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ORIGINAL INVESTIGATION

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Differential modulation of efficiency in a food-rewarded "differential reinforcement of low-rate" 72-s schedule in rats by norepinephrine and serotonin reuptake inhibitors

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Abstract *Rationale:* The differential reinforcement of low-rate 72-s (DRL 72-s) schedule, in which rats must withhold a response for at least 72 s to obtain a reward (generally water), is an attractive procedure for the characterisation of potential antidepressant agents. Indeed, several antidepressants have been shown to improve efficiency (ratio of reinforcement rate to response rate) in this model, either by decreasing response rates and/or by increasing reinforcement rates. *Objective:* Herein, we compared the actions of antidepressants known to inhibit serotonin (5-HT), norepinephrine (NE) and/or dopamine (DA) reuptake in a food-rewarded DRL 72-s schedule. *Methods:* Rats trained in a food-rewarded DRL 72-s schedule and showing stable baseline performance were administered with drugs i.p. once a week. In independent experiments, the influence of drugs on food intake, spontaneous locomotor activity and extracellular levels of monoamines in the frontal cortex was evaluated. *Results:* In confirmation of previous studies, the tricyclic agent imipramine (10.0 mg/kg) and the "atypical" agent mianserin (40.0 mg/kg) significantly increased efficiency. In analogy, the selective NE reuptake inhibitors (NARIs) desipramine (20.0 mg/kg), nortriptyline (2.5 mg/kg) and reboxetine (0.63 mg/kg) all displayed marked enhancements in efficiency. In contrast, the selective 5-HT reuptake inhibitors (SSRIs) citalopram (10.0 mg/kg), fluvoxamine (10.0 mg/kg) and paroxetine (10.0 mg/kg) all significantly decreased efficiency. The mixed 5-HT/NE reuptake inhibitors (SNRIs) venlafaxine (2.5 mg/kg, 10.0 mg/kg) and S33005 (0.16–10.0 mg/kg), likewise, did not increase efficiency. Further, the DA reuptake inhibitors (DARIs) bupropion (0.16–10.0 mg/kg) and GBR12935 (0.63–10.0 mg/kg) had no effect on DRL 72-s performance. All drug classes exerted a similar, mild inhibitory influence on food intake and locomotor behaviour. Imipramine, mianserin and NARIs markedly increased extracellular levels of NE, and SSRIs elevated levels of 5-HT, while SSRIs augmented levels of both. *Conclusions:* The present experimental procedure demonstrates, in analogy to imipramine and mianserin, robust and consistent increases in efficiency with NARIs. Their effects may be distinguished from a decrease in efficiency elicited by SSRIs, and a lack of activity of SNRIs and DARIs. While the reasons underlying the ineffectiveness of SSRIs (in contrast to previous studies) remain to be clarified, these data underline the importance of adrenergic mechanisms in the control of behaviour under conditions of delayed responding. Further, they support the interest of DRL 72-s procedures for the characterisation of diverse classes of antidepressant agent.

Keywords DRL 72-s · Antidepressant · Serotonin reuptake inhibitor · Norepinephrine reuptake inhibitor · Dopamine reuptake inhibitor · Tricyclics

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Introduction

The differential reinforcement of low-rate 72-s (DRL 72-s) is an operant schedule in which a rat is required to withhold a lever press response for at least 72 s in order to obtain a reward. The DRL 72-s schedule has been extensively used as a behavioural screen for antidepressant agents, principally by Seiden and co-workers, although its psychological bases are still debated. Thus, apart from reinforcement per se, behaviour in this experimental procedure may reflect "timing behaviour" (the ability to make a temporal discrimination; Kramer and Rilling 1970; Zeiler 1985; Richards et al. 1993; Wogar et al. 1993; Fletcher 1995; Al-Ruwaitea et al. 1999) and could, as such, be linked to the dysrhythmia (time perception deficits) presented by depressive patients (Healy 1987). However, together with "delayed-reinforcement" models, this "delayed-responding" protocol may incorporate a component of impulsiveness (Richards et al. 1993; Ho et

al. 1998; Bizot et al. 1999; Sokolowski and Seiden 1999), a clinical problem which characterises diverse psychiatric disorders in addition to depressive states (Boix et al. 1998; Ho et al. 1998).

