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Involvement of Catecholamine Receptor Activities in Modulating the Incidence of Yawning in Rats

HIROSHI KIMURA,* KATSUSHI YAMADA,‡
MARIKO NAGASHIMA† AND TATSUO FURUKAWA*[1]

*Department of Pharmacology, †Research Laboratory of Biodynamics, School of Medicine, Fukuoka University, Fukuoka 814-80, Japan and
‡Department of Hospital Pharmacy, Faculty of Medicine, Kagoshima University, Kagoshima 890, Japan

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KIMURA, H., K. YAMADA, M. NAGASHIMA AND T. FURUKAWA. *Involvement of catecholamine receptor activities in modulating the incidence of yawning in rats.* PHARMACOL BIOCHEM BEHAV **53**(4) 1017–1021, 1996.—Possible involvement of catecholamine receptor activities in modulating the incidence of yawning, which involves activation of dopaminergic-cholinergic linked neuronal mechanism, was investigated in rats. Subcutaneous injection of talipexole (B-HT 920), a selective dopamine D_2-receptor agonist, elicited yawning behavior. This behavior was increased by prazosin and bunazosin, α_1-adrenoceptor antagonists, and by pindolol, a β-adrenoceptor antagonist. The yawning induced by physostigmine, an anticholinesterase agent, and pilocarpine, a direct muscarinic receptor agonist, was increased by pindolol, but was unaffected by prazosin and bunazosin. In addition, the yawning induced by the dopaminergic agonists, but not by the cholinergic agonists, was markedly suppressed by ST587, an α_1-adrenoceptor agonist. All the yawning responses to dopaminergic and cholinergic agents were reduced not only by scopolamine, a muscarinic receptor antagonist, but also by idazoxan, rauwolscine, and yohimbine, α_2-adrenoceptor antagonists. The results suggest that catecholamine receptor activities seem to play different roles in inhibitory modulation of the occurrence of yawning caused by dopaminergic and cholinergic stimulation.

Yawning α_1-Adrenoceptors α_2-Adrenoceptors β-Adrenoceptors Dopaminergic stimulation Cholinergic stimulation

WE HAVE PREVIOUSLY demonstrated that the adrenergic mechanism seems to be participated in inhibiting occurrence of yawning because β-adrenoceptor blockades and inhibition of central adrenaline synthesis caused by administration of synthesis enzyme inhibitor similarly facilitate the occurrence of yawning induced by dopaminergic and cholinergic agonists (11,12,26,27).

On the other hand, the noradrenergic mechanism seems to play a very important role in modulating blood pressure responses (14,15), flexor reflex activity (16,19), locomotor behavior (5), postdecapitation convulsions (25), and drinking behavior (2). Regarding behavior, ambulation and rearing were similarly decreased by an α_2-adrenoceptor agonist, clonidine, α_2-adrenoceptor antagonists, yohimbine, rauwolscine, as well as piperoxan, and an α_1-adrenoceptor antagonist, prazosin (3). However, grooming was decreased by clonidine and prazosin but was markedly increased by α_2-adrenoceptor antagonists (3). As for yawning behavior, a few reports have only been presented with different results. SND 919, a dopamine D_2-receptor agonist, derived from an α_2-adrenoceptor agonist, clonidine, produced stretching-yawning behavior that was reduced not only by *l*-sulpiride but also by α_2-adrenoceptor antagonists, yohimbine and idazoxan (7). An α_1-adrenoceptor antagonist, prazosin, was reported to not to affect the yawning induced by apomorphine (9) or antidepressants (18). However, Delini-Stula and Hunn later proposed that the apomorphine-induced yawning is potentiated by α_1-adrenoceptor antagonists and is suppressed by α_1-adreno-

[1] To whom requests for reprints should be addressed.

ceptor agonists (4). These controversial findings have been of interest in view of possible participation of catecholaminergic mechanisms in modulating the yawning.

