The cardiovascular activity of ICI 118,587 a novel β-adrenoceptor partial agonist

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The purpose of this communication is to decribe the cardiovascular activity of ICI 118,587 [1-(*p*-hydroxyphenoxy)-3-β-(morpholinocarbonamido) ethylamino-2-propanol, hemifumarate] a β-adrenoceptor partial agonist. Experiments were performed in beagle dogs anaesthetised with pentobarbitone. In order to examine the direct actions of ICI 118,587 on the heart and circulation uncomplicated by cardiovascular reflexes the dogs were depleted of catecholamines (syrosingopine 5 mg/kg s.c. × 2 days prior to experiment); the cervical vagi and the innervation of the left hind limb at the level of L7 were sectioned. The left hind limb was perfused at constant blood flow and perfusion pressure measured. Heart rate and arterial pressure were also measured.

Dose response curves relating the changes in heart rate (HR) and hind limb perfusion pressure (HLPP) to intravenous injections of both isoprenaline and ICI 118,587 were obtained in 7 dogs. The partial agonist activity of ICI 118,587 was calculated as the maximum increase in HR or decrease in HLPP produced by ICI 118,587 as a percentage of the maximum changes produced by isoprenaline in each dog. The value for ICI 118,587 on HR was found to be 43.4% (s.e. mean ± 1.8) and the ED_{50} to be 3.2 μg/kg (s.e. mean ± 0.41). At doses up to 3 mg/kg i.v. ICI 118,587 had no effect upon HLPP.

In 4 dogs the ability of ICI 118,587 to antagonize the effects of isoprenaline on both HR and HLPP was determined by obtaining dose response curves in the absence and in the presence of increasing doses of ICI 118,587. The effective dissociation constant K′ was calculated in a similar manner to that described by Bilski, Robertson & Wale (1979). The K′ for HR was 7.1 μg/kg (mean range 4.3–11) and for HLPP was 116 μg/kg (mean range 30–199). It is concluded from these results that ICI 118,587 is a cardioselective β-adrenoceptor partial agonist on the heart and at relatively high doses is an antagonist of the vasodilating effects of isoprenaline.

Reference

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The cat isolated trachea, a useful preparation for the study of the smooth muscle relaxant action of prostaglandins

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This communication describes some findings with the cat isolated trachea, a preparation which is suitable for the study of the smooth muscle relaxant action of prostaglandins.

Cat tracheal strips, prepared according to the method of Coburn & Tomita (1973) were suspended in modified Krebs solution (Apperley, Humphrey & Levy, 1976) at 37°C, gassed with 95% O_2, 5% CO_2 and containing indomethacin (2.8×10^{-6} mol/l) phenoxybenzamine (7×10^{-7} mol/l) and atropine (4×10^{-7} mol/l). Prostaglandin E_1 was included in each experiment as a standard. On uncontracted preparations prostaglandins A_1, A_2, B_1, B_2, E_1, E_2, 11-deoxy E_0, $F_1\alpha$, $F_2\alpha$, I_2 up to 3×10^{-4} mol/l, and the PGH_2 analogue U-46619 (Bundy, 1975) up to 9×10^{-5} mol/l, neither contracted nor relaxed the preparation. On preparations contracted with acetylcholine, 9.4×10^{-5} mol/l (atropine being omitted), all prostaglandins caused concentration-dependent relaxation, except for U-46619 which was inactive up to 9×10^{-5} mol/l. With the exception of PGFα (2 series > 1 series, $P < 0.05$) compounds there was no difference in potency between 1- and 2-series prostaglandins and the order of potency was E > 11-deoxy E_0 > A = B > I > Fα (Table 1). These results confirm and extend previous reports (Main, 1964; Horton & Main, 1965) that prostaglandins relax but do not contract cat trachea. Because of the absence of a contractile component in the response the order of agonist potency may be characteristic of the receptors mediating relaxation of this preparation. The smooth

Table 1 Comparison of the relaxant potencies of some prostaglandins on cat isolated trachea contracted with acetylcholine (9.4×10^{-5} mol/l)

Prostaglandin	pD_2* *95% confidence limits*	*Equipotent concentration 95% confidence limits*	*n*
E_1	6.0 (5.9–6.1)	1	54
E_2	6.2 (5.9–6.6)	0.8 (0.4–1.8)	6
11-deoxy E_0	4.2 (3.6–4.9)	20 (13–31)	6
A_1	4.4 (4.2–4.5)	31 (15–65)	6
A_2	4.2 (3.9–4.5)	41 (26–65)	6
B_1	4.2 (3.6–4.9)	50 (35–69)	6
B_2	4.3 (3.8–4.7)	31 (18–50)	6
I_2	4.1 (3.8–4.3)	60 (44–83)	6
$F_2\alpha$	4.2 (3.8–4.3)	108 (67–176)	6
$F_1\alpha$	3.3 (2.7–3.9)	474 (87–2597)	3
U-46619	$\ll$4.1	—	3

* pD_2: negative log of the molar concentration causing 50% of the maximum response.

muscle relaxant action of prostaglandins is believed to be mediated by cyclic AMP (Dunham, Haddox & Goldberg, 1974; Murad & Kimura, 1974) and it is interesting to note that there are similarities between the order of agonist potency described here and those reported elsewhere for stimulation of cyclic AMP formation in some other tissues. These include mouse ovary (Oien, Mandel, Humes, Taub, Hoffsommer & Kuehl, 1975), rat osteogenic sarcoma cells (Atkins & Martin, 1977; Crawford, Atkins & Martin, 1978) and human leucocytes (Lichtenstein, 1973). These effects and relaxation of cat trachea may therefore be mediated by the same receptors. However, more precise comparisons of agonist potency and the development of selective antagonists will be necessary to substantiate this hypothesis.

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