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Oxytocin-Induced Penile Erection and Yawning: Role of Calcium and Prostaglandins

A. ARGIOLAS, M. R. MELIS, R. STANCAMPIANO AND G. L. GESSA

Department of Neurosciences, University of Cagliari, Via Porcell 4, 09124 Cagliari, Italy

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ARGIOLAS, A., M. R. MELIS, R. STANCAMPIANO AND G. L. GESSA. *Oxytocin-induced penile erection and yawning: Role of calcium and prostaglandins*. PHARMACOL BIOCHEM BEHAV **35**(3) 601–605, 1990.—The effect of verapamil, flunarizine, nimodipine, nicardipine, and nifedipine, calcium channel inhibitors, and of indomethacin and aspirin, inhibitors of prostaglandin synthesis, on penile erection and yawning induced by oxytocin was studied in male rats. All calcium channel inhibitors given intraperitoneally (IP) 60 min before the intracerebroventricular (ICV) injection of oxytocin (30 ng) prevented in a dose-dependent manner oxytocin effect. Nimodipine and nicardipine were the most effective being active at doses between 5 and 20 mg/kg, while the others were active at doses higher than 15 mg/kg. Prevention of oxytocin effect was also seen after ICV injection of the above compounds. Unlike calcium channel inhibitors, indomethacin given either IP (10 and 50 mg/kg) or ICV (50 μg), or aspirin (100 mg/kg IP) were ineffective. Microinjection of calcium, but not of prostaglandin E_2 and prostaglandin $F_{2\alpha}$ in the paraventricular nucleus of the hypothalamus, the brain area most sensitive for the induction of the above behavioral responses by oxytocin, induced a symptomatology similar to that induced by oxytocin. The present results suggest that calcium might be the second messenger which mediates the expression of penile erection and yawning induced by oxytocin.

Oxytocin Calcium channel inhibitors Prostaglandins Indomethacin Penile erection Yawning Rat

THE central administration of nanogram amounts of oxytocin induces repeated episodes of penile erection and yawning in male rats (1, 3, 15). This effect seems to be mediated by the stimulation of specific uterine-type oxytocinergic receptors, being induced by oxytocin analogs with a potency that follows their oxytocic potency and prevented by nonapeptide antagonists with a rank order of potency that follows their antioxytocic activity (4). These receptors are probably located in the paraventricular nucleus of the hypothalamus (PVN), since microinjection studies have revealed this nucleus to be the most sensitive brain area for the induction of the above behavioral responses by oxytocin (15), while its destruction causes an almost complete prevention of oxytocin effect (2).

The involvement of uterine-type oxytocinergic receptors in the expression of oxytocin-induced penile erection and yawning raises the possibility that oxytocin is acting in the central nervous system to induce the above responses by a mechanism similar to that responsible for the induction of uterine contraction. In the uterus oxytocin receptor stimulation induces both calcium mobilization and synthesis of prostaglandins, other potent stimulants of the uterus which probably act synergistically with oxytocin during parturition [for a review see (6) and (11)]. In order to verify whether or not calcium and prostaglandins play a role in the expression of oxytocin-induced penile erection and yawning, we have studied the effect of inhibitors of calcium channels and of prostaglandin synthesis on oxytocin-induced penile erection and yawning and the effect of microinjection of calcium and prostaglandins in the PVN on spontaneous penile erection and yawning as well.

METHOD

Male Sprague-Dawley rats (200–250 g, Morini, Bologna, Italy) were used in all the experiments. Rats were caged in groups of 4–6 at 24°C, humidity 60%, with water and standard laboratory food ad lib.

ICV and PVN Injections

Stainless steel guide cannulas (22 gauge) aimed at one lateral ventricle or monolaterally at the PVN were stereotaxically implanted (David Kopf Instruments, USA) under chloral hydrate anaesthesia 5 days before the 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) (21). Substances dissolved in appropriate vehicle or vehicle alone were injected into a lateral ventricle (ICV) via an internal cannula (28 gauge), which 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. Vehicles were saline for oxytocin, distilled water:ethylene glycol:ethanol (60:30:10, V:V:V) for calcium channel inhibitors and 50 mM sodium-potassium phosphate buffer pH = 8.0 for indomethacin. Volumes injected ICV were 5–10 μl in 0.5–1 min. For PVN microinjections prostaglandins were dis-

solved in 50 mM sodium-potassium phosphate buffer pH = 8.0. Calcium gluconate was dissolved in distilled water (mEq/l Ca^{++} = 480). Microinjections were performed by means of an internal cannula (28 gauge) which extended 5.3 mm below the tip of the guide cannula and connected to a 10 μl Hamilton syringe driven by a Stoelting microinfusion pump. Volumes injected were 0.5 μl and 2 μl in 0.5 and 2 min for prostaglandins and calcium gluconate, respectively. The same volume of phosphate buffer or of 11% glucose solution (isoosmotic control) was microinjected in controls. After injection the tip of the cannula was left in the injection side for 30 sec to allow the spread of the injected solution.

