Pergamon

Pharmacology Biochemistry and Behavior, Vol. 50, No. 3, pp. 339-343, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00268-1

Involvement of β-Adrenoceptors in Regulation of the Yawning Induced by Neuropeptides, Oxytocin and α-Melanocyte-Stimulating Hormone, in Rats

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Received 23 December 1993

FUJIKAWA, M., K. YAMADA, M. NAGASHIMA AND T. FURUKAWA. *Involvement of β-adrenoceptors in regulation of the yawning induced by neuropeptides, oxytocin and α-melanocyte-stimulating hormone, in rats.* PHARMACOL BIOCHEM BEHAV **50**(3) 339-343, 1995.—The present study was undertaken to investigate whether β-adrenoceptors are involved in regulation of yawning responses to oxytocin and α-melanocyte-stimulating hormone (α-MSH) in rats. Oxytocin administered intracerebroventricularly (ICV) at doses of 50 and 100 ng/rat elicited yawning. α-MSH (20 μg/rat, ICV) elicited not only yawning but also stretching and body shaking. RS-86 (2-ethyl-8-methyl-2,8-diazaspiro-(4,5)-decan-1,3-dion hydrobromide), a putative muscarinic M_1 receptor agonist, administered ICV at a lower dose of 100 μg/rat and subcutaneously (SC) at doses of 0.25-2.5 mg/kg also elicited yawning. The yawning responses produced by these agents were markedly increased by intraperitoneal (IP) pretreatment with a β-adrenoceptor antagonist, pindolol (20 mg/kg), which per se did not elicit yawning. The yawning induced by oxytocin (50 ng/rat, ICV) plus pindolol, but not that by α-MSH (20 μg/rat, ICV) or RS-86 (0.5 mg/kg, SC) plus pindolol, was inhibited by [d(CH_2)$_5$,Tyr(Me)^2,Orn^8]-vasotocin (100 ng/rat, ICV), an oxytocin receptor antagonist. The yawning induced by oxytocin, α-MSH, or RS-86 administered in combination with pindolol was inhibited by scopolamine (0.5 mg/kg, SC), a muscarinic receptor antagonist, without being affected by spiperone (0.5 mg/kg, SC), a dopamine D_2 receptor antagonist. The results suggest that the yawning produced by the neuropeptides oxytocin and α-MSH is modulated by β-adrenoceptor activity in an inhibitory manner as that produced by muscarinic M_1 receptor agonists, and that it involves cholinergic, but not dopaminergic, activation.

Yawning Oxytocin α-Melanocyte-stimulating hormone RS-86 Muscarinic M_1 receptor agonists Oxytocin receptor antagonists β-Adrenoceptor antagonists

ALTHOUGH physiological significance is uncertain, yawning behavior has received a great deal of attention (3,6). From accumulated behavioral studies, including our previous experimental results, it has been shown that physostigmine, an anticholinesterase agent, and pilocarpine, a muscarinic receptor agonist, induce yawning behavior that is blocked by muscarinic receptor antagonists, but not by dopamine receptor antagonists (5,8,10,18,19,27,28). On the other hand, the yawning induced by dopamine D_2 receptor agonists, such as bromocriptine and talipexole, is antagonized by both dopaminergic and muscarinic receptor antagonists (13,25). On the basis of these findings, the yawning induced by cholinesterase inhibitors and muscarinic receptor agonists appears to involve cholinergic activation, and that in response to dopamine receptor agonists seems to require both dopaminergic and cholinergic activation. Thus, the cholinergic activation followed by unknown yawn-inducing neuronal mechanisms seems to be essential in eliciting yawning behavior (5,10,11,27).

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In addition, yawning behavior seems to involve other neuronal mechanisms. Because the yawning responses to both dopaminergic and cholinergic receptor agonists are increased by β-adrenoceptor blockers (27) and adrenaline synthesis inhibitors (10), the occurrence of yawning evoked by dopaminergic and cholinergic activation seems to be downregulated by the activity of central adrenergic neurons via stimulation of β-adrenoceptors (10,11,27).

On the other hand, central administration of certain peptides, such as α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH), is also capable of inducing a peculiar syndrome characterized by recurrent episodes of yawning, stretching, body shaking, and penile erection (6,7,20,21). Oxytocin has also been reported to elicit yawning behavior (1,2,14) that is inhibited by muscarinic receptor antagonists but not by dopamine receptor antagonists (1).