The present experiments were, therefore, performed to investigate whether catecholamine receptor activity is involved in regulating the occurrence of yawning.

METHODS

Animals

Male Wistar rats (200–230 g) were obtained from Kyudo Animal Laboratory (Kumamoto, Japan). They were kept in an animal room with a 12 L : 12 D 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.

Apparatus

Pairs of rats were placed in a transparent plastic box (33 × 30 × 17 cm) containing wood shavings. They were allowed to become acclimated to the observation box for 30 min prior to drug injection. Yawning is a fixed innate motor pattern characterized by slow, wide opening of the mouth (20,21,23). The total number of yawns was counted for 60 min following the injection.

Drugs and Their Preparation

Rats were intraperitoneally (IP) treated with prazosin (1–8 mg/kg), bunazosin (2.5–20 mg/kg), pindolol (20 mg/kg), ST587 (1–2 mg/kg), idazoxan (2.5–10 mg/kg), rauwolscine (0.1–0.5 mg/kg), yohimbine (0.05–2.5 mg/kg), or scopolamine (0.5 mg/kg) and subcutaneously (SC) injected with talipexole (0.02 mg/kg), physostigmine (0.05 mg/kg), or pilocarpine (2 mg/kg). All of the adrenoceptor agonists and antagonists and muscarinic receptor antagonists were injected 60 min prior to the injection of dopamine receptor agonists, anticholinesterase agents, or muscarinic receptor agonists. The doses were selected on the basis of our previous experiments in which talipexole (0.02 mg/kg, SC) elicited yawning (17,27,28) and pindolol (20 mg/kg, IP) enhanced the yawning response to dopaminergic and cholinergic agonists (11,12,26).

The drugs used were prazosin hydrochloride (Tokyo Kasei, Tokyo, Japan), bunazosin hydrochloride (Eisai, Tokyo, Japan), pindolol (Sigma, St. Louis, MO, USA), ST587 (2-[2-chloro-5-trifluomethyl-phenyl-imino]-imidazolidin) nitrate (Boehringer Ingelheim, Kawanishi, Japan), idazoxan hydrochloride (Sigma, St. Louis, MO), rauwolscine hydrochloride (Extrasynthese, Genay, France), yohimbine hydrochloride (Nacalai tesque, Kyoto, Japan), scopolamine hydrobromide (Nacalai tesque, Kyoto, Japan), talipexole (B-HT 920) dihydrochloride (Boehringer Ingelheim, Kawanishi, Japan), physostigmine sulfate (Wako, Osaka, Japan), and pilocarpine hydrochloride (Nacalai tesque, Kyoto, Japan). Bunazosin, ST587, idazoxan, rauwolscine, yohimbine, scopolamine, talipexole, physostigmine, and pilocarpine were dissolved or diluted in saline. Prazosin and pindolol were dissolved in an excess of equimolar tartaric acid solution with subsequent dilution in saline, respective pH of the solution being 2.2 and 3.5. All drugs were injected into the experimental animals intraperitoneally or subcutaneously.

Statistics

Yawning responses were expressed as mean values ± SEM. Statistical analysis was performed by a one-way analysis of variance followed by the two-tailed Dunnett's test (differences between the control and all groups).

RESULTS

Potentiation of Talipexole-Induced Yawning by α_1-Adrenoceptor Antagonists

Control rats, which were treated subcutaneously with saline or vehicle (1 ml/kg), yawned only occasionally. Talipexole (0.02 mg/kg, SC) produced considerable yawning behavior in the saline-pretreated eight rats, the mean number of yawns in 60 min being 9.3 ± 1.5, as shown in Fig. 1. Talipexole also induced yawning to the same extent in the vehicle-pretreated rats (data not shown). By pretreatment with a wide dose range of prazosin (1–8 mg/kg, IP) or bunazosin (2.5–20 mg/kg, IP), the talipexole-induced yawning was markedly increased with showing bell-shaped dose-response curve and significant increase at 2–4 mg/kg of prazosin and 5–10 mg/kg of bunazosin. The α_1-adrenoceptor antagonists per se were not able to evoke yawning.

