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The effect of adenyl compounds on the rat heart

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1 The effects of adenyl compounds were examined on the rat atrium and ventricle.

2 Adenosine, adenosine 5′-monophosphate, adenosine 5′-diphosphate, adenosine 5′-triphosphate (ATP) and β, γ-methylene ATP (APPCP) produced negative inotropic effects on the rat atrium. These inhibitory effects were antagonized by 8-phenyltheophylline (8-PT), a P_1-purinoceptor antagonist, and potentiated by erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), an adenosine deaminase inhibitor, but were not affected by dipyridamole, which blocks adenosine uptake.

3 α, β-Methylene ATP (APCPP), which is resistant to degradation, did not produce a similar inhibitory response in the rat atrium.

4 Adenosine did not affect the basal developed force of the rat ventricle nor did it affect the β-adrenoceptor-mediated positive inotropic effect.

5 Very high concentrations of ATP (0.1–3 mM) produced negative inotropic effects in the rat ventricle. APPCP (0.3 mM) also produced an inhibitory response, which was significantly smaller than that produced by ATP (0.3 mM). APCPP elicited excitation rather than the expected inhibitory response.

6 The inhibitory effect of ATP in the rat ventricle was not blocked by indomethacin, 8-PT or atropine.

7 It is possible that the action of ATP in the rat ventricle is mediated via P_2-purinoceptors and that the lack of inhibitory action of APCPP on the rat ventricle is due to the difference in structural conformation between ATP and APCPP.

8 It seems likely that inhibitory P_1-purinoceptors are present in the rat atrium and that the inhibitory responses produced by ATP in the rat ventricle may be mediated via P_2-purinoceptors.

Introduction

Rat atria are sensitive to adenyl compounds (Hollander & Webb, 1957; Kolassa, Pfleger & Träm, 1971; Bertelli, Bianchi & Beani, 1972; Meinertz, Nawrath & Scholz, 1973). However, there appear to be no reports in the literature on the responses of the rat ventricle to adenyl compounds.

Two types of 'purinergic' receptors have been proposed, mainly on the basis of the relative potencies of adenosine, adenosine 5′-monophosphate (AMP), adenosine 5′-diphosphate (ADP) and adenosine 5′-triphosphate (ATP) and selectivity of antagonists in a wide variety of tissues (Burnstock, 1976; 1978). P_1-purinoceptors are most sensitive to adenosine and are competitively blocked by methylxanthines; their occupation leads to changes in cyclic adenosine 3′, 5′-monophosphate (cyclic AMP) accumulation. P_2-purinoceptors are most sensitive to ATP and are blocked (although not competitively) by quinidine, 2 substituted imidazolines, 2, 2′-pyridylisatogen, apamin (by blockade of potassium channels) and arylazido aminopropionyl ATP ($ANAPP_3$) which has been claimed to be a specific P_2-purinoceptor antagonist (Hogaboom, O'Donnell & Fedan, 1980; Fedan Hogaboom, O'Donnell, Colby & Westfall, 1981).

The aim of the present study was to examine the responses of the rat heart to adenosine, ATP, the slowly degradable ATP analogue, β, γ-methylene ATP (APPCP) and a degradation-resistant analogue α, β-methylene ATP (APCPP) (Satchell & Maguire, 1975; Maguire & Satchell, 1979) in an attempt to characterize the purinoceptors in the rat heart.

Methods

Wistar rats (250–500 g) of either sex were killed by stunning and cervical dislocation. The hearts were excised and the left atria dissected free in cold modified Krebs-Henseleit solution (Kunos, 1977) which was continuously gassed with a mixture of 95% O_2 and 5% CO_2. The left atrium was mounted on a punctate electrode (Blinks, 1965) and was then transferred to a 10 ml organ bath maintained at 30°C. An initial load of 0.5 g was applied to the preparation. The punctate electrode was used as a cathode (with a distant anode) to deliver electrical stimuli to the muscle (1 Hz, 5 ms duration) at twice threshold voltage. One strip was cut from the right ventricle and this was then suspended in a 10 ml organ bath with a resting tension of 0.5 g. The ventricle strips were electrically stimulated (1 Hz, 5 ms) at twice threshold voltage. The mechanical activity was recorded isometrically by means of a Grass FT 03C force transducer and a Grass model 79D polygraph. The preparations were allowed to equilibrate for 60 min before addition of drugs. The bathing solution was changed every 15 min during the equilibration period.

