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# Existence and pharmacological properties of dopamine $D_4$ receptors in guinea pig vas deferens

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**Abstract**

This study was carried out to identify subtypes of dopamine $D_2$-like receptors in guinea pig isolated vas deferens. Dopamine had no effect on the muscle tone in the presence of prazosin, an $\alpha_1$-adrenoceptor antagonist. However, contractile responses to adenosine triphosphate (ATP), noradrenaline and acetylcholine were potentiated in a concentration dependent manner by dopamine in the presence of prazosin. This potentiation was not inhibited by raclopride, an antagonist for dopamine $D_2$ and $D_3$ receptors. However, the potentiation of ATP- and noradrenaline-induced contraction was inhibited by clozapine and 8-methyl-6-(4-methyl-1-piperazinyl)-11*H*-pyrido[2,3-*b*][1,4]benzodiazepine (JL-18), dopamine $D_4$ receptor antagonists. Further, the potentiation of noradrenaline- and acetylcholine-induced contraction was also inhibited by spiperone, an antagonist for dopamine $D_2$, $D_3$ and $D_4$ receptors. These results suggest that the dopamine $D_4$ receptor is located on the postsynaptic site of guinea pig vas deferens and that activation of the dopamine $D_4$ receptor enhances contractile responses to agonists without affecting muscle tone. 

*Keywords:* Dopamine; Dopamine $D_4$ receptor; ATP; Vas deferens, guinea pig

## 1. Introduction

We suggested that dopamine $D_2$-like receptors exist on the postsynaptic sites of the guinea pig vas deferens. Activation of dopamine receptors does not affect the muscle tone but potentiates the contractile response to adenosine triphosphate (ATP), acetylcholine and transmural nerve stimulation. This potentiation was antagonized by spiperone, a dopamine $D_2$-like receptor antagonist, but not by SCH-23390, an antagonist for dopamine $D_1$-like receptors and α-adrenoceptor antagonists (Morishita and Katsuragi, 1998).

Recently, molecular cloning techniques have revealed five dopamine receptor subtypes (Sibley and Monsma, 1992; Sibley et al., 1993; Sokoloff and Schwartz, 1995). Dopamine $D_1$-like receptors include dopamine $D_1$ and $D_5$ receptors, while dopamine $D_2$-like receptors include dopamine $D_2$, $D_3$ and $D_4$ receptors (Seeman and Van Tol, 1994). Newly developed selective agonists and antagonists for these receptors contribute greatly to the determination of the dopamine $D_1$-like/$D_2$-like receptor classification. Spiperone is an antagonist for dopamine $D_2$, $D_3$ and $D_4$ receptors (Seeman and Van Tol, 1994). Further, raclopride is proposed to be an antagonist for dopamine $D_2$ and $D_3$ receptors (Seeman and Van Tol, 1994; Strange, 1994). Clozapine (Seeman and Van Tol, 1994; Strange, 1994) and its derivative, JL-18 (Liégeois et al., 1995) are antagonists for the dopamine $D_4$ receptor. However, clozapine and JL-18 also interact with other binding sites, such as muscarinic acetylcholine receptors, α-adrenoceptors and others (Coward, 1992; Liégeois et al., 1993; Liégeois et al., 1995). On the other hand, prazosin (Stanaszek et al., 1983) is a selective $\alpha_1$-adrenoceptor antagonist.

We performed this study to identify the subtypes of dopamine $D_2$-like receptors as an enhancer of contractile responses to agonists, such as ATP, noradrenaline and acetylcholine in guinea pig isolated vas deferens by using selective antagonists for central dopamine receptors.

