/or the internal cannula tip positioned correctly in the lateral ventricle, PVN, MS, or CA1 field of the hippocampus were considered for statistical analysis of the results.

Oxytocin Radioimmunoassay

MS-lesioned rats were first divided into two groups, including those animals that were responsive (R-LES) and unresponsive (UR-LES) to apomorphine, respectively (i.e., showed or failed to show penile erection and yawning after apomorphine). Intact and sham-lesioned rats were also used for comparison. Rats were killed by decapitation and the hippocampus was immediately dissected out, and transferred into 16 × 125 mm polypropylene tubes containing 3 ml ice-cold 2 N acetic acid, and boiled for 10 min in a water bath. After homogenization, a small aliquot of each sample was taken for measuring protein content (16). Samples were centrifuged for 15 min at 28,000 × g at 4°C and the clear supernatant transferred to another polypropylene tube and concentrated under vacuum with a Speed Vac (Savant). Samples were dissolved in buffer for oxytocin radioimmunoassay (RIA). Under the above conditions, more than 80% of authentic [^{125}I]oxytocin added to the homogenization medium was recovered. Oxytocin was measured by a well-characterized RIA (14) by using a specific antibody generously provided by Dr. L. Keil (NASA, Ames Research Center, Moffett Field, CA), except for the separation of free and bound [^{125}I]oxytocin, which was performed by means of dextrane-coated charcoal. [^{125}I]oxytocin was prepared by the chloramine T method and purified by gel filtration on Sephadex G25. Synthetic oxytocin was used as the standard. Under our conditions, the linear range of the assay was 0.25–10 pg/tube and the intra- and interassay variation were 10 and 17%, respectively.

Drugs and Peptides

Apomorphine-HCl was purchased from Sigma, (St. Louis, MO). Synthetic oxytocin and $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin were purchased from Peninsula Laboratories (Palo Alto, CA).

Statistics

Statistical evaluation of the results was performed by one-way analysis of variance (ANOVA), followed by Duncan's multiple-range test. A $p < 0.05$ was considered significant.

RESULTS

Effect of $d(CH_2)_5$Tyr(Me)-Orn^8-Vasotocin Microinjected into the PVN on Penile Erection and Yawning Induced by Oxytocin and Apomorphine

As shown in Fig. 1, $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin microinjected in the PVN (0–30 ng/0.3 μl) 5 min before oxytocin

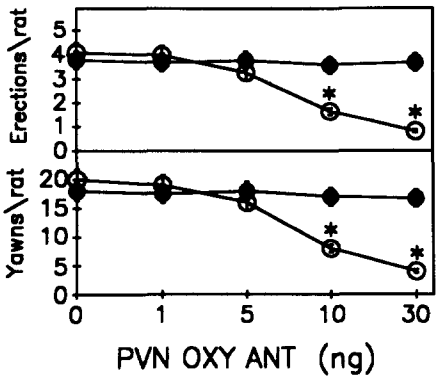

FIG. 1. Effect of the PVN microinjection of $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin on penile erection and yawning induced by (○) ICV oxytocin or (●) SC apomorphine. The oxytocin antagonist (0–30 ng/0.3 μl) was microinjected in the PVN 5 min before oxytocin (30 ng, ICV) or apormorphine (80 μg/kg, SC). Values are means ± SEM of three experiments (10 rats per group). *$p < 0.05$ with respect to PVN saline-treated rats (oxytocin antagonist = 0).

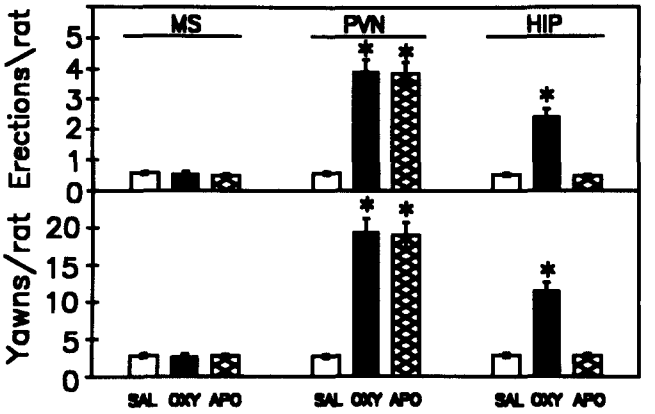

FIG. 2. Effect of saline (0.3 μl, open bars), oxytocin (10 ng/0.3 μl, filled bars), and apomorphine (1 μg/0.3 μl, crosshatched bars) microinjected into the MS, unilaterally into the PVN, and bilaterally into the CA1 field of the hippocampus (HIP) on penile erection and yawning. Each value is the mean ± SEM of 10 rats. *$p < 0.05$ with respect to saline-treated rats.