Cumulative log concentration-response curves were obtained to adenosine, ATP, AMP and APPCP in the atria. Responses to single concentrations of adenosine, AMP, ADP, ATP, APPCP and APCPP were compared in the absence and in the presence of 8-phenyltheophylline (8-PT) (10 μM).

In the ventricle, concentration-response curves were constructed from responses obtained to single additions of ATP and acetylcholine (ACh). In some experiments, responses to single concentrations of adenosine (300 μM), ATP (300 μM), APPCP (300 μM), APCPP (300 μM) and ACh (30 μM) were compared.

When 8-PT (10 μM), dipyridamole (0.5–10 μM), erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) (5 μM) or atropine (1.5 μM) were used, these drugs were added to the organ baths 20 min before the examination of their effects. The tissues were incubated with indomethacin for 1 h before its effect was investigated.

The effect of adenosine was examined on the β-adrenoceptor-mediated positive inotropic effect. Isoprenaline (10–30 nM), a β-adrenoceptor agonist, was added to the organ bath to increase the basal force of contraction. When the response to isoprenaline had reached maximum, adenosine (300 μM) was added. The change in developed force produced by adenosine was compared with the change produced in the absence of adenosine after the response to isoprenaline had reached maximum. In other experiments, adenosine (300 μM) was added to the organ bath 1 min before the addition of isoprenaline (10–30 nM), and the developed force was compared with that obtained when isoprenaline was added alone.

Responses were measured as the percentage changes from basal levels. The mean and standard error of the mean were calculated for each group. Statistical significance was evaluated by the *t* test for paired or unpaired samples, and *P* values of 0.05 or less were considered to be significant.

Drugs and solvents

Adenosine, adenosine 5′-monophosphate (AMP), adenosine 5′-diphosphate (ADP), adenosine 5′-triphosphate (ATP), α, β-methylene adenosine 5′-triphosphate (APCPP), β, γ-methylene adenosine 5′-triphosphate (APPCP), acetylcholine, isoprenaline and indomethacin were obtained from Sigma. Dipyridamole was obtained from Boehringer Ingelheim, 8-phenyltheophylline (8-PT) from Calbiochem, atropine from Antigen Ltd. and erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) from Burroughs Wellcome.

Indomethacin was made up in 0.2 M sodium carbonate solution immediately before use. Ascorbic acid (100 μM) was added to the isoprenaline solution to prevent its oxidation. A stock solution of 10 mM 8-PT was made up in 80% v/v methanol containing 0.2 M NaOH, and aqueous dilutions of this were used. All other drugs were dissolved in distilled water.

Results

Atria

Adenosine, AMP, ADP, ATP and APPCP reduced the force of contraction of rat left atria in a concentration-dependent manner. The effects of adenosine, AMP, ADP, ATP and APPCP were not significantly different from each other at any of the concentrations tested. All five compounds required 50–60 s to produce their maximum effects after a latency of 2–3 s.

APCPP (300 μM) was inactive within the time course of action of the other compounds studied ($n = 4$, see Figure 1Aa). However, after a time lag of 2.8 ± 0.6 min a positive inotropic effect, which required several minutes (18.3 ± 1.9 min) to reach maximum, was observed (Figure 1B).

8-PT antagonized the negative inotropic effects of adenosine, AMP, ADP, ATP and APPCP (Figure 1Ab) but did not affect the positive inotropic effect of APCPP.

Incubation with dipyridamole (0.5 μM), an adenosine uptake blocker, for 20 min did not poten-