## 2. Materials and methods

Male guinea pigs (280–430 g) were killed by stunning and exsanguination and the vasa deferentia were isolated. The preparations were dissected from the surrounding

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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 90 min to obtain a steady tension before the start of the experiment. During this period, the bathing solution was changed two times. 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: acetylcholine chloride (Daiich Pharm.), adenosine 5′-triphosphate disodium salt (ATP) (Boehringer Mannheim), dopamine hydrochloride (Nakarai Chem.), clozapine, 8-methyl-6-(4-methyl-1-piperazinyl)-11*H*-pyrido[2,3-*b*][1,4]benzodiazepine (JL-18), prazosin hydrochloride, *S*(−)-raclopride L-tartrate (Research Biochemicals) and (−)-noradrenaline bitartrate monohydrate (Sigma). Dopamine, noradrenaline and raclopride were dissolved in 0.01 M HCl solution containing $NaHSO_3$ 0.1 mM to prevent oxidation. Clozapine, JL-18 and prazosin were dissolved in 0.01–0.02 M HCl solution; other drugs were dissolved in distilled water. Acetylcholine, ATP, dopamine, noradrenaline, clozapine and raclopride were freshly made daily. The stock solution of JL-18 was kept frozen and used within 3 days. 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

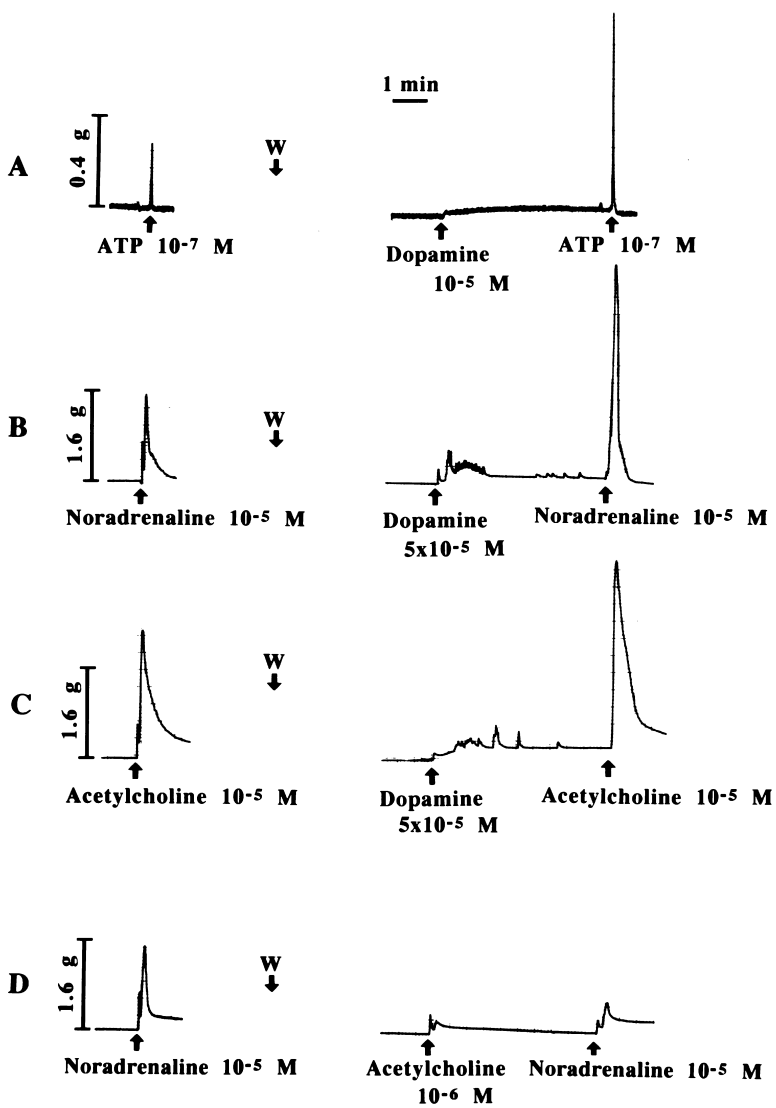


Fig. 1. Typical record showing potentiation of the adenosine triphosphate (ATP)-, noradrenaline- and acetylcholine-induced contraction by dopamine. Left panels (A,B,C and D) show control responses and right panels show the responses after dopamine or acetylcholine. Dopamine was added 5 min before ATP, noradrenaline and acetylcholine. Acetylcholine ($10^{-6}$ M) was also added 5 min before noradrenaline. The arrows indicate drug administration and wash out (W). The calibration marks indicate 1 min (horizontal) and 0.4 to 1.6 g (vertical), respectively.

