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European Journal of Pharmacology 344 (1998) 223–229

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Existence of postsynaptic dopamine D_2 receptor as an enhancer of contractile response in vas deferens

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Received 5 June 1997; revised 3 December 1997; accepted 9 December 1997

Abstract

Effects of dopamine and (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxy-tetralin hydrochloride (N-0434), a dopamine D_2 receptor agonist, in the presence of prazosin on the ATP-and acetylcholine-induced contraction were investigated in the guinea-pig vas deferens in order to test for the existence of postsynaptic dopamine receptors. The contraction induced by ATP was potentiated by dopamine and N-0434. This potentiation was antagonized by spiperone, a dopamine D_2 receptor antagonist, but not by a dopamine D_1 receptor antagonist and an α_2-adrenoceptor antagonist. Similar results were also observed by acetylcholine as well as ATP. The contraction induced by transmural nerve stimulation in the presence of α-adrenoceptor antagonists was also potentiated by N-0434, and this potentiation was antagonized by spiperone. The results suggest that dopamine D_2 receptors are located on the postsynaptic site of guinea-pig vas deferens and that the contractile responses to ATP and acetylcholine are potentiated via activation of dopamine D_2 receptor. © 1998 Elsevier Science B.V.

Keywords: ATP; Dopamine; Acetylcholine; P_{2x} purinoceptor; Dopamine D_2 receptor; Vas deferens, guinea-pig

1. Introduction

It has been suggested that dopamine may be a neurotransmitter in the rat vas deferens and that excitatory dopamine receptors are located on the smooth muscle (Simon and Van Maanen, 1976; Tayo, 1979; Badia et al., 1982). Boadle-Biber and Roth (1975) reported that a high proportion of newly formed catecholamines in the rat vas deferens is present as dopamine. Relja et al. (1982) reported that dopamine receptors are present in rat vas deferens, based on the binding of [^{3}H]haloperidol to plasma membranes. In contrast, some authors reported that the contraction induced by dopamine in the rat vas deferens is mediated by α-adrenoceptors but not by dopamine receptors (Patil et al., 1973; Leedham and Pennefather, 1982). Similar results showing that the contraction induced by dopamine is mediated by α-adrenoceptors but not via dopamine receptors, have also been reported for the vas deferens of mouse and guinea-pig (Gibson and Samini, 1979; Tayo, 1979).

ATP is released as a co-transmitter with noradrenaline from sympathetic nerve endings in the vas deferens (Westfall et al., 1978; Fedan et al., 1981, 1982; Meldrum and Burnstock, 1983; Sneddon and Burnstock, 1984; Katsuragi and Furukawa, 1985; Burnstock, 1990). Exogenous noradrenaline potentiated the ATP-induced contraction in the seminal vesicle (Nakanishi and Takeda, 1973) and vas deferens (Holck and Marks, 1978; Kažić and Milosavljević, 1980) of guinea-pig and in the mouse vas deferens (Witt et al., 1991). However, the effects of dopamine and dopamine agonists on the ATP-induced contraction in the isolated vas deferens have not been reported.

Dopamine receptors have been divided into major subtypes referred to dopamine D_1 and D_2 receptors in the central nervous system (Sibley and Monsma, 1992; Sibley et al., 1993; Sokoloff and Schwartz, 1995). Dopamine D_1 receptors activate adenyl cyclase and thereby increase intracellular levels of cAMP, whereas dopamine D_2 receptors exert an inhibitory influence on this enzyme (Sibley and Monsma, 1992; Sibley et al., 1993; Sokoloff and Schwartz, 1995). Recently, molecular cloning techniques have revealed five dopamine receptor subtypes (Sibley and Monsma, 1992; Sibley et al., 1993; Sokoloff and Schwartz,

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1995). Newly developed selective agonists and antagonists for these receptors contribute greatly to the determination of the dopamine D_1/D_2 receptor classification. N-0434 is a selective dopamine D_2 receptor agonist in the central nervous system (Andersen and Jansen, 1990). SCH-23390 and spiperone are also proposed to be selective dopamine D_1 and D_2 receptor antagonists (Faedda et al., 1989), respectively. On the other hand, prazosin (Stanaszek et al., 1983) and idazoxan (Doxey et al., 1983, 1984) are selective α_1- and α_2-adrenoceptor antagonists, respectively.

