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# Different contributions of ATP and noradrenaline to neurotransmission in the isolated canine intermediate auricular artery

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**Abstract**

Vasoconstrictor responses elicited by periarterial electrical nerve stimulation were analyzed pharmacologically in the canine isolated, perfused intermediate auricular artery. Phentolamine (10 μM) significantly inhibited the vasoconstrictor responses to stimulation at 5 Hz and over but not those to stimulation at frequencies below 5 Hz. Additionally administered α,β-methylene ATP (1 μM) abolished the phentolamine-resistant vasoconstrictions at all frequencies used in this study. In contrast, suramin (100 μM) inhibited the vasoconstrictor responses to stimulation at 5 Hz and below but not those to stimulation at frequencies higher than 5 Hz. Phentolamine abolished the suramin-resistant vasoconstriction at all frequencies. Phentolamine and α,β-methylene ATP selectively abolished the vasoconstrictor responses to exogenous noradrenaline and ATP, respectively. These results show that the co-transmission of noradrenaline and ATP exists at sympathetic nerve terminals in the canine intermediate auricular artery, and that purinergic transmission is mainly involved in the vasoconstrictor responses to low-frequency nerve stimulation. © 1997 Elsevier Science B.V.

*Keywords:* Auricular artery; Sympathetic nerve stimulation; Purinergic transmission; $P_{2x}$ purinoceptor

## 1. Introduction

There is a considerable body of evidence that adenosine 5′-triphosphate (ATP) acts as a co-transmitter with noradrenaline at sympathetic nerve terminals in the vas deferens and many blood vessels (see Burnstock, 1990; Von Kügelgen and Starke, 1991). Noradrenaline-ATP co-transmission has also been shown in isolated canine blood vessels including the basilar artery (Muramatsu et al., 1981), cerebral artery (Muramatsu and Kigoshi, 1987), mesenteric artery (Muramatsu, 1987; Machaly et al., 1988), lateral saphenous vein (Flavahan and Vanhoutte, 1986) and splenic artery (Ren et al., 1996). We have reported the vascular responsiveness to many vasoactive substances of the isolated canine auricular artery (Ito and Chiba, 1984a,b, 1985) and have shown that this artery might be a useful model for investigating the responses of skin vasculature to vasoactive substances. Chiba and Ito (1985) reported that isolated and perfused canine auricular arteries responded well to periarterial electrical stimulation and were more responsive than those of mesenteric arteries at lower frequencies. In the present study, we made an attempt to investigate whether the vasoconstriction produced by electrical stimulation has a purinergic component in the isolated and perfused intermediate auricular artery of the dog.

## 2. Materials and methods

### 2.1. Arterial preparations

Mongrel dogs of either sex, weighing 8 to 17 kg, were anesthetized with sodium pentobarbital (30 mg/kg i.v.). After treatment with sodium heparin (200 units/kg i.v.), the dogs were killed by rapid exsanguination from the right femoral artery. The intermediate auricular arteries of either ear were then carefully isolated and cleaned of connective tissues in cold Krebs–Henseleit solution (4°C). The isolated arteries were cut into one or two segments, without branches, 0.5–0.7 mm in outer diameter and 5–7 mm in length. As described previously (Chiba and Tsukada, 1985; Ren et al., 1994, 1996), each segment was cannulated and set up for perfusion (see Fig. 1 of Chiba and Tsukada, 1985). Briefly, a stainless steel cannula was inserted into the arterial segment from the distal to the proximal end. The cannula was 3 cm long and 0.4 mm in outer diameter and had a small hole at 5 mm distance from