The present experiments were therefore performed to investigate whether β-adrenoceptor activity is involved in regulation of the yawning induced by the neuropeptides oxytocin and α-MSH in rats.

METHOD

Animals

Male Wistar rats (200–230 g) were obtained from Kyudo Animal Laboratory (Kumamoto, Japan). They were kept in an animal room with a 12L : 12D cycle (lights on at 0700 h). Commercial food (CE-2, Clea Japan Ltd.) and tap water were freely available except during the experiments. All experiments were carried out at an environmental temperature of 23 ± 1°C.

Behavioral Observations

Pairs of rats were placed in transparent plastic boxes (33 × 30 × 17 cm) containing wood shavings. They were allowed to habituate to the observation boxes for 30 min prior to drug injection. The stretching–yawning syndrome is a fixed innate motor pattern; the stretch phase consists of a stretching of the forelimbs and hindlimbs, and the yawn is a slow, wide opening of the mouth (6,20,21). "Wet-dog body-shake behavior" in the rat is a paroxysmal shudder of the head, neck, and trunk, reminiscent of the deliberate movement observed in dogs when wet (12,20,24). Yawns were counted immediately after SC or ICV injection of oxytocin or RS-86 for 60 min, whereas the counting started 60 min after ICV injection of α-MSH followed by a 60-min observation period.

Administration of Drugs

For the ICV injection of oxytocin, [d(CH$_2$)$_5$,Tyr(Me)^2, Orn^8]-vasotocin, α-MSH, and RS-86, rats were anesthetized with pentobarbital sodium and placed on a stereotaxic apparatus (Narishige). Stainless steel guide cannulas were implanted into the lateral ventricles using stereotaxic coordinates according to the atlas of Pellegrino et al. (17) (0.2 mm posterior to bregma, 1.5 mm lateral to midline, and 2.5 mm ventral to dura). The cannulas were fixed to the skull with dental cement. At least 2 weeks after surgery, oxytocin (50 and 100 ng in 20 μl of 0.9% NaCl), [d(CH$_2$)$_5$,Tyr(Me)^2,Orn^8]-vasotocin (100 ng in 20 μl of 0.9% NaCl), α-MSH (20 μg in 20 μl of 0.9% NaCl), or RS-86 (100 μg in 20 μl of 0.9% NaCl) was administered for 60 s using a Hamilton syringe (100 μl) connected through polyethylene tubing to an internal cannula that extended 1.0 mm beyond the tip of the guide cannula. After injection, the tip of the cannula was left in the injection site for 60 s to allow spread of the injected solution. For systemic administration of RS-86, the agent (0.25–2.5 mg/kg) was SC injected. Time intervals between treatment with respective receptor antagonists and the yawn inducers (SC or ICV) were 30 min for pindolol (20 mg/kg, IP), spiperone (0.5 mg/kg, SC), and scopolamine (0.5 mg/kg, SC), and 15 min for [d(CH$_2$)$_5$, Tyr(Me)^2,Orn^8]-vasotocin (100 ng/rat, ICV). Dosages of oxytocin and the oxytocin antagonist were selected according to the previous reports by Argiolas et al. (1,2), and those of other drugs, α-MSH, pindolol, spiperone, and scopolamine were chosen according to our previous experiments (10,13,20,21,27).

Drugs

The following drugs were used: oxytocin (Peptide Institute, Osaka, Japan), α-MSH (Peptide Institute), RS-86 (2-ethyl-8-methyl-2,8-diazaspiro-(4,5)-decan-1,3-dion hydrobromide) (Sandoz, Basel, Switzerland), pindolol (Sigma, St. Louis, MO), [d(CH$_2$)$_5$,Tyr(Me)^2,Orn^8]-vasotocin (Peninsula Laboratories, Inc., Belmont, CA), spiperone (Spiropitan Injection, Eisai, Tokyo, Japan), and scopolamine hydrobromide (Nacalai tesque, Kyoto, Japan). Pindolol was dissolved in an excess of equimolar tartaric acid solution with subsequent dilution in saline and was injected IP into experimental animals. The other drugs dissolved in saline were injected SC or ICV into experimental animals as mentioned above. Doses are expressed in terms of respective salts, with the exception of oxytocin, α-MSH, [d(CH$_2$)$_5$,Tyr(Me)^2,Orn^8]-vasotocin, pindolol, and spiperone.