We performed this study to show the existence of postsynaptic dopamine receptors in the guinea-pig vas deferens by using selective agonists and antagonists for central dopamine receptors.

2. Materials and methods

Male guinea-pigs (370–420 g) were killed by stunning and exsanguination and the vasa deferentia were isolated. The preparations were dissected from the surrounding connective tissue and suspended in a 20-ml muscle chamber containing Krebs–bicarbonate solution (pH 7.35 to 7.40) maintained at 37°C, with a gas mixture of 5% CO_2 in O_2 continuously bubbled through the fluid. Longitudinal contractions of vas deferens were recorded isometrically with a force displacement transducer (Nihon Kohden, SB-1T) linked to a polygraph. The resting tension was adjusted to 0.80 g and the preparation was allowed to equilibrate for 120–150 min to obtain a steady tension before the start of the experiment. During this period, the bathing solution was changed three times. Intramural nerves of the vas deferens were stimulated by delivering 10 Hz for 7 s (rectangular pulse of 0.1 ms duration and supramaximal voltage). The composition of the Krebs–bicarbonate solution used was (mM): NaCl 117.7, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 24.4 and dextrose 10.0.

The drugs used were: (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxy-tetralin hydrochloride (N-0434), *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH-23390), idazoxan hydrochloride, prazosin hydrochloride, spiperone hydrocloride (Research Biochemicals), dopamine hydrochloride (Nakarai), adenosine 5′-triphosphate disodium salt (ATP) (Boehringer Mannheim), α,β-methylene adenosine 5′-triphosphate lithium salt (α,β-methylene ATP) (Sigma Chem.), acetylcholine chloride (Daiich Pharm.) and tetrodotoxin (Sankyo). Dopamine, N-0434 and SCH-23390 were dissolved in 0.01 M HCl solution containing $NaHSO_3$ 0.1 mM to prevent oxidation; other drugs were dissolved in distilled water. Dopamine, acetylcholine and ATP were freshly made daily. α,β-Methylene ATP and SCH-23390 were kept frozen and other drugs were kept at 5°C. These stock solutions were used within one week. Working solutions of the desired concentration for experimental use were freshly prepared by diluting the stock solution with Krebs–bicarbonate solution before the experiments. Drugs were added to the organ bath in a volume of 0.2 ml or less. Prazosin was always added to the bathing solution 10 to 15 min before ATP, acetylcholine and transmural nerve stimulation to block the α_1-adrenoceptor agonistic activity of dopamine and N-0434. To observe the effects of dopamine and N-0434 on the ATP-induced contraction, dopamine and N-0434 were added to the organ bath 5 min prior to ATP (10^{-7} M) in the presence of prazosin. Further, to observe antagonisms to effects of dopamine and N-0434, antagonists were added 5 min prior to dopamine and N-0434. A concentration–response curve for N-0434 to transmural nerve stimulation was obtained by cumulative addition of N-0434 to the organ bath at intervals of 5 min. The contraction induced by ATP (10^{-7} M), α,β-methylene ATP (10^{-7} M) and acetylcholine (10^{-5} M) in the presence of prazosin (10^{-7} M) was regarded as the control (100%), respectively. Further, the contraction induced by transmural nerve stimulation in the presence of prazosin (10^{-7} M) and idazoxan (10^{-7} M) was regarded as the control (100%). The results are expressed as mean values ± standard error of the mean. The significance of differences was determined with Student's paired *t*-test. *P* values of 0.05 or less were considered to be significant.

3. Results

3.1. The contraction induced by dopamine and effects of prazosin on the contraction

Dopamine at concentrations of 10^{-5}, 5×10^{-5} and 10^{-4} M produced a contraction of the guinea-pig vas deferens in a concentration dependent manner (data not shown). The contraction induced by dopamine was abolished by prazosin (10^{-7} M), an α_1-adrenoceptor antagonist (Fig. 1).

