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Do α_2-adrenoceptors play an integral role in the antinociceptive mechanism of action of antidepressant compounds?

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Abstract

Antidepressants are analgesic in the absence or presence of depression. The underlying mechanisms probably involve a complex interplay between several neurotransmitter systems and neuroreceptors. α-Adrenoceptors play an important role in pain processing and α_2-adrenoceptor agonists have been used in clinical pain management so we have investigated whether α-adrenoceptor sub-types mediate the antinociceptive activity of antidepressants. Thus, the abdominal constriction assay in mice was used to examine the antinociceptive responses of a diverse range of antidepressants following α_1- or α_2-adrenoceptor antagonism. The antidepressants or monoamine reuptake inhibitors included the serotonin selective reuptake inhibitor paroxetine, the serotonin–noradrenaline reuptake inhibitor sibutramine, the resolved (+)- and (−)-enantiomers of the noradrenaline reuptake inhibitor oxaprotiline, plus the tricyclics amitriptyline and dothiepin. All these compounds have been previously shown to be antinociceptive in this paradigm. The respective α_1- and α_2-adrenoceptor antagonists prazosin and RX821002 ([2-(2-methoxy-1,-4-benzodioxan-2-yl)-2-imidazoline]) did not produce antinociception though at 1.0 mg kg^{-1}; s.c., RX821002 but not prazosin blocked clonidine antinociception. The antinociceptive activity produced by sub-maximal doses of amitriptyline, dothiepin, sibutramine, paroxetine, (+)- and (−)-oxaprotiline were all blocked by RX821002 but not by prazosin. Additionally, both morphine and aspirin antinociception was resistant to α_1- and α_2-adrenoceptor antagonism. Thus, α_2- rather than α_1-adrenoceptors may play an integral role in antidepressant antinociception irrespective of the propensity for inhibiting reuptake of not only noradrenaline but also serotonin. It is probable, however, that other differing pharmacological properties of some antidepressants, such as opioid-like activity, may complicate any empirical correlation between monoamine uptake and analgesia.

Keywords: Antidepressant; α_2-Adrenoceptor; Antinociception; Analgesia; Amitriptyline; Dothiepin; Paroxetine; Oxaprotiline enantiomer; Sibutramine

1. Introduction

Pain is often accompanied by depression, the incidence of which ranges from 10% upwards to 100% in chronic pain patients (Pilowsky et al., 1977; Turkington, 1980). Consequently, in the clinical literature, antidepressant therapy has been advocated in the management of some pain conditions both in the absence (Gomersall and Stuart, 1978) and presence (Ward et al., 1979; Feinmann and Harris, 1984; Max et al., 1987) of concomitant depression.

There has been considerable discussion at the experimental level about the nature and underlying mechanisms of antidepressant analgesia (Biegon and Samuel, 1979, 1980; Ögren and Hölm, 1980; Botney and Fields, 1983; Tura and Tura, 1990). In the light of this debate, we have recently shown that there is an involvement of opioidergic systems in the dose-dependent analgesic profiles induced by several types of antidepressant in laboratory studies (Gray et al., 1998). There are, however, other modulatory neurotransmitter systems implicated in pain processes. A classic example of this is provided by noradrenergic neuronal pathways, where at least four major separate systems are thought to modulate nociception (Proudfit, 1988: Sewell, 1991). In this context, we have demonstrated that agonists at α_2-adrenoceptors produce graded analgesia with varying degrees of opioid-, 5-hydroxytrytamine- (serotonin- or 5-HT-) and α-adrenoceptor involvement (Dobson et al., 1997).

It is clear that central α_2-adrenoceptors play an important role in pain processing. Indeed, α_2-adrenoceptor agonists have been employed clinically in the management of

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pain, either alone or in combination with opioids (Davis et al., 1991; Eisenach, 1994; Eisenach et al., 1995). The aim of the present experimental study was to address the question whether mechanisms involving α-adrenoceptor sub-types mediate any analgesic activity of antidepressants. To this end, we have investigated the antinociceptive responses of a range of diversely designated antidepressants. This included the serotonin selective reuptake inhibitor paroxetine, the serotonin–noradrenaline reuptake inhibitor sibutramine, the resolved enantiomers of the noradrenaline reuptake inhibitor oxaprotiline plus the tricyclics amitriptyline and dothiepin to a chemical stimulus (an algogenic agent; 1% acetic acid). Subsequently, the effects of these antidepressant agents were examined following pretreatment with the adrenoceptor antagonists prazosin (α_1) (Rochford et al., 1993) or RX821002 ([2-(2-methoxy-1,-4-benzodioxan-2-yl)-2-imidazoline]) (α_2) (Langin et al., 1989).

