J. Pharm. Pharmacol. 1992, 44: 836–840
Received September 3, 1991

The Interaction between Noradrenaline and ATP upon Polyphosphoinositide Metabolism and Contraction in Tail Arteries from Normo- and Hypertensive Rats

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Abstract—The effects of, and interaction between, noradrenaline and α,β-methylene ATP upon polyphosphoinositide (PPI) breakdown, investigated by measuring the accumulation of inositol phosphates, and contraction, were studied in tail arteries from normo- (WKY) and spontaneously-hypertensive (SHR) rats. Noradrenaline (10^{-7}–10^{-3} M) evoked a prazosin (10^{-6} M)-sensitive, concentration-dependent increase in total inositol phosphate accumulation in both WKY and SHR rats. No significant differences were observed in either the maximal response or in the concentration range over which noradrenaline evoked this response, between these two populations. Noradrenaline (5×10^{-7}–5×10^{-5} M) evoked a concentration-dependent contraction of arteries from both SHR and WKY rats. The responses to noradrenaline were about 2-fold greater at all effective concentrations of noradrenaline in SHR compared with WKY rats. α,β-Methylene ATP (10^{-6} M) did not alter noradrenaline-stimulated total inositol phosphate accumulation, in arteries from either SHR or WKY rats, measured either as the maximal response or as the EC50. α,β-Methylene ATP (5×10^{-6}M), by itself, evoked a contractile response, which was quantitatively similar in SHR and WKY rats, and was additive with the contractile responses to noradrenaline (5×10^{-7}–5×10^{-5} M). The maximum response produced by a combination of noradrenaline and α,β-Methylene ATP was quantitatively similar to that produced by noradrenaline alone. No evidence of synergism between α,β-Methylene ATP and noradrenaline upon contraction was observed. Nerve stimulation (50 V, 16 Hz, 0·5 ms for 5 min) evoked a prazosin (10^{-6} M)-sensitive significant ($P < 0.001$) increase in total inositol phosphate accumulation in arteries from WKY rats. α,β-Methylene ATP did not modulate noradrenaline-elicited increases in either contraction or PPI metabolism in either SHR or WKY rats. The postsynaptic modifications responsible for the previously reported enhanced contraction to sympathetic nerve stimulation in this tissue are not due to changes in purinergic influence upon either noradrenaline-stimulated PPI metabolism or upon contraction.

A well-characterized feature of essential hypertension is the enhanced contractility of the vasculature to nerve stimulation in hypertensive compared with normotensive rat models (for review see Reid 1988). Alterations in both tone and postsynaptic activity have been proposed by way of explanation. Increased sympathetic activity in tissues from hypertensive animals involving central cardiovascular arteries (Juskevich et al 1978; Saavedra et al 1978; Takeda & Bunag 1978) or locally at the level of the postganglionic sympathetic neurone (Westfall & Meldrum 1985) could increase transmitter release and explain the increased response. The involvement of ATP in the increased release has been proposed by Vidal et al (1986). On the other hand, there was no significant difference in the evoked ^{3}H overflow between tail arteries from normal and spontaneously hypertensive rats preloaded with [^{3}H]noradrenaline. These results led Muir & Wardle (1989) to conclude that the increased pressor responses evoked by field stimulation in tail arteries from hypertensive rats was not due to an increased noradrenaline release but was mediated postsynaptically. Postsynaptically, an increased receptor sensitivity (Haeusler & Haefely 1970; Lais & Brody 1978; Ekas & Lokhandwala 1981) to the transmitters including ATP (Vidal et al 1986) has been proposed.

It is now recognized that, in response to stimulation, certain sympathetic nerves release more than one excitatory substance (Burnstock 1976, 1985), usually noradrenaline and ATP (or a closely related substance), each with a potential neurotransmitter or neuromodulatory role—the phenomenon of co-transmission (Campbell 1987; Bartfai et al 1988).