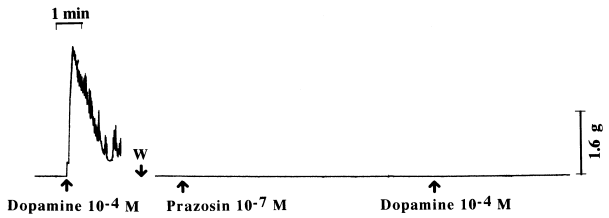

Fig. 1. Typical record showing the contraction induced by dopamine and effects of prazosin on the contraction. Left panel shows a control response to dopamine (10^{-4} M) and right panel, the response to dopamine after prazosin (10^{-7} M) which was added to the bathing solution 10 min before dopamine (10^{-4} M). The arrows indicate drug administration and wash out (W). The calibration marks indicate 1 min (horizontal) and 1.6 g (vertical), respectively.

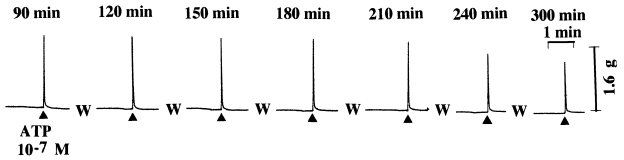

Fig. 2. Typical record showing the change in sensitivity to ATP with time. Prazosin (10^{-7} M) was added to the organ bath 15 min before ATP (10^{-7} M). Triangle and W indicate ATP administration and wash out, respectively. Each time represents time-course after mounting a vas deferens in an organ bath. The calibration marks indicate 1 min (horizontal) and 1.6 g (vertical).

3.2. Effects of dopamine and N-0434 on the contractile responses to ATP and α,β-methylene ATP

ATP at a concentration of 10^{-7} M induced a transient phasic contraction in the presence of prazosin (10^{-7} M) as seen in Fig. 2, the mean increase in tension being 1.11 ± 0.05 g from 63 preparations. The amplitude of this contraction was matched by that of the contraction induced by a single pulse field stimulation (data not shown). If ATP (10^{-7} M) in the presence of prazosin (10^{-7} M) is tested at intervals of 30 min after mounting the vas deferens in an organ bath, the contractile response to ATP reaches a maximum in 90 to 120 min. Once maximal sensitivity has been attained, the response to ATP remains essentially constant for 2 h (Fig. 2). Similar results were observed on the contractile responses to noradrenaline, acetylcholine and α,β-methylene ATP (data not shown). α,β-Methylene ATP (10^{-7} M) which activates and then desensitizes P_{2x} purinoceptors, also induced a contraction (Fig. 3).

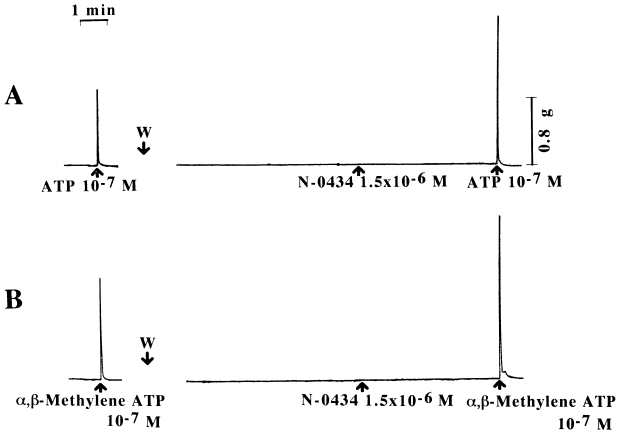

Fig. 3. Typical record showing potentiation of the ATP- and α,β-methylene ATP-induced contraction by N-0434. Prazosin was added to the bathing solution 10 min before ATP (10^{-7} M) or α,β-methylene ATP (10^{-7} M) to block the α_1-adrenoceptor agonistic activity of N-0434. Left panels (A and B) show control responses to ATP and α,β-methylene ATP in the presence of prazosin (10^{-7} M), right panels, the responses to ATP and α,β-methylene ATP after N-0434 (1.5×10^{-6} M) in the presence of prazosin (10^{-7} M). N-0434 (1.5×10^{-6} M) was added 5 min before ATP or α,β-methylene ATP. The arrows indicate drug administration and wash out (W). The calibration marks indicate 1 min (horizontal) and 0.8 g (vertical), respectively.