prevented in a dose-dependent manner penile erection and yawning induced by oxytocin (30 ng, ICV). A 50% prevention of the oxytocin response was obtained with the dose of 10 ng, *df* 49, $F(2, 52) = 31$ and 44, $p < 0.05$. In contrast, $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin was ineffective against penile erection and yawning induced by apomorphine (80 μg/kg, SC). Similar results were found when penile erection and yawning were induced by the PVN injection of oxytocin (10 ng/0.3 μl), *df* 31, $F(2, 92) = 34$ and 54, $p < 0.05$, or of apomorphine (50 ng/0.3 μl) (Table 1).

Effect of MS Injections of Oxytocin and Apomorphine on Penile Erection and Yawning

Oxytocin (10 ng/0.3 μl) or apomorphine (1 μg/0.3 μl) injected into the MS was unable to induce penile erection and yawning in male rats. In contrast, the above responses were observed when oxytocin or apomorphine was injected unilaterally into the PVN [*df* 29, $F(3, 33) = 23$ and 45, and 21 and 55 after oxytocin and apomorphine, respectively, $p < 0.05$] or oxytocin was injected bilaterally into the CA1 field of the hippocampus, *df* 29, $F(3, 33) = 21$ and 32, $p < 0.05$. Unlike oxytocin, apomorphine did not induce penile erection or yawning when injected bilaterally into the CA1 field of the hippocampus (Fig. 2).

Effect of MS Lesion on Oxytocin- and Apomorphine-Induced Penile Erection and Yawning

Figure 3 shows the effect of MS lesion on penile erection and yawning induced by oxytocin or apomorphine. In sham-MS-lesioned rats, both oxytocin (30 ng, ICV) and apomorphine (80 μg/kg, SC) induced penile erection and yawning [*df* 44, $F(3, 23) = 35$ and 32, and 30 and 55 after oxytocin and apomorphine, respectively, $p < 0.05$]. In MS-lesioned rats, while oxytocin induced penile erection and yawning, *df* 44, $F(3, 23) = 23$ and 32, $p < 0.05$, apomorphine was inactive in about 75% of MS-lesioned rats. Similar results were also found when oxytocin or apomorphine was unilaterally injected directly in the PVN. In fact, while oxytocin (10 ng/0.3 μl) and apomorphine (50 ng/0.3 μl) induced a similar number

TABLE 1

EFFECT OF PVN $d(CH_2)_5$TYR(ME)-ORN^8-VASOTOCIN ON PENILE ERECTION AND YAWNING INDUCED BY PVN OXYTOCIN OR APOMORPHINE

PVN Treatment	Erections/Rat	Yawns/Rat
Saline + oxytocin	3.87 ± 0.36	18.00 ± 1.60
Saline + apomorphine	3.95 ± 0.37	19.50 ± 1.75
$d(CH_2)_5$Tyr(Me)-Orn^8-VT + oxytocin	0.60 ± 0.05*	2.00 ± 0.18*
$d(CH_2)_5$Tyr(Me)-Orn^8-VT + apomorphine	3.90 ± 0.37	19.75 ± 1.77

Saline (0.3 μl) or oxytocin antagonist (30 ng/0.3 μl) was microinjected unilaterally in the PVN 5 min before oxytocin (10 ng/0.3 μl) or apomorphine (50 ng/0.3 μl). Values are means ± SEM of four experiments (eight rats per group).

*$p < 0.05$ with respect to PVN saline-pretreated rats (oxytocin antagonist = 0).