Differences in Potentiation by α_1-Adrenoceptor and β-Adrenoceptor Antagonists of the Yawning Induced by Dopaminergic and Cholinergic Agonists

Subcutaneous injection of physostigmine (0.05 mg/kg) and pilocarpine (2 mg/kg) also elicited yawning, the mean number of yawns during 60 min in eight rats being 7.3 ± 1.4 and 8.1 ± 2.1, respectively. Pretreatment with pindolol (20 mg/kg, IP) markedly increased all these yawning responses to talipexole, physostigmine, and pilocarpine. The β-adrenoceptor antagonist did not elicit yawning when given alone. On the other hand, prazosin (4 mg/kg, IP) and bunazosin (5 mg/kg, IP) increased the yawning responses to talipexole but failed to affect the responses to physostigmine or pilocarpine (Fig. 2).

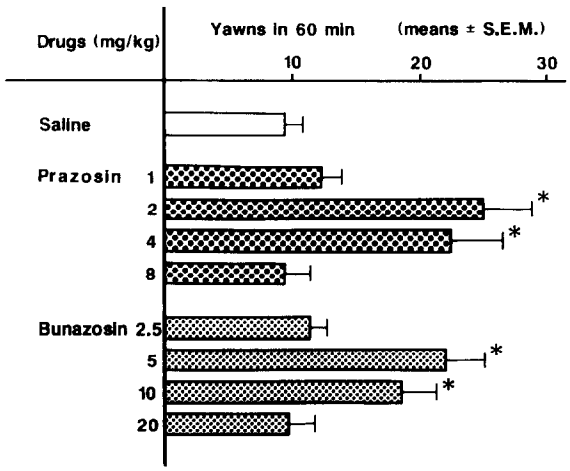

FIG. 1. Dose responses to prazosin and bunazosin of facilitative effects on the yawning induced by talipexole. Control saline, prazosin (1–8 mg/kg, IP) or bunazosin (2.5–20 mg/kg, IP) was given 1 h before talipexole (0.02 mg/kg, SC). Columns represent means ± SEM (horizontal bars) of the number of yawns during a 60-min observation period in eight rats. *$p < 0.01$; significant difference from the saline-pretreated group.

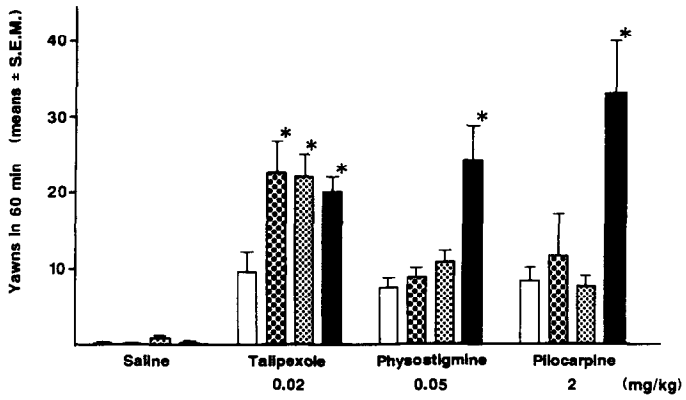

FIG. 2. Differences in effects of prazosin, bunazosin, and pindolol on the yawning induced by talipexole, physostigmine, and pilocarpine. Open columns: saline (1 ml/kg, IP) as control and for pretreatment; big dot columns: prazosin (4 mg/kg, IP); small dot columns: bunazosin (5 mg/kg, IP); and closed columns: pindolol (20 mg/kg, IP) for pretreatment. These antagonists were given 1 h before talipexole (0.02 mg/kg, SC), physostigmine (0.05 mg/kg, SC), or pilocarpine (2 mg/kg, SC) for pretreatment. Columns represent means ± SEM (vertical lines) of the number of yawns in eight rats. *$p < 0.01$; significant difference from the respective control groups (open columns).

