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Existence of dopamine D_1 receptor on the sympathetic nerve endings in the guinea-pig vas deferens

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Abstract

The effects of selective dopamine receptor agonists and antagonists on sympathetic neuromuscular transmission were investigated in the guinea-pig vas deferens in order to test for the presence of presynaptic dopamine receptors. A single-pulse field stimulus induced a rapid monophasic contraction which was strongly inhibited by α,β-methylene ATP, a P_{2X} purinoceptor desensitizing agent. The contraction was also inhibited by 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalinamine (UK 14,304), a selective α_2-adrenoceptor agonist. This inhibition was antagonized by idazoxan, an α_2-adrenoceptor antagonist, but not by *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (SCH-23390), a dopamine D_1 receptor antagonist. Furthermore, the contractions were inhibited in a dose-dependent manner by *R*(+)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride (SKF-38393) and (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-82958), dopamine D_1 receptor agonists, and the inhibition was antagonized by both SCH-23390 and idazoxan, but not by spiperone, a dopamine D_2 receptor antagonist. The results suggest that dopamine D_1 receptors are located on the sympathetic nerve endings of guinea-pig vas deferens.

Keywords: ATP; Neurotransmission; Dopamine D_1 receptor; α_2-Adrenoceptor; Vas deferens, guinea-pig

1. Introduction

It is generally accepted that α_2-adrenoceptors located presynaptically trigger negative feedback control by inhibiting transmitter release from sympathetic nerve terminals (Langer, 1981; Starke et al., 1989). In the guinea-pig vas deferens, contractile responses to low frequency sympathetic nerve stimulation were depressed by exogenous dopamine, and this effect was prevented by phentolamine, an α_2-adrenoceptor antagonist, but not affected by haloperidol, a dopamine receptor antagonist (Bell and Matalanis, 1977; Bell, 1980). It has therefore been believed that, in the guinea-pig vas deferens, the presynaptic effect of dopamine is mediated via α_2-adrenoceptors. Similar results showing that presynaptic inhibiting effects of dopamine and dopamine receptor agonists on nerve stimulation-evoked twitch contraction are mediated by α_2-adrenoceptors but not via dopamine receptors, have also been reported for the vas deferens of mouse and rat (Hurst et al., 1979; Gibson and Samini, 1979; Badia et al., 1982; Leedham and Pennefather, 1982; Willems et al., 1985). On the other hand, Tayo has suggested the possibility that prejunctional dopamine receptors seem to exist in the rat vas deferens (Tayo, 1979, 1981).

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 Jr., 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 Jr., 1992; Sibley et al., 1993; Sokoloff and Schwartz, 1995). Newly developed agonists and antagonists for these receptors contribute greatly to the determination of the dopamine D_1/D_2 receptor classification. SKF-38393 and SKF-82958 are selective dopamine D_1 receptor agonists in the central nervous system (Andersen and Jansen, 1990). SCH-23390 is also proposed to be a selective dopamine D_1 receptor antagonist (Faedda et al., 1989). On the other hand, the imidazoline derivative, UK

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14,304, has been reported to act as a full agonist at α_2-adrenoceptors on human platelets (Grant and Scrutton, 1980), fat cells (Galitzky et al., 1989) and the colon adenocarcinoma cell line (HT29 cell) (Paris et al., 1989). Idazoxan is a more potent and selective α_2-adrenoceptor antagonist than yohimbine or phentolamine (Doxey et al., 1983, 1984).