The importance and relevance of co-transmission to hypertension is unclear. The pressor responses to noradrenaline were enhanced in arteries from spontaneously-hypertensive (SHR) rats (Muir & Wardle 1989) compared with normotensive (WKY) controls, but the contribution of the purinergic component to the enhanced contractile response of hypertensive arteries to nerve stimulation remains unclear and controversial. Either an increase in the release of, or in the response to, ATP has been proposed to occur in hypertension (Vidal et al 1986), although no significant differences in the evoked [^{3}H]noradrenaline or [^{3}H]ATP overflow, or in the pressor responses to ATP between SHR and WKY rats (Muir & Wardle 1988, 1989) were found in this laboratory. These observations provide no support for the involvement of an enhanced purinergic component of sympathetic co-transmission in hypertension. However, one important potential purinergic contribution to nerve-evoked

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contraction remains to be investigated. If, as might be anticipated (Campbell 1987), sympathetically released co-transmitters act synergistically, the question arises as to whether an interaction between them upon stimulus-contraction mechanisms exists in this tissue and if so whether this is modified in hypertension.

The signal-transduction mechanism most closely associated with contraction in vascular smooth muscle, including the rat tail artery (Bao et al 1989; Schwarze et al 1990) involves stimulation of polyphosphoinositide (PPI) metabolism (Abdel-Latif 1986). The PPI transduction system was therefore an obvious target for study, particularly since pressor responses to exogenous noradrenaline, as well as those to nerve stimulation, were enhanced in arteries from SHR rats (Fouda et al 1987; Muir & Wardle 1989), strongly implicating a postsynaptic locus for the enhanced responsiveness of tissues from SHR rats. Accordingly, the effects of and interaction between noradrenaline and co-transmitter ATP upon inositol phosphate accumulation (taken as a measure of PPI metabolism) and contraction were examined in rat tail arteries, a tissue where the electrical and mechanical responses to noradrenaline and ATP have been well characterized (Sneddon & Burnstock 1984; Muir & Wardle 1989). This was done to determine whether the purinergic component of sympathetic nerve stimulation acted as a modulator of the biochemical and contractile responses to noradrenaline and if differences existed in any such interaction between the normo- and hypertensive states.

Materials and Methods

Preparation of arteries

Age-matched albino WKY and SHR rats were killed by stunning followed by exsanguination. The tail was severed, the cornified epithelium removed and a length (7–8 cm) of artery dissected out from the proximal end (Holman & Surprenant 1980). Arteries were then cleaned of connective tissue and cut into segments (1 cm long, 5 mg wet wt).

Effects of noradrenaline and ATP on contraction

Artery segments (8 × 1 mm) were sleeved over two stainless steel wires which formed part of a perspex assembly. One wire was fixed and the other attached to an isometric strain gauge (FT03) so that changes in arterial diameter could be measured in terms of force displacement. The strain gauge was attached to a polygraph to record tension changes. Each assembly and artery segment was placed in a water-jacketed organ bath containing aerated (95%O_2–5%CO_2) Krebs bicarbonate buffer of the following composition (mM): NaCl 118, $NaHCO_3$ 25, KCl 4, $CaCl_2$ 2·6, $MgCl_2$ 1·2, NaH_2PO_4 1, glucose 11, pH 7·4, at 37°C ± 1°C. Following an equilibration period of at least 30 min, cumulative dose-response curves to increasing concentrations of noradrenaline, alone or in the presence of α,β-methylene ATP at a concentration (5×10^{-6} M) previously known to be effective in stimulating contraction of this tissue, were constructed using arteries from SHR and WKY rats.