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the distal blind end. The segment was fixed to the distal portion of the cannula with cotton threads. The cannulated arterial segment was placed in a cup-shaped glass container and perfused at a constant flow rate by means of a micro-tube pump (MP-3A, Tokyo Rikakikai, Tokyo, Japan) with Krebs–Henseleit solution. The solution contained (in mM): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; $KH_2PO_4$, 1.2; $NaHCO_3$, 25 and glucose, 5.6, gassed with 95% $O_2$ and 5% $CO_2$ and maintained at a constant temperature of 37°C with a circulator pump (FE2, Haake). The flow rate was kept at 0.6 ml/min. The perfusion pressure was measured with an electronic manometer (TP-400T, Nihon Kohden, Tokyo, Japan) and recorded by a rectigraph (WT-685GH, Nihon Kohden). After a stabilization period of 60 min, the preparation was removed from the bath solution and fixed in a horizontal position. The preparation was perfused at a constant flow rate during the experiment. The basal perfusion pressure was within 80–110 mmHg.

For electrical stimulation of the adrenergic nerve endings, two platinum electrodes were placed on the extraluminal side of the artery wall. Electrical impulses (10 V, 1 ms, 0.3–30 Hz, 10 s) were provided by an electric stimulator (SEN-7203, Nihon Kohden). The organ bath was sealed with plastic film to maintain the preparation at 37°C. 10-min intervals between electrical stimulation periods were needed to obtain reproducible responses. The intervals between frequency–response curves were 60 min. Each agonist was administered, by microsyringe (MS-50, Ito Seisakujyo) into rubber tubing attached to the cannula, in a volume of 0.01–0.03 ml for 4 s. The intervals between agonist injections and agonist dose–response curves were 5 min and 20 min, respectively. Antagonists and inhibitors were dissolved in perfusate and given 60 min before (except for tetrodotoxin, 10 min before) the second response curves were made for electrical stimulation and agonists. The perfusion with 1 μM $\alpha,\beta$-methylene ATP initially induced a great increase in perfusion pressure. The increased perfusion pressure gradually decreased to the previous basal pressure in 30 min and the perfusion pressure never changed after that. The perfusion with 4 μM guanethidine induced a vasoconstriction which was abolished by 10 μM phentolamine. Electrical stimulation was performed after 60 min of perfusion with guanethidine and the perfusion pressure remained stable during the experiment. The other antagonists did not significantly affect the basal perfusion pressure.

### 2.2. Drugs

The drugs used were: DL-noradrenaline hydrochloride (Sankyo, Tokyo, Japan); disodium adenosine 5′-triphosphate (ATP, Sigma, St. Louis, MO, USA); $\alpha,\beta$-methylene ATP (Research Biochemicals International, Natick, MA, USA); atropine sulfate (Wako, Osaka, Japan); DL-propranolol hydrochloride (Sumitomo, Tokyo, Japan); phentolamine mesylate (Ciba Geigy, Basel, Switzerland); guanethidine sulfate (Sigma); tetrodotoxin (Sigma) and suramin hexasodium (Wako). All drugs were dissolved in physiological saline before the start of the experiment. The stock solutions were kept at −80°C until used.

### 2.3. Statistical analyses

Vascular responses to drugs and electrical stimulation are expressed as the maximal changes in perfusion pressure (mmHg) from their control levels. The data are shown as means ± S.E.M. An analysis of variance with Bonferroni's test was used for the statistical analysis of multiple comparisons of data. *P*-values less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Vascular responses to electrical nerve stimulation and effects of tetrodotoxin and guanethidine on the vasoconstrictor responses

Periarterial electrical nerve stimulation (1 ms pulse duration, 10 V for 10 s) produced an increase in perfusion pressure with a monophasic, gradually developing response in canine auricular arteries. Although definite biphasic responses were not recognized, a notch was observed on the top of the responses in half of the preparations at 5 Hz or lower. Vasoconstrictor responses to electrical stimulation were elicited in a frequency-dependent manner (Figs. 1 and 2). The second and third response curves for electrical stimulation were not significantly different from the first one (data not shown). Tetrodotoxin (0.1 μM) abolished the vasoconstrictor responses to 1–10 Hz stimulation and significantly inhibited those to 20 and 30 Hz by 90.6 ± 6.8% and 81.9 ± 7.2%, respectively ($n$ = 10). Tetrodotoxin did not significantly affect the responses to exogenously applied noradrenaline and ATP (data not shown). An adrenergic neuron blocker, guanethidine (4 μM), significantly inhibited the vasoconstrictor responses to electrical stimulation at all used frequencies and additional phentolamine (10 μM) significantly inhibited the residual responses (Fig. 2). Atropine (1 μM) and propranolol (1 μM) did not affect the vasoconstriction induced by electrical stimulation (data not shown).