We performed this study to show the presence of presynaptic 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 (400–550 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 maintained at 37°C, with a gas mixture of 5% CO_2 in O_2 continuously bubbled through the fluid. The preparation was attached to an electrode assembly from which one platinum wire passed through the lumen of the vas deferens and a second wire, parallel to the first, dipped into 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 with a single shock (rectangular pulse of 2 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: *R*(+)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride (SKF38393), (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-82958), *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (SCH-23390), 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalinamine (UK 14,304), spiperone hydrochloride (Research Biochemicals International), (−)-noradrenaline bitartrate monohydrate, α,β-methylene adenosine 5′-triphosphate lithium salt (α,β-methylene ATP) and idazoxan hydrochloride (Sigma). Noradrenaline, SKF-38393, SKF-82958 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. These stock solutions were kept frozen and 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 muscle chamber in a volume of 0.2 ml or less. To observe effects of drugs on contractile

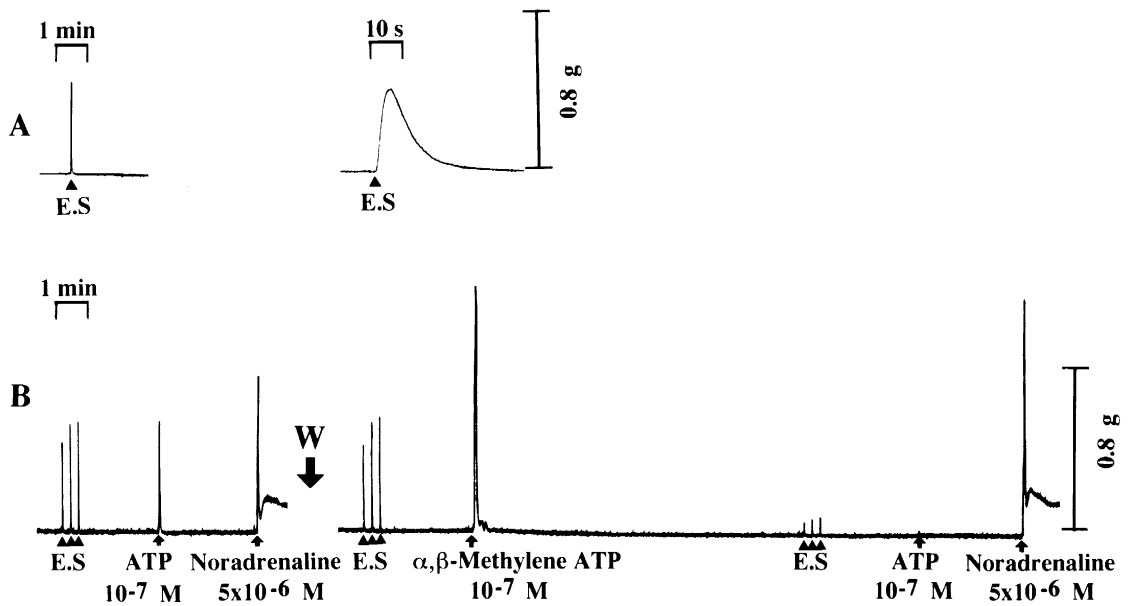

Fig. 1. (A) Typical record showing shape of the twitch contraction caused by a single-pulse field stimulus. The triangle (E.S.) indicates a single-pulse stimulus (2-ms duration, supramaximal voltage). Left and right panels show a slow and fast contraction trace recorded in the same preparation, respectively. The calibration marks indicate 1 min or 10 s (horizontal) and 0.8 g (vertical), respectively. (B) Effects of α,β-methylene ATP on the contractile responses to single pulses, ATP and noradrenaline. The left panel indicates control responses and the right panel the responses after treatment with α,β-methylene ATP (10^{-7} M). The twitches were elicited three times at 15-s intervals by single-pulse field stimulation as shown by the triangles (E.S.). Drugs were added directly into the bathing fluid. The arrows indicate drug administration and washout (W).

responses to electrical stimulation, the drugs were added to the bathing solution 5 min prior to electrical stimulation, with the exception of α,β-methylene ATP which was added to the bathing solution 10 min before electrical stimulation. Dose-response curves for dopamine agonists were obtained by cumulative addition of dopamine agonists to the organ bath. At the beginning of the experiments, a single pulse was applied three times at intervals of 15 s in the absence of drugs and the arithmetic mean of the three contractions 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 twitch contraction induced by single-pulse field stimulation and effects of α,β-methylene ATP on the contraction

As seen in Fig. 1A, a single-pulse field stimulus produced a monophasic rapid contraction in the guinea-pig vas deferens, the mean increase in tension being 0.58 ± 0.01 g from 91 preparations.

