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The antinociceptive action of some β-adrenoceptor agonists in mice

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1 The antinociceptive actions of several β-adrenoceptor agonist drugs have been studied in mice by use of a modified abdominal constriction test.

2 All the drugs studied had high antinociceptive activity, with ID_{50} values in the nmol kg^{-1} range. (−)-Isoprenaline and (±)-isoxsuprine were the most potent, being about ten times more active than salbutamol, the least potent drug studied. All these drugs produced their action very rapidly and appear to act within the peritoneum.

3 (−)-Isoprenaline had about six times the potency of the (+)-isomer.

4 (±)-Propranolol caused rightward shifts, usually parallel, of the dose-response curves for (−)-isoprenaline. (+)-Propranolol was more than ten times less potent than the racemic drug.

5 Practolol also caused parallel, rightward shifts of the dose-response curves for (−)-isoprenaline, and was about twice as potent as (±)-propranolol, whether given by subcutaneous or intraperitoneal injection. Atenolol and ICI 118551 had intermediate potencies.

6 Propranolol, practolol and ICI 118551 were all considerably less potent in antagonizing the antinociceptive actions of fenoterol and RO363, than (−)-isoprenaline. None of these antagonist drugs showed more than a slight ability to discriminate between the β_1- and β_2-selective agonist drugs.

7 No evidence was found for the involvement of opioid, dopamine, or α-adrenoceptors in the antinociceptive action of the β-adrenoceptor agonist drugs. Evidence for and against the involvement of β-adrenoceptors is discussed, and it is concluded that if these receptors do mediate the antinociceptive action they appear to be atypical.

Introduction

Bentley *et al.* (1981, 1983) using a modified abdominal constriction test, presented evidence that various opioid drugs, as well as both α- and β-adrenoceptor agonists could produce a marked antinociceptive effect by an action within the mouse peritoneum. They postulated that this effect involved an action on opioid receptors and adrenoceptors, which they considered were most likely to be situated on sensory nerve endings. The study of the α-adrenoceptor agonists (Bentley *et al.*, 1983) indicated that those compounds with high α_2-activity were more potent than those favouring α_1-adrenoceptors.

Isoprenaline was the only β-adrenoceptor agonist studied. It was found to have the highest antinociceptive potency of the catecholamines tested, and was only a little less active than clonidine. This paper describes studies using other β-adrenoceptor agonists, and their interaction with several β-adrenoceptor antagonists and with opioid drugs.

Methods

Male Balb-C mice were used, weighing between 20 and 25 g. These were obtained from the Monash University Central Animal House. They were housed for about 24 h before use in the departmental animal rooms, with free access to food and water.

The method of testing for antinociceptive activity was the abdominal constriction test, as modified by Bentley *et al.* (1981). Acetic acid, 0.6%, 1.0 ml per 100 g body weight i.p. was used for most experiments as the irritant stimulus. Six min after this was injected, the number of abdominal constrictions was counted for two min, and the mice were then injected intraperitoneally with either saline or catecholamine diluent for the control group, or with various doses of the agonist drugs dissolved in saline. The mice were randomized into four groups of twelve animals, one acting as the saline control, while the three other groups received ascending doses of the agonist drugs, given in a geometric ratio. The number of abdominal

constrictions was then counted for two or more further periods of two min, beginning immediately after the injection of the agonist. For one experiment, acetylcholine, 3.2 mg kg^{-1} i.p., was used as the noxious stimulus (Collier *et al.*, 1968). In this case isoprenaline was mixed with the acetylcholine and the two drugs were injected simultaneously. The abdominal constrictions were counted for two periods of two min, beginning immediately after the injection.

In the studies using antagonist drugs, these were given s.c. 15 or 30 min before acetic acid, that is 23, or 38 min before injecting the β-adrenoceptor agonist drugs. In addition, experiments were also conducted in which various antagonist drugs were injected intraperitoneally together with the acetic acid. Six min later, the abdominal constrictions were counted for two min, the β-adrenoceptor agonist was injected (i.p.) and the abdominal constrictions were counted again for two further periods of two min, as described above.