added to the organ bath in a volume of 0.25 ml or less. All concentrations in the text refer to final concentrations of drugs in the muscle chamber and are expressed in terms of molarity. Prazosin ($10^{-7}$ M) was added to the bathing solution 15 min before agonists, such as ATP, noradrenaline and acetylcholine to block the $\alpha_1$-adrenoceptor agonistic activity of dopamine. To observe effects of dopamine on the agonist-induced contraction, dopamine was added to the organ bath 5 min prior to agonists. Further, to observe antagonisms to potentiating effects of dopamine, dopamine antagonists were added 5 min prior to dopamine. Concentration-dependent potentiating effects of dopamine on the agonist-induced contraction was obtained by noncumulative methods (Fig. 3). After mounting the vas deferens in a organ bath, the sensitivity of the vas deferens to ATP ($10^{-7}$ M), noradrenaline ($3.75 \times 10^{-5}$ M) or acetylcholine ($10^{-5}$ M) increased with time and reached the maximum in 90 to 120 min. After that, responses to these agonists were reproducible during a 2-h experiment (data not shown). Therefore, the maximum contraction induced by ATP ($10^{-7}$ M), noradrenaline ($3.75 \times 10^{-5}$ M or $5 \times 10^{-5}$ M) and acetylcholine ($10^{-5}$ M) at 120 min was regarded as the control (100%), respectively. The results are expressed as mean values or mean values ± standard error of the mean. Statistical significance of differences between values was determined with analysis of variance (ANOVA) followed by Dunnett's test for multiple comparisons with single control or with Student's paired *t*-test for paired values. $P$ values of 0.05 or less were considered to be significant.

## 3. Results

### *3.1. Effects of dopamine on the contraction induced by ATP, noradrenaline and acetylcholine*

The ATP ($10^{-7}$ M) induced a transient phasic contraction (Fig. 1A). Noradrenaline ($10^{-5}$ M) and acetylcholine ($10^{-5}$ M) induced a phasic contraction followed a tonic contraction (Fig. 1B and C). The muscle tone was elevated by dopamine ($10^{-5}$ to $5 \times 10^{-5}$ M). The ATP-induced contraction was potentiated by dopamine($10^{-5}$ M), the potentiation being $199.82 \pm 12.70\%$ of the control ($P < 0.01$, $n = 4$). The contractile responses to noradrenaline and acetylcholine were also potentiated by dopamine ($5 \times 10^{-5}$ M), the potentiation being $100.15 \pm 23.96\%$ ($P < 0.01$, $n = 5$) and $53.53 \pm 10.21\%$ ($P < 0.01$, $n = 4$) of the control, respectively. However, the noradrenaline-induced contraction was inhibited by acetylcholine ($10^{-6}$ M), the

