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Do antidepressants affect motivation in conditioned place preference?

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Abstract

The positive motivational effects of a range of antidepressants/neurotransmitter reuptake inhibitor compounds were studied using conditioned place preference. These agents included amitriptyline (2.5–10 mg/kg), venlafaxine (5 and 10 mg/kg), sibutramine (5 and 10 mg/kg), fluoxetine (2.5–10 mg/kg), paroxetine (5–15 mg/kg) and sertraline (2.5–10 mg/kg). Male Wistar rats were place conditioned in a three-compartment box to vehicle or drug alternately for 8 days using a 30-min pretreatment time. Control animals received vehicle only. Cocaine (5 mg/kg) was used as a positive control for the procedure. Significant place preference ($P < 0.05$) was observed with paroxetine (15 mg/kg), fluoxetine (5 and 10 mg/kg), sertraline (2.5–10 mg/kg) and cocaine. Venlafaxine and sibutramine, serotonin/noradrenaline reuptake inhibitors, produced no place conditioning, while the highest dose of the tricyclic antidepressant, amitriptyline (10 mg/kg), produced signs of place aversion. The role of serotonin in reward pathways and differences in serotonin, noradrenaline and dopamine reuptake-inhibiting properties of these compounds may explain why only the serotonin-selective reuptake inhibitors produced place preference in this study.

Keywords: Conditioned place preference; Amitriptyline; Antidepressant; 5-HT (5-hyroxytryptamine, serotonin) reuptake inhibitor, selective

1. Introduction

Chronic antidepressant treatment increases brain serotonergic activity, and this concurs with the concept that reduced serotonergic function within the central nervous system (CNS) is implicated in the pathogenesis of depression. (Meltzer and Lowry, 1987; Delgado et al., 1989, 1990). It has also been postulated that dopamine plays a significant role in the aetiology of depression (Willner, 1983, 1990; Jimerson, 1987) and that antidepressants may, therefore, interact with dopaminergic systems (Borsini et al., 1985; DeMontis et al., 1990; Brown and Gershon 1993). Tricyclic antidepressants increase the ability of the dopamine agonist, apomorphine, to stimulate locomotor activity as well as stereotyped behaviour (Maj et al., 1984) and also potentiate the release of dopamine associated with amphetamine administration (Brown et al., 1991; Nomikos et al., 1991). Furthermore, several studies have indicated an involvement of mesolimbic dopaminergic systems in the action of antidepressants (e.g., Papp, 1989; Collu et al., 1997a).

Neurones within the mesocorticolimbic dopaminergic system are considered important in mediating the rewarding effects of drugs and other stimuli. The ventral tegmental area is the origin of dopaminergic fibres (designated A10 neurones) that project to the nucleus accumbens, this pathway being considered crucial to the reward process (see Koob, 1992 for review). The ventral-tegmental area is itself innervated by serotonergic neurones arising in the raphe nuclei (Herve et al., 1987), which appear to exert a tonic inhibitory effect on the firing activity of dopaminergic neurones, possibly through 5-$HT_{2C/2B}$ receptors (Prisco et al., 1994). Electrophysiological studies have shown that serotonin-selective reuptake inhibitors reduce the spontaneous activity of dopamine neurones in the ventral-tegmental area, an effect apparently mediated through 5-HT (Prisco and Esposito, 1995; Di Mascio et al., 1998).

Thus, both serotonergic and dopaminergic systems are involved with regulation of the reward pathway. Consistent with this theory, there is an increasing number of anecdotal reports that some commonly used antidepressants are abused by patients (Delisle, 1991; Pagliaro and Pagliaro,

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1993; Tinsley et al., 1994). In fact, withdrawal reactions, often characteristic of addictive drugs, have also been reported after discontinuation of antidepressant treatments, particularly with serotonin-selective reuptake inhibitors (Lane, 1996; Black et al., 1997). The aim of this study was to determine whether compounds, with well-defined amine reuptake inhibitory profiles, could generate conditioned place preference, an established behavioural paradigm for examining the positive motivational properties of drugs. Cocaine, generally regarded as a dopamine reuptake inhibitor, was employed as a positive control in order to validate the methodology.