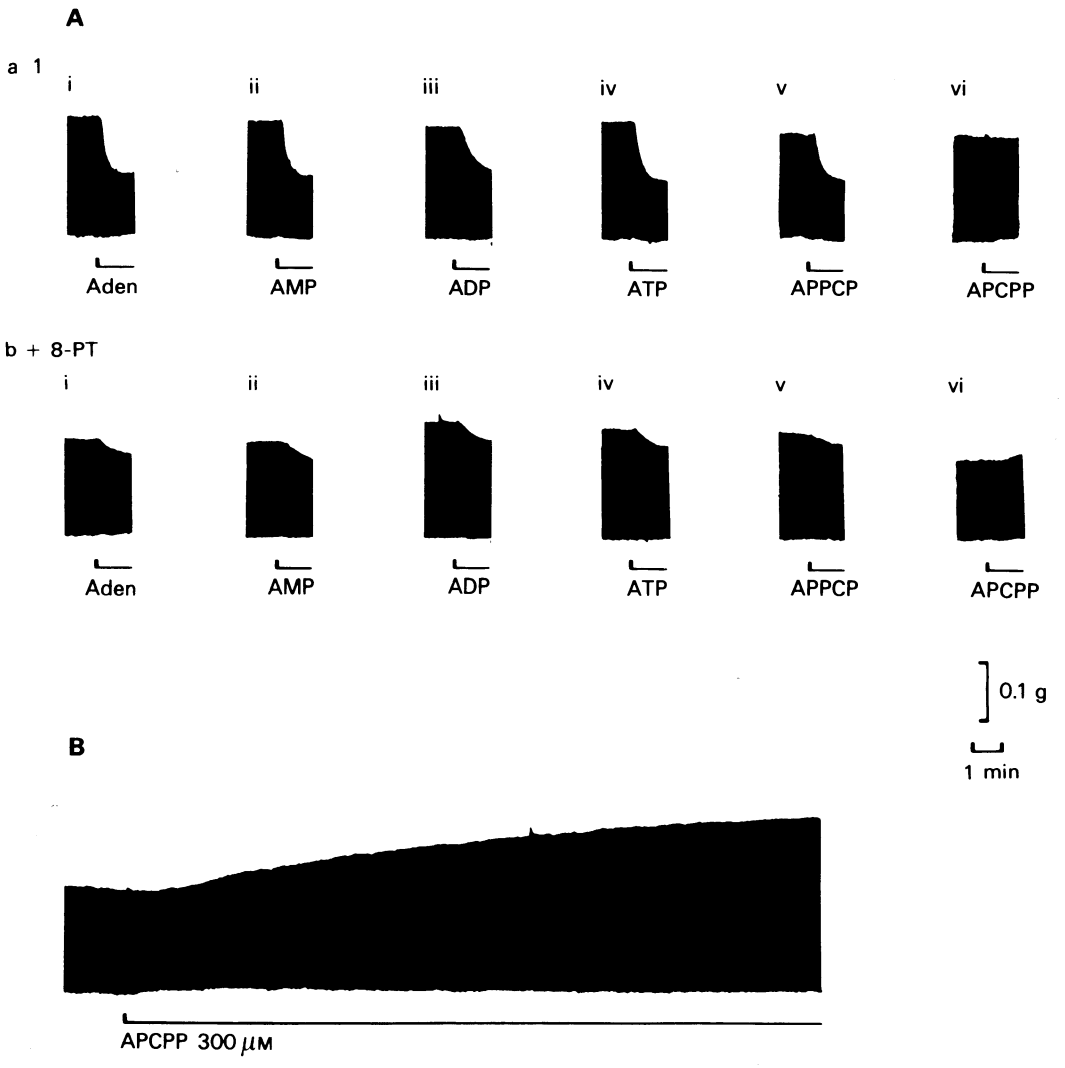

Figure 1 (A) Responses of electrically-driven rat atria to 300 μM of the following purines: (i) adenosine (Aden), (ii) AMP, (iii) ADP, (iv) ATP, (v) β, γ-methylene ATP (APPCP) and (vi) α, β-methylene ATP (APCPP), in the absence (a) and presence (b) of 10 μM 8-phenyltheophylline (8-PT). (B) The response of electrically-driven rat atria to APCPP (300 μM) over a longer time period.

tiate the negative inotropic effects of adenosine, ATP or APPCP. Dipyridamole, in concentrations as high as 10 μM, did not potentiate the effects of adenosine. The effect of 0.5 μM dipyridamole on the negative inotropic effects of adenosine is illustrated in Figure 2a.

EHNA (5 μM), an adenosine deaminase inhibitor, potentiated the effects of adenosine (Figure 2b). Similar results were obtained with AMP and ATP.