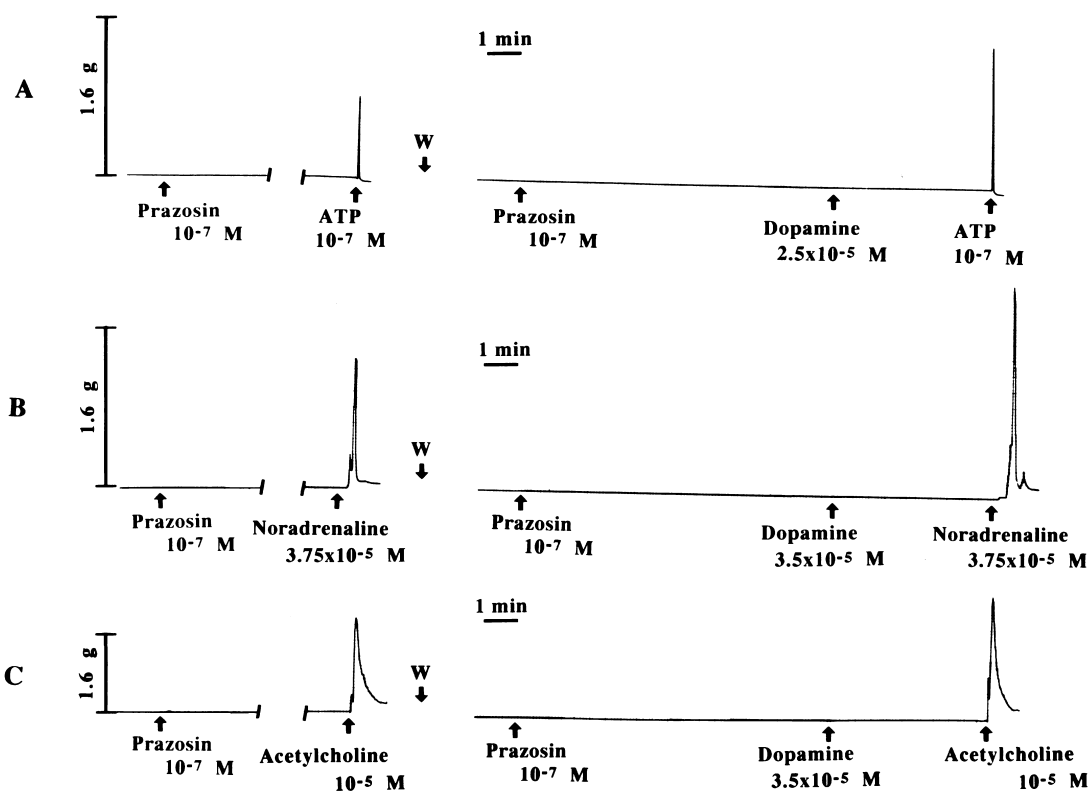


Fig. 2. Typical record showing potentiation of the ATP-, noradrenaline- and acetylcholine-induced contraction by dopamine in the presence of prazosin. Prazosin ($10^{-7}$ M) was added to the bathing solution 15 min before ATP($10^{-7}$ M), noradrenaline ($3.75 \times 10^{-5}$ M) and acetylcholine ($10^{-5}$ M). Left panels (A, B and C) show control responses to ATP, noradrenaline and acetylcholine in the presence of prazosin ($10^{-7}$ M) and right panels, the responses to ATP, noradrenaline and acetylcholine after dopamine ($2.5 \times 10^{-5}$ M) in the presence of prazosin ($10^{-7}$ M). Dopamine ($2.5 \times 10^{-5}$ M) was added 5 min before ATP, noradrenaline and acetylcholine. The arrows indicate drug administration and wash out (W). The calibration marks indicate 1 min (horizontal) and 1.6 g (vertical), respectively.

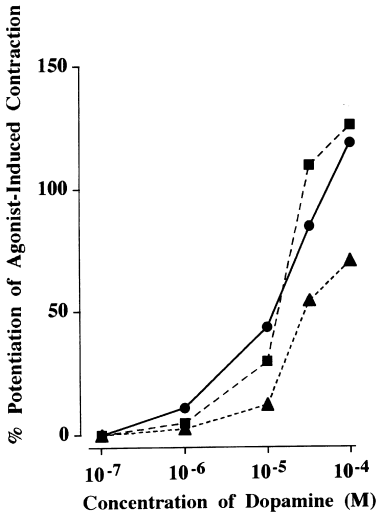


Fig. 3. Concentration-dependent potentiating effects of dopamine on the contraction induced by ATP, noradrenaline and acetylcholine. Results are expressed as percentage potentiation of the contraction induced by ATP ($10^{-7}$ M), noradrenaline ($3.75\times10^{-5}$ M) and acetylcholine ($10^{-5}$ M) in the presence of prazosin ($10^{-7}$ M). ●: ATP ($10^{-7}$ M, $n=8$), ■: noradrenaline ($3.75\times10^{-5}$ M, $n=6$), ▲: acetylcholine ($10^{-5}$ M, $n=5$). Concentration-dependent potentiating curves of dopamine were obtained by noncumulative methods. After the contractile responses to agonists were observed in the absence and presence of dopamine, preparations were washed out with Krebs-bicarbonate solution. Contractile responses to agonists were observed at intervals of 30 min. Dopamine was added as a single concentration to the bath solution 5 min before agonists in the presence of prazosin ($10^{-7}$ M). Each curve represents the mean values of five to eight experiments.

inhibition being $53.12 \pm 6.70\%$ ($P < 0.01$, $n = 4$) of the control(Fig. 1D).