2. Materials and methods

2.1. Subjects

Male Wistar rats, weighing 180–210 g at the start of behavioural experiments, were used. All animals were housed four per cage, maintained on a 12-h light/dark cycle and allowed food and water ad libitum. Each animal was handled daily for 5 days prior to commencement of the conditioned place preference procedure to allow acclimatisation. Behavioural experiments were conducted during the light phase between 1000 and 1600 h.

2.2. Drugs

Cocaine hydrochloride (McFarlan Smith, UK), fluoxetine hydrochloride (Lilly, USA), amitriptyline (Sigma, UK), venlafaxine (Wyeth, UK), sibutramine (Knoll, UK) and paroxetine (SmithKline Beecham, UK) were dissolved in sterile saline. Sertraline hydrochloride (Pfizer, USA) was suspended in sterile saline containing Tween 80. All drugs were administered intraperitoneally (i.p.) 30 min before conditioning.

2.3. Place conditioning procedure

A three-compartment conditioning chamber measuring $88 \times 36 \times 34$ cm (length $\times$ width $\times$ height) was used, consisting of two compartments measuring $39 \times 36 \times 34$ cm (length $\times$ width $\times$ height), one having grey sides and stippled floor, the other having black and white stripes (2 cm wide) and a smooth floor. The third compartment consisted of a white central platform 10 cm in length, 36 cm wide and raised by 2 cm, which separated the two main compartments. During the conditioning phase, compartments were isolated using guillotine doors.

At the start of the experiment, subjects were habituated to the boxes for 20 min on 2 consecutive days, being allowed free access to all compartments. On the third day, the time spent in each compartment was recorded and the least preferred side determined for each animal. Place conditioning involved an 8-day counterbalanced schedule, with animals (7–9 per treatment group) being placed into the boxes 30 min after drug administration. Animals were given drug and confined (paired) to their least preferred compartment, or given saline and paired with their preferred compartment on alternate days (counterbalancing). Control animals received vehicle each day, with half of the group paired to the preferred side and half to the least preferred side, alternating for the 8 days of pairing. Following conditioning, subjects had a drug-free day (receiving neither vehicle nor drug for 24 h), before being allowed free access to both compartments on the final day, and the mean time spent in each compartment recorded as before. Place preference was calculated as the mean difference in time spent in the initially least preferred side before and after conditioning (occupancy in s). The number of entries into each conditioning compartment was also recorded, and the difference between the total number of entries pre- and post-conditioning used to provide an approximate index of locomotor activity.

2.4. Data analysis and statistics

Results were expressed as mean $\pm$ S.E.M. difference in time (s) spent in the least preferred compartment before and after conditioning (occupancy). This difference indicated the change in preference induced by the drug: positive difference reflecting reward, negative difference suggesting aversion. All treatment groups were compared against their respective vehicle control groups. Data was analysed by one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test, or Student's *t*-test (cocaine treatment group only). Where appropriate, significance was assumed at the $P < 0.05$ level.

3. Results

3.1. Effect of cocaine on place conditioning

Cocaine produced conditioned place preference, as defined by a statistically significant increase in occupancy of the least preferred side, at 5 mg/kg ($F[6,7] = 2.9$; $P < 0.05$, $n = 7–8$; see Fig. 1A).

3.2. Effect of amitriptyline on place conditioning

At the highest dose (10 mg/kg), amitriptyline caused apparent place aversion. Occupancy times for saline and amitriptyline 10 mg/kg are 54 ± 41 and -166 ± 38 s, respectively ($F[3,27] = 6.4$; $P < 0.01$, one-way ANOVA with Dunnett's post hoc analysis).