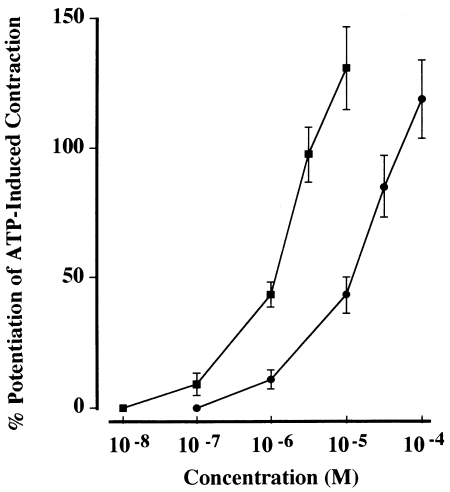

Fig. 4. Concentration-dependent potentiating effects of dopamine and N-0434 on the ATP-induced contraction. Results are expressed as percentage potentiation of the contraction induced by ATP (10^{-7} M) in the presence of prazosin (10^{-7} M). (●); dopamine, (■); N-0434. Concentration-dependent potentiating curves of dopamine and N-0434 were obtained by non-cumulative methods. After the contractile response to ATP (10^{-7} M) was observed in the absence and presence of dopamine or N-O434, preparations were washed out with Krebs–bicarbonate solution. Contractile responses to ATP (10^{-7} M) were observed at intervals of 30 min. Dopamine and N-0434 were added as a single concentration to the bath solution 5 min before ATP (10^{-7} M) in the presence of prazosin (10^{-7} M). Each curve represents the mean values of eight experiments. Vertical bars represent standard errors.

Dopamine and N-0434 had no effect on the muscle tone in the presence of prazosin (10^{-7} M) (Figs. 1 and 3). However, the contractions induced by ATP and α,β-methylene ATP in the presence of prazosin (10^{-7} M) were significantly potentiated by N-0434 (1.5×10^{-6} M), the potentiation of the ATP- and α,β-methylene ATP-induced contraction being 59.5 ± 3.7% ($P < 0.01$, $n = 20$) and 59.9 ± 8.8% ($P < 0.01$, $n = 6$) of the control, respectively. Further, the ATP-induced contraction in the presence of prazosin (10^{-7} M) was potentiated in a concentration dependent manner by dopamine or by N-0434 (Fig. 4).

3.3. Effects of spiperone, SCH-23390 and idazoxan on the potentiation of the ATP-induced contraction by dopamine or by N-0434

Spiperone (5×10^{-7} to 10^{-6} M), SCH-23390 (5×10^{-7} M) and idazoxan (5×10^{-7} M) had no effect on the muscle tone (data not shown). Further, the ATP-induced contraction was not significantly ($P > 0.05$) altered by spiperone (10^{-6} M), SCH (5×10^{-7} M) and idazoxan (5×10^{-7} M), the alteration being −1.84 ± 1.30% (n = 5), 6.46 ± 3.21% ($n = 7$) and 3.39 ± 5.25% ($n = 5$) of the control, respectively. As seen in Fig. 5, the potentiation of the ATP-induced contraction by dopamine or by N-0434 in the presence of prazosin (10^{-7} M) was antagonized by spiperone (5×10^{-7} to 10^{-6} M), a dopamine D_2 receptor antagonist, but not by SCH-23390 (5×10^{-7} M), a

