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The negative inotropic effect of nicorandil is independent of cyclic GMP changes: a comparison with pinacidil and cromakalim in canine atrial muscle

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1 The negative inotropic effects of nicorandil, a nitrate with K-channel opening properties, have been compared with those of pinacidil, cromakalim and nifedipine, in canine right atrial muscle.

2 Cromakalim, pinacidil and nicorandil all produced a negative inotropic effect. However, even at their maximally effective concentrations, the force of contraction remained at about 10% of control levels, whereas contraction was abolished by nifedipine.

3 The pD_2 values for the negative inotropic effects of cromakalim, pinacidil and nicorandil were 5.93, 5.37 and 4.35, respectively.

4 The negative inotropic effects of cromakalim (3×10^{-5} M), pinacidil (3×10^{-5} M and 3×10^{-4} M) and nicorandil (3×10^{-5} M) were not accompanied by changes in cyclic AMP and cyclic GMP levels, whereas that of 3×10^{-4} M nicorandil was accompanied by an increase in cyclic GMP but not cyclic AMP concentrations.

5 The negative inotropic effect produced by 3×10^{-4} M nicorandil was greatly reduced by 10^{-2} M tetraethylammonium, whereas the increase in cyclic GMP produced by this concentration of nicorandil was not significantly changed. Sodium nitroprusside (10^{-3} M) produced a large increase in cyclic GMP concentrations but had no significant negative inotropic effect.

6 It is concluded that the negative inotropic effects of nicorandil like those of cromakalim and pinacidil do not result from an increase in cyclic GMP concentrations. Instead these effects may be due to their action as K-channel openers.

Introduction

Unlike classical nitrates such as nitroglycerin, nicorandil, an antianginal drug with vasodilator properties (Uchida *et al.*, 1977; Sakai *et al.*, 1983), produces a negative inotropic effect (Taira *et al.*, 1979; Yanagisawa *et al.*, 1979; Endoh & Iijima, 1983), although it is a nitrate in chemical structure. This cardiac effect of nicorandil was thought to be secondary to an abbreviated action potential duration caused by an increase in potassium (K) conductance of the cardiac sarcolemma (Yanagisawa *et al.*, 1979; Yanagisawa & Taira, 1980; Iijima & Taira, 1986). On the other hand, like classical nitrates, nicorandil increases guanosine 3′ : 5′-cyclic monophosphate (cyclic GMP) in both vascular (Endoh & Taira, 1983; Holzmann, 1983) and cardiac (Endoh & Iijima, 1983) muscle. Consequently a possible causal relationship between the increase in cyclic GMP and the negative inotropic effects of nicorandil has been tentatively suggested (Endoh & Iijima, 1983).

In order to determine whether this proposal is correct, it would be helpful to compare the effects of nicorandil on the force of contraction and cyclic GMP levels in cardiac muscle with those of other agents which increase K-conductance in the cardiac sarcolemma. The present experiments were designed for this purpose. Pinacidil (Arrigoni-Martelli *et al.*, 1980) and cromakalim (Buckingham *et al.*, 1986), both new antihypertensive agents, appear to be suitable reference agents for this purpose. Pinacidil has been shown to open ^{86}Rb-permeable K-channels in rat vascular smooth muscle (Bray *et al.*, 1987) and to increase membrane K-conductance in guinea-pig single ventricular cells (Iijima & Taira, 1987). However, pinacidil does not increase cyclic GMP concentrations in vascular smooth muscle (Kauffman *et al.*, 1986). Cromakalim is believed to cause the opening of K-channels in both vascular

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smooth muscle (Hamilton *et al.*, 1986; Weir & Weston, 1986) and in guinea-pig papillary muscle (Cain & Metzler, 1985; Scholtysik, 1987).

In the present experiments the effects of nicorandil on force of contraction and on cyclic nucleotide levels were compared with those of cromakalim and pinacidil. The action of tetraethylammonium (TEA), a K-channel blocker (Coraboeuf & Vassort, 1968), on the mechanical and biochemical effects of these agents was also investigated. In some experiments, the effects of nifedipine and of sodium nitroprusside were also determined for comparative purposes. In this way it was hoped to clarify the role of cyclic GMP in the negative inotropic action of nicorandil. In the present work nicorandil, pinacidil and cromakalim will be called K-channel openers (Weston & Abbott, 1987).