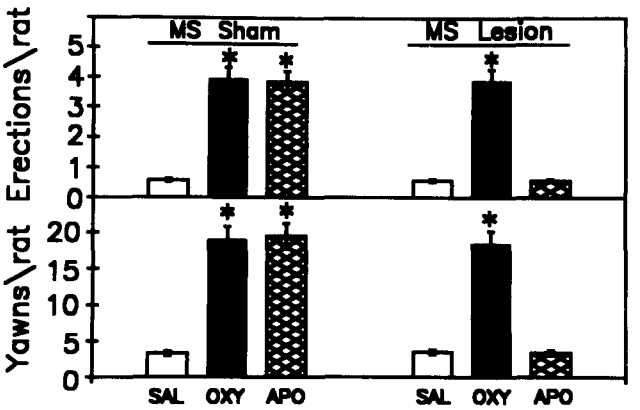

FIG. 3. Effect of MS lesion on penile erection and yawning induced by ICV saline (5 μl, open bars), oxytocin (30 ng, filled bars), or SC apomorphine (80 μg/kg, crosshatched bars). Values are means ± SEM of three experiments (15 rats per group). *$p < 0.05$ with respect to saline-treated rats.

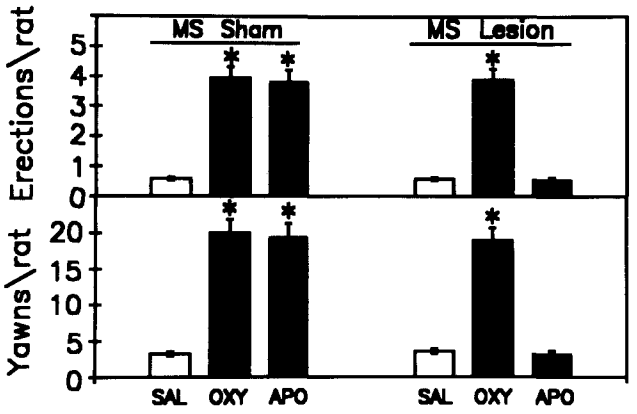

FIG. 4. Effect of MS lesion on penile erection and yawning induced by the PVN microinjection of saline (0.3 μl, open bars), oxytocin (10 ng/0.3 μl, crosshatched bars), or apomorphine (50 ng/0.3 μl, filled bars). Values are means ± SEM of three experiments (21 rats per group). *$p < 0.05$ with respect to saline-treated rats.

of penile erection and yawning episodes in sham-MS lesioned rats [df 62, $F(3, 15) = 27$ and 36, and 33 and 63 after oxytocin and apomorphine respectively, $p < 0.05$], in MS-lesioned rats oxytocin, but not apomorphine, induced the behavioral responses, df 62, $F(3, 15) = 23$ and 44, $p < 0.05$ (Fig. 4).

Effect of MS Lesion on Oxytocin Concentration in the Hippocampus

Figure 5 shows the oxytocin content in the hippocampus of intact, sham-lesioned, and MS-lesioned rats that were responsive (R-LES) and unresponsive (UR-LES), respectively, to apomorphine. Lesioned rats were killed 2 days after apomorphine challenge. In UR-LES MS-lesioned rats, oxytocin content was decreased by about 45% with respect to sham-lesioned rats and to the R-LES MS-lesioned rats, df 63, $F(2, 76) = 33.85$, $p < 0.05$. These two latter groups showed oxytocin levels similar to those of control rats.

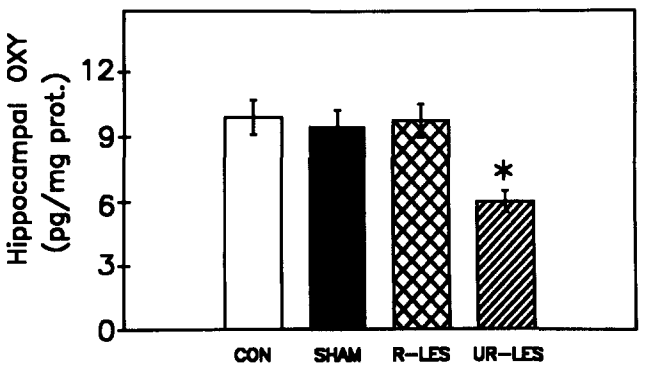

FIG. 5. Effect of MS lesion on oxytocin concentration in the hippocampus. The hippocampal concentration of immunoreactive oxytocin was measured by RIA in intact control (open bars), sham-lesioned (filled bars), and MS-lesioned rats, previously divided in apomorphine-responsive (R-LES) (crosshatched bars) and apomorphine-unresponsive (UR-LES)(diagonal bars). Values are means ± SEM of three experiments (16 rats per group). *$p < 0.05$ with respect to control rats.