Ventricular strips

Adenosine (0.3 mM) slightly enhanced the contractile force of the rat ventricle (Figure 3), but this effect was not significant. ATP (0.1–3 mM) reduced the force of contraction of the rat right ventricular strip in a concentration-dependent manner (Figure 4). APPCP (0.3 mM) also produced a negative inotropic response (Figure 3) but the response produced by

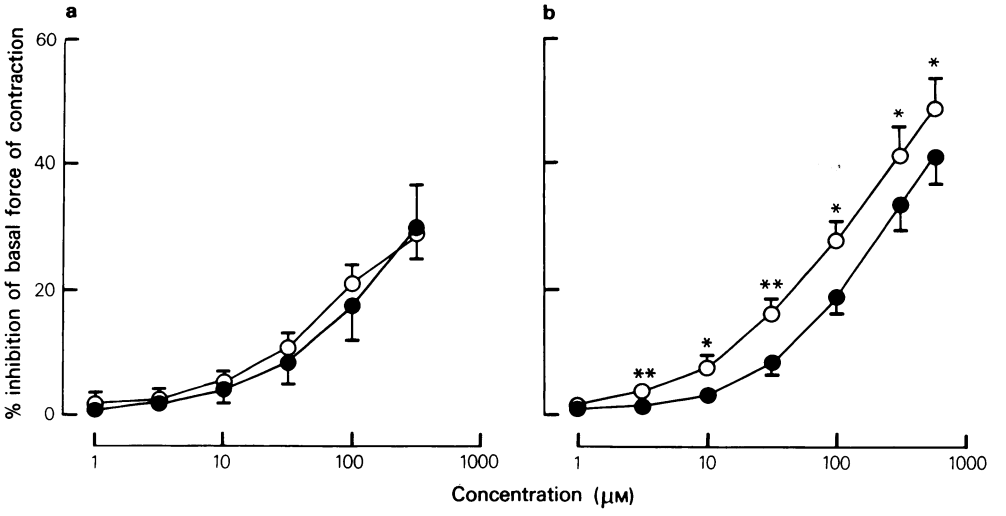

Figure 2 Log concentration-response curves of the electrically-driven rat atria to the negative inotropic effect of adenosine (●) in the absence and (○) in the presence of (a) dipyridamole (0.5 μM) and (b) erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) (5 μM). Each point is the mean of observations from 6 preparations. Vertical bars show s.e.mean. Asterisks indicate the significance of the differences between control responses and responses obtained in the presence of dipyridamole or EHNA using the paired *t* test. * $P<0.05$; ** $P<0.01$.

APPCP (0.3 mM) was significantly smaller than that produced by the same concentration of ATP ($P<0.01$). APCPP (0.3 mM) increased the force of contraction of the rat right ventricular strip (Figure 3).

ACh (1–300 μM) produced a negative inotropic effect (Figure 4). The responses to ATP (300 μM) were not affected by the concentration of atropine (1.5 μM) that completely blocked the response to ACh (30 μM). A combination of atropine (1.5 μM) and indomethacin (20 μM) slightly potentiated ($P<0.05$) the response to ATP (300 μM). 8-PT (10 μM) did not affect the responses to ATP.

Isoprenaline (10–30 nM) increased the force of contraction to 174.2 ± 27.8% of the basal developed force ($n=9$). Adenosine (300 μM) did not affect the positive inotropic action of isoprenaline whether it was added before isoprenaline or after the response to isoprenaline had reached maximum.

Discussion

The effects of adenyl compounds on the rat atrium and ventricle are described in this study. Adenosine, AMP, ADP, ATP and APPCP produced negative inotropic effects on the driven rat atrium, a finding consistent with previous reports (Hollander & Webb, 1957; Kolassa *et al.*, 1971; Bertelli *et al.*, 1972; Meinertz *et al.*, 1973). The effects of adenosine, AMP, ADP, ATP and APPCP were not significantly different from each other. The effects of adenosine, AMP, ADP, ATP and APPCP are probably mediated via P_1-purinoceptors since 8-PT antagonized their effects. Further, APCPP, which is resistant to degradation to adenosine (Satchell & Maguire, 1975; Maguire & Satchell, 1979), was inactive within the time course of action of ATP and APPCP, suggesting that ATP and APPCP are metabolised to adenosine and AMP before acting on P_1-purinoceptors. The mode of action of APCPP in producing slowly developing excitation after a long latency is not known.

EHNA (5 μM), an adenosine deaminase blocker, potentiated the negative inotropic effects of adenosine, AMP and ATP, supporting the view that ATP is metabolised to adenosine and AMP before acting on P_1-purinoceptors and suggesting that extracellular deamination may be an important route for inactivation of adenosine.