Effects of noradrenaline, α,β-methylene ATP and nerve stimulation on PPI metabolism

Changes in PPI metabolism in the segments were quantified by measuring inositol phosphate accumulation in the presence of LiCl to inhibit the enzyme inositol monophosphatase and prevent the recycling of inositol phosphates into PPIs (Akhtar & Abdel-Latif 1984). The segments were transferred to a single glass vial containing Krebs bicarbonate buffer saturated with 95% O_2–5% CO_2, to which was added myo-[2-^{3}H]inositol (8 μCi mL^{-1}). This vial was incubated (37°C, 3 h), then individual segments transferred to another single vial containing Krebs bicarbonate buffer supplemented with LiCl (10 mM and myo-[2-^{3}H]inositol (8 μCi mL^{-1}). This vial and contents were then incubated together for a further 15 min at 37°C.

After this preliminary incubation, segments were divided among a number of identical glass vials (3–4 segments per vial) at 37°C in the same medium as before. The effects of noradrenaline or α,β-methylene ATP upon inositol phosphate accumulation were examined 30 min after their addition to this medium and of nerve stimulation (50 V, 16 Hz, 0·5 ms) following continuous application of square wave pulses for 5 min. Incubations were terminated by transferring segments to ice-cold trichloroacetic acid (1 mL, 10% w/v).

The effect of prazosin (10^{-6} M) was investigated. It was added during the pre-incubation procedures 15 min before the commencement of the incubations with noradrenaline. The arteries were then transferred to Li-containing Krebs buffer and the protocol completed as above.

Trichloroacetic acid was extracted from the samples (1 mL) by repeated (3 times) addition and thorough mixing of water-saturated diethylether. The pH of the samples was then adjusted to pH 7 with NaOH (0·2 mL, 0·1 M). The inositol phosphates were extracted and separated from the samples by anion exchange chromatography (Berridge 1983) using Dowex 1-X8 anion exchange columns (100–200 mesh, formate form). Inositol trisphosphates, bisphosphates and monophosphates were eluted together, giving an indication of total inositol phosphate accumulation. The eluted inositol phosphates were measured by liquid scintillation counting.

Measurement of systolic blood pressure

Systolic blood pressure was measured in conscious rats, acclimatized to 37°C for 15 min. Readings were made, without anaesthesia, by inflating a tail cuff and using a piezoelectric crystal detector connected to a storage oscilloscope to determine when the systolic blood pressure had been reached and to a sphygmomanometer to measure blood pressure. The mean systolic blood pressure was: 125 ± 3·0 mm Hg (± s.e.m.) (n = 10) in WKY rats and 195 ± 1·9 mm Hg in SHR rats.

Analysis of results

Results were expressed as the mean ± s.e.m. of a number (n) of observations. Student's *t*-test was used to test for significance between means. Data that showed a non-parametric distribution were analysed using the Mann Whitney U-test. A *t*-value of $P < 0.05$, or less, was taken as significant.

Drugs and chemicals

Myo-[2-^{3}H]inositol (18·3 Ci $mmol^{-1}$, in an aqueous ethanol solution (10% v/v)) was purchased from Amersham International Plc, UK. (−)-Noradrenaline bitartrate, α,β-methylene ATP (lithium salt) and nifedipine were obtained from

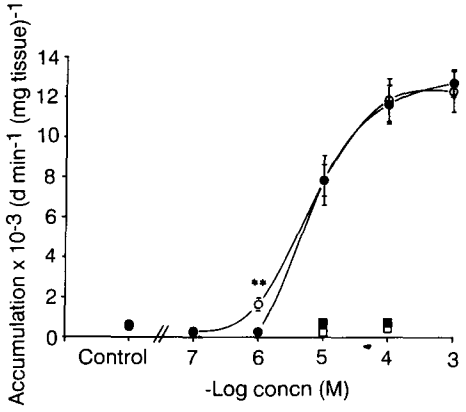

FIG. 1. The effect of noradrenaline upon inositol phosphate accumulation (mean ± s.e.m., n = 7) in tail arteries from WKY (○) and SHR (●) rats. Prazosin (10^{-6} M) abolished the effects of noradrenaline in arteries from both WKY (□) and SHR (■) rats. Control indicates incubations in the absence of drugs.