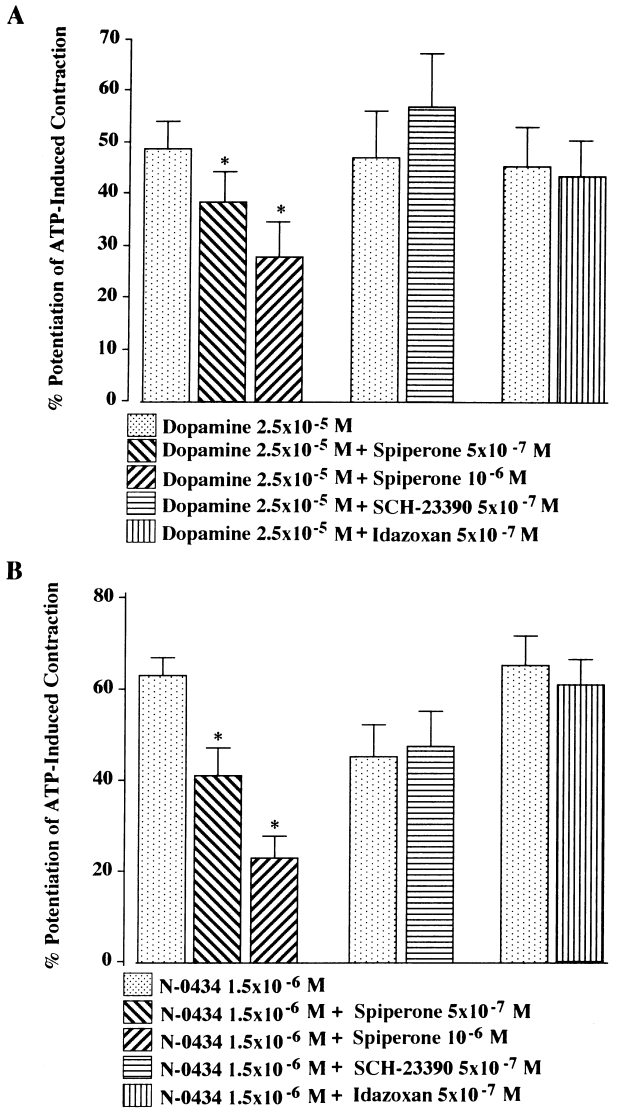

Fig. 5. Effects of spiperone, SCH-23390 and idazoxan on the potentiation of the ATP-induced contraction by dopamine and N-0434. Upper panel A: dopamine (2.5×10^{-5} M). Lower panel B: N-0434 (1.5×10^{-6} M). Prazosin (10^{-7} M) was added to bathing solution 15 min before ATP (10^{-7} M). Spiperone (5×10^{-7} to 10^{-6} M), SCH-23390 (5×10^{-7} M) and idazoxan (5×10^{-7} M) were added 10 min before ATP. Dopamine or N-0434 was added 5 min before ATP. Results are expressed as percentage potentiation of the contraction induced by ATP (10^{-7} M). Each column represents the mean percentage potentiation from five to eight experiments. Vertical bars indicate standard errors. Significant difference from dopamine or N-0434 ($^{*}P < 0.01$).

dopamine D_1 receptor antagonist and idazoxan (5×10^{-7} M), an α_2-adrenoceptor antagonist.

3.4. Effects of N-0434 on the contraction induced by transmural nerve stimulation

Transmural nerve stimulation of the vas deferens produced a transient twitch contraction. The contraction induced by transmural nerve stimulation was abolished by a neuronal blocking agent, tetrodotoxin (10^{-6} M) and a P_{2x}-purinoceptor desensitizing agent, α,β-methylene ATP (2.5×10^{-6} M) which were added to the bathing solution 5 min and 10 min before transmural nerve stimulation, respectively (data not shown).

When transmural nerve stimulation was applied at intervals of 6 min in the presence of prazosin (10^{-7} M) and idazoxan (10^{-7} M), the contraction induced by transmural nerve stimulation remained constant during experiments (data not shown). However, the contraction induced by transmural nerve stimulation was potentiated in a concentration dependent manner by cumulative addition of N-0434 (10^{-7} to 10^{-5} M) (Fig. 6).