2. Methods

2.1. Animals

Male GB1 mice (ICI derived strain, bred in our own animal facility) weighed 20 ± 2 g at the beginning of the experiments. The mice were housed in groups of eight per cage at a constant temperature of 22.0 ± 1.0°C, with food and water available ad libitum. A 12 h/12 h light/dark cycle was employed with lights on at 0800 h, all experiments being conducted during the light phase of the cycle. Animals were habituated to the experimental environment 2 h prior to the commencement of the experiments and during this period food and water were withdrawn.

2.2. Nociceptive test

The abdominal constriction assay (Alhaider, 1991) was chosen as an appropriate algogenic paradigm since it is capable of detecting antinociception produced not only by α_2-adrenoceptor agonists (Dobson et al., 1997) but also opioids (Hayes et al., 1986), non-steroidal anti-inflammatory agents and a range of antidepressant compounds (Gray et al., 1998).

The animals were randomly assigned into treatment groups of eight mice (with appropriate controls). Thirty minutes prior to 1% acetic acid challenge (10 mg kg^{-1}; i.p.), the mice were pretreated with one of the antidepressant compounds, morphine, aspirin or saline. The α-adrenoceptor antagonists or their vehicle were administered subcutaneously as a contralateral injection concomitant to the prospective analgesic agent. Following the i.p. administration of acetic acid, the mice were placed in individual observation chambers and the number of abdominal constrictions in the ensuing 20-min period was recorded simultaneously for treated and control groups. An abdominal constriction was defined as a posture with the abdomen flattened, the back depressed and the hind limbs extended. Each abdominal constriction was taken to have occurred with the adoption of this position and to have terminated with the resumption of the 'normal' position (Millan et al., 1994).

Subcutaneously administered doses of antidepressants producing sub-maximal antinociceptive responses in the abdominal constriction assay were determined from dose–response relationships generated in a previous study in this laboratory (Gray et al., 1998). Parenteral doses of prazosin (1.0 mg kg^{-1}; s.c.) and RX821002 (1.0 mg kg^{-1}; s.c.) were chosen for their reported in vivo selectivity at α_1-adrenoceptors (Rochford et al., 1993) and α_2-adrenoceptors (Jackson et al., 1991), respectively. It should be noted at this juncture that RX821002 has also been shown to possess affinity at non-adrenoceptor imidazoline binding sites (Callado et al., 1996) while prazosin, in addition to its antagonist action at α_1-adrenoceptors, does display some differential affinity at α_{2B}- and α_{2A}-adrenoceptor sites (Bylund et al., 1988).

The antinociceptive test was conducted following the ethical guidelines laid down by the Committee for Research and Ethical Issues of the International Association for the Study of Pain (Zimmermann, 1983).

2.3. Drugs

Amitriptyline hydrochloride (Sigma, Poole, UK), aspirin (McCarthy's, Bristol, UK), clonidine hydrochloride (ICN, UK), dothiepin hydrochloride (Knoll Pharmaceuticals, Nottingham, UK), (+)-oxaprotiline and (−)-oxaprotiline (Ciba-Geigy, Basle, Switzerland), morphine hydrochloride (Vestric, Bristol, UK), paroxetine (SmithKline-Beecham, Harlow, UK), prazosin hydrochloride (Pfizer, UK), RX821002 (2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline) (Reckitt and Coleman, UK) and sibutramine hydrochloride (Knoll Pharmaceuticals, Nottingham, UK), were all freshly dissolved in normal apyrogenic saline (0.9 w/v NaCl). All drug doses relate to the salt where appropriate, and they were injected subcutaneously (s.c.) in weight-related dose volume of 5 ml kg^{-1} body weight.

2.4. Data analysis

The data are presented as % protection (i.e., a compound producing 100% protection prevents or abolishes acetic acid-induced abdominal constriction). Hence, % protection = 100 − ([mean number of abdominal constrictions of drug treated/mean number of abdominal constrictions of control] × 100). All analyses were conducted on untransformed raw data and mean values were compared