Sigma (St Louis, MO, USA). Prazosin hydrochloride was a gift from Pfizer Research, UK.

Results

The effect of noradrenaline and of α,β-methylene ATP upon total inositol phosphate accumulation

Noradrenaline (10^{-6}–10^{-3} M) evoked a concentration-dependent, prazosin (10^{-6} M)-sensitive, increase in total inositol phosphate accumulation in both SHR and WKY rats compared with the respective controls (Fig. 1). With the exception of noradrenaline at 10^{-6} M, where the effect in WKY rats was significantly greater, no significant difference was found between normo- and hypertensive animals either in the maximal response observed (17-fold increase over basal accumulation) or in the EC50 values (mean EC50 = $6{\cdot}6 \pm 1{\cdot}5 \times 10^{-6}$ M, n = 5, for WKY rats and $5{\cdot}5 \pm 1{\cdot}0 \times 10^{-6}$ M, n = 5, for SHR rats).

In both WKY and SHR rats, α,β-methylene ATP, up to a concentration of 10^{-3} M, did not stimulate a significant increase in total inositol phosphate accumulation, compared with the respective controls (data not shown).

The interaction between noradrenaline and α,β-methylene ATP upon inositol phosphate accumulation

Noradrenaline (10^{-6}–10^{-3} M) evoked a concentration-dependent increase in total inositol phosphate accumulation in both SHR and WKY rats (Fig. 2) which was unaffected by the co-addition of α,β-methylene ATP (10^{-6} M), the EC50 value for contraction in this tissue (Schwarze et al unpublished). α,β-Methylene ATP (10^{-6} M), alone, had no effect upon total inositol phosphate accumulation in tissues from either SHR or WKY rats.

The interaction between noradrenaline and α,β-methylene ATP upon contraction

Noradrenaline (5×10^{-7}–5×10^{-5} M) evoked a concentration-dependent contraction of tail artery rings from both SHR and WKY rats (Fig. 3). Noradrenaline-stimulated contractile responses were about 2-fold greater in SHR than

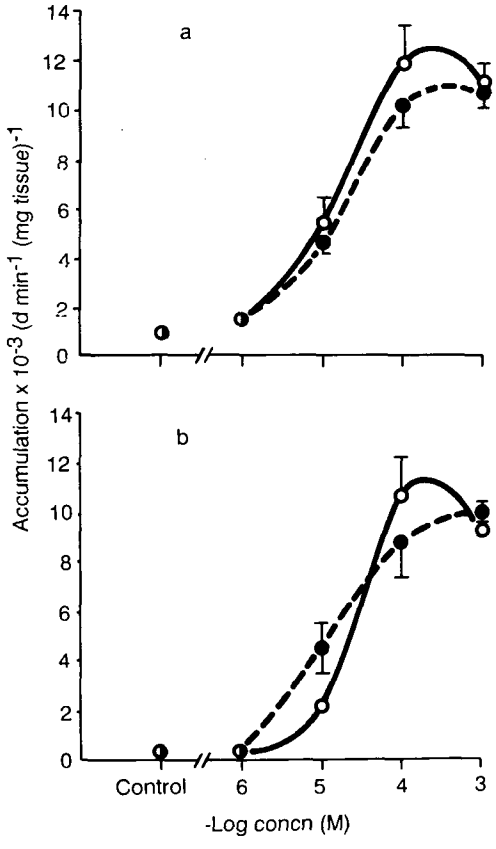

FIG. 2. Noradrenaline-stimulated increases in inositol phosphate (mean ± s.e.m., n = 7) in tail arteries from WKY (a) and SHR (b) rats in the presence (●) and in the absence (○) of α,β-methylene ATP (10^{-6} M). Control indicates incubations in the absence of noradrenaline.