Irrespective of the conceptual and psychological foundations of DRL 72-s procedures, antidepressant agents characteristically increase reinforcement rates and, generally, decrease response rates. Correspondingly, one parameter proposed for characterisation of their actions is an increase in efficiency: that is, the ratio of reinforcement to response rates (Bright et al. 1997; Sokolowski and Seiden 1999; Wong et al. 2000). A shift in the inter-response time (IRT) distribution towards longer durations (O'Donnell and Seiden 1982, 1983; Richards et al. 1993; Sokolowski and Seiden 1999) has also been exploited for evaluation of antidepressant agents. Although the specificity of the DRL 72-s model has been questioned (Pollard and Howard 1986; Britton and Koob 1989; Jackson et al. 1995), other classes of psychoactive drug display contrasting profiles of performance (O'Donnell and Seiden 1983; Seiden et al. 1985; Britton and Koob 1989; Li et al. 1989; Marek et al. 1993; Sabol et al. 1995), and the responsiveness of DRL procedures to antidepressant agents is reasonably well established.

Thus, monoamine oxidase inhibitors (O'Donnell and Seiden 1982; Marek and Seiden 1988a) and electroconvulsive shock (Seiden et al. 1985) enhance efficiency both by an increase in reinforcement rates and a simultaneous decrease in response rates. Further, the "atypical" agents mirtazapine and mianserin, which possess 5-HT_{2C} and α_2-adrenoceptor (AR) antagonist properties, similarly improve DRL 72-s performance by increasing reinforcement rates and/or decreasing response rates (O'Donnell and Seiden 1983; Marek et al. 1989b; Hand et al. 1991; Jackson et al. 1995; Jones et al. 1998). Tricyclic agents, such as clomipramine, amitriptyline and imipramine, are also effective as shown by a decrease in response rates, which may or may not be accompanied by an increase in reinforcement rates (McGuire and Seiden 1980a, 1980b; O'Donnell and Seiden 1983; Howard and Pollard 1984; Danysz et al. 1988; Van Hest et al. 1992; Olivier et al. 1993; Borsini et al. 1997).

Tricyclic antidepressants inhibit reuptake of both 5-HT and norepinephrine (NE). Indicative of the significance of serotonergic mechanisms in the actions of antidepressant in the DRL 72-s procedure, 5-HT reuptake inhibitors (SSRIs) have been shown to be effective as judged by an increase in reinforcement rates and/or a decrease in response rates (Seiden et al. 1985; Danysz et al. 1988; Marek et al. 1989a; Olivier et al. 1993; Richards et al. 1993; Bright et al. 1997; Jones et al. 1998; Cousins and Seiden 2000; Wong et al. 2000), as well as by "peak deviation analysis of IRT distribution" (Sokolowski and Seiden 1999). In support of a role of serotonergic pathways, serotonin $(5\text{-HT})_{1A}$ agonists display an antidepressant-like profile in the DRL 72-s procedure, while depletion of central pools of 5-HT interferes with performance in the DRL 72-s protocol and in models of delayed reinforcement (Fletcher 1995; Ho et al. 1998; Bizot et al. 1999; Jolly et al. 1999). Nevertheless, there are marked differences amongst SSRIs as concerns their behavioural profiles in the DRL 72-s procedure and the precise significance of serotonergic mechanisms remains to be further clarified (see Discussion).

Like tricyclic agents, SSRIs and 5-HT_{1A} agonists elevate extracellular levels of NE in corticolimbic structures (Millan et al. 2000b) and adrenergic mechanisms may similarly control behaviour in the DRL 72-s procedure and models of delayed reinforcement. Correspondingly, the NE reuptake inhibitors (NARIs) desipramine and nortriptyline increase reinforcement rates and decrease response rates (O'Donnell and Seiden 1983; Bizot et al. 1988; Britton and Koob 1989; Bright et al. 1997; Evenden 1999; Wong et al. 2000). Although desipramine and nortriptyline interact with 5-$HT_{2A/2C}$ receptors, antagonists of which are active in the DRL 72-s model (Marek and Seiden 1988b), the more selective NARI reboxetine, likewise, increased efficiency in a recent study of Wong et al. (2000).