3.3. Effect of serotonin-selective reuptake inhibitors on place conditioning

Fluoxetine produced conditioned place preference at both 5 and 10 mg/kg ($F[3,27] = 5.6$, $P < 0.05$, $n = 7–8$;

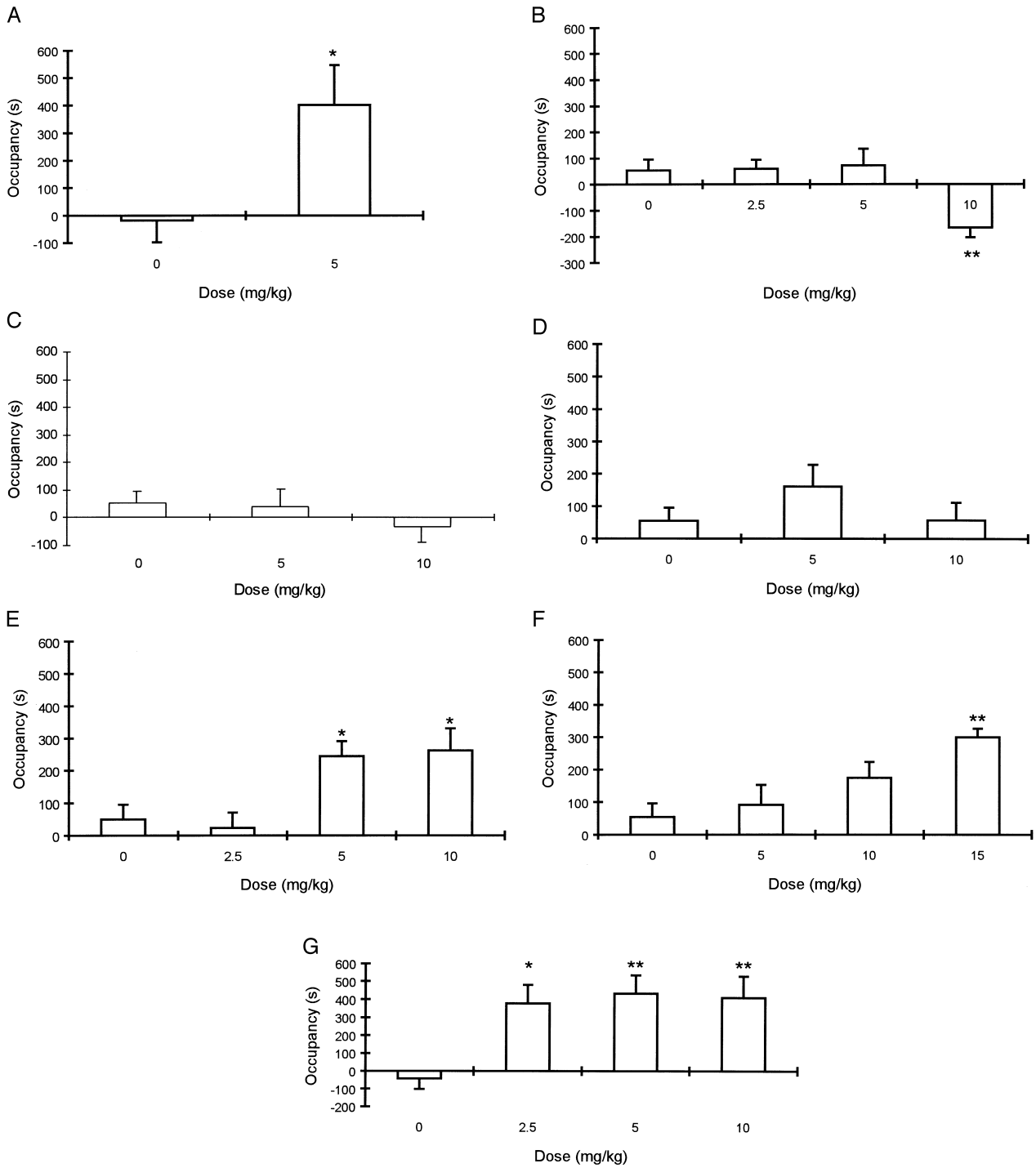

Fig. 1. Compartment occupancies following drug treatment. Occupancy represents the mean change in time ([s] ± S.E.M.) spent in the initially least preferred compartment between the pre- and post-conditioning values: (A) cocaine (0 and 5 mg/kg); (B) amitriptyline (0, 2.5, 5 and 10 mg/kg); (C) venlafaxine (0, 5, and 10 mg/kg); (D) sibutramine (0, 5 and 10 mg/kg); (E) fluoxetine (0, 2.5, 5 and 10 mg/kg); (F) paroxetine (0, 5, 10, or 15 mg/kg); (G) sertraline (0, 2.5, 5 or 10 mg/kg). $^{**}P < 0.01$, one-way ANOVA followed by Dunnett's post hoc test, $^{*}P < 0.05$, one-way ANOVA followed by Dunnett's post hoc test. Cocaine treatment group: $^{*}P < 0.05$, Student *t*-test; $n = 7–9$).

Fig. 1E). Paroxetine produced conditioned place preference at the highest dose level used, 15 mg/kg, although the response suggested a dose-dependent relationship ($F[3,26] = 5.3$, $P < 0.01$, $n = 7–8$; Fig. 1F). Sertraline produced conditioned place preference at all doses used in this study ($F[3,30] = 4.8$; $P < 0.05$, 2.5 mg/kg; $P < 0.01$, 5 and 10 mg/kg; one-way ANOVA followed by Dunnett's post hoc test; Fig. 1G).

3.4. Effect of mixed serotonin / noradrenaline reuptake inhibitors

Neither venlafaxine (Fig. 1C) nor sibutramine (Fig. 1d) produced place conditioning ($F[3,27] = 1.2$ and 0.8, respectively).

3.5. Number of entries into conditioning compartments

This parameter was taken as an approximate guide to general locomotor activity. The difference between the total number of entries, pre- and post-conditioning, into the two conditioning compartments showed no significant differences in any of the treatment groups.

4. Discussion

The results of this study demonstrated that, at the dose ranges used, amitriptyline, venlafaxine and sibutramine did not produce significant conditioned place preference. Venlafaxine exhibited a tendency towards place aversion, although this was not significant, while amitriptyline showed significant place aversion at the highest dose (10 mg/kg) tested. Although this aversion data should be treated with caution considering the bias nature of the paradigm used, it is consistent with reports that suggest short-term treatment with tricyclic antidepressants produces conditioned place aversion (Papp, 1988).