For constructing dose-response curves, the mean number of abdominal constrictions was determined for the two min period immediately before giving the agonist. The score for each individual mouse for the two min period immediately following the injection of the agonist drug was subtracted from the mean predosing value, and these values for the reduction in number of abdominal constrictions were analysed by a computer programme to obtain ID_{50} values with 95% confidence limits. Where antagonist drugs were used, the resulting dose-response curve was compared with the appropriate control curve, and again, using a computer programme, an analysis of variance (ANOVA) was performed (Colquhoun, 1971) to calculate the dose-ratio and its 95% confidence limits.

Drugs

Acetylcholine (BDH), (±)-atenolol base (ICI), dopamine hydrochloride (Sigma), (±)-fenoterol hydrobromide (Boehringer-Ingelheim), (+)-isoprenaline bitartrate (Sigma), (−)-isoprenaline bitartrate (Sigma), (±)-ICI 118551 (erythro-DL-1(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol; ICI), (±)-isoxsuprine hydrochloride (Duvadilan, Mead Johnson), morphine hydrochloride (Macfarlane Smith), naloxone hydrochloride (Endo Labs), (±)-orciprenaline sulphate (Metaproterenol, Boehringer Ingelheim), piperoxan hydrochloride (May & Baker), (±)-practolol base (ICI), (±)-propranolol hydrochloride (ICI), (+)-propranolol hydrochloride (ICI), (±)-RO363 oxalate ((±)-1-(3,4 dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol; synthesized in the School of Chemistry, Victorian College of Pharmacy), (±)-salbutamol sulphate (Glaxo), (±)-terbutaline sulphate (Astra).

All drugs were made as stock solutions of 0.1% (expressed as the free base) in distilled water. For the catecholamines, 1 mg ml^{-1} sodium metabisulphite, and 0.1 ml of 0.1 N hydrochloric acid was added. These were held at −4°C until used, when they were diluted appropriately in 0.9% w/v NaCl solution or, for the catecholamines, in a special diluent containing (mM): NaCl 154, NaH_2PO_4 0.012 and ascorbic acid 0.17.

Results

β-Adrenoceptor agonists

All the β-adrenoceptor agonists tested had potent antinociceptive activity, with ID_{50} values in the nmol kg^{-1} range. Isoxsuprine, (±)-isoprenaline, and fenoterol were the most potent, while terbutaline and salbutamol had the lowest activity. Some degree of stereospecificity was shown, as (+)-isoprenaline was about six times less potent than the (−)-isomer.

It was found that all these drugs produced their antinociceptive action very quickly, and, with doses which were adequate to block the abdominal constrictions completely, this effect occurred within 10 s of the injection. ID_{50} values were calculated for all the agonists for the first and second two min periods and for additional periods for several of these agonists. With most of the drugs tested, the effect was maximal in the first two min period and did not change significantly during the second two min. There were two exceptions to this. With fenoterol, the ID_{50} value was a little lower in the second than in the first two min period, but there was no further change at the third two min period. Isoxsuprine was the only drug whose action diminished with time over three successive two min periods; its effect was not tested beyond this time. Furthermore, the dose-response curve for isoxsuprine was less steep than those for the other agonist drugs tested. (−)-Isoprenaline was the only drug investigated for longer periods. It was found that the ID_{50} values for this agonist drug did not vary significantly over the ten min period following its injection.

In one experiment, the antinociceptive potency of (−)-isoprenaline was estimated using acetylcholine, 3.2 mg kg^{-1} i.p., as the noxious stimulus. The two drugs were injected simultaneously. It was found that the ID_{50} value for (−)-isoprenaline for the first two min period was only slightly greater than when acetic acid was used as the noxious stimulus, while the values were identical for the second two min period. These results are presented in Table 1.

β-Adrenoceptor antagonists

Five β-adrenoceptor antagonists were tested, (±)- and (+)-propranolol, practolol, atenolol and ICI 118551 (Bilski *et al.*, 1980; 1983; O'Donnell & Wanstall, 1980; Hartley & Pennefather, 1985). With the exception of

Table 1 ID_{50} values (mol $kg^{-1} \times 10^{-9}$) with 95% confidence limits of various β-adrenoceptor agonist drugs