Systemic Treatments

Verapamil, flunarizine-2HCl, nimodipine, nicardipine-HCl and nifedipine-HCl were dissolved in distilled water:ethylene glycol: ethanol (60:30:10, V:V:V) and injected intraperitoneally (IP) in a volume of 1 ml/rat. Indomethacin and aspirin were dissolved in 50 mM sodium-potassium phosphate buffer pH = 8.0 and pH = 8.9, respectively, and injected IP in a volume of 2 ml/rat. Controls received 2 ml IP of the corresponding vehicle.

Behavioral Studies

Calcium channel inhibitors were administered IP or ICV 60 min or 15 min, respectively, before ICV oxytocin. Indomethacin and aspirin were administered IP 30 min before oxytocin. Soon after treatment, the 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, the animals were killed by decapitation, the brains were removed and visually inspected to ascertain the correct position of the cannula tip into the lateral ventricle. In the experiments in which PVN microinjections were made, at the end of the experiment rats were killed by decapitation, the brains removed and stored in saline containing 2% formaldehyde for 12–15 days. In order to localize the 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. Only those animals that were found to have the cannula tip positioned correctly were considered for statistical analysis of the results (Duncan's multiple range test).

Drugs

(±)Verapamil, flunarizine-2HCl, nifedipine-HCl, nicardipine-HCl, indomethacin, aspirin, prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were purchased from Sigma (St. Louis, MO), nimodipine from Bayer (Italy), calcium gluconate from Carlo Erba (Milan, Italy) and oxytocin from Peninsula Laboratories (San Carlos, CA).

RESULTS

Prevention of Oxytocin-Induced Penile Erection and Yawning by Calcium Channel Inhibitors

As shown in Fig. 1, 30 ng of ICV oxytocin induced repeated episodes of penile erection and yawning in male rats. Both responses were prevented by IP pretreatment with the calcium channel inhibitors verapamil, flunarizine, nimodipine, nicardipine and nifedipine in a dose-dependent manner. Nimodipine and nicardipine were found to be the most effective, being the dose of 10 mg/kg of both compounds capable of inducing a 30–40% prevention of oxytocin-induced response. A total prevention was found with doses of 10–20 mg/kg of either compound. Nifedipine,

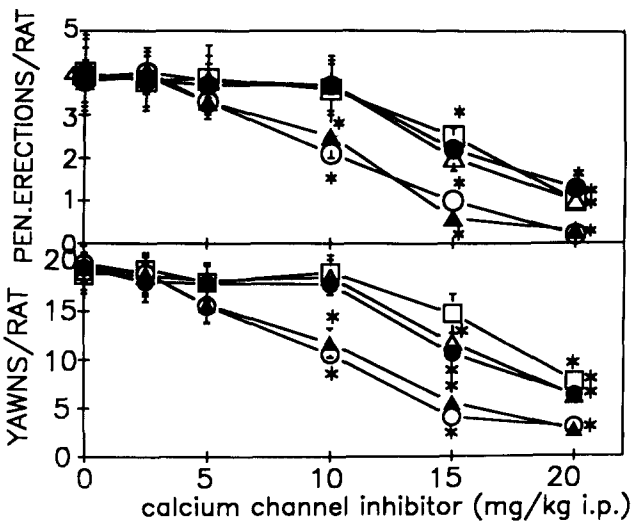

FIG. 1. Prevention of oxytocin-induced penile erection and yawning by calcium channel inhibitors: systemic administration. All rats received oxytocin (30 ng ICV). Verapamil (●), flunarizine (△), nifedipine (□), nimodipine (▲) and nicardipine (○) or vehicle alone were administered IP 60 min before oxytocin. After treatment, the animals were placed individually into Plexiglas cages and observed for 60 min during which penile erection and yawning episodes were counted. Each value is the mean ± S.E.M. of 3 experiments (20 rats per group). *$p<0.001$ with respect to controls (calcium antagonist = 0).

verapamil and flunarizine were also active, but their smaller active dose was 15 mg/kg, which prevented oxytocin effect by about 25–30%. The highest dose used (20 mg/kg) prevented penile erection and yawning induced by oxytocin by about 85–90%. A 75% or higher prevention of oxytocin effect was also seen when verapamil, flunarizine and nicardipine were injected ICV at the dose of 50 μg in 10 μl vehicle 10 min before oxytocin in 80% of the treated rats (Fig. 2). At the above IP and ICV doses, calcium channel inhibitors failed to induce any overt behavioral change.