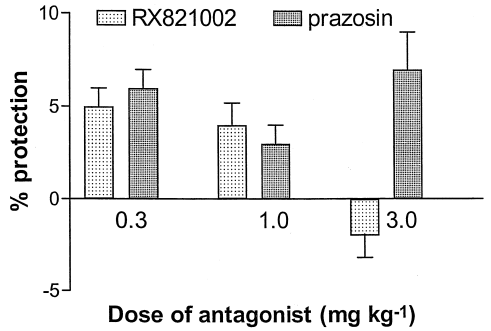

Fig. 1. Activity of α-adrenoceptor agents in the mouse abdominal constriction assay. (A) The effect of the α_1-adrenoceptor antagonist prazosin (0.3–3.0 mg kg^{-1}; s.c.) or the α_2-adrenoceptor antagonist RX821002 (0.3–3.0 mg kg^{-1}; s.c.) on visceral nociception in the mouse abdominal constriction assay. Neither of the adrenergic antagonists had any appreciable activity in this nociception paradigm. Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

using one-way analysis of variance followed by the post-hoc Tukey test. The level of statistical significance was assumed at the $P < 0.05$ level.

3. Results

3.1. Are the α-adrenoceptor antagonists RX821002 and prazosin, or the α-adrenoceptor agonist clonidine inherently protective in the abdominal constriction assay?

Neither of the α-adrenoceptor antagonists RX821002 nor prazosin at doses up to 3 mg kg^{-1} when administered by themselves subcutaneously produced any inherent significant ($P > 0.05$) inhibition of acetic acid-induced abdominal constriction (Fig. 1). The α_2-adrenoceptor agonist clonidine, on the other hand, yielded a dose-dependent inhibition of abdominal constriction over the dose range 0.01 up to 1.0 mg kg^{-1} (s.c.) and at the highest dose level, it totally abolished the abdominal constriction response, thus affording 100% protection against the algogenic stimulus (Fig. 2a).

3.2. Are α_2- to the exclusion of α_1-adrenoceptors involved in the antinociceptive response produced by clonidine?

The antinociceptive effects induced by clonidine at 0.3 and 1.0 mg kg^{-1} were markedly attenuated ($P < 0.01$) by