### *3.2. Effects of dopamine on the contraction induced by ATP, noradrenaline and acetylcholine in the presence of prazosin*

The ATP ($10^{-7}$ M) induced a transient phasic contraction in the presence of prazosin ($10^{-7}$ M) which was added to bath solution 15 min before ATP (Fig. 2A). Noradrenaline ($3.75 \times 10^{-5}$ M) induced a contraction in the presence of a low concentration of prazosin ($10^{-7}$ M) (Fig. 2B). However, the contractile response to noradrenaline ($3.75 \times 10^{-5}$ M) was abolished in the presence of a high concentration of prazosin ($10^{-6}$ M) (data not shown). Amplitude of the noradrenaline-induced contraction ($3.75 \times 10^{-5}$ M) was $38.34 \pm 3.76\%$ ($n = 16$) of the normal contraction in the absence of prazosin. Acetylcholine ($10^{-5}$ M) induced a phasic contraction followed by a tonic contraction in the presence of prazosin ($10^{-7}$ M) (Fig. 2C). The mean tension developed by ATP, noradrenaline and acetylcholine was $0.52 \pm 0.04$ g ($n = 31$), $1.05 \pm 0.07$ g ($n = 33$) and $1.60 \pm 0.01$ g ($n = 31$), respectively. As seen in Fig. 2, the muscle tone was not affected by dopamine in the presence of prazosin ($10^{-7}$ M). However, the contractile responses to ATP, noradrenaline and acetylcholine were potentiated in a concentration-dependent manner by dopamine (Fig. 3).

### *3.3. Effects of clozapine and raclopride on the potentiation of the ATP-induced contraction by dopamine*

The muscle tone was not affected by clozapine ($10^{-6}$ M) and raclopride ($10^{-6}$ M) (data not shown). Further, the contractile response to ATP ($10^{-7}$ M) was not significantly ($p > 0.05$) altered by clozapine ($10^{-6}$ M) and raclopride ($10^{-6}$ M), the alteration being $2.90 \pm 1.39\%$ ($n = 6$) and $-0.45 \pm 2.03\%$ ($n = 5$) of the control, respectively. As seen in Fig. 4, the potentiation of the ATP-induced contraction by dopamine in the presence of prazosin ($10^{-7}$ M) was antagonized by clozapine ($5 \times 10^{-7}$ to $10^{-6}$ M), a dopamine $D_4$ receptor antagonist, but not by raclopride ($10^{-6}$ M), an antagonist for dopamine $D_2$ and $D_3$ receptors.

### *3.4. Effects of spiperone, JL-18 and raclopride on the potentiation of the noradrenaline-induced contraction by dopamine*

The muscle tone was not affected by spiperone ($10^{-6}$ M), JL-18 ($5 \times 10^{-7}$ M) and raclopride ($10^{-6}$ M) (data not shown). Further, the contractile response to noradrena-