Failure of Indomethacin and Aspirin to Alter Oxytocin-Induced Penile Erection and Yawning

Table 1 shows the effect of the systemic pretreatment with indomethacin and aspirin, potent inhibitors of prostaglandin synthesis (8), on penile erection and yawning induced by oxytocin. Indomethacin (10 and 50 mg/kg IP) and aspirin (100 mg/kg IP) given 30 min before oxytocin (30 ng ICV), were unable to alter oxytocin-induced responses. Indomethacin (50 μg) was ineffective also when given ICV 15 min before oxytocin. At the above doses, indomethacin and aspirin failed to induce any overt behavioral change.

Effect of Calcium Gluconate, Prostaglandin E_2 and Prostaglandin $F_{2\alpha}$ Microinjection in the PVN on Spontaneous Penile Erection and Yawning

As shown in Fig. 3, the microinjection of 2 μl of a calcium gluconate solution containing 0.96 μEq of Ca^{++}, but not 0.48 μEq, in the PVN induces repeated episodes of penile erection and yawning in 80% of the treated rats. The effect of 0.96 μEq Ca^{++} was comparable to that induced by ICV oxytocin. No effect was observed when 2 μl of the isoosmotic control solution (11% glucose) was injected. Calcium gluconate was ineffective when

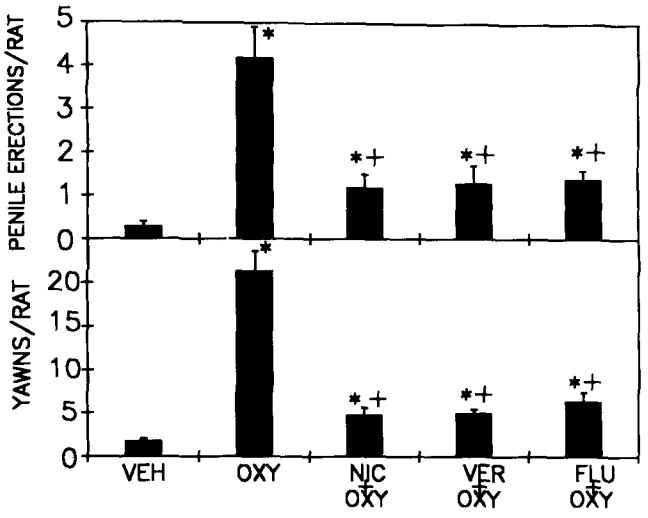

FIG. 2. Prevention of oxytocin-induced penile erection and yawning by calcium channel inhibitors: ICV administration. All rats received oxytocin (30 ng ICV). Fifty μg of either nicardipine, or verapamil, or flunarizine or vehicle alone (5 μl) were administered ICV 10 min before oxytocin. After treatment, the animals were placed individually into Plexiglas cages and observed for 60 min during which penile erection and yawning episodes were counted. Each value is the mean ± S.E.M. of 3 experiments (12 rats per group). *$p<0.001$ with respect to controls; +$p<0.001$ with respect to oxytocin-treated rats.