in WKY rats confirming the previously reported enhanced adrenergic contractile response in hypertensive tissues. α,β-Methylene ATP (5×10^{-6} M) alone, contracted arteries from both SHR and WKY rats; the maximum contractile response was not significantly different between the two populations thus confirming the lack of an enhanced purinergic response in hypertensive tissues. Co-addition of α,β-methylene ATP (5×10^{-6} M) with increasing concentrations of noradrenaline resulted in a simple additive effect between the two agents producing a maximum response which could be evoked by noradrenaline acting alone. α,β-Methylene ATP (5×10^{-6} M) did not potentiate the noradrenaline-evoked contraction of arteries from either SHR or WKY rats. No evidence of synergism between noradrenaline and α,β-methylene ATP upon contraction was observed in either normo- or hypertensive tissues.

The effect of nerve stimulation upon inositol phosphate accumulation

Electrical field nerve stimulation (50 V, 16 Hz, 0·5 ms) evoked a significant, prazosin (10^{-6} M)-sensitive increase in total inositol phosphate accumulation in arteries from normotensive WKY control rats (Table 1). The inositol phosphate response is thus mainly adrenergic.

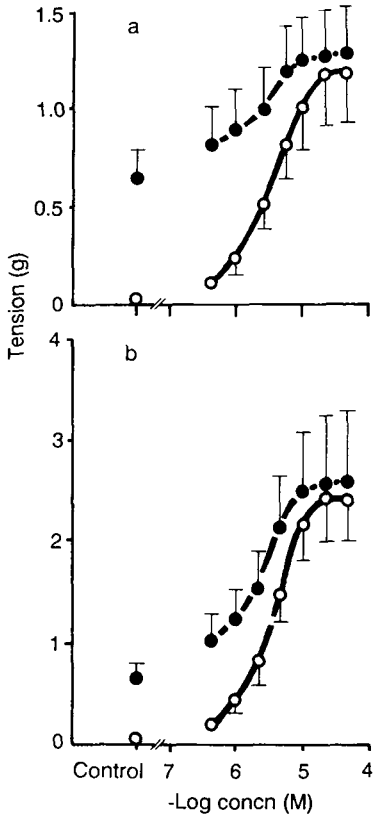

FIG. 3. Contractile responses (mean ± s.e.m., n = 4), expressed as tension developed, in tail arteries from WKY (a) and SHR (b) rats to noradrenaline in the presence (●) and absence (○) of α,β-methylene ATP (5×10^{-6} M). Control indicates incubations in the absence of noradrenaline.

Table 1. The effect of nerve stimulation alone and in the presence of prazosin upon total inositol phosphate accumulation in tail arteries.

Treatment	Inositol phosphate accumulation (d min^{-1} (mg wet wt)$^{-1}$)
Control	493 ± 40
Nerve stimulation	1053 ± 99***
Nerve stimulation + prazosin (10^{-6} M)	684 ± 67

***$P < 0.001$ compared with control.

Discussion

The present study has modelled the hypertensive state closely in a well-characterized system by monitoring the effects of neuronally released transmitters in an artery in which an enhanced pressor response to nerve stimulation exists. In the rat tail artery, noradrenaline, via α_1-adrenoceptors, and α,β-methylene ATP, via P_{2x}-purinoceptors, contribute to the contraction while the electrical response is entirely purinergic (Sneddon & Burnstock 1984; Muir & Wardle 1989).