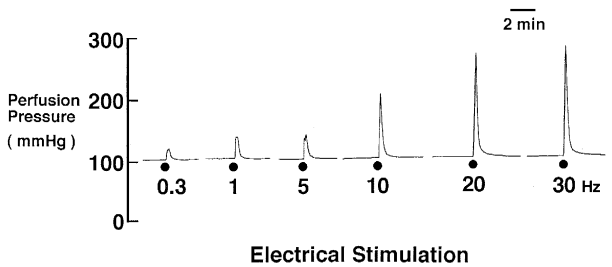


Fig. 1. Traces showing frequency-dependent vasoconstrictor responses to electrical periarterial nerve stimulation with 0.3–30 Hz in an isolated canine auricular artery.

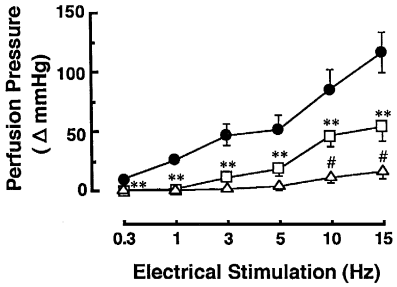


Fig. 2. Effects of guanethidine and phentolamine on the vasoconstrictor responses to electrical stimulation. (●) Control, $n = 8$; (□) guanethidine 4 μM, $n = 8$; (△) guanethidine 4 μM and phentolamine 10 μM, $n = 5$. Points represent the mean values with S.E.M. $^{**}$ $P < 0.01$ as compared with the control group and $^{\#}$ $P < 0.05$ as compared with the guanethidine group.

### 3.2. Effects of phentolamine and α,β-methylene ATP on the vasoconstrictor responses to electrical nerve stimulation, noradrenaline and ATP

10 μM phentolamine significantly reduced the vasoconstrictor responses to electrical stimulation at high frequencies, 5 Hz and higher, but it did not affect the responses elicited at low frequencies, 0.3–3 Hz (Fig. 3a). Phentolamine-resistant vasoconstriction was abolished by additional perfusion with α,β-methylene ATP (1 μM) for desensitization of $P_{2x}$ purinoceptors. Perfusion with α,β-methylene ATP alone failed to shift the frequency–response curve for electrical stimulation (Fig. 3b) even though the vasoconstrictor responses to 0.3 and 1 Hz stimulation were non-significantly reduced by $10.1 \pm 7.3\%$ ($n = 6$) and $32.8 \pm 18.6\%$ ($n = 6$), respectively. α,β-Methylene ATP-resistant vasoconstriction was abolished by additional phentolamine. Phentolamine (10 μM) completely blocked the vasoconstrictor responses to exogenous noradrenaline (0.01–1 nmol) and did not significantly