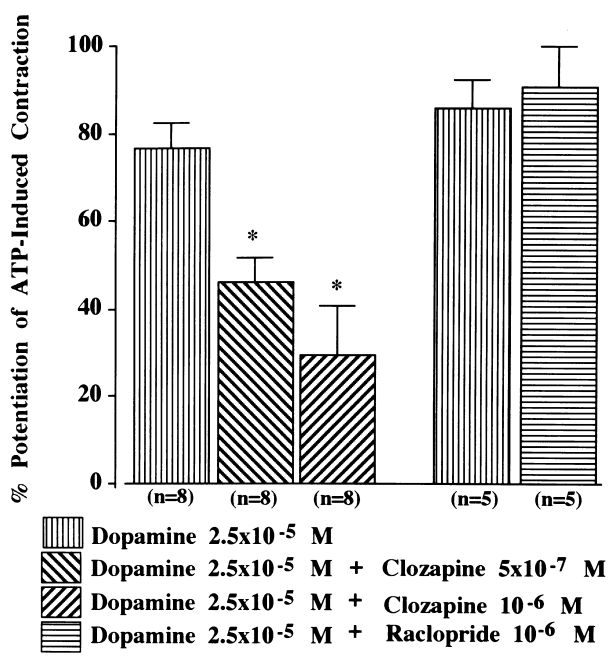


Fig. 4. Effects of clozapine and raclopride on the potentiation of the ATP-induced contraction by dopamine. Prazosin ($10^{-7}$ M) was added to bathing solution 15 min before ATP ($10^{-7}$ M). Clozapine ($5\times10^{-7}$ to $10^{-6}$ M) and raclopride ($10^{-6}$ M) were added 10 min before ATP. Dopamine was added 5 min before ATP ($10^{-7}$ M). 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. The number of experiments is shown in parentheses. Vertical bars indicate standard errors. Significant difference from dopamine ($^*P < 0.01$).

line ($3.75 \times 10^{-5}$ M) was not significantly ($p > 0.05$) altered by spiperone ($10^{-6}$ M), JL-18 ($5 \times 10^{-7}$ M) and raclopride ($10^{-6}$ M), the alteration being $2.32 \pm 4.44\%$ ($n = 5$), $-4.46 \pm 4.67\%$ ($n = 7$) and $-1.63 \pm 2.84\%$ ($n = 5$) of the control, respectively. As seen in Fig. 5, the potentiation of the noradrenaline-induced contraction by dopamine in the presence of prazosin ($10^{-7}$ M) was antagonized by spiperone ($5 \times 10^{-7}$ to $10^{-6}$ M) and JL-18 ($5 \times 10^{-7}$ M), a dopamine $D_4$ receptor antagonist, but not by raclopride ($10^{-6}$ M), the antagonist for dopamine $D_2$ and $D_3$ receptors.

### 3.5. Effects of spiperone and raclopride on the potentiation of the acetylcholine-induced contraction by dopamine

The muscle tone was not affected by spiperone ($10^{-6}$ M) and raclopride ($10^{-6}$ M) (data not shown). Further, the contractile response to acetylcholine ($10^{-5}$ M) was also unaffected ($P > 0.05$) by spiperone ($10^{-6}$ M) and raclopride ($10^{-6}$ M), the alteration being $-2.44 \pm 2.44\%$ ($n = 5$) and $-0.76 \pm 1.45\%$ ($n = 5$) of the control, respectively. However, the contraction induced by acetylcholine ($10^{-5}$ M) was strongly inhibited by clozapine ($5 \times 10^{-7}$ M) and JL-18 ($5 \times 10^{-7}$ M) (data not shown). As seen in Fig. 6, the potentiation of the acetylcholine-induced contraction by dopamine ($3.5 \times 10^{-5}$ M) in the presence of prazosin ($10^{-7}$ M) was antagonized by spiperone ($5 \times 10^{-7}$ to $10^{-6}$ M), but not by raclopride ($10^{-6}$ M).