Methods

Mongrel dogs of either sex, weighing 5 to 13 kg were anaesthetized with pentobarbitone sodium (30 mg kg^{-1}, i.v.) and their hearts were removed. Trabecular muscles were excised from the right atrial wall in oxygenated cold (ca. 7°C) Krebs-Henseleit solution and mounted in 20 ml organ baths. The composition of this solution was as follows (mM): NaCl 118, $NaHCO_3$ 24.9, KCl 4.7, KH_2PO_4 1.2, $CaCl_2$ 2.5, $MgSO_4$ 1.2, glucose 11.1, ascorbic acid 0.057 and Na_2EDTA (disodium ethylenediaminetetraacetic acid) 0.027. The solution was equilibrated with 95% O_2 and 5% CO_2 at a temperature of 37°C (pH 7.4). Muscles were stretched to a resting tension of about 0.5 g and were stimulated with rectangular pulses of a voltage of twice the threshold and 5 ms duration at a frequency of 0.5 Hz. During an equilibration period of about 1 h, the length of the muscle was adjusted to produce the maximum force of contraction which was recorded on thermal pen-writing oscillographs (NEC San-ei, Recti-Horiz-8K) by means of strain-gauge transducers (Shinkoh, UL-10230).

The effects of the K-channel openers on the force of contraction were observed during their cumulative administration. Concentrations of nicorandil and pinacidil were increased at 5 min intervals, and those of cromakalim and nifedipine at 10 or 30 min intervals, respectively. In experiments in which adenosine 3':5'-cyclic monophosphate (cyclic AMP) and cyclic GMP contents were measured, all muscles were treated with both 10^{-6} M nadolol and 10^{-6} M atropine to eliminate possible effects of noradrenaline and acetylcholine released by electrical stimuli on the concentrations of cyclic nucleotides. Usually 4–8 muscles obtained from one and the same heart were run in parallel, and one of them always served as control. In these experiments, atrial muscles were removed from the bath 5 min after administration of cromakalim, pinacidil, nicorandil or sodium nitroprusside, or 20 min after administration of tetraethylammonium (TEA), and immediately frozen in liquid nitrogen. Frozen muscles were stored overnight at −30°C. Cyclic AMP and cyclic GMP contents of these frozen muscle samples were measured with sensitive radioimmunoassay methods as previously reported (Endoh *et al.*, 1982; Yanagisawa *et al.*, 1984).

The drugs and chemicals used were as follows: nicorandil hydrochloride (Chugai), pinacidil (Shionogi), cromakalim (BRL 34915, Beecham), nifedipine (0.1 mg ml^{-1} in ampoule, Bayer), sodium nitroprusside (Wako), tetraethylammonium chloride (TEA, Wako), (±)-nadolol base (Squibb), atropine sulphate (Wako). Pinacidil was dissolved in 0.1 M HCl to give a concentration of 200 mM. Cromakalim was dissolved in 70% ethanol to give a concentration of 10 mM. Nadolol base was dissolved in 0.5 M HCl to give a concentration of 32 mM. Other drugs were dissolved in distilled water. From these stock solutions and from the ampoule of nifedipine, the desired concentrations were obtained by diluting with distilled water. The antiserum to cyclic AMP, to cyclic GMP, [^{125}I]-succinyl cyclic AMP and cyclic GMP tyrosine methyl ester were prepared and supplied by Yamasa Shoyu Co.

In concentration-response curves for the negative inotropic effect of K-channel openers or nifedipine, responses were expressed as % (basal force = 100%) and computer fitted to a logistic equation:

$$E = 100 - M \times A^p/(A^p + K^p)$$

where E is normalized response, M is the maximum response to each drug, A is drug concentration, K is EC_{50} value of each drug and p is the slope parameter (Parker & Waud, 1971). EC_{50} values are presented as pD_2 ($pD_2 = -\log EC_{50}$).

Experimental values are given as mean ± s.e.mean. Statistical significance of differences between mean values was estimated by Student's *t* test. A *t* test for the paired comparison was used when it was applicable. A *P* value smaller than 0.05 was considered to be significant.