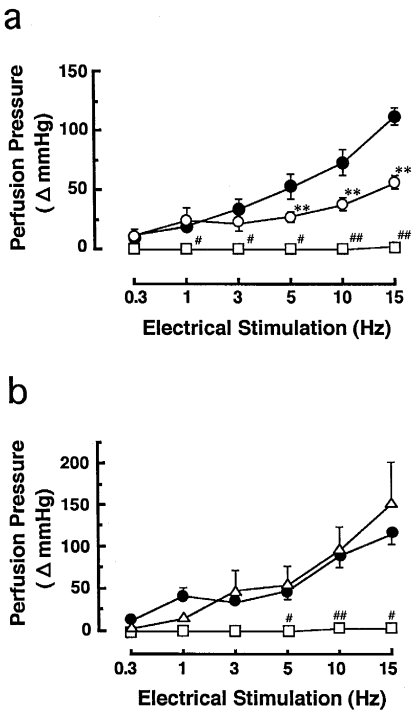


Fig. 3. Effects of phentolamine and α,β-methylene ATP on the vasoconstrictor responses to electrical stimulation. (a) ●, control; ○, phentolamine 10 μM; □, phentolamine 10 μM and α,β-methylene ATP 1 μM, $n = 6$. Points represent the mean values with S.E.M. $^{*}$ $P < 0.05$; $^{**}$ $P < 0.01$ as compared with the control group, and $^{\#}$ $P < 0.05$; $^{\#\#}$ $P < 0.01$ as compared with the phentolamine group. (b) ●, control; △, α,β-methylene ATP 1 μM; □, α,β-methylene ATP 1 μM and phentolamine 10 μM, $n = 6$–8. Points represent the mean values with S.E.M. $^{\#}$ $P < 0.05$; $^{\#\#}$ $P < 0.01$ as compared with the α,β-methylene ATP group.

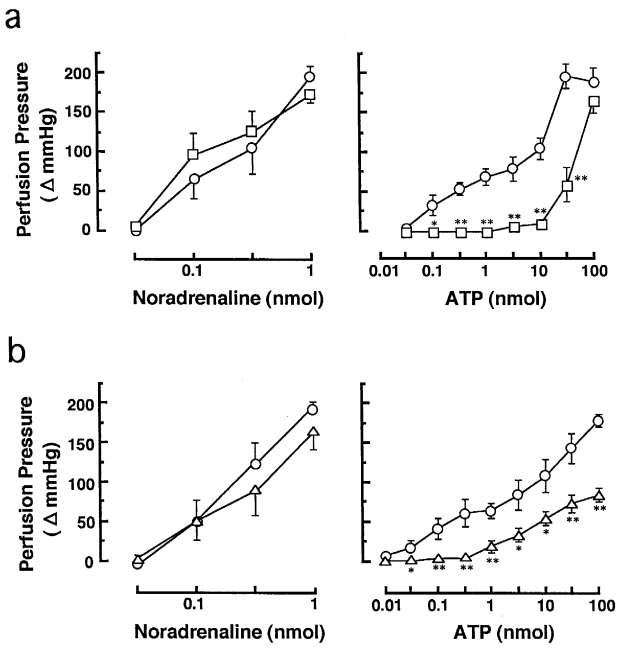


Fig. 4. Effects of α,β-methylene ATP (a) and suramin (b) on the vascular responses to noradrenaline and ATP in the canine auricular artery. (a) ○, control; □, α,β-methylene ATP 1 μM, $n = 6$. (b) ○, control; △, suramin 100 μM, $n = 7$–8. Points represent the mean values with S.E.M. $^{*}$ $P < 0.05$; $^{**}$ $P < 0.01$.

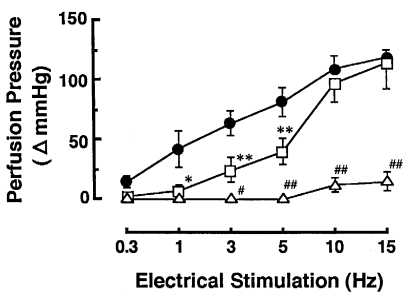


Fig. 5. Effects of suramin and phentolamine on the vasoconstrictor responses to electrical stimulation. (●) Control, $n = 8$; (□) suramin 100 μM, $n = 8$; (△) suramin 100 μM and phentolamine 10μM, $n = 6$. Points represent the mean values with S.E.M. $^{*}$ $P < 0.05$; $^{**}$ $P < 0.01$ as compared with the control group and $^{\#}$ $P < 0.05$; $^{\#\#}$ $P < 0.01$ as compared with the suramin group.

change those to ATP (data not shown). Perfusion with $\alpha,\beta$-methylene ATP significantly inhibited the responses to exogenous ATP (Fig. 4a) and did not affect those to noradrenaline (Fig. 4a).