Agonist drug	*1st 2 min*	*2nd 2 min*
Isoxsuprine	4.5 (3.1–5.7)	11.7 (10.6–12.8)
	3rd 2 min	14.9 (13.1–17.2)
(−)-Isoprenaline	6.6 (6.3–6.9)	6.5 (6.2–6.8)
	5th 2 min	6.3 (5.9–6.7)
Fenoterol	7.6 (6.8–8.5)	6.4 (5.8–7.0)
	3rd 2 min	6.2 (5.3–7.1)
Orciprenaline	18.7 (17.2–20.3)	18.3 (16.9–19.7)
RO363	32.4 (30.0–35.0)	33.0 (30.6–35.8)
(+)-Isoprenaline	41.1 (37.4–44.9)	41.0 (37.7–44.4)
Terbutaline	47.6 (43.0–52.3)	46.9 (43.9–49.9)
Salbutamol	70.1 (65.9–74.4)	70.8 (66.5–75.2)
(−)-Isoprenaline (ACh as the noxious stimulus)	7.7 (7.2–8.2)	6.3 (5.8–6.8)

Potency ratio (−)-: (+)-isoprenaline = 6.08 (5.57–6.64)

(+)-propranolol, which was given only by the i.p. route, all these antagonists were injected s.c. 15 min before the acetic acid. At the doses used, none of these drugs had any significant effect on the abdominal constrictions, but all antagonized the antinociceptive action of (−)-isoprenaline, given 23 min later. In most cases, the dose-response curve to (−)-isoprenaline was shifted to the right in parallel. Practolol was the most effective antagonist, being about twice as potent as (±)-propranolol, which was the weakest antagonist tested (Table 2).

The relatively low potency of (±)-propranolol compared with practolol was surprising (see Barrett *et al.*, 1973), even allowing for the fact that it was a racemic mixture, and so experiments were conducted to investigate the possibility that it was being metabolized more rapidly than practolol. Accordingly, dose-ratios against (−)-isoprenaline were prepared for both these antagonists given 30 min after acetic acid, and these were compared with the 15 min period. It was found that the antagonist potency of both drugs was not significantly less at 30 min than at 15 min, that is, practolol was still more potent than (±)-propranolol (Table 2).

In another series of experiments, the effects of (±)- and (+)-propranolol, practolol, and ICI 118551, given by i.p. injection, were tested. The antagonists were mixed with the acetic acid and given simultaneously, so that the (−)-isoprenaline was given eight min after the antagonists. (+)-Propranolol was given

Table 2 The antagonist potency of various β-adrenoceptor antagonist drugs against (−)-isoprenaline

Antagonist drug	*Route of administration*	*Dose* (mol kg^{-1})	*Time before (−)-isoprenaline* (min)	*Dose-ratio (95% confidence limits)*
(±)-Propranolol	s.c.	6.8×10^{-6}	23	49.5 (45.9–53.9)*
	s.c.	1.36×10^{-5}	23	111.7 (103.3–120.8)
	s.c.	1.36×10^{-5}	38	108.2 (100.6–116.4)
	i.p.	6.8×10^{-8}	8	10.0 (9.3–10.8)*
Practolol	s.c.	6.8×10^{-6}	23	96.8 (88.2–106.2)
	s.c.	6.8×10^{-6}	38	101.3 (92.8–110.6)
	i.p.	6.8×10^{-8}	8	16.5 (15.1– 18.1)
Atenolol	s.c.	6.8×10^{-6}	23	61.4 (59.5–63.4)
ICI 118551	s.c.	6.8×10^{-6}	23	54.7 (50.0–60.0)*
	i.p.	6.8×10^{-8}	8	9.1 (8.4–9.9)*
(+)-Propranolol	i.p.	1.36×10^{-7}	8	1.5 (1.4–1.7)*

*Denotes significant deviation from parallelism with the control dose-response curve.

Table 3 The antagonist potency of propranolol, practolol and ICI 118551, 6.8×10^{-8} mol kg^{-1} i.p., against RO363, and fenoterol

Antagonist drug	*Agonist drug*	*Dose-ratio (95% confidence limits)*
Propranolol	RO363	0.8 (0.7–0.9)
	Fenoterol	1.7* (1.5–1.9)
Practolol	RO363	1.9* (1.7–2.1)
	Fenoterol	1.1 (0.95–1.2)
ICI 118551	RO363	1.4 (1.3–1.5)
	Fenoterol	3.4 (2.8–4.1)

*Denotes significant deviation from parallelism with the control dose-response curve.