The contraction induced by transmural nerve stimulation in the presence of prazosin (10^{-7} M) was not significantly ($P > 0.05$) altered by spiperone (5×10^{-7} M) which was added to bathing solution 5 min before transmural nerve stimulation, the alteration being $-0.39\pm0.98\%$ ($n=5$) of the control. In an additional set of experiments, N-0434 (5×10^{-6} M) in the presence of prazosin (10^{-7} M) and idazoxan (10^{-7} M) potentiated the nerve stimulation-induced contraction by $19.12\pm3.15\%$ This potentiation was significantly reduced to $4.62\pm1.97\%$ ($P < 0.01$, $n=5$) by spiperone 5×10^{-7} M which was added 6 min after N-0434.

3.5. Effects of dopamine on the contractile responses to acetylcholine

Acetylcholine (10^{-5} M) induced a phasic contraction followed by a tonic contraction in the presence of prazosin

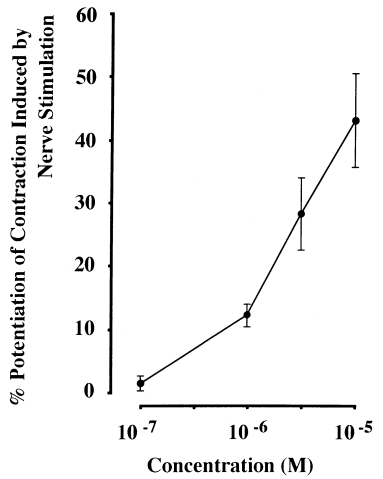

Fig. 6. Concentration-dependent potentiating effects of N-0434 on the contractile response to transmural nerve stimulation. Results are expressed as percentage potentiation of the contraction induced by transmural nerve stimulation in the presence of prazosin (10^{-7} M) and idazoxan (10^{-7} M). (●); N-0434. Prazosin (10^{-7} M) and idazoxan (10^{-7} M) were added to the bathing fluid 15 and 10 min prior to transmural nerve stimulation. The twitches were elicited at intervals of 6 min. N-0434 was added cumulatively to the bath solution 5 min before transmural nerve stimulation in the presence of prazosin (10^{-7} M) and idazoxan (10^{-7} M). The curve represents the mean values of eight experiments. Vertical bars represent standard errors.

(10^{-7} M) which was added to bath solution 15 min before acetylcholine. The phasic contraction induced by acetylcholine (10^{-5} M) in the presence of prazosin (10^{-7} M) was significantly potentiated by dopamine (2.5×10^{-5} M), the potentiation of the acetylcholine-induced contraction being $25.12 \pm 6.84\%$ ($P < 0.01$, $n = 6$) of the control. This potentiation was significantly reduced to $11.03 \pm 4.06\%$ ($P < 0.05$, $n = 6$) by spiperone (5×10^{-7} M) which was added to bath solution 5 min before dopamine (2.5×10^{-5} M).

4. Discussion

It is well known that dopamine and dopamine agonists have a weak α-adrenoceptor stimulating action (Willems et al., 1985). In this study, dopamine produced a contraction in the isolated guinea-pig vas deferens. This contraction was abolished by prazosin, an α_1-adrenoceptor antagonist, indicating that the contraction induced by dopamine is mediated via stimulation of α_1-adrenoceptors.

It has been generally accepted that the ATP-induced contraction is mediated through stimulation of P_{2x} purinoceptors in the isolated guinea-pig vas deferens (Burnstock and Kennedy, 1985). We found that the contraction induced by ATP was potentiated in a concentration-dependent manner by dopamine or by N-0434, a dopamine D_2 receptor agonist. The possibility that the degradation of exogenously added ATP is reduced by dopamine and N-0434 should be taken into consideration. Ecto-ATPase, which is present on cells such as vascular endothelial cells, smooth muscle cells and others (Pearson, 1985). α,β-Methylene ATP is a potent P_{2x} purinoceptor agonist and stable to enzymic hydrolysis (Cusack et al., 1988). In this study, the contractions induced by α,β-methylene ATP as well as ATP were potentiated by N-0434. Thereby, the potentiation of the ATP-induced contraction by dopamine or by N-0434 seems not to result from an inhibition of ecto-ATPase activity.