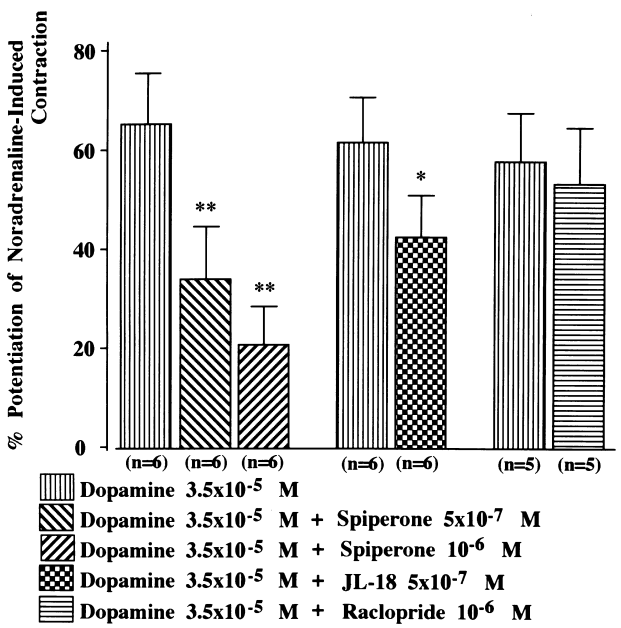


Fig. 5. Effects of spiperone, JL-18 and raclopride on the potentiation of the noradrenaline-induced contraction by dopamine. Prazosin ($10^{-7}$ M) was added to bathing solution 15 min before noradrenaline ($3.75 \times 10^{-5}$ M). Spiperone($5 \times 10^{-7}$ to $10^{-6}$ M), JL-18 ($5 \times 10^{-7}$ M) and raclopride ($10^{-6}$ M) were added 10 min before noradrenaline. Dopamine was added 5 min before noradrenaline ($3.75 \times 10^{-5}$ M). Results are expressed as percentage potentiation of the contraction induced by noradrenaline ($3.75 \times 10^{-5}$ M). Each column represents the mean percentage potentiation from five to six experiments. The number of experiments is shown in parentheses. Vertical bars indicate standard errors. Significant difference from dopamine ($^{*}P < 0.05$, $^{**}P < 0.01$).

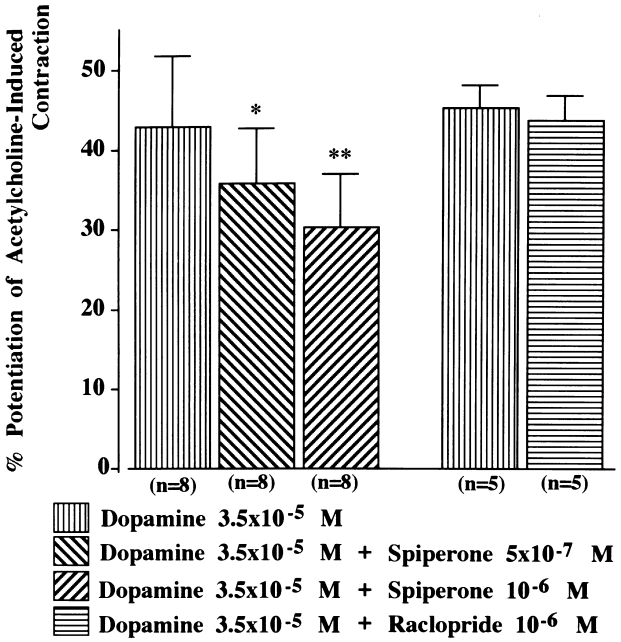


Fig. 6. Effects of spiperone and raclopride on the potentiation of the acetylcholine-induced contraction by dopamine. Prazosin ($10^{-7}$ M) was added to bathing solution 15 min before acetylcholine ($10^{-5}$ M). Spiperone ($5 \times 10^{-7}$ to $10^{-6}$ M), and raclopride ($10^{-6}$ M) were added 10 min before acetylcholine ($10^{-5}$ M). Dopamine was added 5 min before acetylcholine ($10^{-5}$ M). Results are expressed as percentage potentiation of the contraction induced by acetylcholine ($10^{-5}$ M). Each column represents the mean percentage potentiation from five to eight experiments. The number of experiments is shown in parentheses. Vertical bars indicate standard errors. Significant difference from dopamine ($^{*}P < 0.05$, $^{**}P < 0.01$).

## 4. Discussion

It has been generally accepted that the contractile response to ATP is mediated through activation of $P_{2x}$ purinoceptors in guinea pig isolated vas deferens (Burnstock and Kennedy, 1985). As described in Section 1, activation of dopamine $D_2$-like receptors does not affect the muscle tone but potentiates the contractile response to ATP. This potentiation was antagonized by spiperone, a dopamine $D_2$-like receptor antagonist. However, spiperone possesses a high affinity for dopamine $D_2$, $D_3$ and $D_4$ receptors (Seeman and Van Tol, 1994). In this study, the potentiation of the ATP-induced contraction by dopamine was not antagonized by raclopride, an antagonist for dopamine $D_2$ and $D_3$ receptors, indicating that potentiating effect is not mediated through activation of dopamine $D_2$ and $D_3$ receptors. The muscle tone and ATP-induced contraction were unaffected by clozapine, a dopamine $D_4$ receptor antagonist. However, the potentiation of the

ATP-induced contraction by dopamine was effectively antagonized by clozapine. This fact shows that the dopamine $D_4$ receptor exists on the smooth muscle of the guinea pig vas deferens, and that activation of the dopamine $D_4$ receptor potentiates the ATP-induced contraction.