As seen in Fig. 1B, after the contractile responses to single pulses, ATP and noradrenaline had been observed, the preparation was washed out with Krebs-bicarbonate solution. The responses to single pulses returned to their normal value 30 min later. After the single-pulse stimulation, addition of α,β-methylene ATP (10^{-7} M) to the bathing solution caused a transient contraction. After treatment with α,β-methylene ATP for 10 min, the contractions induced by single pulses were strongly inhibited, the inhibition being 85.7 ± 4.6% of the control ($n = 4$). Also, the ATP-induced contraction was completely abolished, while the noradrenaline-induced contraction was significantly potentiated, by 45.8 ± 4.8% ($P < 0.01$, $n = 4$).

3.2. Effects of idazoxan and SCH-23390 on the inhibition by UK 14,304

UK 14,304 had no effect on muscle tone. However, as seen in Fig. 2, the contraction induced by single-pulse stimulation was inhibited by UK 14,304 at a concentration of 2.5×10^{-9} M, the inhibition being 52.1 ± 5.8% ($n = 10$) of the control. This inhibition was antagonized by idazoxan (10^{-7} M), but not by SCH-23390 (5×10^{-7} M).

3.3. Effects of SKF-38393 and SKF-82958 on twitch contractions caused by single-pulse stimulation

SKF-38393 and SKF-82958 had no effect on muscle tone. However, SKF-38393 and SKF-82958 at the high concentration of 10^{-6} M enhanced the ATP-induced contraction by 26.8 ± 6.0% and 32.2 ± 7.0% ($P < 0.02$, $n = 5$), respectively. As seen in Fig. 3, the contractions induced by single-pulse field stimulation were inhibited in a concentration-dependent manner by SKF-38393 and SKF-82958. The concentrations of SKF-38393 and SKF-82958 producing half-maximum inhibition (EC_{50}) were 5.8 ± 0.5 × 10^{-7} M and 1.1 ± 0.2 × 10^{-7} M ($n = 8$), respectively. Thus, the inhibitory action of SKF-82958 was five times stronger than that of SKF-38393.

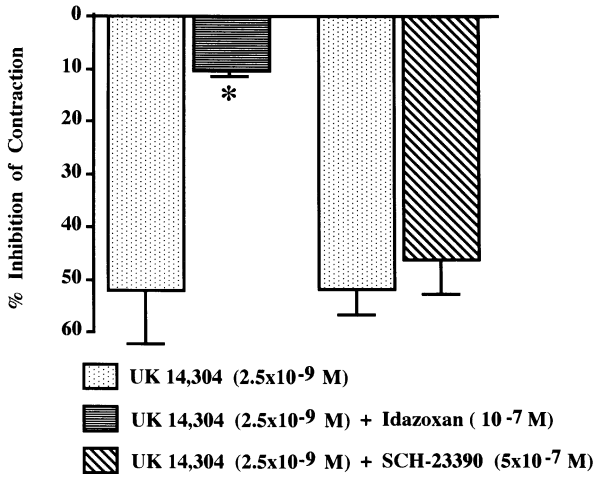

Fig. 2. Statistical data showing antagonism by idazoxan and SCH-23390 of the inhibitory response to UK 14,304. Idazoxan (10^{-7} M) or SCH-23390 (5×10^{-7} M) was applied in the presence of UK 14,304 (2.5×10^{-9} M). Results are expressed as percentage inhibition of the contraction induced by electrical stimulation. Each column represents the mean percentage inhibition from five experiments. Vertical bars indicate standard errors. Significant difference from UK 14,304 in the absence of antagonists (* $P < 0.01$).