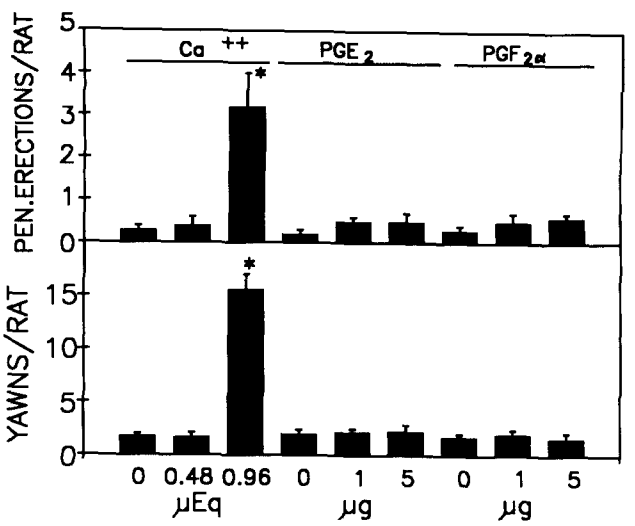

FIG. 3. Effect of calcium, prostaglandin E_2 and prostaglandin $F_{2\alpha}$ microinjection in the PVN on spontaneous penile erection and yawning. For calcium microinjection, 2 μl of an aqueous solution containing calcium gluconate (0.48 or 0.96 μEq Ca^{++}) or 11% glucose (isoosmotic control) was injected in 2 min as described in the Method section. Prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were dissolved in 50 mM sodium-potassium phosphate buffer pH = 8.0 and injected in a volume of 0.5 μl in 2 min. The same volume of buffer was injected in controls. After microinjection, the animals were placed individually in Plexiglas cages and observed for 60 min during which penile erection and yawning episodes were counted. Each value is the mean ± S.E.M. of 3 experiments (15 rats per group). *$p<0.001$ with respect to vehicle-treated rats.

injected 2 mm lateral or dorsal to the PVN. Ineffective were also the microinjections of 0.5, 1 and 5 μg of either prostaglandin E_2 or prostaglandin $F_{2\alpha}$ or their vehicle. At the above doses both prostaglandins failed to induce any overt behavioral change.

DISCUSSION

The present results show that organic calcium channel inhibitors prevent in a dose-dependent manner penile erection and yawning induced by oxytocin. Such effect of calcium channel inhibitors seems to be central, since it is observed not only after IP administration of the drugs, but also after their ICV injection. The finding suggests that oxytocin exerts its effect on penile erection and yawning by increasing calcium influx in some neuronal population of the rat brain. Indeed, verapamil, flunarizine, nifedipine, nimodipine and nicardipine are thought to be rather selective calcium channel inhibitors, although they belong to different chemical classes and differentially affect calcium channel

TABLE 1

FAILURE OF INDOMETHACIN AND ASPIRIN TO ALTER OXYTOCIN-INDUCED PENILE ERECTION AND YAWNING IN MALE RATS

		ICV Injections			
Pretreatment IP	Dose mg/kg	Saline[a]	Oxytocin	Saline[a]	Oxytocin
		Pen. Erections/Rat		Yawns/Rat	
Phosphate buffer	2 ml	0.3 ± 0.1	3.8 ± 0.6*	1.8 ± 0.7	21.3 ± 2.0*
Indomethacin	10	0.4 ± 0.05	3.5 ± 0.8*	1.5 ± 0.5	20.1 ± 3.0*
Indomethacin	50	0.3 ± 0.1	3.4 ± 1.0*	1.2 ± 0.5	19.5 ± 2.0*
Indomethacin	50 μg ICV	0.4 ± 0.1	3.6 ± 0.7*	1.3 ± 0.2	18.5 ± 3.4*
Aspirin	100	0.3 ± 0.1	3.8 ± 1.0*	1.6 ± 0.1	18.9 ± 2.0*

Indomethacin and aspirin were dissolved in 50 mM sodium-potassium phosphate buffer, pH = 8.0 and pH = 8.9, respectively, and injected IP in a volume of 2 ml/rat 30 min before ICV oxytocin (30 ng/5 μl) or saline (5 μl). When injected ICV, indomethacin was administered 15 min before oxytocin. After treatment, the animals were placed individually in Plexiglas cages and observed for 60 min during which penile erection and yawning episodes were counted. Each value is the mean ± S.E.M. of 3 experiments (15 rats per group). *$p<0.001$ with respect to the corresponding group treated with ICV saline.

[a] = saline was replaced by 50 mM phosphate buffer in rats pretreated with ICV indomethacin.