The negative inotropic effects of adenosine, ATP and APPCP were not potentiated by dipyridamole (0.5–10 μM). This is consistent with the results of Stafford (1966) and Kolassa *et al.* (1971) who have reported the failure of dipyridamole in potentiating the negative chronotropic effect of adenosine in the rat heart. This is in contrast to the guinea-pig, where the effects of adenosine are potentiated by dipyridamole (Stafford, 1966, Kolassa *et al.*, 1971; Burnstock & Meghji, 1981). It has been shown that less adenosine is taken up in rat hearts than in guinea-pig hearts (Hopkins & Goldie, 1971). Hopkins &

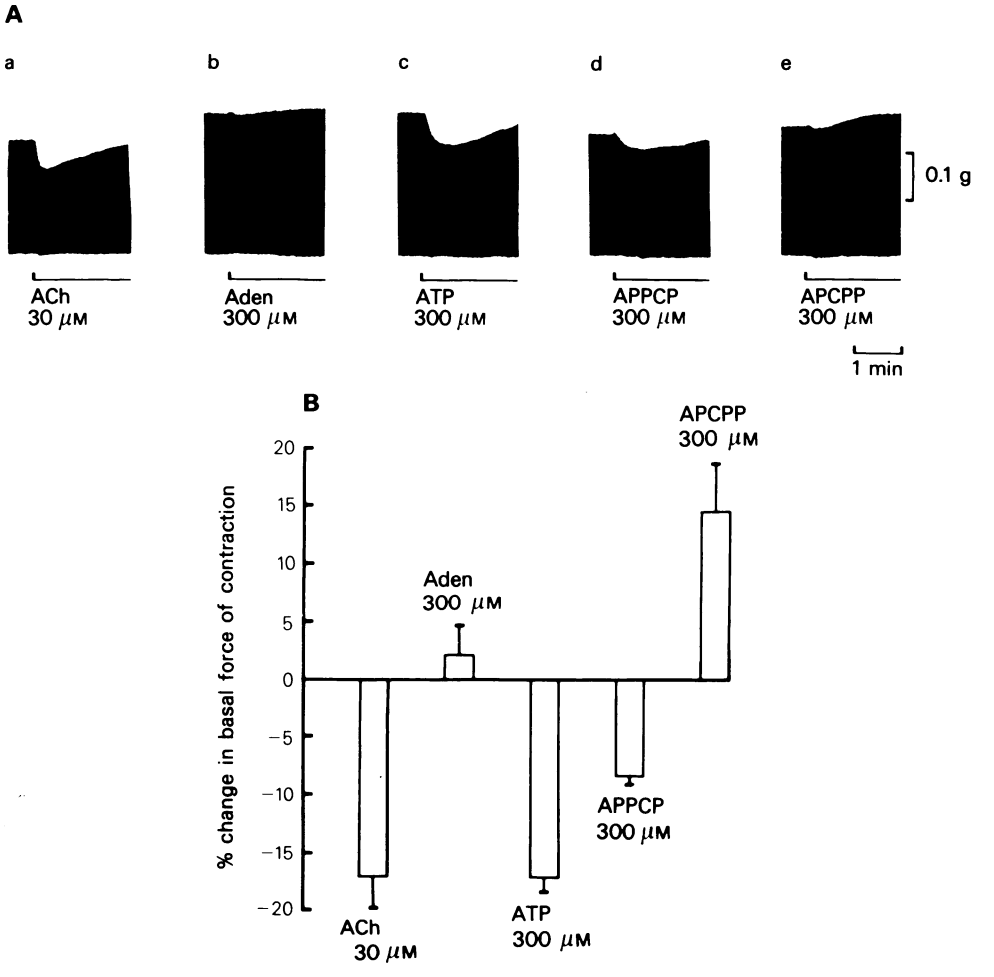

Figure 3 (A) Responses of the electrically stimulated rat ventricular strip to: (a) acetylcholine (ACh), (b) adenosine, (c) ATP, (d) β, γ-methylene ATP (APPCP) and (e) α, β-methylene ATP (APCPP). (B) Vertical columns, which show the percentage changes in the basal force of contraction caused by ACh, adenosine, ATP, APPCP and APCPP, were constructed from the means of observations from at least 4 preparations. Vertical bars show s.e.mean.