Difference in Suppression of the Yawning Induced by Dopaminergic and Cholinergic Agonists by the α_1-Adrenoceptor Agonist

As shown in Fig. 3, after ST587 (1-2 mg/kg), an α_1-adrenoceptor agonist, the yawning responses to talipexole, but not those to physostigmine and pilocarpine, were dose-dependently suppressed.

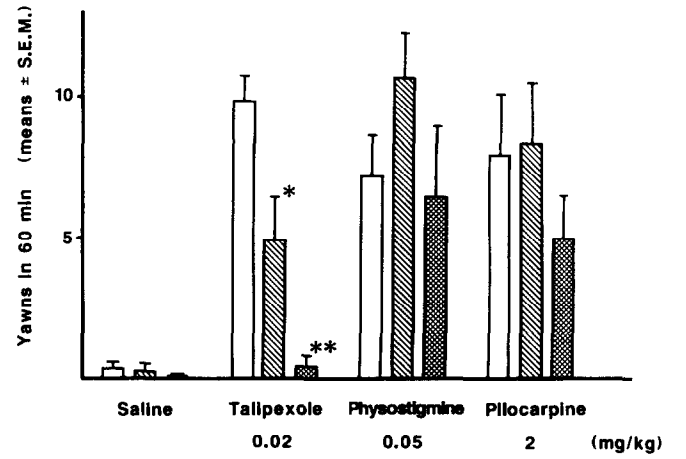

FIG. 3. Effects of ST587 on the yawning induced by talipexole, physostigmine and pilocarpine. Open columns: saline (1 ml/kg, IP) as control and for pretreatment; striped columns: ST587 (1 mg/kg, IP); checked columns: ST587 (2 mg/kg, IP) for pretreatment. They were given 1 h before talipexole (0.02 mg/kg, SC), physostigmine (0.05 mg/kg, SC), or pilocarpine (2 mg/kg, SC) for pretreatment. Columns represent means ± SEM (vertical lines) of the number of yawns in eight rats. *$p < 0.05$, **$p < 0.01$; significant difference from the respective control groups (open columns).

Suppression of the Yawning Induced by Dopaminergic and Cholinergic Agonists by α_2-Adrenoceptor and Muscarinic Receptor Antagonists

As seen in Fig. 4, the talipexole-induced yawning was dose dependently reduced by pretreatment with idazoxan (2.5-10 mg/kg, IP), rauwolscine (0.1-0.5 mg/kg, IP), and yohimbine (0.05-2.5 mg/kg, IP), α_2-adrenoceptor antagonists. Moreover, at these maximal doses of idazoxan (10 mg/kg), rauwolscine (0.5 mg/kg), and yohimbine (2.5 mg/kg), the yawning responses to physostigmine and pilocarpine were strongly depressed as well (Table 1).

DISCUSSION

Previous experiments have shown that the yawning induced by dopamine D_2 receptor agonists is antagonized by both dopamine and muscarine receptor antagonists (17,24,26), and that by cholinesterase inhibitors and muscarine receptor agonists is inhibited by muscarine receptor antagonists, but not by dopamine receptor antagonists (1,10,12,20,22,29). These findings imply that the yawning induced by dopamine receptor agonists involves activation of dopaminergic and cholinergic neuronal mechanisms and that by cholinesterase inhibitors and direct muscarinic receptor agonists involves activation of cholinergic neuronal mechanisms. Consequently, it has been proposed that the dopaminergic-cholinergic neuronal link is essentially participated in the occurrence of yawning behavior (1,12,26).