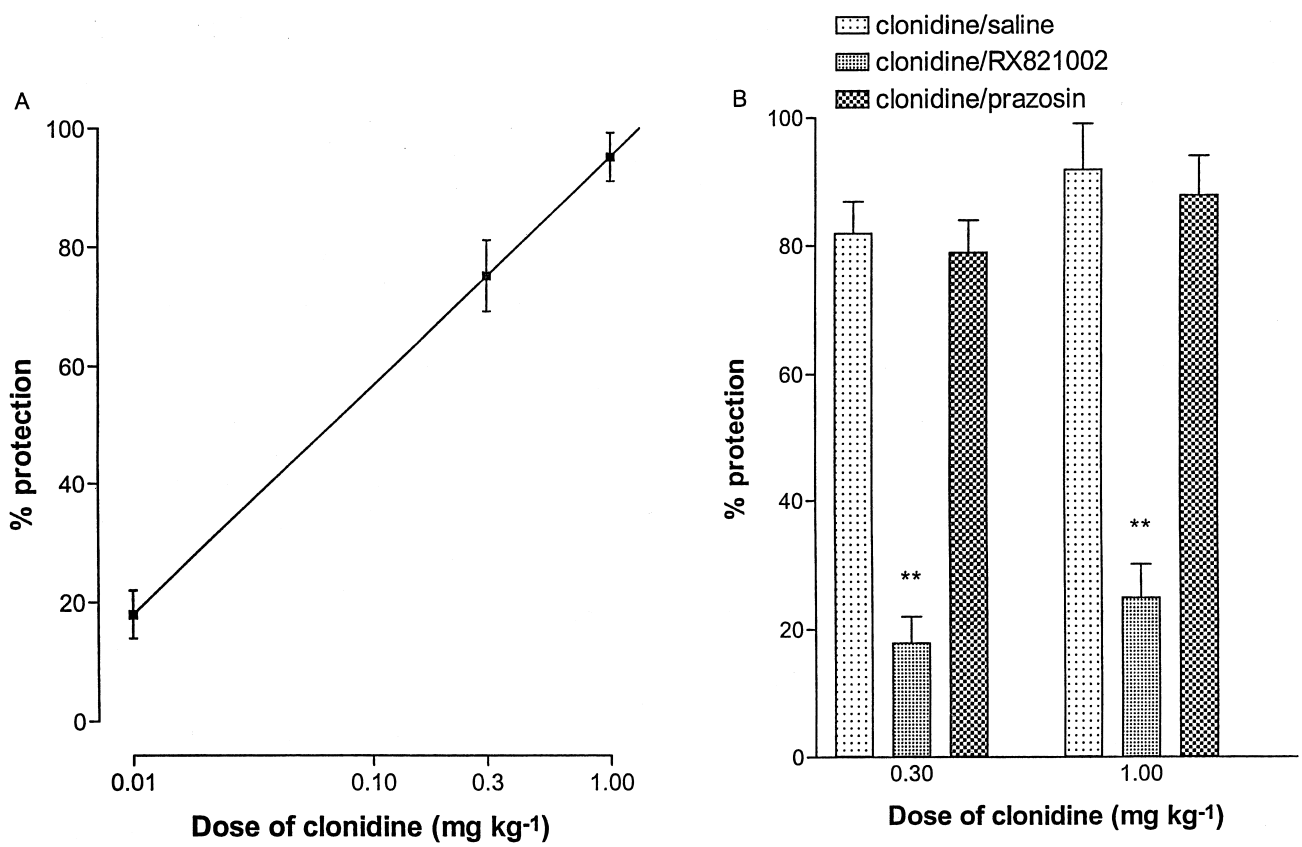

Fig. 2. The effect of α-adrenoceptor antagonists on clonidine antinociception in the mouse abdominal constriction assay. (A) Dose–response study of clonidine against visceral nociception in the mouse abdominal constriction paradigm. Clonidine produced graded protection against acetic acid nociception. (B) Clonidine antinociception was antagonised by the α_2-adrenoceptor antagonist, RX821002 (1 mg kg^{-1}; s.c.) but was insensitive to administration of the α_1-adrenoceptor antagonist, prazosin (1 mg kg^{-1}; s.c.). Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

concurrent subcutaneous administration of RX821002 (1 mg kg^{-1}) emphasising that the clonidine response in this test involved α_2-adrenoceptors and further suggesting that the dose of RX821002 employed was adequate for α_2-adrenoceptor blockade. In contrast, It was also observed that prazosin (1.0 mg kg^{-1}) did not significantly modify ($P > 0.05$) clonidine antinociception at either of the doses described above (Fig. 2b).

3.3. Are α_2- and / or α_1-adrenoceptors implicated in morphine or aspirin antinociception?

Both morphine and aspirin produced dose-dependent inhibitory or protective activity in the abdominal constriction assay and this activity against visceral antinociception is well established in this test (Gray et al., 1998). Moreover, the antinociceptive effects of neither morphine (0.3 or 2.0 mg kg^{-1}; $P > 0.05$) nor aspirin at 22.5 or 100 mg kg^{-1} ($P > 0.05$) were reversed by RX821002 (1.0 mg kg^{-1}) or prazosin (1.0 mg kg^{-1}) in this test for nociception (Fig. 3a and b).

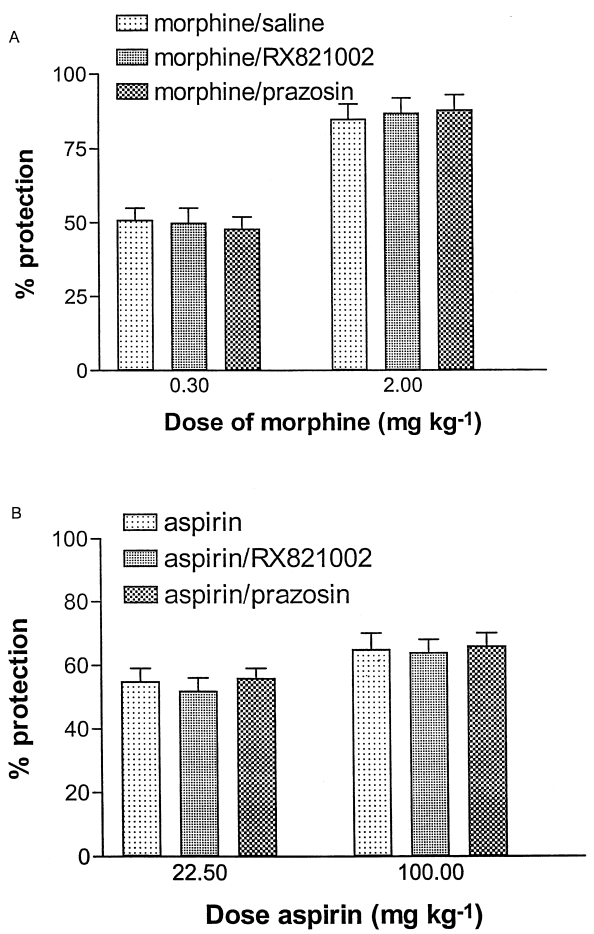

Fig. 3. The effect of morphine or aspirin in the mouse abdominal constriction assay. (A) Morphine produced robust dose-dependent protective effect in the mouse abdominal constriction assay. Neither prazosin (1 mg kg^{-1}; s.c.) nor RX821002 (1 mg kg^{-1}; s.c.) reversed morphine antinociception. (B) Aspirin produced minimal protection against acetic acid-induced visceral nociception in this model at the two doses examined. Aspirin antinociception was not subject to either α_1- or α_2-adrenoceptor antagonist reversal. Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