Goldie (1971) and Kolassa *et al.* (1971) have shown, with the use of [^{14}C]-adenosine, that the adenosine uptake process in rats, unlike the guinea-pig, was not blocked by dipyridamole. It is likely that these observations account for the inability of dipyridamole to potentiate adenosine actions in the rat heart.

Rat right ventricular strips did not respond to adenosine. This is consistent with other reports where adenosine does not modify the action potentials or contractile properties of the ventricle of guinea-pig (Johnson & McKinnon, 1956; Schrader, Gerlach & Baumann, 1979), cat (Shah, Kechejian, Kavaler & Fisher, 1974), dog (Lammerant & Becsei, 1973) and rabbit (Endoh & Yamashita, 1980). However, adenosine has been shown to have an effect on ventricular preparations in other studies. Adenosine exerted a depressant effect on the spontaneous firing rate of ventricular pacemaker cells of the guinea-pig (Szentmiklósi, Németh, Szegi, Papp & Szekeres, 1980; West, Belardinelli & Berne, 1982). In Langendorff rabbit hearts, adenosine increased the left ventricular contractile force secondary to the release of noradrenaline (Buckley, 1970a, b) and in the dog ventricle it induced a small negative inotropic effect followed by a marked positive inotropic response (Chiba & Himori, 1975).

Although adenosine does not appear to produce a direct effect on the mechanical activity of many mam-