Cocaine, fluoxetine, paroxetine, and sertraline all produced significant conditioned place preference, and this accords with the conditioned place preference activity observed with cocaine (e.g., Spyraki et al., 1982) and fluoxetine (Collu et al., 1997b; Subhan et al., 2000). It was noteworthy that no change in the number of entries made into the two conditioning compartments was observed. This suggests that locomotor activity was unaffected by drug doses capable of inducing conditioned place preference and, therefore, modification of motoric behaviour was unlikely to account for any place preference conditioning reported in this study.

There are several possible explanations for the observed differences between the classic tricyclic antidepressant (amitriptyline), the serotonin/noradrenaline reuptake inhibitors (sibutramine and venlafaxine) and the serotonin-selective reuptake inhibitors (fluoxetine, paroxetine and sertraline) on conditioned place preference. Amitriptyline is associated with side effects resulting from a less specific pharmacological profile. In addition to inhibition of noradrenaline and serotonin reuptake, this drug is a potent inhibitor of the binding of specific ^{3}H-radioligands to histamine H_1 receptors, 5-HT_2 receptors and muscarinic receptors, and α_1- and α_2-adrenoceptors (Thomas et al., 1987; Owens et al., 1997). Antagonism of histamine receptors has been linked to sedation (Hall and Ögren, 1984), while muscarinic receptor blockade produces classical anticholinergic side effects, such as dry mouth, constipation and blurred vision (Hall, 1983), all of which may counter any conditioned place preference tendency in favour of conditioned place aversion. In contrast, the serotonin-selective reuptake inhibitors are relatively specific and do not appear to bind significantly to a range of CNS receptors (Thomas et al., 1987). Accordingly, they are associated with fewer, potentially aversive, side effects. However, like serotonin-selective reuptake inhibitors, venlafaxine and sibutramine exhibit little affinity for muscarinic and histamine receptors (Stock, 1997) yet neither induce place preference. This absence of positive motivational effects concurs with clinical trials involving sibutramine tested on recreational drug users (Cole et al., 1998; Schuh et al., 2000). This suggests that side-effect incidence alone cannot explain the failure for venlafaxine and sibutramine to produce place preference in this study.