Results

Negative inotropic effects of K-channel openers or nifedipine in atrial muscles

Nifedipine (10^{-8} to 3×10^{-6} M), cromakalim (10^{-8} to 10^{-4} M), pinacidil (10^{-7} to 3×10^{-4} M) and nicorandil (10^{-6} to 3×10^{-3} M) caused a concentration-dependent decrease in the force of contraction in

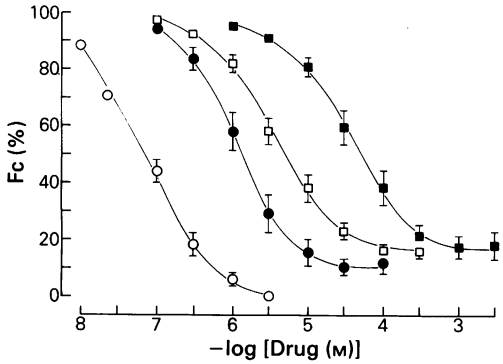

Figure 1 Log concentration-response curves for the negative inotropic effect of nifedipine, cromakalim, pinacidil and nicorandil in canine atrial muscle: (○) nifedipine, (●) cromakalim, (□) pinacidil and (■) nicorandil. The force of contraction (Fc) is presented as % of the basal force. Data points are means of 6–17 muscles, with s.e.mean shown by vertical bars.

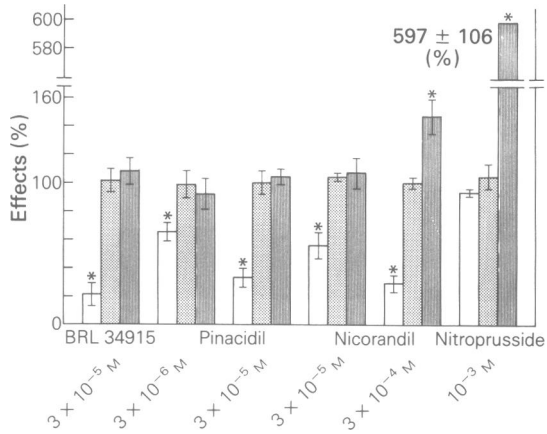

Figure 2 Effects of cromakalim, pinacidil, nicorandil and sodium nitroprusside on the force of contraction and cyclic nucleotide levels in canine atrial muscle. The values are expressed as % of either the basal force or control nucleotide values. Experimental numbers were 5 to 14. The force (Fc) of contraction (open columns), cyclic AMP (stippled columns) and cyclic GMP (lined columns) level in control muscles were 530 ± 93 mg, 0.92 ± 0.04 pmol mg^{-1} wet weight and 27.7 ± 2.1 fmol mg^{-1} wet weight, respectively ($n = 14$). * $P < 0.05$ compared to the basal force or control nucleotide values.

canine right atrial muscles (Figure 1). The summarized data obtained from the computer fitting to the logistic equation are shown in Table 1. When compared at the EC_{50} level, cromakalim was about 3.5 times more potent than pinacidil which was about 10 times more potent than nicorandil. Nifedipine abolished contractions at the highest concentration used, whereas the three K-channel openers failed to abolish it; about 10% of the basal force of contraction remained even in the presence of the highest concentrations of these agents.

Effects of K-channel openers on the force of contraction and cyclic nucleotide levels in atrial muscles

Figure 2 shows the effects of K-channel openers and sodium nitroprusside on the force of contraction and cyclic nucleotide levels in atrial muscles. Although 3×10^{-5} M cromakalim, 3×10^{-5} and 3×10^{-4} M pinacidil and 3×10^{-5} M nicorandil decreased the force of contraction in atrial muscles, the cyclic AMP and cyclic GMP levels in the tissues were not changed significantly. Nicorandil at 3×10^{-4} M decreased the force of contraction by 71 ± 6% and increased cyclic GMP by 47 ± 12% ($n = 13$; $P < 0.05$). Sodium nitroprusside at 10^{-3} M increased cyclic GMP by 497 ± 106% ($P < 0.05$) but had no significant effect on the force of contraction

Table 1 Negative inotropic effects of cromakalim, pinacidil, nicorandil and nifedipine in canine right atrial muscles

	n	*Basal force* (mg)	*Maximum effect* (%)	pD_2	*Slope factor* (p)
Cromakalim	7	1,351 ± 177	92.4 ± 2.2	5.93 ± 0.12	1.38 ± 0.13
Pinacidil	17	790 ± 109	87.9 ± 2.1	5.37 ± 0.09	1.13 ± 0.06
Nicorandil	14	901 ± 161	90.3 ± 2.6	4.35 ± 0.13	1.24 ± 0.11
Nifedipine	6	961 ± 163	99.4 ± 0.9	7.14 ± 0.08	1.10 ± 0.25

Maximum effect, pD_2 values and slope factors (p) were obtained by computer fitting to the logistic equation of the concentration-effect curves for cromakalim, pinacidil, nicorandil and nifedipine (see Methods).