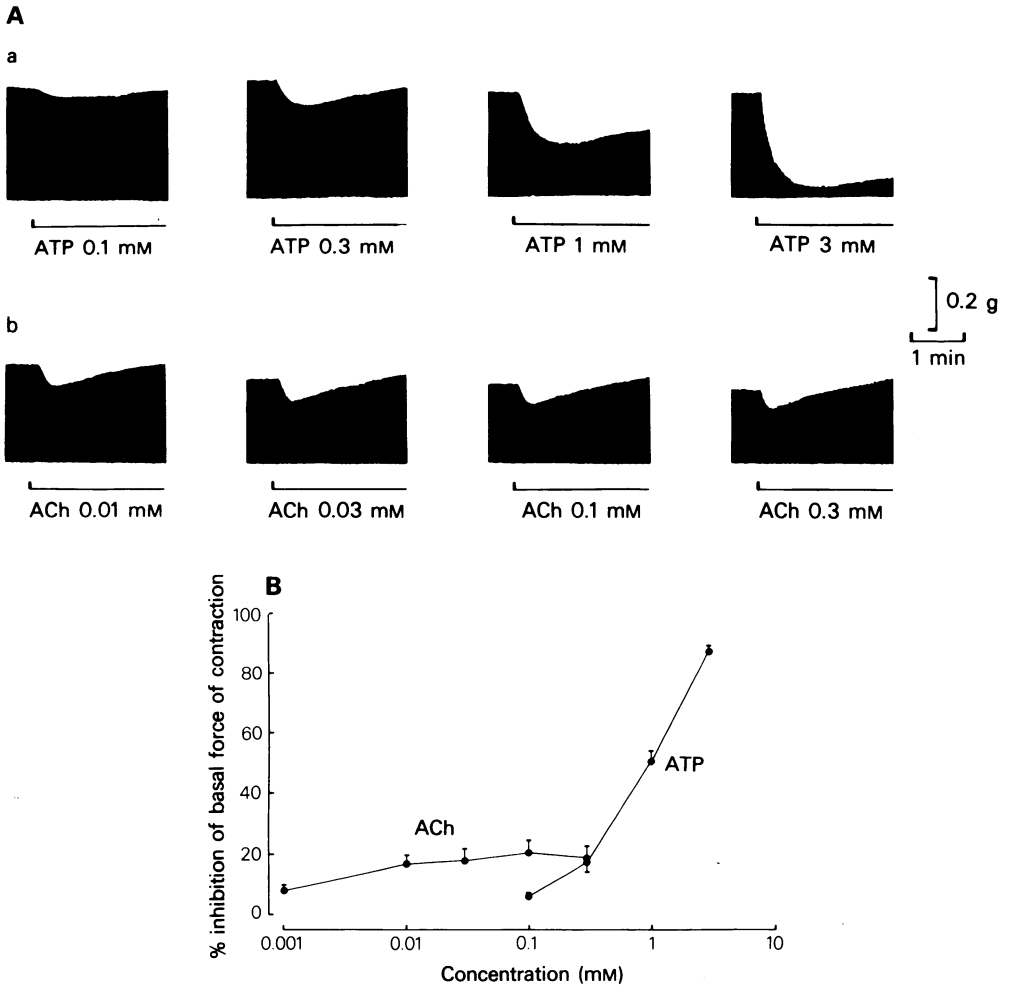

Figure 4 (A) Responses of the electrically stimulated rat ventricular strip to various concentrations of: (a) ATP and (b) acetylcholine (ACh). (B) Log concentration-response curves of electrically stimulated rat ventricular strips to the negative inotropic effects of ATP and ACh. Each point is the mean of observations from at least 4 preparations. Vertical bars show s.e.mean.

malian ventricular preparations, it has been shown to inhibit the β-adrenoceptor-mediated increase of developed tension in the left ventricle of guinea-pig hearts (Schrader, Baumann & Gerlach, 1977; Schrader *et al.*, 1979) and in the isolated papillary muscle of rabbit (Endoh & Yamashita, 1980). Adenosine also reduced the isoprenaline-induced increase in cyclic AMP concentration in the rat ventricle (Dobson, 1978) and in the guinea-pig ventricle (Schrader *et al.*, 1977; 1979). However, Huang & Drummond (1978) found that both adenosine and catecholamines stimulated cyclic AMP accumulation in the guinea-pig heart and that the combined action of adenosine and β-adrenoceptor agonist on cyclic AMP levels was additive. Theophylline antagonized the adenosine-mediated inhibition of isoprenaline-induced cardiac adenylate cyclase activity and myocardial contractile force development in the guinea-pig (Schrader *et al.*, 1977). It has been suggested that adenosine may act on the ventricular myocardium as a negative feed-back inhibitor of sympathetic overstimulation (Schrader *et al.*, 1977; 1979; Dobson, 1978). However, in the study described here, no evidence was found for the action of adenosine on β-adrenoceptor-mediated positive inotropic effects in the rat ventricle.

Very high concentrations of ATP (0.1–3 mM) produced marked negative inotropic effects on the rat

ventricle. In contrast, ACh (0.01–0.3 mM) produced little effect. The relative insensitivity of the mammalian ventricle to ACh has been observed in other studies (Blinks & Koch-Weser, 1963). It is unlikely that the responses to ATP are mediated via release of endogenous ACh since they were not affected by a concentration of atropine which completely antagonized the effects of ACh.

APPCP (300 μM) produced a significantly smaller response than did ATP at the same concentration ($P<0.01$). However, APCPP, which is resistant to degradation (Satchell & Maguire, 1975; Maguire & Satchell, 1979), produced an excitatory response rather than the expected inhibitory response. This may suggest that the inhibitory actions of ATP were mediated via P_1-purinoceptors. However, this was not found to be the case since the P_1-purinoceptor agonist, adenosine, was inactive on the rat ventricle and, furthermore, the responses to ATP were not inhibited by 8-PT.

Analogues in which the polyphosphate chain is altered (e.g. APPCP and APCPP) are unable to stimulate prostaglandin synthesis, unlike ATP (Brown & Burnstock, 1981). Responses to ATP have been found to be mediated either partly or wholly by prostaglandins in a number of preparations (Burnstock, Cocks, Paddle & Staszewska-Barczak, 1975; Kamikawa & Shimo, 1976; Brown & Burnstock, 1981). However, the effects of ATP in the rat ventricle do not appear to be mediated via prostaglandins since indomethacin, a prostaglandin synthetase inhibitor (Vane, 1971), failed to antagonize them.

It is possible that the inhibitory action of ATP is mediated via P_2-purinoceptors and that the excitatory action of APCPP on the rat ventricle is due to an additional unknown action of this compound resulting from the difference in structural conformation. The distance between the α and β phosphorus atoms is lengthened in APCPP, in comparison to ATP, by the replacement of an anhydride oxygen with a methylene group.

It seems likely that inhibitory P_1-purinoceptors are present in the rat atrium and that the inhibitory responses produced by ATP in the rat ventricle may be mediated via P_2-purinoceptors.

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