In our previous reports the yawning responses to dopaminergic and cholinergic agonists were increased by pretreatment with various β-adrenoceptor antagonists, such as pindolol, propranolol, and indenolol, which block central β-adrenoceptors after reaching the brain through the blood-brain barrier, but not by peripheral β-adrenoceptor antagonists, carteolol and atenolol (12,26,27). We have also found that administration of phenylethanolamine, *N*-methyltransferase inhibitors, which reduce central adrenaline synthesis without

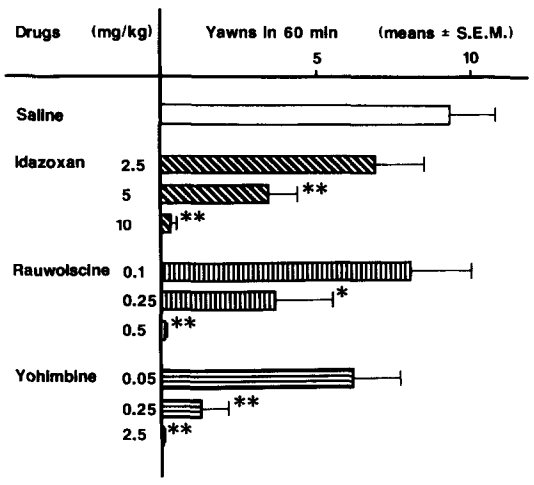

FIG. 4. Inhibitory effects of idazoxan, rauwolscine, and yohimbine on the yawning induced by talipexole. Saline (1 ml/kg, IP), idazoxan (2.5-10 mg/kg, IP), rauwolscine (0.1-0.5 mg/kg, IP), and yohimbine (0.05-2.5 mg/kg, IP) were given 1 h before talipexole (0.02 mg/kg, SC). Columns represent means ± SEM (horizontal bars) of the number of yawns in eight rats. *$p < 0.05$, **$p < 0.01$; significant difference from the saline-injected group.

TABLE 1

SUPPRESSIVE EFFECTS OF α_2-ADRENOCEPTOR AND MUSCARINIC RECEPTOR ANTAGONISTS ON THE YAWNING INDUCED BY DOPAMINERGIC AND CHOLINERGIC AGONISTS

		Yawns in 60 min			
Drugs	(mg/kg)	Saline	Talipexole	Physostigmine	Pilocarpine
Saline		0.4 ± 0.2	9.3 ± 1.5*	7.3 ± 1.4*	8.1 ± 2.1*
Idazoxan	10	0.0 ± 0.0	0.3 ± 0.2†	3.1 ± 1.4‡	1.8 ± 1.0‡
Rauwolscine	0.5	0.0 ± 0.0	0.1 ± 0.1†	1.8 ± 0.9†	0.1 ± 0.1†
Yohimbine	2.5	0.0 ± 0.0	0.0 ± 0.0†	0.4 ± 0.2†	0.6 ± 0.3†
Scopolamine	0.5	0.0 ± 0.0	0.3 ± 0.3†	0.0 ± 0.0†	0.0 ± 0.0†

Receptor antagonists were given intraperitoneally 1 h before the yawning inducers, talipexole (0.02 mg/kg, SC), physostigmine (0.05 mg/kg, SC), and pilocarpine (2 mg/kg, SC). Values represent means ± SEM of the number of yawns by 8–10 rats.

*$p < 0.01$; significant difference from the saline-saline group.

†$p < 0.01$, ‡$p < 0.05$; significant difference from the respective control groups.

affecting noradrenaline levels, similarly increases the yawning induced by tacrine, a cholinesterase inhibitor (11,12), thus suggesting that the occurrence of yawning evoked by both dopaminergic and cholinergic activation is downregulated by activity of central adrenergic neurons via β-adrenoceptor stimulation (11,12,26). Indeed, the present experiment also confirmed that pindolol increased the yawning induced by talipexole, physostigmine, and pilocarpine.