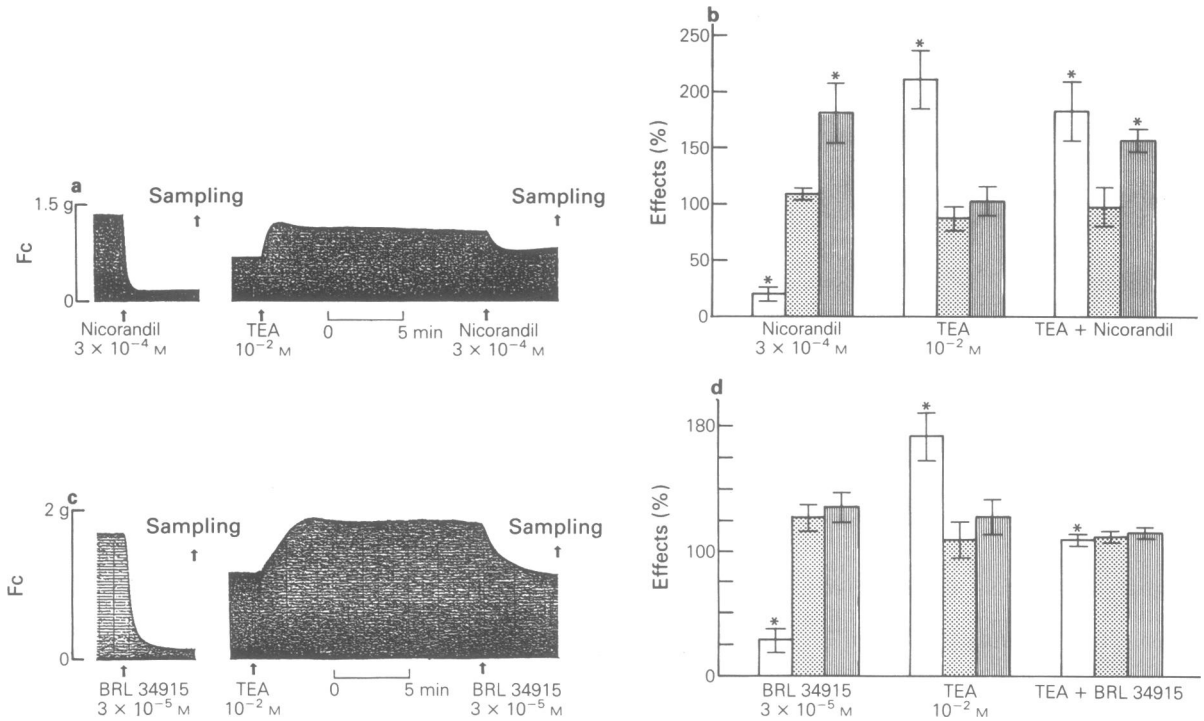

Figure 3 Influence of tetraethylammonium (TEA) on the effects of nicorandil and cromakalim on the force of contraction and cyclic nucleotide levels in canine atrial muscle. (a) Typical mechanical recordings with nicorandil. Drug administrations and sampling for the measurement of cyclic nucleotides are indicated by arrows. (b) Effects (%) on the force of contraction (open columns), cyclic AMP (stippled columns) and cyclic GMP (lined columns) levels. (c) Typical mechanical recordings with cromakalim. Drug administrations and sampling for the measurement of cyclic nucleotides are indicated by arrows. (d) Effects (%) on the force of contraction (open columns), cyclic AMP (stippled columns) and cyclic GMP (lined columns) levels. Numbers of muscles were 6 to 8. Force of contraction, cyclic AMP and cyclic GMP levels in control muscles were 628 ± 137 mg, 0.93 ± 0.16 pmol mg^{-1} wet weight, 26.2 ± 2.8 fmol mg^{-1} wet weight, respectively ($n = 7$). * $P < 0.05$ compared to the basal force or control nucleotide values.

(92 ± 4%, $n = 5$; $P > 0.05$). Cyclic AMP levels were not changed either by the K-channel openers or by sodium nitroprusside.

Differential modification by TEA of the negative inotropic effect and effects on cyclic nucleotide levels produced by nicorandil or cromakalim in atrial muscles

Figure 3 shows the % changes in the force of contraction and cyclic nucleotide levels in the presence of 3×10^{-4} M nicorandil alone, 10^{-2} M TEA alone or both TEA and nicorandil. In the presence of nicorandil alone, the force of contraction was decreased to 20 ± 7%, cyclic AMP levels were not changed and cyclic GMP levels were increased by 80 ± 27% ($n = 6$; $P < 0.05$). In the presence of TEA alone, the force of contraction increased by 110 ± 24%, whereas cyclic AMP and cyclic GMP levels did not change ($n = 7$). When nicorandil was administered after the steady state positive inotropic effect of TEA had been attained, the negative inotropic effect of nicorandil was attenuated greatly (−17 ± 8%, $n = 7$; $P > 0.05$ compared with the force just before administration of nicorandil in the presence of TEA), whereas the increase in cyclic GMP produced by nicorandil (69 ± 14%, $n = 7$; $P < 0.05$) was not affected.