That PPI metabolism was indeed a postsynaptic, largely adrenergic, effect, involved in nerve-evoked stimulus-contraction coupling in this artery, was confirmed by the ability of nerve stimulation to increase total inositol phosphate accumulation in a prazosin-sensitive manner. This confirms our previous work, in normal Wistar rats, that neuronally-mediated vasoconstriction in tail arteries is largely adrenergic with no major contribution from co-released ATP in either vasoconstriction or the associated PPI response (Schwarze et al 1990). In the present study, exogenously-added noradrenaline also produced a dose-dependent increase in total inositol phosphate accumulation in tail arteries from both SHR and WKY rats, there being no significant difference between these two populations. The concentration ranges over which noradrenaline increased total inositol phosphate accumulation (10^{-6}–10^{-4} M) and contracted this tissue (5×10^{-7}–5×10^{-5} M) were consistent with the involvement of PPI metabolism in the effects of noradrenaline upon muscle tone. The enhanced contractile responses to noradrenaline in arteries from SHR when compared with those obtained from WKY rats confirmed the previous reports of an enhanced adrenergic contractile response in the hypertensive state (Fouda et al 1987; Muir & Wardle 1989). However, the lack of any difference in the absolute levels of total inositol phosphate accumulation between SHR and WKY rats suggests no difference occurred either in the degree of stimulation of phospholipase C or in the hydrolysis of PPIs by noradrenaline in this enhanced contractile response during the development of hypertension. Previously reported results from investigations of the effects of agonists on the vasculature of hypertensive model systems are conflicting and do not clarify the picture. Increases (Resink et al 1987, 1989; Takata et al 1989; Huzoor-Akhbar et al 1989), decreases (Heagerty et al 1986; Socorro et al 1990) and no changes (Jones et al 1988) in total inositol phosphate accumulation have been reported. These variations may have arisen from differences in methodology, tissues, contractile substances or the hypertensive model used.

α,β-Methylene ATP, a stable selective P_{2x}-purinoceptor agonist (Burnstock & Kennedy 1985; Burnstock 1990), up to a concentration of 10^{-3} M, did not significantly increase total inositol phosphate accumulation in either SHR or WKY rats. Significantly, α,β-methylene ATP (5×10^{-6} M) evoked a contractile response in both SHR and WKY rats which was not significantly different between the two strains. The lack of correlation between the biochemical and physiological responses suggests that PPI metabolism is not a signal-transduction mechanism utilized by purinergic receptors in this tissue. Indeed, when both mechanical and electrical responses evoked by noradrenaline and ATP in the rat tail artery are considered, noradrenaline evoked a slow but sustained contraction with no electrical accompaniment, whereas ATP evoked a smaller and more rapid contraction with a large electrical response. ATP may, therefore, produce contraction in the rat tail artery, as in the rabbit ear artery (Benham & Tsien 1987), by opening cation channels in the plasma membrane, depolarizing the cell and allowing the entry and release of Ca^{2+} to permit contraction.

Implicit in co-transmission, is the concept that noradrenaline and ATP are synarchic regulators of vascular smooth muscle tone. The hypothesis tested in this study was that a contribution of the purinergic component to nerve-evoked

contraction was a modulation of the stimulus-contraction coupling mechanisms utilized by noradrenaline and that this interaction may be altered in the hypertensive state. Previous studies focusing upon the action of purines acting in isolation may have missed such a purinergic influence and the postulated enhanced purinergic component to nerve stimulation reported by Vidal et al (1986) may reflect an indirect action of ATP through modulation of the actions of noradrenaline. There was no evidence, however, from the present study that an interaction between the co-transmitters upon PPI metabolism or contraction occurs in the normotensive state or that any alteration in an interaction between the co-transmitters could account for the enhanced contractile responses produced in hypertensive rats in-vitro by ATP (Vidal et al 1986). α,β-Methylene ATP did not significantly enhance the total inositol phosphate accumulation or the contractile responses evoked by noradrenaline in either SHR or WKY rats. These findings, consistent with the failure of α,β-methylene ATP to potentiate either noradrenaline-stimulated contraction or PPI-metabolism in Wistar rats (Schwarze et al 1990), provide no support for a purinergic involvement in the development of hypertension.

Acknowledgements

The authors gratefully acknowledge the technical help of J. W. Craig in the contractile experiments and the support of the Scottish Home and Health Department, the Nuffield Foundation, the Wellcome Trust, the SmithKline Foundation and the medical research funds of the University of Glasgow.

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