### *3.3. Effects of suramin on the vasoconstrictor responses to electrical nerve stimulation, noradrenaline and ATP*

Suramin (100 μM), a $P_2$-purinoceptor antagonist, significantly inhibited the vascular responses to electrical stimulation at 5 Hz and lower frequencies (Fig. 5), while it did not reduce the responses elicited at 10 and 15 Hz. Suramin-resistant vasoconstriction was significantly inhibited by additional perfusion with phentolamine (10 μM). Suramin significantly inhibited the vascular responses to exogenous ATP and failed to shift the dose–response curve for noradrenaline (Fig. 4b).

## 4. Discussion

The present study shows the co-transmission of noradrenaline and ATP of sympathetic nerve terminals in the isolated, canine intermediate auricular artery. A pharmacological analysis of the vasoconstrictor responses to electrical nerve stimulation suggests that purinergic transmission is mainly involved in the vasoconstrictor responses to low-frequency stimulation in the canine intermediate auricular artery.

In the present study, tetrodotoxin abolished the electrical stimulation-induced vasoconstriction at 10 Hz or lower. Phentolamine (10 μM) and $\alpha,\beta$-methylene ATP (1 μM) together abolished the vasoconstrictor responses to 15 Hz stimulation. Moreover, guanethidine (4 μM), a sympathetic neuron blocking agent (Burnstock and Warland, 1987; Muramatsu, 1987), significantly inhibited the vasoconstrictor responses to electrical stimulation, although it never caused complete inhibition. These findings suggest that the vasoconstriction evoked by electrical stimulation at frequencies lower than 15 Hz is due to an activation of periarterial sympathetic nerves.

Atropine (10 μM) did not modify the frequency–response curve for electrical stimulation. Furthermore, a combined treatment with phentolamine and $\alpha,\beta$-methylene ATP, a $P_{2x}$ purinoceptor desensitizing agent (Kasakov and Burnstock, 1983; Sneddon and Burnstock, 1985), abolished the vasoconstriction elicited by electrical stimulation. These findings indicate that not only noradrenaline but also ATP (or related purines) might be released as transmitters from sympathetic nerve endings to cause vascular contractions. We used phentolamine as an adrenoceptor antagonist since there are abundant $\alpha_1$ and $\alpha_2$ adrenoceptors postsynaptically in the canine intermediate auricular artery (Ito and Chiba, 1985).

Electrical stimulation parameters affect the ratio of neurally released noradrenaline and ATP. Generally, short pulse trains at a low frequency favor the purinergic component of the response (Kennedy et al., 1986; Ramme et al., 1987; Evans and Cunnane, 1992; Ren et al., 1996) and the adrenergic component becomes greater at higher frequencies (Muramatsu et al., 1989; Sjöblom-Widfeldt et al., 1990; Ren et al., 1996). In the present study, phentolamine, which selectively antagonized the responses to exogenous noradrenaline but not ATP, did not reduce the vasoconstrictor responses to electrical stimulation at low frequencies (0.3–3 Hz). In contrast, suramin, a $P_2$-purinoceptor antagonist, (Dunn and Blakeley, 1988; Leff et al., 1990; McLaren et al., 1995), which selectively inhibited the vasoconstrictor responses to exogenous ATP but not noradrenaline, significantly inhibited the vasoconstriction evoked by electrical stimulation at low frequencies. Moreover, suramin did not inhibit the vasoconstrictor responses to high-frequency stimulation (10 and 15 Hz) but additional phentolamine did. These findings strongly suggest that purinergic and adrenergic transmission may be predominantly involved in the vasoconstrictor responses to low- and high- frequency stimulation, respectively, in the canine intermediate auricular artery.