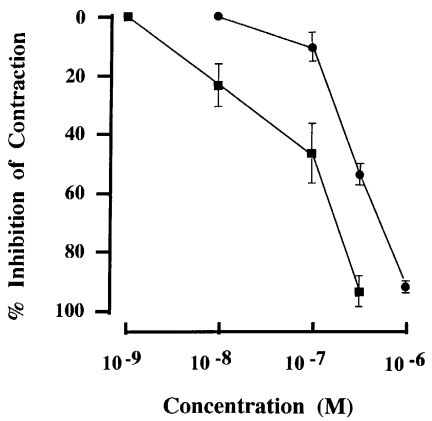

Fig. 3. Dose-dependent inhibitory effects of SKF-38393 and SKF-82958 on the contractile response to single-pulse field stimulation. Results are expressed as percentage inhibition of the contraction induced by single-pulse field stimulation. (●) SKF-38393; (■) SKF-82958. Drugs were added cumulatively to the bath solution 5 min before single-pulse field stimulation. Each curve is the mean of eight experiments. Vertical bars represent standard errors.

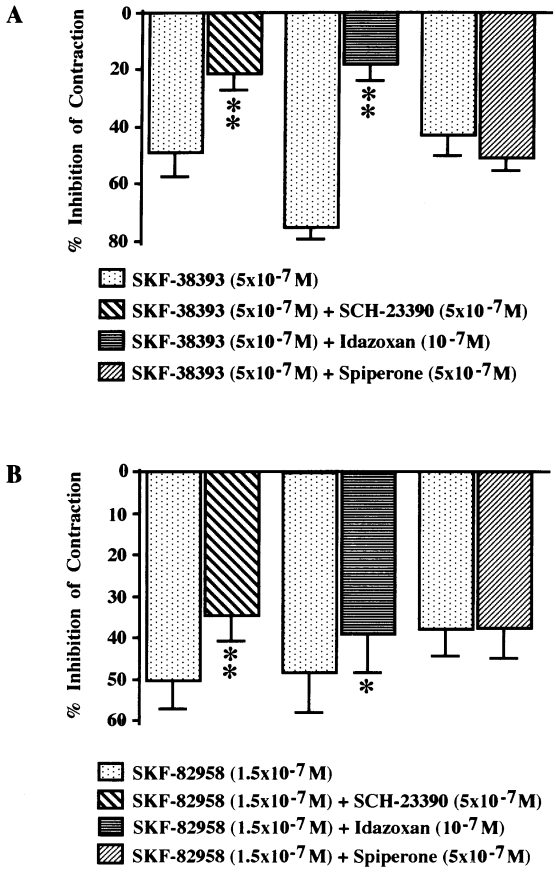

Fig. 4. Effects of SCH-23390, idazoxan and spiperone on the inhibition by SKF-38393 and SKF-82958 of the single-pulse-induced twitches. (A) SKF-38393; (B) SKF-82958. Experimental methods were the same as for Fig. 2. Results are expressed as percentage inhibition of the contraction induced by single-pulse field stimulation. Each column represents the mean percentage inhibition from five to eight experiments. Vertical bars indicate standard errors. Significant difference from SKF-38393 or SKF-82958 (** $P < 0.01$, * $P < 0.05$).

3.4. Effects of SCH-23390, spiperone and idazoxan on the inhibition by SKF-38393 and SKF-82958

As seen in Fig. 4A, the contractions induced by single-pulse field stimulation were inhibited by SKF-38393 (5×10^{-7} M). This inhibition was antagonized by SCH-23390 (5×10^{-7} M) and idazoxan (10^{-7} M), but not by spiperone (5×10^{-7} M). Similar results were obtained with SKF-82958 (Fig. 4B).

4. Discussion

We have previously reported that the contraction of guinea-pig vas deferens induced by single-pulse stimulation is mediated by activation of the sympathetic nervous system because the contraction is blocked by the adrenergic neuron blocking agents, guanethidine and bretylium, and by a neuronal blocking agent, tetrodotoxin (Morishita et al., 1983). Similar results were reported by other investigators (Burnstock and Holman, 1964; Swedin, 1971; Westfall et al., 1978; Lew and White, 1987).