It might be tentatively proposed that the positive motivational drive of serotonin-selective reuptake inhibitors are derived from their ability to modify dopaminergic neurotransmission. In this respect, it is commonly accepted that administration of abused drugs such as morphine, cocaine, nicotine and ethanol cause an increase in extracellular dopamine release, particularly in the nucleus accumbens. This capacity to modulate dopamine neurotransmission is thought to account for the rewarding properties of drugs of abuse (Di Chiara and Imperato, 1988). Fluoxetine has been associated with changes in dopaminergic neurotransmission, having been shown to potentiate dopamine transmission (Serra et al., 1992), to augment cocaine-induced conditioned place preference (Collu et al., 1996) and also to enhance cocaine drug discrimination (Cunningham and Callahan, 1991, 1995). The serotonin-selective reuptake inhibitors studied here may have the ability to modulate the activity of the mesolimbic dopaminergic system through serotonergic innervation of the ventral-tegmental area. In this context, electrophysiological studies have revealed a reduction in the firing of dopaminergic neurones in the ventral-tegmental area following acute fluoxetine challenge and this finding may possibly be ascribed to facilitation of an inhibitory serotonergic influence arising from the dorsal raphe nucleus (Prisco and Esposito, 1995). Regulation of the ventral-tegmental area nucleus-accumbens pathway by serotonin-selective reuptake inhibitors would tend to be more pronounced than with the serotonin–noradrenaline reuptake inhibitors, due to their increased relative 5-HT reuptake inhibitory selectivity vs. that for noradrenaline (Table 1), and this factor may well underlie the rewarding effects seen here.

In addition to an inhibitory action on the reuptake of noradrenaline and 5-HT, the antidepressants studied display some direct ability to block the reuptake of dopamine (see Table 1). The affinities for the dopamine transporter were generally weak, but in some cases may have been sufficient to contribute to the positive motivational proper-

Table 1
Reuptake inhibitor constants (K_i's) of compounds studied on noradrenergic, serotonergic, and dopaminergic transporters in brain tissue homogenates

Drug	Reuptake inhibitor constants, K_i [nM]		
	Noradrenaline	5-HT	Dopamine
Amitriptyline[a]	24 ± 6	66 ± 3	2300 ± 400
Amitriptyline[b]	13.9 ± 0.8	84 ± 1	600 ± 600
Venlafaxine[b]	210 ± 20	39 ± 3	5300 ± 600
Sibutramine[c]	283 ± 25	1811 ± 193	2309 ± 104
BTS 54,354[c]	17 ± 2	2.7 ± 0.3	24 ± 1
BTS 54,505[c]	25 ± 1	4.9 ± 0.3	31 ± 2
Fluoxetine[a]	280 ± 70	12 ± 1	1600 ± 200
Fluoxetine[b]	143 ± 6	14 ± 3	3050 ± 70
Fluoxetine[c]	320 ± 33	11 ± 1	2025 ± 85
Paroxetine[b]	33 ± 2	0.73 ± 0.04	1700 ± 300
Sertraline[b]	220 ± 40	3.4 ± 0.4	260 ± 40
Cocaine[a]	155 ± 9	180 ± 10	270 ± 20

BTS 54,354 and BTS 54,505 are the secondary and primary amine metabolites of sibutramine, respectively.
[a] Values were reported by Richelson and Pfenning (1984).
[b] Values were reported by Bolden-Watson and Richelson (1993).
[c] Values were reported by Heal et al. (1998).