Noradrenaline and dopamine produced contractions of guinea pig isolated vas deferens, but dopamine was considerably less potent than noradrenaline (Tayo, 1979). In our previous report, the contractile response to dopamine ($10^{-4}$ M) was abolished by prazosin ($10^{-7}$ M), an $\alpha_1$-adrenoceptor antagonist, in guinea pig isolated vas deferens (Morishita and Katsuragi, 1998). In this study, the contractile response to noradrenaline was inhibited by 62% in the presence of a low concentration of prazosin ($10^{-7}$ M) and was abolished in the presence of a high concentration of prazosin ($10^{-6}$ M). These results indicate that the contractions induced by noradrenaline and dopamine were mediated via stimulation of $\alpha_1$-adrenoceptors. On the other hand, the muscle tone and noradrenaline-induced contraction in the presence of prazosin ($10^{-7}$ M) were unaffected by spiperone, an antagonist for dopamine $D_2$, $D_3$ and $D_4$ receptors and JL-18, a dopamine $D_4$ receptor antagonist. The contractile response to noradrenaline in the presence of prazosin was also potentiated by dopamine. This potentiation was antagonized by spiperone and JL-18, but not by raclopride, an antagonist for dopamine $D_2$ and $D_3$ receptors. These results support above conclusion that the dopamine $D_4$ receptor exists on the postsynaptic sites of guinea pig vas deferens and that the potentiating effect is mediated via stimulation of the dopamine $D_4$ receptor.

Furthermore, the potentiation of acetylcholine-induced contraction by dopamine was antagonized by spiperone, but not by raclopride, indicating that the potentiating effect is mediated via activation of the dopamine $D_4$ receptor which is located on the postsynaptic site of the guinea pig vas deferens.

It has been reported that ATP and noradrenaline interact in a synergistic manner at postsynaptic sites in guinea pig and mouse vas deferens (Holck and Marks, 1978; Kažić and Milosavljević, 1980; Witt et al., 1991). In our study, the contractile responses to ATP, noradrenaline and acetylcholine were potentiated by dopamine in the absence or presence of prazosin. However, although the muscle tone was slightly elevated by acetylcholine, the contractile response to noradrenaline in the absence of prazosin was inhibited by acetylcholine. Thus, stimulation of postsynaptic dopamine $D_4$ receptors does not affect the muscle tone, but potentiates the contractile response to ATP, noradrenaline and acetylcholine. Therefore, potentiating effects of agonists by dopamine appear to be unique phenomena.

The ATP is released as a co-transmitter with noradrenaline from sympathetic nerve endings in the vas deferens (Fedan et al., 1981, 1982; Sneddon et al., 1982; Burnstock, 1990). We previously reported that the contraction of vas deferens induced by transmural nerve stimulation in the presence of $\alpha_1$- and $\alpha_2$-adrenoceptor antagonists was potentiated via activation of postsynaptic dopamine $D_2$-like receptors (Morishita and Katsuragi, 1998). On the other hand, dopamine normally circulates in plasma (Bühler et al., 1978; Van Loon, 1983). The plasma concentration of the free form of dopamine is approximately equivalent to that of adrenaline and 20% that of noradrenaline (Van Loon, 1983). As dopamine acts on presynaptic dopamine $D_1$-like receptors (Furukawa and Morishita, 1997) and postsynaptic dopamine $D_4$ receptors in guinea pig isolated vas deferens, it is possible that plasma dopamine exerts autoinhibitions at presynaptic sites and potentiating effects of the contraction induced by neuronally-released ATP and noradrenaline at postsynaptic sites.

The results suggest that the dopamine $D_4$ receptor exists on postsynaptic sites of guinea pig vas deferens and that activation of postsynaptic dopamine $D_4$ receptors potentiates the contractile responses to ATP, noradrenaline and acetylcholine without affecting the muscle tone.

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