The discovery of presynaptic α_2-adrenoceptors, which play a role in inhibition of noradrenaline release from noradrenergic neurons, has permitted subclassification of α-adrenoceptors into α_1- and α_2-subtypes (15). As to α_1-adrenoceptors, there have been reports describing that the yawning induced by talipexole (6) and apomorphine (9,26) was unaffected by prazosin at a lower dose of 1 mg/kg, IP, whereas that by apomorphine was potentiated by prazosin at a higher dose of 2.5 mg/kg, IP (4). In this study, we used prazosin, 1–8 mg/kg, IP, and bunazosin, 2.5–20 mg/kg, IP, at wide range of dose, and the yawning produced by a dopamine D_2-receptor agonist, talipexole, was increased after treatment with α_1-adrenoceptor antagonists, such as prazosin (2–4 mg/kg) and bunazosin (5–10 mg/kg), while the yawning induced by physostigmine and pilocarpine was not increased by the antagonists. Moreover, the α_1-adrenoceptor agonist ST587 markedly suppressed the yawning induced by the dopaminergic agonists, but not by the cholinergic agonists. Consequently, the noradrenergic neuronal mechanism seems to be participated via α_1-adrenoceptors in decreasing the incidence of yawning caused by the dopaminergic agonists, without influencing the behavior induced by the cholinergic agonists.

Interestingly, in the present experiment, the β-adrenoceptor antagonist, pindolol, increased all the yawning responses to talipexole, physostigmine, and pilocarpine, whereas the α_1-adrenoceptor antagonists and agonists affected the responses to the dopaminergic agonist, but not those to the cholinesterase inhibitor and the direct muscarinic receptor agonist. In addition, as mentioned above, central adrenaline synthesis inhibitors, which decrease adrenaline level without changing noradrenaline level, potentiate the yawning elicited by a cholinesterase inhibitor (11,12). Therefore, it is presumed that, in the dopaminergic-cholinergic neuronal link, which is involved in causing the yawning behavior, the noradrenergic mechanism inhibits incidence of the behavior via α_1-adrenoceptor activity by interacting with dopaminergic neurons that precede cholinergic neurons, and the adrenergic mechanism inhibits the incidence via β-adrenoceptor activity by interacting with cholinergic neurons.

As for α_2-adrenoceptor antagonists, the yawning evoked by talipexole was inhibited by yohimbine (6) and that by apomorphine and physostigmine was reported to be reduced not only by idazoxan and piperoxan, the α_2-adrenoceptor antagonists, but also by clonidine, an α_2-adrenoceptor agonist (9). In the present experiment, selective α_2-adrenoceptor antagonists such as idazoxan, rauwolscine, and yohimbine (14,15) dose dependently suppressed the yawning responses not only to dopaminergic agonists but also to cholinergic agonists. It has been proposed that α_2-adrenoceptors are located on noradrenergic and/or adrenergic neuronal pathways and that α_2-adrenoceptor antagonists increase both noradrenaline and adrenaline release via blockade of α_2-adrenoceptors at central catecholaminergic nerve terminals (8,13). Therefore, although real mechanisms still remain uncertain, the results may suggest a possibility that the stimulation of noradrenergic and adrenergic mechanisms elicited by an increase in noradrenaline and adrenaline release induced by α_2-adrenoceptor blockade might result in inhibition of the yawning evoked by both dopaminergic and cholinergic activation.

In order to know more about the role of the adrenoceptors on yawning from a physiological point of view, it might be very important to determine possible areas in the brain where the yawning is involved, because of differential distribution of adrenoceptors in the brain. We have investigated that intracerebral injection of dopamine receptor agonists into the striatum and septum at low doses evoked yawning (24), but the studies with other brain areas have not been presented. Accordingly, this problem still remain to be solved in future.

Although believed to be selective for a specific receptor subtype, α-agonists and antagonists act also on the other receptor subtypes and/or receptors of other transmitters, and the results, therefore, represent the algebraic sum of their actions at the various receptors involved. This will leave the interpretation of the results speculative to a certain extent until the neuronal pathways that participate in the dopamine-acetylcholine link in the control of the yawning response are well identified.

In summary, the present findings suggest that the catecholamine receptor activity is involved in modulating the occurrence of yawning in different manner.

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