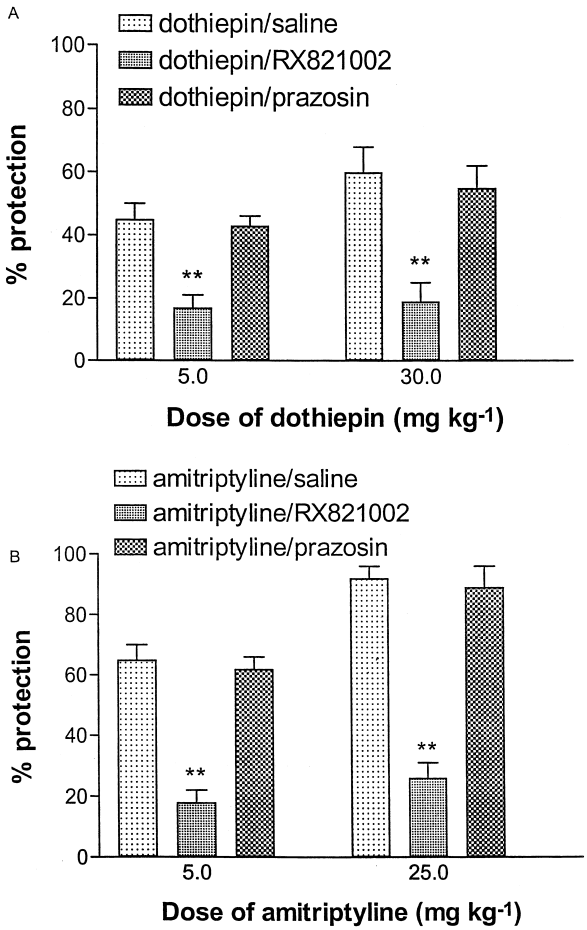

Fig. 4. The effect of α-adrenoceptor antagonists on tricyclic antidepressant-induced antinociception in the mouse acetic acid-induced abdominal constriction assay. (A) The effect of RX821002 or prazosin on dothiepin-induced antinociception. Dothiepin displayed some dose-dependent activity against acetic acid-induced abdominal constrictions. The α_2-adrenoceptor antagonist, RX821002 (1 mg kg^{-1}; s.c.), antagonised dothiepin-induced antinociception. However, this action was specific to the α_2-adrenoceptor antagonist, since the α_1-adrenoceptor antagonist (prazosin; 1 mg kg^{-1}; s.c.) failed to modify dothiepin-induced antinociception in this paradigm. (B) The effect of RX821002 or prazosin on amitriptyline-induced antinociception. Amitriptyline produced robust activity in the mouse abdominal constriction assay which was insensitive to antagonism by the α_1-adrenoceptor antagonist, prazosin (1 mg kg^{-1}; s.c.), but was significantly reversed by the α_2-adrenoceptor antagonist, RX821002 (1 mg kg^{-1}; s.c.). Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

3.4. Do α_2- and / or α_1-adrenoceptors mediate the antinociceptive activity of tricyclic antidepressants, and if so, are they specific to an individual tricyclic enantiomer?

The antinociceptive responses induced by sub-maximal doses (Gray et al., 1998) of both amitriptyline (5.0 and