at a dose of 1.36×10^{-7} mol kg^{-1} but the doses of the other antagonists were 6.8×10^{-8} mol kg^{-1}. It was found that none of these antagonists, given i.p. at the above doses, had any effect on the abdominal constrictions. However, they all antagonized the antinociceptive effect of (−)-isoprenaline. As with the s.c. injection, practolol was again about twice as potent as ICI 118551 and (±)-propranolol, while (+)-propranolol, 1.36×10^{-7} mol kg^{-1}, had negligible antagonistic activity. Higher doses were not tested to avoid problems caused by the local anaesthetic action of the drug. Further experiments were conducted to determine whether there was any correlation between β_1- or β_2-adrenoceptor selectivity and antinociceptive potency. For these, practolol (β_1-selective, Dunlop & Shanks, 1968), ICI 118551 (β_2-selective, Bilski *et al.*, 1980, 1983; O'Donnell & Wanstall, 1980; Hartley & Pennefather, 1985) and (±)-propranolol (non-selective) were interacted with RO363 (β_1-selective, Raper *et al.*, 1978; Iakovidis *et al.*, 1980) fenoterol (β_2-selective, Lands *et al.*, 1967; Brittain *et al.*, 1976) and (−)-isoprenaline. The antagonist drugs were mixed with the acetic acid and given i.p. at a dose of 6.8×10^{-8} mol kg^{-1} eight min before the agonist drugs.

It was found that (±)-propranolol, practolol and ICI 118551 all had considerably less antagonist action against fenoterol and RO363 than against (−)-isoprenaline. In fact (±)-propranolol actually caused a small potentiation of the effect of RO363, although it produced a slight antagonism of fenoterol. In addition, practolol showed very little ability to discriminate between fenoterol and RO363, while ICI 118551 was only a little more potent in antagonizing fenoterol than RO363. (±)-Propranolol was also a little more effective against fenoterol than against RO363 (see Table 3).

Table 4 Interaction of naloxone and piperoxan with (−)-isoprenaline, and of propranolol with morphine

Antagonist drug	*Agonist drug*	*Dose-ratio (95% confidence limits)*
Naloxone 3.0×10^{-5} mol kg^{-1}	(−)-Isoprenaline	1.1 (1.05–1.2)
Piperoxan 3.0×10^{-5} mol kg^{-1}	(−)-Isoprenaline	1.8 (1.7–2.0)
Propranolol 6.8×10^{-5} mol kg^{-1}	Morphine	3.1 (2.9–3.3)

Interactions of (−)-isoprenaline with piperoxan and naloxone

In mice pretreated with the α-adrenoceptor antagonist piperoxan, or with naloxone, both at a dose of 3.0×10^{-5} mol kg^{-1} s.c. given 15 min before the acetic acid, the antinociceptive action of (−)-isoprenaline was only slightly antagonized. Dose-ratios of 1.45 and 1.70, were produced by these two antagonists (Table 4).

Interactions of propranolol with morphine

The earlier study by Bentley *et al.* (1983) had shown that piperoxan had almost half the antagonist potency of naloxone against morphine. Therefore the ability of propranolol to antagonize morphine was tested. Because (±)-propranolol itself has antinociceptive effect, probably because of its local anaesthetic action (Ishida *et al.*, 1980), doses above 6.8×10^{-5} mol kg^{-1} s.c. could not be used. However, at this dose, given s.c. 15 min before the acetic acid, propranolol caused no significant reduction in the abdominal constriction score, but produced a dose-ratio with morphine of only about 3 (Table 4).

Interactions of (+)-propranolol with dopamine

Dopamine was a less potent anticiceptive agonist than any of the β-adrenoceptor agonists tested, with an ID_{50} value of 1.08×10^{-7} mol kg^{-1} (Bentley *et al.*, 1983). This effect was not antagonized at all by (±)-propranolol, 1.36×10^{-7} mol kg^{-1}, i.p.