Histology

In a separate experiment, the histological analysis revealed that in UR-LES MS-lesioned rats the whole region of the MS was damaged in both lateral and rostrocaudal directions (Fig. 6). The lesion extended from the plane in which the anterior commissure begins to the plane in which the anterior commissure ends and involved parts of both lateral septi, the medial paraolfactory area, and the rostral hippocampus (Cornu Ammonis) [see (25)]. In contrast, in R-LES MS-lesioned rats the MS lesion was complete but localized more caudally than that found in UR-LES MS-lesioned rats, involving mainly the surrounding lateral septi.

DISCUSSION

The present study shows that the oxytocin antagonist $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin injected into the PVN prevents penile erection and yawning induced by oxytocin but not by apomorphine, while MS lesions that decrease hippocampal oxytocin concentration prevent the above behavioral responses induced by apomorphine but not by oxytocin. These

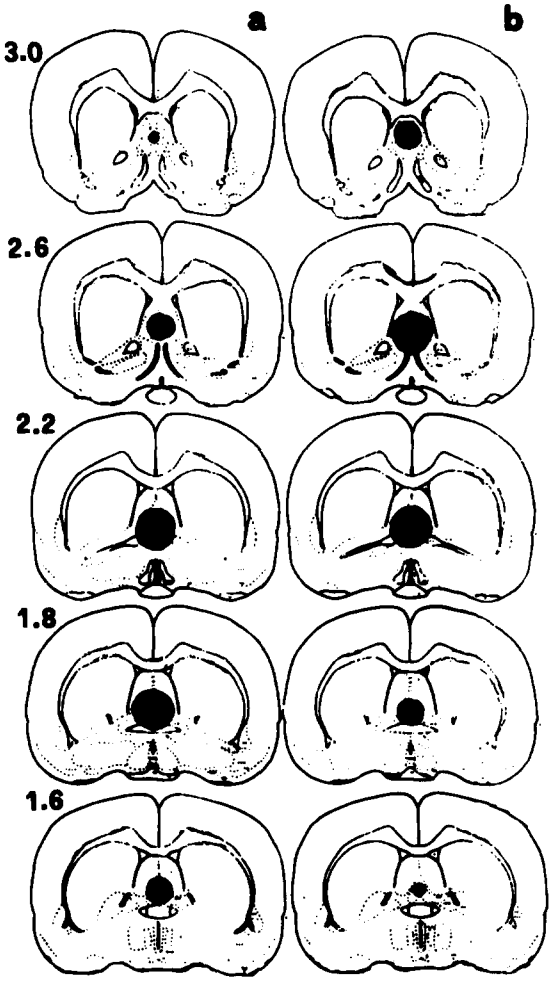

FIG. 6. Schematic representation of MS lesion in (a) apomorphine-responsive and (b) unresponsive rats through serial transverse brain sections [see (25) for coordinates].

results extend previous findings suggesting that the dopaminergic agonist apomorphine induces penile erection and yawning by releasing oxytocin in the CNS. In particular, the failure of $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin to prevent apomorphine response when injected in the PVN, in spite of its efficacy when given ICV [see (21)], suggests that apomorphine induces penile erection and yawning by increasing oxytocinergic activity by acting directly on dopaminergic receptors at the level of the oxytocinergic cell bodies or indirectly by removing some inhibitory input on oxytocinergic neurons, rather than by releasing oxytocin in the PVN. On the other hand, the ability of $d(CH_2)_5$Tyr(Me)-Orn^8-vasotocin injected into the PVN to prevent ICV or PVN oxytocin response confirms that oxytocin acts mainly in the PVN to induce penile erection and yawning (19) possibly by stimulating specific oxytocinergic receptors located in this hypothalamic nucleus. In line with the hypothesis that apomorphine induces penile erection and yawning by activating oxytocinergic neurons, it is likely that oxytocin also induces the above responses by increasing its own transmission, perhaps by stimulating oxytocinergic receptors located in the cell bodies of its own neurons in the PVN. Accordingly, exogenous oxytocin injected in the PVN has been found capable of activating its own release in vivo (10,11) and in vitro (23) from magnocellular neurons, and immunoreactive oxytocinergic synapses have been found to impinge on the cell bodies of oxytocinergic neurons in both hypothalamic supraoptic and paraventricular nuclei (30).

In agreement with the above hypotheses, the failure of apomorphine to induce penile erection and yawning when injected directly in the MS or in the hippocampus or in MS-lesioned rats [(18) and the present results], although effective when injected in the PVN, suggests that apomorphine induces the above responses by activating those oxytocinergic pathways originating in the PVN that reach the medial septum or the rostral hippocampus (tenia tectae) passing rostrally to the septum (6). The second possibility is the most likely, being favored by the failure of oxytocin to induce penile erection and yawning when injected in the MS, by the finding showing that MS lesions decrease hippocampal oxytocin concentration only in those animals found unresponsive to apomorphine and by the failure of iontophoretically applied oxytocin to activate MS neurons (13).