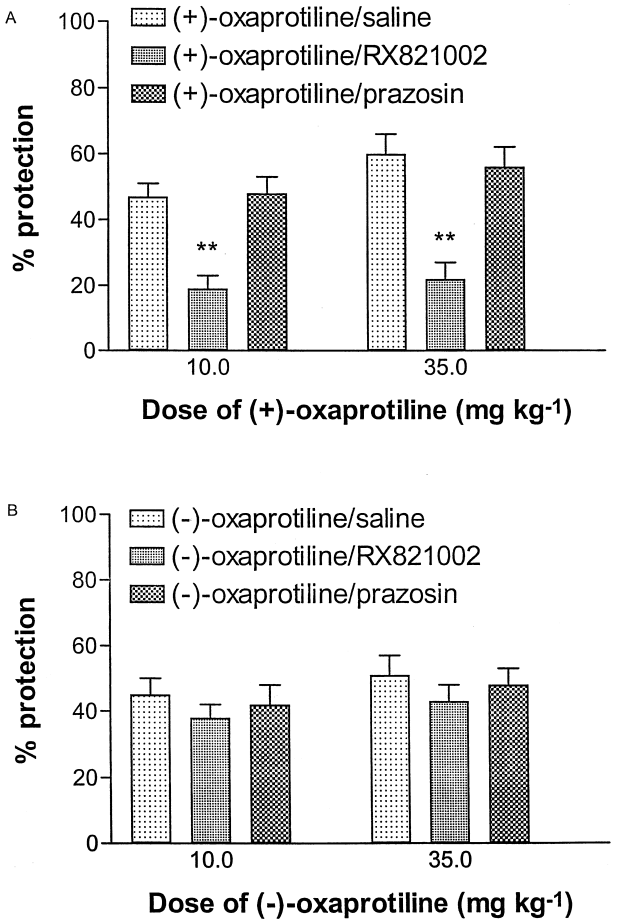

Fig. 5. The effect of α-adrenoceptor antagonists on the resolved isomers of (±)-oxaprotiline antinociception in the mouse abdominal constriction paradigm. (A) The effect of RX821002 or prazosin against (+)-oxaprotiline antinociception. (+)-Oxaprotiline has significant noradrenergic reuptake activity and produced antinociceptive activity in this model. The antinociception produced by (+)-oxaprotiline was α_2-adrenoceptor antagonist reversible (RX821002, 1 mg kg^{-1}; s.c.) but not α_1-adrenoceptor antagonist reversible (prazosin, 1 mg kg^{-1}; s.c.). Each bar represents the mean ± S.E.M. % protection in groups of eight mice. (B) The effect of RX821002 or prazosin against (−)-oxaprotiline antinociception. (−)-Oxaprotiline possesses little blockade activity against the noradrenergic transporter, however, it still produced appreciable antinociception in this paradigm. The antinociceptive response from (−)-oxaprotiline was not α-adrenoceptor antagonist-reversible (RX821002 or prazosin, 1 mg kg^{-1}; s.c.). Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

25.0 mg kg^{-1}) and dothiepin (5.0 and 30 mg kg^{-1}) were significantly antagonised by RX821002 (1.0 mg kg^{-1}; $P < 0.01$) but not by prazosin (1.0 mg kg^{-1}; $P > 0.05$; see Fig. 4a and b). In addition, the antinociception evoked by (+)-oxaprotiline (10 and 35 mg kg^{-1}; $P < 0.01$) was blocked by RX821002 (1.0 mg kg^{-1}). However, RX821002 failed to antagonise the laevo- or *R*-enantiomer, of oxaprotiline (10 and 35 mg kg^{-1}). These data are shown in Fig. 5a and b. Furthermore, the antinociceptive action of both oxaprotiline enantiomers remained unmodified ($P > 0.05$) by prazosin (1.0 mg kg^{-1}) co-administration (Fig. 5a and b).

3.5. Are the antinociceptive actions of newer antidepressants α_2- and / or α_1-adrenoceptor-mediated?

The protective action of paroxetine in the abdominal constriction assay at a dose of 2.0 mg kg^{-1} was not affected by RX821002 (1.0 mg kg^{-1}; s.c.) treatment, though at a higher dose of 10 mg kg^{-1} for paroxetine, its protective action was significantly attenuated ($P < 0.05$)