Statistical Analysis

Yawning responses are expressed as mean values ± SEM. Statistical analysis was performed using either two-tailed Student's *t*-test (differences between two groups) or one-way anal-

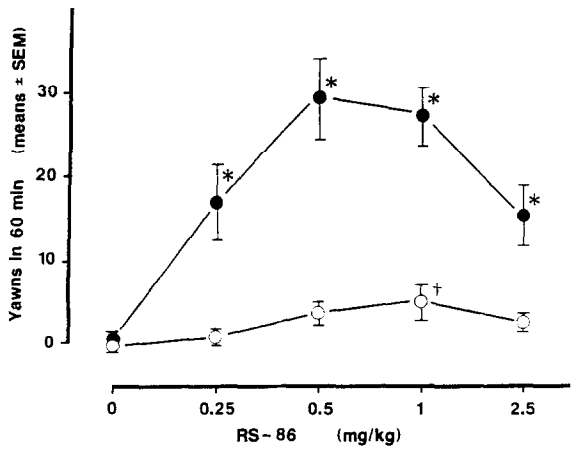

FIG. 1. Dose–response curve of yawning to RS-86 in saline- or pindolol-pretreated rats. The number of yawns was counted for 60 min following injection of RS-86 (0.25–2.5 mg/kg, SC). Pindolol (20 mg/kg, IP) (●) or saline (1 ml/kg, IP) (○) was administered 30 min before RS-86. SC: subcutaneous injection, IP: intraperitoneal injection. Points represent means ± SEM (vertical lines) of the number of yawns from eight rats during a 60-min observation period. †$p < 0.05$, significant difference from saline plus saline-injected group, determined by one-way ANOVA followed by Dunnett's test. *$p < 0.01$, significant difference from respective control groups, determined by Student's *t*-test.

TABLE 1

YAWNING INDUCED BY OXYTOCIN, α-MSH, OR RS-86 IN SALINE- AND PINDOLOL-PRETREATED RATS

Drugs	Yawns in 60 Min	
	Saline	Pindolol
Saline (20 μl/rat)	0.5 ± 0.5	1.1 ± 0.7
Oxytocin (50 ng/rat)	4.0 ± 1.0	17.1 ± 1.9*
Oxytocin (100 ng/rat)	4.7 ± 1.5	18.2 ± 3.7*
α-MSH (20 μg/rat)	12.0 ± 1.8	21.4 ± 3.0†
RS-86 (100 μg/rat)	1.8 ± 0.8	12.8 ± 2.4*

Oxytocin (50, 100 ng/rat), α-MSH (20 μg/rat), and RS-86 (100 μg/rat) were administered intracerebroventricularly to rats. Pindolol (20 mg/kg, IP) was administered 30 min before yawn inducers. Values represent means ± SEM of the number of yawns from 8–12 rats.

Significant difference from respective control groups, determined by Student's *t*-test: $*p < 0.01$, $†p < 0.05$.

ysis of variance (ANOVA) followed by two-tailed Dunnett's test (differences between a control and all groups).

RESULTS

The Yawning Induced by ICV Injection of Oxytocin, α-MSH, or RS-86

Control rats treated with saline (1 ml/kg) administered SC yawned only occasionally. As shown in Fig. 1, RS-86 (0.25–2.5 mg/kg, SC) induced a small number of yawning responses in saline-pretreated rats, the maximal effect being observed at a dose of 1 mg/kg. Control rats treated with saline (20 μl/rat) administered ICV yawned only occasionally. In saline-pretreated rats, RS-86 administered ICV at a dose of 100 μg/rat elicited a slight yawning response (Table 1). Oxytocin (50, 100 ng/rat, ICV) and α-MSH (20 μg/rat, ICV) evoked the yawning behavior (Table 1). The yawning induced by oxytocin and RS-86 appeared 5–10 min and terminated within 60 min after injection, whereas that by α-MSH occurred about 60 min after administration and terminated within a further 60 min. In addition, α-MSH evoked not only yawning but also stretching and body shaking; the body shaking appeared immediately and terminated within 120 min after injection, and the stretching occurred about 60 min after injection and terminated within 60 min (data not shown). Oxytocin and RS-86 caused no such stretching or body-shake behavior.