The ineffectiveness of apomorphine to induce penile erection and yawning when injected into the MS is in contrast with previous studies showing that the bilateral injection of apomorphine into the lateral septum induces yawning (35). The discrepancy might be explained by the fact that in those studies doses of apomorphine (10 μg and higher per site) were used that were too high and probably resulted in the spread of the drug to the active site. Accordingly, it is unlikely that apomorphine acts directly in the MS, although a septohippocampal dopamine-acetylcholine link has been supposed to be involved in the expression of yawning and penile erection (34). In fact, if the latter hypothesis were correct, the stimulation of dopaminergic receptors in the MS would induce a cholinergic inhibition mediating in turn penile erection and yawning. Against such hypothesis, muscarinic agonists induce the above behavioral responses (34), possibly acting in the hippocampus (18,32), and blockade of cholinergic transmission by muscarinic antagonists atropine and scopolamine, as well as by MS lesions, which decrease hippocampal acetylcholine content [see (18)], prevent apomorphine response (18,32, 34,35).

Taken together with the inability of MS lesion to prevent oxytocin response, the above results suggest that apomorphine induces penile erection and yawning by activating selectively the hypothalamic-hippocampal oxytocinergic projection. In this respect, it is noteworthy that the hippocampus plays a key role in the expression of penile erection and sexual behavior [see (17)], apomorphine increases oxytocin content in this brain area at doses that induce penile erection and yawning (22), oxytocin induces these behavioral responses when injected in the CA1 field of the hippocampus (19), and oxytocin excites hippocampal neurons by acting on uterine-type oxytocinergic receptors (9,24), those that mediate penile erection and yawning (3). Nevertheless, it is likely that this hypothalamic-hippocampal oxytocinergic pathway plays only a minor role or is not involved at all in the oxytocin response. In fact, the inability of MS lesion to prevent the effect of oxytocin injected in the PVN raises the possibility that oxytocin may act in the PVN to induce penile erection and yawning by stimulating other neuronal pathways not involving the hippocampus, that is, the oxytocinergic projections reaching the pons, medulla, and spinal cord (5,6,26,28). Accordingly, the PVN is considered a sort of integration center between the central and autonomic nervous systems (29). In view of the prevention of oxytocin effect by PVN lesions but not by MS lesions, it is tempting to speculate that a hippocampal-hypothalamic pathway, whose activity is modified by apomorphine treatment, mediates in turn the activity of the same neuronal circuits modified by PVN oxytocin and controlling the above behavioral responses. In agreement with this hypothesis, neuronal pathways originating in the hippocampus and septum that exert an excitatory input on vasopressinergic and oxytocinergic neurons in the PVN have been described (27,31).

The involvement of oxytocin in different central neuronal pathways that control penile erection and yawning deserves some comment. One of these pathways, that is, the hypothalamic-hippocampal oxytocinergic pathway, is activated by apomorphine and probably by other dopaminergic agonists through the stimulation of D_2 dopamine receptors in the PVN [see (20)]. Interestingly, the PVN contains the A14 group of the so-called incertohypothalamic dopaminergic system (8). These small dopaminergic neurons arborize extensively and surround the oxytocinergic neuronal cell bodies in the PVN (7,15). This suggests that this still poorly characterized hypothalamic dopaminergic system plays a major role in the expression of yawning and penile erection. Since the hypothalamus, the first developed brain structure from a phylogenetic point of view, plays a primary role survived during evolution from fishes to primates in reproduction, it is easy to speculate that hypothalamic oxytocin is involved in the control of penile erection in mammals. The involvement of oxytocin in the expression of penile erection in brain areas phylogenetically developed later, but strictly connected to the hypothalamus (i.e., the limbic system), might be one of those mechanisms by means of which high brain centers control such a primary sexual function. In particular, the activation of central oxytocinergic pathways by dopamine, a neurotransmitter involved in motivation and rewarding mechanisms [see (33)], raises the possibility that oxytocin in the limbic system plays a role in sexual arousal and motivation (libido in men), while its action in the hypothalamus may be related mainly to erectile and ejaculatory performance (potency in men).

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