ties of these compounds. In particular, sertraline possessed the lowest inhibitor constant for dopamine reuptake, although any interpretation derived from such a comparison must be treated with caution because the quoted values were derived from different studies. In an attempt to determine whether the place preference conditioning produced by these agents was related to their propensity to inhibit dopamine reuptake, we have ranked each compound for place preference efficacy at the 5 mg/kg dose level against the rank order for dopamine reuptake inhibitory K_i values (Fig. 2). Analysis by Spearman's rank correlation for this data revealed that there was a significant correlation between the two sets of values ($r = -0.93$; $P < 0.01$) for the parent compounds. However, it must be noted that any contribution to dopamine reuptake inhibition by the metabolites of the drugs studied is difficult to establish, since their concentrations cannot be determined under the present experimental conditions.

It has also been reported that antidepressants increase the levels of enkephalin (De Felipe et al., 1985) and pre-proenkephalin mRNA (Dziedzicka-Wasylewska and Rogoz, 1995) in the nucleus accumbens, ventral-tegmental area and striatum. Rossby et al. (1996) recently demonstrated that fluoxetine increases pre-proenkephalin mRNA by more than 200% via a serotonin-dependent mechanism. If this increase in mRNA is accompanied by a subsequent increase in enkephalin levels, rewarding effects may ensue due to an interaction with opioid systems. Previous work in our laboratory has provided further evidence for an interaction between antidepressants and opioid systems (Rafieian-Kopei et al., 1995). Moreover, naloxone and naltrindole attenuate the analgesic effects of both serotonin-selective and serotonin–noradrenaline reuptake inhibitors and this may well implicate endogenous opioids in antidepressant-induced antinociception (Gray et al., 1998).

The possible relationship between serotonin-selective reuptake inhibitors, opioids and reward systems, may explain the conditioned place preference induced by serotonin-selective reuptake inhibitors. In contrast, the failure to induce conditioned place preference by amitriptyline might be attributed to its actions at multiple receptors leading to side effects and subsequent place aversion. Thus, we would conclude that conditioned place preference can be produced by certain antidepressants and this activity appears to be contingent upon their pharmacological profile, particularly with respect to serotonin, dopamine and opioid mechanisms. It is not yet clear whether such positive motivational effects are widespread with respect to the clinical usage of antidepressants, although as noted earlier, there have been some anecdotal reports. Certain individuals may have an increased propensity towards abuse but such individuals might be potentially difficult to predict. Furthermore, these compounds are administered clinically over long periods and our study makes no attempt to determine whether the positive motivational effects persist. This is the subject of further work.

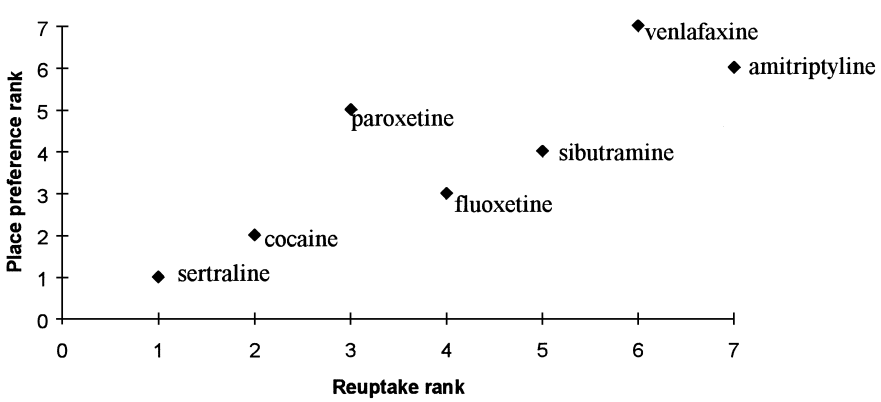

Fig. 2. Plot of dopamine reuptake inhibitory K_i rank (abscissa) against conditioned place preference efficacy rank at 5 mg/kg dose level (ordinate; $r = -0.93$, $P < 0.01$).

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