Curiously, despite the impressive therapeutic efficacy of the mixed 5-HT/NE reuptake inhibitor (SNRI) venlafaxine, apart from a preliminary communication (Jones et al. 1998), no information is available concerning DRL 72-s or delayed reinforcement experimental procedures. Further, despite the substantial number of drugs evaluated in the DRL 72-s procedure, few data are available for different classes of drug concurrently evaluated with a common protocol. This is of importance since procedural differences may account for contrasting actions of drugs between individual studies.

In light of the above observations, the present investigation systematically examined the influence of diverse classes of antidepressant agent, focussing on the relative significance of 5-HT relative to NE reuptake sites. First, in line with many previous studies (Bright et al. 1997; Jones et al. 1998; Wong et al. 2000), we employed efficiency as a parameter for characterisation of "antidepressant" properties. Second, we established the validity of the present model with two, mechanistically distinct antidepressant agents (vide supra), imipramine and mianserin (Owens et al. 1997; Tatsumi et al. 1997; Millan et al. 2000b). Three chemically distinct NARIs were employed – desipramine, nortriptyline and reboxetine – as well as three chemically distinct SSRIs – fluvoxamine, paroxetine and the highly selective agent citalopram, which has yet to be evaluated in the present model. We also examined the actions of venlafaxine and the highly potent SNRI, S33005 (Schweizer et al. 1997; Millan et al. 2001a, 2001b; Table 1). To explore a possible contribution of dopamine (DA) reuptake inhibition to behaviour in the DRL 72-s model, the selective DA reuptake inhibitor (DARI), GBR12935 was used, as well as bupropion, a DARI of modest selectivity and potency but established clinical efficacy as an antidepressant (Table 1; Owens et al. 1997; Rahman et al. 2001). Third, the great majority of previous investigations of the DRL 72-s procedure have utilised water reward. To expand the data base available for this procedure (Sanger 1988;

Table 1 Interaction of the antidepressant agents used in the differential reinforcement of low-rate (DRL) 72-s study with native rat and cloned human serotonin, norepinephrine and dopamine transporters. Affinities are expressed as pK_is. *r* rat, *h* human, *SERT* serotonin transporter, *NET* norepinephrine transporter, *DAT* dopamine transporter, *NT* not tested. Data are from this laboratory (Millan et al. 2000a, 2001b; Newman-Tancredi, A. et al. unpublished observations)

Drug	rSERT	hSERT	rNET	hNET	rDAT	hDAT
Imipramine	7.7	8.2	7.9	7.4	<6.0	NT
Mianserin	<5.0	<5.0	7.3	6.7	<6.0	NT
Desipramine	6.4	6.8	9.1	9.1	4.7	<5.0
Reboxetine	6.8	7.0	8.3	7.8	<5.0	<5.0
Nortriptyline	6.7	7.1	8.6	8.5	<6.0	NT
Citalopram	8.8	8.3	5.4	<5.0	<5.0	<5.0
Paroxetine	9.4	9.8	7.0	6.8	<6.0	6.0
Fluvoxamine	8.3	8.0	<6.0	5.4	NT	<5.0
Venlafaxine	7.6	7.1	6.0	5.2	<5.0	<5.0
S33005	8.7	8.7	6.8	5.8	<5.0	<5.0
Bupropion	<4.0	<5.0	<5.0	<5.0	6.5	6.2
GBR12935	<6.0	NT	6.2	NT	8.5	8.2

Britton and Koob 1989; Van Hest et al. 1992; Bright et al. 1997; Jones et al. 1998), and in analogy to certain delayed reinforcement models (Bizot et al. 1988, 1999; Al-Ruwaitea et al. 1999), we employed a food reward. Fourth, inasmuch as monoamine reuptake inhibitors modulate food intake and motor behaviour (Bray and Greenway 1999; Carek and Dickerson 1999; Rowland et al. 2000; Millan et al. 2001a), in independent experiments, the influence of drugs on these parameters was examined. Finally, in parallel studies, we examined the influence of key drugs on extracellular levels of 5-HT, NE and DA in the frontal cortex of freely moving rats (Millan et al. 2000b, 2001b).