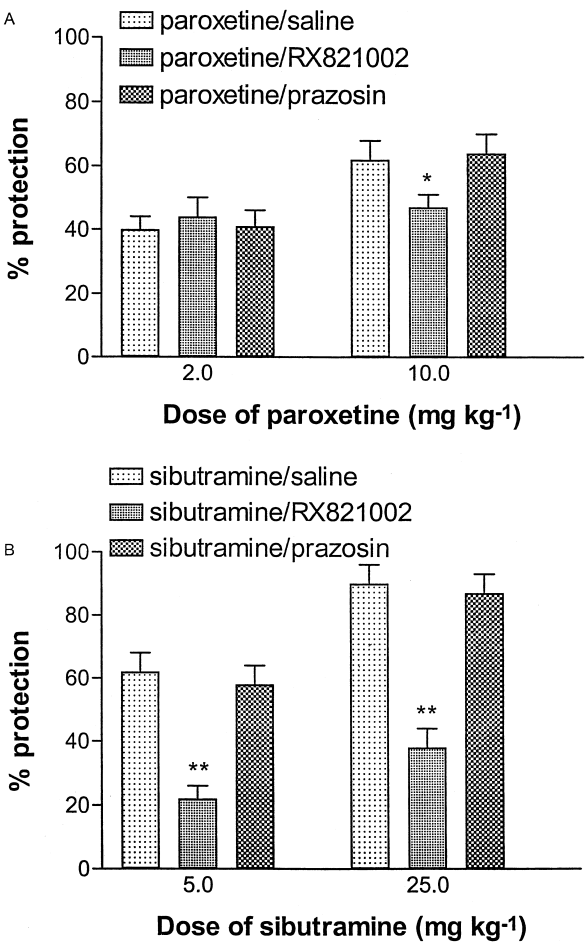

Fig. 6. The effect of the α-adrenoceptor antagonists, RX821002 and prazosin on paroxetine and sibutramine antinociception in the mouse abdominal constriction assay. (A) Paroxetine antinociception was not subject to α-adrenoceptor antagonism (RX821002 or prazosin, 1 mg kg^{-1}; s.c.) at the lowest dose examined. However, the higher dose of paroxetine (10 mg kg^{-1}; s.c.) did display α_2-adrenoceptor antagonism (RX821002, 1 mg kg^{-1}; s.c.) but did not exhibit α_1-adrenoceptor antagonist-reversible antinociception (prazosin, 1 mg kg^{-1}; s.c.). (B) The effect of α-adrenoceptor antagonists on sibutramine antinociception. Both doses of sibutramine examined in this study displayed α_2-adrenoceptor antagonist-reversible antinociception (RX821002, 1 mg kg^{-1}; s.c.), while neither dose produced α_1-adrenoceptor antagonist-reversible (prazosin, 1 mg kg^{-1}; s.c.) antinociception in this nociceptive paradigm. Each bar represents the mean ± S.E.M. % protection in groups of eight mice. RX821002 and prazosin were given 25 min before the intraperitoneal injection of 1% acetic acid.

by α_2-adrenoceptor antagonism (Fig. 6a). In a similar fashion, sibutramine antinociception (5.0 and 25 mg kg^{-1}) was inhibited by RX821002 though the degree of reduction was much more marked ($P < 0.01$) than that observed with paroxetine. In contrast, both paroxetine and sibutramine protection against abdominal constriction remained unmodified by concurrently administered prazosin (1 mg kg^{-1}; s.c.) such that the levels of percentage protection given by these two antidepressant agents were not significantly different ($P > 0.05$) in the absence or presence of the α_1-adrenoceptor blocker (Fig. 6a and b).

4. Discussion

Clinical treatment of pain frequently involves the use of cyclooxygenase inhibitors (aspirin or other non-steroidal anti-inflammatory agents) and the opioids (morphine or similar compounds) though sympathomimetic agents and monoamine uptake inhibitors also occupy a place in pain management (Schmitt et al., 1974; Valeri et al., 1991; Ardid et al., 1992; Pick et al., 1992; De Kock et al., 1997).

In this study, we have observed that clonidine possesses dose-related inhibitory activity against visceral nociception and this supports the view that this particular α_2-adrenoceptor agonist is not only a useful adjunct to opioid analgesia, but is also intrinsically analgesic when administered epidurally (Eisenach et al., 1995; Patel et al., 1996) in a dose-dependent fashion acutely following abdominal surgery (De Kock et al., 1997) or chronically in the treatment of neuropathic and cancer pain (Kulka, 1996). Indeed, α-adrenoceptor subtypes are distributed both spinally (ventral and dorsal horn) and supraspinally (Sewell, 1991; Mallard et al., 1992) and at least some of these sites in the dorsal horn of the spinal cord and other locations may be potential target sites mediating clonidine-induced analgesia (Patel et al., 1996).

The abolition of clonidine antinociception by RX821002, and the failure of prazosin in this respect would suggest that α_2 — rather than α_1 — adrenoceptors are chiefly responsible for mediating clonidine protection against abdominal constriction and this accords with the reports from Millan (1992) and Millan et al. (1994). In contrast, it has been suggested that the analgesic action of accepted α_2-adrenoceptor agonists has both α_2- and α_1-adrenoceptor-mediated components (Howe et al., 1982; Hayes et al., 1986) and that the relative contribution of these two receptor subtypes is largely dependent on the type of analgesic paradigm used (Tasker and Melzack, 1989). Moreover, it must be emphasised that additional α_1- and α_2-adrenoceptor antagonists should be studied on potential adrenoceptor-mediated antinociception in view of the reported affinity of RX821002 and prazosin at imidazoline sites and α_2-adrenoceptor sites, respectively (Bylund et al., 1988; Callado et al., 1996).