Discussion

This study has demonstrated that several β-adrenoceptor agonist drugs have antinociceptive activity when measured with the modified abdominal constriction test. In this respect, they resemble the α-adrenoceptor agonists reported in the earlier study by Bentley *et al.* (1983) and show similar potencies to noradrenaline, clonidine and morphine, with ID_{50} values in the nmol kg^{-1} range. However, the range of potencies shown by the β-adrenoceptor agonists tested was only about 15, as compared with a 60 fold potency range amongst the α-adrenoceptor agonists studied previously (Bentley *et al.*, 1983). The β-adrenoceptor agonists further resemble their α-adrenoceptor analogues in that their antinociceptive action was apparent within seconds of injecting these drugs, and this, together with the very high potency, points to an action exclusively within the peritoneum. (−)-Isoprenaline also resembled (−)-noradrenaline in that it was almost equally potent against both acetic acid and acetylcholine. Collier *et al.* (1968) have discussed the irritant action of these substances, and suggest that acetic acid acts indirectly, via the production of kinins, while acetylcholine appears to stimulate the sensory nerves directly. Bentley *et al.* (1983) argued that since noradrenaline was equally effective as an antinociceptive agent against both these noxious stimuli its action did not involve a reduced production of kinins, but was more likely to depend on a direct action on the sensory nerve endings, possibly to depress the generation of pain impulses. A similar argument could be advanced to explain the antinociceptive action of (−)-isoprenaline.

Another question arising from this study is whether β-adrenoceptors are involved in the antinociceptive action, or whether some other, unknown mechanism is causing the effect. No unequivocal evidence to resolve this ambiguity has been obtained from this study. Evidence against the receptor hypothesis is principally the very low isomeric potency ratio of (−)- to (+)-isoprenaline. Buckner & Patil (1971) determined the isomeric activity difference for (−)- and (+)-isoprenaline on guinea-pig atria and trachea, and found factors of 1000 and 500 respectively. Similarly McPherson *et al.* (1984), who studied binding affinities of atrial and uterine membrane preparations, reported isomeric binding ratios for isoprenaline of 44.7 and 13.8 respectively. In the present study it was found that (−)-isoprenaline was only about six times more potent than the (+)-isomer as an antinociceptive agent.

However, there are several other findings which may suggest that β-adrenoceptors are involved in the antinociceptive action. Firstly, all of the eight β-adrenoceptor agonists tested had high activity in the test, and (−)-isoprenaline was in fact as active as morphine and clonidine, while salbutamol, the least potent substance tested, was only about ten times less active. The second piece of evidence suggesting adrenoceptor involvement is that the dose-response curves for the antinociceptive action of (−)-isoprenaline were shifted to the right, usually in a parallel manner, by all the four β-adrenoceptor antagonists tested. Propranolol, the only antagonist available as the (+)-isomer, showed a considerable degree of stereospecificity to a much greater extent than isoprenaline. It was not possible to estimate the isomeric dose-ratio accurately for this drug since propranolol in doses above 1.36×10^{-7} i.p. has antinociceptive activity of its own probably because of its membrane-stabilizing property (Ishida *et al.*, 1980). However the (±)-isomer was clearly ten times more potent than the (+)-isomer. Harms *et al.* (1977) have reported isomeric dose-ratios for propranolol acting on rat atria and diaphragm of around 100, though the ratio was only about 20 with adipocytes.

There was also clear evidence that the antinociceptive action of the β-adrenoceptor agonists did not involve interaction with α-adrenoceptors, since it was shown previously (Bentley *et al.*, 1983) that propranolol caused only a slight antagonism of clonidine. In the present study it caused very little antagonism of either morphine or dopamine, while naloxone and piperoxan were similarly inactive against (−)-isoprenaline.

On the other hand, there is evidence from this study that, if β-adrenoceptors do indeed mediate the antinociceptive response, there does not appear to be any selective involvement of β_1- or β_2-receptors; (−)-isoprenaline and fenoterol, which had the highest antinociceptive potency of the drugs studied, both have high activity at β_2-adrenoceptors (Lands *et al.*, 1967; Brittain *et al.*, 1976), and isoxsuprine, which also had high antinociceptive activity is also said to have β_2-adrenoceptor activity (Bowman & Rand, 1980) although there is controversy here (see later). However, RO363, a drug specific for β_1-adrenoceptors (Raper *et al.*, 1978; McPherson *et al.*, 1984) was only a little less potent than fenoterol, and was more potent than other selective β_2-adrenoceptor agonists, including salbutamol.