Potentiation of the Yawning by the β-Adrenoceptor Antagonist Pindolol

Pindolol (20 mg/kg, IP) administered alone evoked no behavioral changes, including yawning. After pretreatment with pindolol (20 mg/kg, IP), RS-86 (0.25–2.5 mg/kg, SC) elicited marked yawning behavior, forming a bell-shaped curve with a maximal effect at 0.5 mg/kg (Fig. 1). Furthermore, the yawning responses induced by ICV oxytocin, α-MSH, and RS-86 were markedly potentiated in pindolol-pretreated rats (20 mg/kg, IP) (Table 1). On the other hand, the stretching caused by α-MSH was unchanged and body shaking was slightly decreased (not significant) by pindolol (data not shown).

Effects of Oxytocin and Muscarinic Receptor Antagonists on the Yawning Induced by Oxytocin and RS-86 Administered in Combination With Pindolol

As shown in Table 2, the yawning produced by oxytocin (50 ng/rat, ICV) administered after pindolol (20 mg/kg, IP) was markedly inhibited by treatment with [d(CH_2)$_5$,Tyr(Me)^2,Orn^8]-vasotocin (100 ng/rat, ICV), an oxytocin receptor antagonist, but that by α-MSH (20 μg/rat, ICV) or RS-86 (0.5 mg/kg, SC) after pindolol was unaltered. In addition, the yawning behavior induced by oxytocin, α-MSH, or RS-86 administered after pindolol was strongly inhibited by pretreatment with scopolamine (0.5 mg/kg, SC) but was unaffected by spiperone (0.5 mg/kg, SC). None of these receptor antagonists administered alone elicited yawning.

DISCUSSION

Previous studies have shown that a muscarinic receptor agonist, pilocarpine, induces yawning behavior in rats (18). Muscarinic receptors have been designated as either M_1 or M_2 receptors, depending on whether they have high or low affinity for pirenzepine (9), although such classification is as yet tentative (4). In the present study, RS-86, a centrally acting potent muscarinic M_1 receptor agonist (16), administered SC produced yawning in rats, as reported previously by Gower

TABLE 2

EFFECTS OF VARIOUS RECEPTOR ANTAGONISTS ON YAWNING INDUCED BY OXYTOCIN, α-MSH, OR RS-86 IN PINDOLOL-PRETREATED RATS

Drugs	Yawns in 60 Min			
	Saline	Oxytocin Antagonist	Spiperone	Scopolamine
Pindolol + oxytocin	15.0 ± 2.2	2.5 ± 1.1*	11.6 ± 2.6	0.3 ± 0.3*
Pindolol + α-MSH	16.6 ± 2.5	15.9 ± 2.6	10.1 ± 1.7	0.6 ± 0.3*
Pindolol + RS-86	24.1 ± 1.8	23.8 ± 3.3	25.4 ± 3.6	0.1 ± 0.1*

Oxytocin (50 ng/rat), α-MSH (20 μg/rat), and the oxytocin receptor antagonist (100 ng/rat) were administered intracerebroventricularly. RS-86 (0.5 mg/kg) was administered subcutaneously (SC). Pindolol (20 mg/kg, IP) was administered 30 min, oxytocin receptor antagonist (100 ng/rat) 15 min, and spiperone (0.5 mg/kg, SC) as well as scopolamine (0.5 mg/kg, SC) 30 min before yawn inducers. Values represent means ± SEM of the number of yawns from 8–12 rats.

*Significant difference from respective control groups, determined by Dunnett's test: $*p < 0.01$.

(8), suggesting that the muscarinic receptors participating in the induction of yawning may be M_1 receptors. From such dose-response studies on systemic administration of RS-86, 100 μg/rat was selected for ICV administration in the present study. On the other hand, central administration of nanogram amounts of oxytocin was reported to produce yawning in rats (1). For ICV administration of the peptides, oxytocin was given at doses of 50 and 100 ng/rat according to the previous reports by Argiolas et al. (1,2), and α-MSH was administered at 20 μg/rat from the results of our previous experiments (20,21). In the present study, oxytocin and α-MSH injected ICV evoked yawning behavior, but the potency of oxytocin seemed to be less effective in causing yawning compared with the previous report by Argiolas et al. (1). We have no adequate explanation for this difference in effect at present, but it may be due, at least in part, to differences in species and/or strains used in both studies.