In the abdominal constriction assay, α_2- rather than α_1-adrenoceptors also appear to play an integral role in antidepressant antinociception since it was RX821002 once again and not prazosin, which produced a decrement in the protective action of amitriptyline, dothiepin, paroxetine, sibutramine, and (+)-oxaprotiline. In contrast, the visceral antinociception produced by morphine and aspirin remained insensitive to both α_1- and α_2-adrenoceptor antagonism, thus indicating a fundamental difference between the classical centrally or peripherally acting analgesics and antidepressants. It must be added, however, that endogenous opioidergic systems are involved in the antinociceptive mechanism(s) of antidepressants (Gray et al., 1998). Furthermore, pharmacological and autoradiographic studies have demonstrated that opioid and α_2-adrenoceptors

Table 1
Uptake selectivity ratios calculated from in vitro inhibition of radiolabelled noradrenaline and 5-HT uptake in brain tissue
Although the active primary and secondary amine metabolites of sibutramine were more powerful inhibitors of noradrenaline and 5-HT uptake than sibutramine itself, the ratios of selectivity between noradrenaline over 5-HT were comparable for sibutramine and its metabolites. Data for the racemate (±)-oxaprotiline are provided for comparison with its resolved enantiomers and clearly show the noradrenaline selectivity of this compound. ND = not determined

Drug	Noradrenaline uptake		5-HT uptake		Selectivity ratios
	K_i (nM)	IC_{50} (μM)	K_i (nM)	IC_{50} (μM)	Noradrenaline over 5-HT
Amitriptyline	13.9[a]	–	8.4[a]	–	0.6
Dothiepin	28.0[a]	–	170[a]	–	6.1
Sibutramine	283[b]		1811[b]		6.4
Sibutramine (2^0 amine metabolite)	2.7[b]		17[b]		6.3
Sibutramine (1^0 amine metabolite)	4.9[b]		25[b]		5.1
Paroxetine	33.0[a]	–	0.73[a]	–	0.022
(+)-Oxaprotiline	–	0.0036[c]	–	ND[c]	–
(−)-Oxaprotiline	–	3.0[c]	–	ND[c]	–
(±)-Oxaprotiline	–	0.0046[c]	–	25.0[c]	5435

Inhibitor constants (K_i in nM) were taken from data according to [a]Bolden-Watson and Richelson (1993) and [b]Heal et al. (1998).
Concentrations required to inhibit noradrenaline or 5-HT uptake by 50% (IC_{50} in μM) were taken from data according to [c]Waldmeier et al. (1982).

are co-localised within the same laminae of the dorsal horn further suggesting a possibility of an opioid-adrenoceptor interaction at the spinal level (Sullivan et al., 1987).

The selection of antidepressants studied in this investigation have varying propensities for inhibiting neuronal uptake of not only 5-HT but also noradrenaline (Table 1). This latter action, in particular, may well be a principal underlying mechanism by which these compounds elevate noradrenaline intrasynaptically to generate α_2-adrenoceptor-mediated antinociception (Sewell, 1991). However, the inhibitory ratios of noradrenaline to 5-HT uptake into brain synaptosomes range widely from 6.4 for the serotonin–noradrenaline reuptake inhibitor sibutramine to 0.022 for the serotonin selective reuptake inhibitor paroxetine, and yet the antinociception yielded by all the antidepressants was α_2-adrenoceptor antagonist sensitive.

Finally, it is notable that there is an 833-fold difference in the noradrenaline uptake inhibitory potency of (+)-oxaprotiline compared to (−)-oxaprotiline (Waldmeier et al., 1982) but the antinociception produced by identical doses of both enantiomers was comparable. However, the laevo enantiomer's antinociception was not α_2-adrenoceptor antagonist-reversible. It appears therefore that there is a relative lack of overall correlation between antinociception and noradrenaline or 5-HT reuptake potency (see Table 1). This is somewhat surprising since monoamines are involved in the expression of analgesia and their uptake is considered to be a major element of the pharmacology of antidepressant agents. It is probable, however, that other differing pharmacological properties of some antidepressants, such as opioid-like activity, may complicate any empirical correlation between monoamine uptake and analgesia (Rafieian-Kopaei and Sewell, 1994) though diversity of pharmacokinetic characteristics must also be considered as a complicating factor.

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