Other evidence from this study suggests that if the antinociceptive effect involves β-adrenoceptors, these appear to be atypical. For example, as mentioned above, while isoprenaline did show stereospecificity this was considerably less than in some other tissues. Similarly, the studies concerned with the interactions of various selective β-adrenoceptors agonists and antagonists could also cast doubt on the involvement of β-adrenoceptors, or at least, indicate that they are atypical. For example, the studies in which (±)-propranolol, practolol and ICI 118551 were interacted with RO363 and fenoterol produced unexpected results, since none of these antagonists was as effective

against RO363 or fenoterol as it was against isoprenaline. In fact, (±)-propranolol actually potentiated the antinociceptive action of RO363. It was to be expected that practolol would be a considerably more effective antagonist of RO363 than of fenoterol but there was only a minimal difference between the dose-ratios produced against these two agonist drugs. Similarly, while ICI 118551 was a more potent antagonist of fenoterol than of RO363, the differential was only about 2.5 times.

These results are capable of three explanations. It is possible that the antinociceptive actions of all the β-adrenoceptor agonists is entirely independent of β-adrenoceptors, and depends on some other, as yet undefined, mechanism, perhaps involving prostaglandins. But, if it is accepted that β-adrenoceptors are involved, it would appear either that they form a mixed β_1- and β_2-population, or that they are atypical.

Evidence favouring a mixed population comes from the finding that ICI 118551 (a β_2-selective antagonist) is a little more effective in antagonizing fenoterol (β_2-selective) than RO363 (β_1-selective). On the other hand, there are three findings that are more compatible with the suggestion that atypical β-adrenoceptors are present. Firstly, (−)-isoprenaline, the non-selective antagonist, was not significantly more effective than fenoterol, and was only about five times more potent than RO363. Other β_2-selective agonists, such as salbutamol and terbutaline, were a little weaker than RO363. Isoxsuprine may be a special case. Although it is said to have β_2-activity (Bowman & Rand, 1980), various authors have suggested that the effects of this drug on the uterus and vascular tissue do not involve β-adrenoceptors (see Manley & Lawson, 1968; Berg-Johnsen & Nesheim, 1976; Ikeda *et al.*, 1984). Other findings suggesting atypical β-adrenoceptors include (i) the low isomeric dose-ratio of (−)- to (+)-isoprenaline, (ii) the poor ability of practolol to discriminate between RO363 and fenoterol, and (iii) the greater antagonist potency of practolol compared to (±)-propranolol against (−)-isoprenaline. This was seen after both s.c. and i.p. injections of the antagonists, and thus does not seem to depend on different rates of metabolism of the drugs, nor on different abilities to penetrate to the site of action within the peritoneum.

It is possible that this unexpectedly high potency of practolol may depend on its intrinsic sympathomimetic agonist action (Dunlop & Shanks, 1968), although, at the doses used, there was no sign of any antinociceptive activity in the control groups of mice that received the antagonist drug alone.

There are other reports in the literature indicating the presence of atypical β-adrenoceptors, at least on adipocytes. Harms *et al.* (1977) showed that while the isomeric dose-ratios for propranolol were identical on diaphragm and atria (about 100 fold), on adipocytes, the ratio was about five times lower. de Vente *et al.* (1980) found that the lipolysis stimulated in rat isolated adipocytes by (−)-noradrenaline and salbutamol (selective for β_1- and β_2-adrenoceptors respectively) was not preferentially antagonized by practolol (β_1-selective) or H35/25 (β_2-selective). This led these workers to conclude that the adipocyte did not have a mixed population of β_1- and β_2-adrenoceptors and they suggested, from a study of several chemically related β-adrenoceptor antagonists, that the receptor on the adipocyte had dualistic β_1- and β_2-properties. Bojanic *et al.* (1985) found that the stimulation of cyclic AMP by isoprenaline in rat adipocytes, as well as lipolysis, showed pA_2 values for antagonism by betaxolol, ICI 118551 and propranolol which also suggested an atypical β-adrenoceptor in this tissue. These results are similar to those of the present study. To examine the two possibilities more accurately would require the measurement of pA_2 values of the three antagonists against (−)-isoprenaline, RO363, and fenoterol.

This study suggests that some of the β-adrenoceptor agonists may be of possible therapeutic use as locally acting analgesic drugs. However, it is likely that their actions on the cardiovascular system might detract from their use in this context. But if an atypical β-adrenoceptor is in fact involved, it may be possible to develop some analogues of isoprenaline with relatively greater selectivity for the 'analgesic β-adrenoceptor'. The relatively high antinociceptive potency of (+)-isoprenaline might provide clues.

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