It has also been reported that the contractile response of vas deferens to a single stimulus exhibits two phases, with differing time courses (McGrath, 1978). The differing time courses of the two phases were clear-cut in rat and mouse vasa deferentia whereas, in guinea-pig vasa, both phases of the response had a relatively slower time course and were less distinct from each other (McGrath, 1978). In the prostatic portion of guinea-pig vas, a second component in the response to a single stimulus could not be distinguished (McGrath, 1978). In our present study, similar results, that is a single-pulse stimulus producing a monophasic contraction, were observed in the guinea-pig vas deferens. 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; Allcorn et al., 1986; Burnstock, 1990). ATP mediates the initial rapid phase, whereas noradrenaline mediates the secondary slow phase. α,β-Methylene ATP blocks only contractions induced by ATP but not those induced by noradrenaline and carbachol (Meldrum and Burnstock, 1983). After desensitization of the P_{2X} purinoceptor by α,β-methylene ATP in this study, not only the contraction induced by exogenously added ATP but also the twitch contraction induced by single-pulse stimulation was almost abolished. Therefore, the contraction induced by a single pulse seems to be mediated largely via ATP release from sympathetic nerves of guinea-pig vas deferens.

In the present study, the contraction induced by a single pulse was inhibited by UK 14,304, an α_2-adrenoceptor agonist. This inhibition was antagonized by idazoxan (10^{-7} M), an α_2-adrenoceptor antagonist, but not by SCH-23390 (5×10^{-7} M), a dopamine D_1 receptor antagonist, indicating that presynaptic α_2-adrenoceptors are present on sympathetic nerve terminals of guinea-pig vas deferens. The results also showed that SCH-23390 has little activity as α_2-adrenoceptor antagonist at low concentrations.

We found that the contraction induced by single-pulse stimulation was inhibited in a concentration-dependent manner by SKF 38393 and SKF-82958, dopamine D_1 receptor agonists. This inhibition is due to inhibition of ATP release from sympathetic nerve endings, because SKF 38393 and SKF-82958 do not inhibit the contraction induced by exogenously added ATP. The inhibition induced by SKF 38393 and SKF-82958 was effectively antagonized by SCH-23390 at a concentration that lacked α_2-adrenoceptor blocking activity, but was not antagonized by spiperone, a dopamine D_2 receptor antagonist (Faedda et al., 1989). These results suggest that dopamine D_1 receptors exist on the presynaptic terminals of sympathetic nerves of the guinea-pig vas deferens. Activation of presynaptic dopamine D_1 receptors inhibits the release of ATP

as well as of noradrenaline from sympathetic nerve endings.

As described in Section 1, the depression by dopamine of contractile responses to nerve stimulation was antagonized by phentolamine, an α_2-adrenoceptor antagonist, but was unaffected by haloperidol, a dopamine D_2 receptor antagonist. These results are similar to those of our present study, in that the depression by SKF-38393 and SKF-82958 of nerve-mediated responses was also antagonized by idazoxan, an α_2-adrenoceptor antagonist, without being affected by spiperone, a dopamine D_2 receptor antagonist. Phentolamine and idazoxan are imidazoline derivatives. Phentolamine has been reported to exhibit both dopamine receptor and α_2-adrenoceptor antagonist properties (Castelli and Genedani, 1982; Koons et al., 1983). Therefore, the antagonism by α_2-adrenoceptor antagonists of the inhibition caused by dopamine or dopamine receptor agonists may be explained by the dopamine D_1 receptor antagonist action rather than the α_2-adrenoceptor antagonist action of phentolamine or idazoxan. The validity of this explanation is supported by the fact that the presynaptic inhibition by dopamine D_1 receptor agonists was antagonized by SCH-23390 at a concentration that lacked an α_2-adrenoceptor antagonistic action.

The results suggest that presynaptic dopamine receptors exist on sympathetic nerve endings in guinea-pig vas deferens and that these dopamine receptors can be classified as dopamine D_1 receptor such as located in the central nervous system.

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