Materials and methods

Animals

Experiments were carried out on male Wistar rats (220–240 g body weight upon arrival; supplier Iffa-Credo, l'Arbresle, France). They were housed in sawdust-lined polycarbonate cages with, unless otherwise specified, unrestricted access to food and water. They were kept under a 12-h/12-h light/dark cycle with lights on at 0700 hours. Laboratory temperature was 21±1.0°C and humidity 60±5%. All animal use procedures conformed to international European ethics standards (86/609-CEE) and the French National Committee (décret 87/848) for the care and use of laboratory animals.

DRL 72-s

Apparatus

The experiment was conducted in eight, standard operant conditioning boxes (model E10–10, Coulbourn Instruments, Lehigh Valley, Pa.) placed in sound-attenuated, fan-ventilated chambers. Each box was equipped with a house-light mounted above a food-pellet receptacle. Food pellets (45 mg, Noyes, Lancaster, N.H.) were delivered by a pellet dispenser (model ENV-203, Med Associates, Georgia, Vt.). A lever was located on the left of the receptacle 2.5 cm from the grid floor. Water was available through the spout of a water bottle located on the right of the receptacle 6 cm above the floor. Scheduling of reinforcement contingencies, reinforcement delivery and data recording were controlled by the Schedule Manager for Windows software (Med Associates).

Training

The procedure employed was adapted from that described by Seiden et al. (1985), with food instead of water employed as the reward. Twenty-four rats were housed individually with free access to water and restricted access to chow (10–11 g per day) in order to maintain their weight at approximately 80% of unrestricted weight. Daily sessions in the operant conditioning boxes were conducted from Monday to Friday as follows. During the first sessions (30 min in duration), the rats were trained to lever press for food under a fixed ratio 1/fixed time 1-min schedule until they had obtained 50 pellets during a session. Then, a DRL 18-s schedule was introduced for 10 days (ten 1-h sessions), followed by the DRL 72-s schedule (1-h sessions) over 8–12 weeks. During the first month of DRL 72-s, four to eight overnight 8-h sessions – with water available – were added in order to accelerate training (Bright et al. 1997; Jones et al. 1998). Data recorded during a session were the number of pellets obtained (reinforcement rate) and the number of lever presses (response rate). Efficiency was calculated as 100 × pellets/responses. The testing period began when stable individual baseline performance was achieved. That is, drug testing took place each Friday only for rats that earned at least five pellets per session on Tuesday, Wednesday and Thursday sessions, and for which the variability in response was not greater than ten during these sessions. On the test day, drugs were administered i.p. 30 min prior to the session with at least five rats tested at each dose. In a randomised design, the animals were tested once with vehicle (control test session).

Data analysis

All data (reinforcement rate, response rate and efficiency) obtained during a test session were expressed as the percentage of the preceding training session. This increased precision by taking into account the baseline values for each subject. Dose–effects were analysed by means of one-way analysis of variance (ANOVA) followed by Dunnett's test.

Dialysis studies

In independent experiments, the influence of drugs on levels of 5-HT, NE and DA in single dialysate samples of the frontal cortex was determined as detailed previously (Millan et al. 2001b), employing high-performance liquid chromatography (HPLC) plus coulometric detection in freely-moving rats implanted 1 week prior to testing with a guide cannula. Samples were taken every 20 min. Basal 5-HT, NE and DA levels were monitored for 1 h, then drugs were injected, and samples taken for a further 3 h. Changes were expressed relative to basal values (defined as 0%). The maximal effect observed is indicated in Table 2. Where possible, drugs were evaluated at a dose that exerted a significant effect in the DRL 72-s procedure. Data were analysed using an unpaired *t*-test.

Spontaneous locomotion

In an independent experiment, rats were given (i.p.) drug or vehicle and individually placed for a 30-min habituation period in transparent polycarbonate cages (45×30×20 cm) located in activity chambers. Then, locomotion was monitored for 60 min. A locomotion count corresponded to the consecutive interruption of two infrared beams situated 24 cm apart and 4 cm above the cage floor. Data were analysed using an unpaired *t*-test.