For the frequency–response curves of the present study, the duration of the stimulation period was kept constant at 10 s so that, with an increase in frequency from 0.3 to 15 Hz, the number of pulses increased from 3 to 150. One might argue that it was the small number of pulses that made the response to low-frequency stimulation phentolamine-resistant. This alternative seems unlikely, however. When the arteries were stimulated with 100 pulses at 1 Hz, giving a stimulation period of 100 s, the vasoconstriction was as resistant to phentolamine (10 μM) as when the arteries were stimulated with the usual 10 pulses at 1 Hz (authors' unpublished observation).

In the present study, the vasoconstrictor responses elicited by electrical stimulation were usually monophasic. Biphasic neurogenic contractions have been observed in the rabbit central ear artery (Kennedy et al., 1986), the dog mesenteric artery (Machaly et al., 1988), the largest rami caecales of the rabbit ileocolic artery (Bulloch and Starke, 1990) and the rat mesenteric artery (Sjöblom-Widfeldt et al., 1990). It has been proposed that the early phase is largely purinergic and the later phase is predominantly noradrenergic (Machaly et al., 1988; Bulloch and Starke, 1990; Sjöblom-Widfeldt et al., 1990). It was impossible to differentiate the vasoconstriction into an early phase and a late phase in this study, since longer periods of stimulation are required to cause biphasic contractions (Bulloch and Starke, 1990). Further studies will be needed to investigate the notches seen in the top of the vasoconstrictor responses in several experiments.

Phentolamine alone failed to inhibit the vasoconstrictor responses to low-frequency stimulation (Fig. 3a). However, adrenergic transmission may also be involved in the vasoconstriction evoked by stimulation at a low frequency, because vasoconstrictor responses to low-frequency stimu-

lation still remained after perfusion with suramin and after the suramin-resistant vasoconstriction was abolished by additional phentolamine. It has been reported that presynaptic $\alpha_2$-adrenoceptors modulate the neurogenic release of both noradrenaline and ATP and that co-released noradrenaline might inhibit the release of purinergic transmitters as well as noradrenaline through presynaptic $\alpha_2$-adrenoceptors (Von Kügelgen and Starke, 1985; Bulloch and Starke, 1990; MacDonald et al., 1992; Driessen et al., 1993; Ren et al., 1996). In this study, phentolamine may also have antagonized the presynaptic $\alpha_2$-adrenoceptors to increase the release of ATP, so that phentolamine might fail to reduce the vasoconstrictor responses induced by low-frequency stimulation. Similarly, the increase in purinergic transmitters as a result of inhibition of presynaptic $\alpha_2$-adrenoceptors may leave almost one-half of the responses to high-frequency stimulation even after perfusion with phentolamine, although adrenergic transmission may play a significant role in the vasoconstriction induced by high-frequency stimulation.

$\alpha,\beta$-Methylene ATP (1 μM), which selectively inhibited the responses to exogenous ATP but not noradrenaline, failed to inhibit the frequency–response curves for electrical stimulation and additional phentolamine abolished the $\alpha,\beta$-methylene ATP-resistant vasoconstriction. $\alpha,\beta$-Methylene ATP abolished the phentolamine-resistant vasoconstrictor responses to electrical stimulation, suggesting that 1 μM $\alpha,\beta$-methylene ATP could definitely desensitize postsynaptic $P_{2x}$ purinoceptors. Therefore, the remaining vasoconstrictor responses after prior perfusion with $\alpha,\beta$-methylene ATP might be elicited by another transmitter, noradrenaline. It has been reported that $\alpha,\beta$-methylene ATP can potentiate the noradrenaline-mediated neurogenic contraction in other vascular tissues (Bulloch et al., 1990; MacDonald et al., 1992; Bao and Stjärne, 1993).

In conclusion, purinergic transmission co-exists in the sympathetic nerve stimulation-induced vasoconstriction of canine intermediate auricular arteries. Purinergic transmission contributes predominantly to the vasoconstrictor responses to periarterial sympathetic nerve stimulation at a low frequency.

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