Previous experiments have shown that the yawning responses to dopaminergic agonists were increased by administration of β-adrenoceptor antagonists such as pindolol and propranolol (27). The yawning responses to cholinergic agents such as physostigmine, pilocarpine, and tacrine were also increased by treatment with the β-adrenoceptor antagonist, pindolol (10,27). Moreover, the potentiation was elicited by central β-adrenoceptor blockers such as propranolol and others, which reach the brain through the blood-brain barrier, but not by peripheral β-adrenoceptor blockers (carteolol and atenolol), indicating that potentiation by β-blockers occurs in the brain (27). The yawning induced by RS-86 administered SC and ICV was potentiated by treatment with the β-adrenoceptor blocker pindolol in the present study. In addition, the occurrence of yawning behaviors produced by the neuropeptides oxytocin and α-MSH given ICV was markedly potentiated by treatment with pindolol.

It has been reported that oxytocin-induced yawning is inhibited by [d(CH_2)$_5$,Tyr(Me)^2,Orn^8]-vasotocin, an oxytocin receptor antagonist (1). In the present study, the yawning produced by oxytocin administered in combination with pindolol was also blocked by [d(CH_2)$_5$,Tyr(Me)^2,Orn^8]-vasotocin, whereas that by α-MSH or RS-86 plus pindolol was unaffected, suggesting that the yawning responses are elicited via different receptor mechanisms. The yawning evoked by ACTH, an α-MSH-related peptide, was also reported to be unaffected by oxytocin receptor antagonists (2).

The yawning induced by muscarinic receptor agonists was reported to be blocked by muscarinic receptor antagonists, but was unaffected by dopamine receptor antagonists (8,19, 25,28). In the present study, the yawning behavior elicited by RS-86, a muscarinic M_1 receptor agonist, administered in combination with pindolol was inhibited by scopolamine, a muscarinic receptor antagonist, but not by spiperone, a dopamine D_2 receptor antagonist. The yawning produced by oxytocin after pindolol was also antagonized by scopolamine, without being affected by spiperone. These results seem to be in agreement with the previous proposal that the expression of yawning induced by dopaminergic agonists involves dopamine–oxytocin, but not oxytocin–dopamine, linkage (15). The yawning evoked by an α-MSH-related peptide, ACTH, which was unaffected by oxytocin receptor antagonists, was also reported to be prevented by cholinergic receptor antagonists (2,6). Our previous results also indicated that none of the responses to α-MSH, yawning, stretching, and body shaking, are associated with changes in the activities of the nigrostriatal, mesolimbic, tuberoinfundibular, or tuberohypophyseal dopaminergic neurons (20,21), and that α-MSH-induced yawning is decreased by administration of cholinergic receptor antagonists (20). In the present study, the yawning evoked by α-MSH administered after pindolol was antagonized by scopolamine, but not by spiperone. From such findings, the oxytocin- and α-MSH-induced yawning responses appear to involve cholinergic, but not dopaminergic, activation, although further investigation is warranted to identify the neuronal circuit between the peptidergic–cholinergic-linked neuronal system involved in causing yawning behavior. It is also suggested that the activation of a muscarinic receptor constitutes the expression of yawning as a common mechanism. Moreover, the present results also indicate that β-adrenoceptors seem to be involved in the yawn-inducing neuronal mechanism linked to cholinergic neurons and thereby play an inhibitory role in modulation of occurrence of the behavior.

Body shaking was reported previously after administration of various drugs such as α-MSH (20,21), thyrotropin-releasing hormone (23,24,26), and 5-hydroxytryptophan (20), and after electrical stimulation of the hippocampus in rats (22). The present study also confirmed that ICV administration of α-MSH induced body shaking.

The present results suggest that the neuropeptides oxytocin and α-MSH and the muscarinic M_1 receptor agonists produce yawning via activation of cholinergic mechanisms, and that β-adrenoceptors are involved in regulation of the yawning induced by the neuropeptides.

ACKNOWLEDGEMENTS

This work was supported by Grants in Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan (60570103, 62570098, and 01570119).

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