subtypes [for a review see (12)]. The prevention of penile erection and yawning is observed at relatively high doses of calcium channel inhibitors. The requirement of such high doses probably reflects the presence of a subtype of calcium channel in the central nervous system different from that found in cardiac and smooth muscle tissue (13), which makes the nervous tissue poorly sensitive to the action of these compounds [for a review see (12)]. The slightly higher potency of nimodipine and nicardipine might also be due to the greater affinity of these dihydropyridines for the nervous tissue than that of the other dihydropyridine nifedipine, the phenylalkylamines (i.e., verapamil) or the diphenylpiperazines (i.e., flunarizine). Accordingly, autoradiographic studies revealed high density of binding sites for nitrendipine in brain synaptosomes, which are not labeled by verapamil or diltiazem (19). However, the possibility that the prevention of penile erection and yawning is due to unspecific effects of calcium channel inhibitors cannot be completely ruled out from the present results. At high doses, in fact, these compounds have been found able to inhibit not only calcium channels, but also sodium and potassium channels (20) and to interact, at least in vitro, with central and peripheral α_2-adrenergic and muscarinic receptors (5, 7, 12). However, it is unlikely that the prevention of oxytocin effect is due to adrenergic or muscarinic receptor blockade since α_2-adrenergic antagonists have a facilitatory role on sexual activity [see (23)] and the interaction with muscarinic receptors is seen only at very high doses (7). Despite the above possibility, further support for a role of calcium in the expression of penile erection and yawning induced by oxytocin is provided by the finding that elevation of calcium concentration in the PVN region, the most sensitive brain area for the induction of the above responses by oxytocin (15) induces a similar symptomatology. In contrast, inhibition of prostaglandin synthesis by indomethacin or by aspirin was unable to alter oxytocin-induced penile erection and yawning, suggesting that prostaglandins are not involved in the expression of these behavioral responses. Accordingly, microinjection of prostaglandins in the PVN, unlike oxytocin or calcium gluconate, was unable to induce penile erection and yawning.

Taken together, the ability of calcium channel inhibitors to prevent oxytocin-induced penile erection and yawning and of calcium microinjections in the PVN to induce an oxytocin-like effect suggest that oxytocin induces the above behavioral responses by acting in the PVN by a mechanism similar to that operating in the uterus or mammary gland. Accordingly, oxytocin action on these peripheral tissues is dependent on the presence of intra- and extracellular calcium, but not of cyclic adenosine-monophosphate (c-AMP), and calcium channel inhibitors prevent oxytocin-induced uterine contractions [for a review see (9) and (11)]. This correlates well with our recent findings showing that uterine-type oxytocin receptors are involved in the induction of penile erection and yawning by oxytocin. Indeed, the structure-activity relationship of oxytocin and related peptides for the induction of the above behavioral responses was found to be similar to that reported for the induction of uterine contraction or milk ejection [see (4)]. As to the mechanism by which oxytocin mobilizes calcium to induce the above responses, only some speculation is possible at present. One possibility is that oxytocin activates directly calcium channels or influences one of the various biochemical systems known to modify calcium homeostasis, such as phosphoinositide turnover, ATPase activity or calcium binding to calmodulin-like proteins. Some of these mechanisms have been reported to be operative in the uterus (9, 11, 14, 24), but have not been yet demonstrated in brain. In particular, the data available so far in the literature suggest that oxytocin, unlike vasopressin, is unable to alter phosphoinositide breakdown in brain tissue even at relatively high doses (25). In spite of the lack of biochemical correlates, electrophysiological studies have shown that oxytocin is able to activate several neuronal populations in different rat brain areas including the hypothalamic supraoptic nucleus and PVN (10,26), the hippocampus (18) and the dorsal motor nucleus of the vagus nerve (22). Interestingly, in the PVN, where oxytocin seems to act to induce penile erection and yawning (15), oxytocin excites its own neurons (10,26) and this effect is strongly reduced in presence of low calcium/high magnesium media (26), suggesting the involvement of calcium influx in the above responses.

In addition to oxytocin, other substances induce repeated episodes of penile erection and yawning in rats. Among them are dopaminomimetic drugs, such as apomorphine [see (16)]. Recently, we have provided experimental evidence showing that this dopaminergic agonist induces these behavioral responses by releasing oxytocin in the central nervous system. Accordingly, apomorphine-induced penile erection and yawning are prevented by oxytocin receptor antagonists with a rank order of potency that follows their antioxytocic potency (17); the brain area most sensitive for the induction of the above effects either by oxytocin or apomorphine is the PVN (15,16); destruction of oxytocinergic neurons within the brain and spinal cord by electrolytic lesion of the PVN abolishes apomorphine-induced responses (2). If the above hypothesis were correct, apomorphine-induced response would be antagonized in a dose-dependent manner by calcium channel inhibitors, as found for oxytocin effect. Accordingly, we have found that calcium channel inhibitors prevent apomorphine-induced penile erection and yawning (Argiolas *et al.*, submitted).

In conclusion, although further studies are necessary to clarify the mechanism responsible for calcium mobilization, the present data suggest that calcium is the second messenger which mediates oxytocin-induced penile erection and yawning.

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