It has been reported that postjunctional α_2-adrenoceptor as well as α_1-adrenoceptor may exist in the mouse vas deferens (Von Kügelgen et al., 1989). In the present study, the potentiation of the ATP-induced contraction by dopamine and N-0434 was not affected by idazoxan, an α_2-adrenoceptor antagonist, indicating that postsynaptic α_2-adrenoceptors are not involved in the potentiating response to ATP.

The potentiation of the ATP-induced contraction by dopamine and N-0434 was effectively antagonized by spiperone, a dopamine D_2 receptor antagonist, but not by SCH-23390, a dopamine D_1 receptor antagonist. These results suggest that dopamine D_2 receptors exist on smooth muscle of the guinea-pig vas deferens and that activation of dopamine D_2 receptor enhances the ATP-induced contraction. Interestingly, stimulation of postsynaptic dopamine D_2 receptors does not affect the muscle tone, but enhances the ATP-induced contraction. Stimulation of dopamine receptors located on the dog renal and mesenteric artery produces a vasodilatation (Lokhandwala and Barrett, 1982). Therefore, function of postsynaptic dopamine D_2 receptor in the guinea-pig vas deferens seems to largely differ from that of vascular dopamine receptors.

It has been reported that the contractile response of the isolated vas deferens to field stimulation is divided into two separate contractions, consisting of an initial twitch contraction followed by a slower maintained contraction, when the usual 5 s period of stimulation is extended to 30 s (Swedin, 1971a,b). As described in Section 1, sympathetic transmission in the vas deferens is now known to be due to at least two co-transmitter substances, noradrenaline and ATP (Fedan et al., 1981; Sneddon et al., 1982; Meldrum and Burnstock, 1983; Sneddon and Burnstock, 1984; Katsuragi and Furukawa, 1985; Burnstock, 1990). ATP mediates the initial twitch contraction, whereas noradrenaline mediates the secondary slow contraction. In our study, the preparations have been stimulated for a short period (7 s) at 10 Hz. In this case, the contraction induced by transmural stimulation for 7 s corresponds to the initial twitch contraction induced by field stimulation for a long period (30 s) as has been reported by Swedin (1971a,b) and other investigators (Fedan et al., 1981; Sneddon et al., 1982; Stjärne and Åstrand, 1985; Allcorn et al., 1986). In fact, the contraction induced by transmural nerve stimulation was abolished by pretreatment with α,β-methylene ATP, a P_{2x} purinoceptor desensitizing agent (Meldrum and Burnstock, 1983), in our study. Recently, it has been also reported that ATP is released from smooth muscles by stimulation of postsynaptic α_1-adrenoceptors and P_2 purinoceptors (Westfall et al., 1987; Vizi and Burnstock, 1988; Katsuragi et al., 1990, 1991; Kurz et al., 1994). Therefore, it is necessary to think that the contraction induced by transmural nerve stimulation is mediated by ATP released from both sympathetic nerve endings and smooth muscles. In this study, the contraction induced by transmural nerve stimulation in the presence of prazosin and idazoxan was potentiated by N-0434, a dopamine D_2 receptor agonist. This potentiation is due to postsynaptic action, because activation of presynaptic dopamine receptors inhibits the contraction induced by transmural nerve stimulation in the guinea-pig vas deferens (Furukawa and Morishita, 1997). This potentiating effect was antagonized by spiperone, a dopamine D_2 receptor antagonist, suggesting that the contractile responses to transmural nerve stimulation is enhanced via activation of postsynaptic dopamine D_2 receptors.

The contractile response to acetylcholine was also potentiated by dopamine. This potentiation was antagonized by spiperone, indicating that the potentiating effect is mediated via stimulation of dopamine D_2 receptors. Thus, there is no evidence at all suggesting that the potentiating effect is due to a specific interaction between dopamine D_2- and P_{2x}-receptor.

The results suggest that the contractile responses to ATP and acetylcholine are potentiated by activation of postsynaptic dopamine receptors in the guinea-pig vas deferens and that these dopamine receptors can be classified as dopamine D_2 receptors such as located in the central nervous system.

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