The influence of TEA on the negative inotropic effect of cromakalim and its effects on cyclic nucleotide levels in atrial muscle is shown in Figure 3. Cromakalim at 3×10^{-5} M decreased the force of contraction to 22 ± 8% of the basal force without changing cyclic nucleotide levels ($n = 8$). In the pre-

sence of TEA, cromakalim decreased the force of contraction to $56 \pm 5\%$ of that before administration of cromakalim ($n = 5$). In the presence of TEA the % decrease in force of contraction produced by cromakalim was significantly ($P < 0.05$) smaller than that observed in the absence of TEA. Thus, TEA antagonized the negative inotropic effect of cromakalim. The cyclic nucleotide levels in atrial muscles were not changed in the presence of either TEA or cromakalim.

Discussion

In the present experiments cromakalim, pinacidil and nicorandil, agents known to be capable of opening K-channels in the vascular and cardiac sarcolemma, all produced a negative inotropic effect in canine atrial muscle such that the force of contraction was reduced to about 1/10 of the basal force at their maximally effective concentrations. When their EC_{50} values were compared, cromakalim was about 3.5 times more potent than pinacidil which was about 10 times more potent than nicorandil. These potency ratios are similar to those derived from the cardiac and vasodilator effects of these agents in isolated, blood-perfused heart preparations of the dog (Gotanda *et al.*, 1988).

As described above, at their maximally effective concentrations, the three K-channel openers did not abolish contraction which remained at about 1/10 of the basal force. This contrasts with the effect of nifedipine, a dihydropyridine calcium (Ca) channel blocker (Fleckenstein *et al.*, 1972) which was able to abolish contraction. The resistant component of the force of contraction observed in the presence of the K-channel openers is understandable, because their main effects are to increase outward K^+-currents in cardiac muscle cells (Taira, 1987 for nicorandil; Iijima & Taira, 1987 for pinacidil; Sato, personal communication, for cromakalim) and the inward Ca^{2+}-current is not affected by them (Iijima & Taira, 1986; Taira, 1987 for nicorandil; Sato, personal communication, for pinacidil and cromakalim). Nicorandil at 10^{-3} M shortened the duration of the action potential to about 1/3 of the control in canine atrial muscle being about 10 ms against 35 ms in control at 50% repolarization (Yanagisawa & Taira, 1980). It has been shown that a depolarization of 5 ms duration is capable of initiating a twitch contraction amounting to 10–15% of the control in various mammalian cardiac muscles (Morad & Trautwein, 1968). Thus the residual 1/10 of basal force seen in the presence of nicorandil, pinacidil and cromakalim is consistent with a shortening of action potential duration which restricts the Ca^{2+}-influx.

The negative inotropic effects of all the three K-channel openers were antagonized by TEA, although TEA *per se* produced a positive inotropic effect. Although not specifically investigated, this antagonism is probably due to an inhibitory effect of TEA on the opening of K-channels, as observed in trachealis smooth muscles (Allen *et al.*, 1986a,b).

In the present experiments, high concentrations of nicorandil increased cyclic GMP without affecting the level of cyclic AMP in canine atrial muscle as previously reported (Endoh & Iijima, 1983). In this respect nicorandil differed from pinacidil and cromakalim both of which failed to change either cyclic GMP or cyclic AMP levels. TEA also did not change cyclic nucleotide levels. In the presence of TEA, however, the negative inotropic effect of nicorandil was almost abolished, whereas the nicorandil-induced increase in cyclic GMP levels was not affected. Thus, it seems reasonable to conclude that the negative inotropic effect of nicorandil in canine atrial muscle is not a result of an increase in cyclic GMP. The possibility of a causal relationship between cyclic GMP levels and negative inotropy in atrial muscle is controversial (Endoh & Yamashita, 1981; Groschner *et al.*, 1986). In the present experiments, sodium nitroprusside produced a large increase in cyclic GMP but the force of contraction was not decreased significantly. Thus, it seems unlikely that major changes in cyclic GMP levels are involved in force development in canine atrial muscles.

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