Table 2 Influence of antidepressant agents on levels of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) simultaneously quantified in single dialysate samples of the frontal cortex of freely moving rats. Data are mean±SEM values of the (maximal) increase in 5-HT, NE and DA levels expressed as a percentage change from baseline (0%). Absolute (basal) levels of 5-HT, NE and DA were 0.68±0.06, 1.02±0.08 and 1.22±0.14 pg/20 µl dialysate, respectively. *n* number of animals per dose

	Dose (mg/kg, i.p.)	*n*	5-HT	NE	DA
Vehicle	–	6	+ 1±13	+ 9±12	+ 4±10
Imipramine	10.0	7	+ 41±7 *	+ 382±27*	+ 168±45*
Mianserin	10.0	6	+ 50±13 *	+ 897±131*	+ 621±82*
Desipramine	20.0	6	+ 52±8 *	+ 254±16*	+ 365±65*
Reboxetine	0.63	6	+ 18±3	+ 328±58*	+ 156±22*
Citalopram	2.5	7	+ 172±18 *	+ 27±13	+ 22±1
Paroxetine	10.0	6	+ 250±33 *	+ 89±13*	+ 27±7
Fluvoxamine	10.0	5	+ 185±28 *	+ 112±19*	+ 52±10*
Venlafaxine	10.0	5	+ 200±39 *	+ 310±30*	+ 144±15*
S33005	10.0	6	+ 173±11 *	+ 229±7*	+ 208±21*

*$P<0.05$; significance of drug to vehicle values in unpaired *t*-test

Food intake

In an independent experiment, individually housed rats were food deprived for 24 h prior to the experiment. Drugs or vehicle were administered i.p. 30 min prior to re-access to a pre-weighed quantity of food (standard chow). One hour later, chow was re-weighed and food intake calculated. Data were analysed using an unpaired *t*-test.

Drugs

Drugs were prepared in sterile water with a few drops of Tween 80 and administered i.p. in a volume of 1 ml/kg. All drug doses are in terms of the base. Drug sources, salts and structures were as follows: bupropion HCl (Burroughs Wellcome CO., N.C.); desipramine HCl, imipramine HCl and nortriptyline HCl (Sigma, Chesnes, France); fluvoxamine maleate (Solvay Duphar, Weesp, the Netherlands); GBR12935 {1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenylpropyl)-piperazine} diHCL (Research Biochemicals International, Natick, Mass.) and paroxetine HCl (Beecham Pharmaceticals, Brentford, UK). S33005 [(–)1-(1-dimethylaminomethyl 5–methoxybenzocyclobutan-1-yl) cyclohexanol] HCl, citalopram HBr, mianserin HCl, reboxetine methane sulfonate and venlafaxine HCl were synthetised by Servier chemists (G. Lavielle and J.-L. Péglion).

Results

Influence of the antidepressant agents imipramine and mianserin on DRL 72-s performance

Imipramine elicited a dose-dependent and marked increase in reinforcement rates. However, its dose–response curve was biphasic with statistical significance obtained only for the dose of 10.0 mg/kg. Further, imipramine elicited a dose-dependent and monophasic decrease in response rates with statistical significance obtained at a dose of 40.0 mg/kg. Correspondingly, efficiency was dose-dependently increased up to the dose of 10.0 mg/kg. Efficiency was not computable at 40.0 mg/kg since certain animals failed to emit a response at this dose (Fig. 1).

Mianserin dose dependently and monophasically increased reinforcement rates and, at the highest dose tested (40.0 mg/kg), decreased the response rates, although this effect failed to reach statistical significance. This profile of performance was associated with a significant increase in efficiency at the highest dose tested.

Influence of the NARIs desipramine, nortriptyline and reboxetine on DRL 72-s performance

Desipramine, nortriptyline and reboxetine displayed the same general profile as imipramine on DRL 72-s performance. That is, they elicited a dose-dependent, though biphasic, increase in reinforcement rates that was associated with a dose-dependent and monophasic decrease in response rates. Like imipramine, increases in reinforcement rates were significant only for a single dose (20.0, 2.5 and 0.63, respectively). At these doses, desipramine, nortriptyline and reboxetine improved efficiency. At high doses, desipramine (20.0 mg/kg and 40.0 mg/kg), nortriptyline (2.5 mg/kg and 10.0 mg/kg) and reboxetine (10.0 mg/kg) significantly decreased response rates. As for imipramine, at the highest dose of desipramine (40.0 mg/kg), some rats failed to respond: consequently, efficiency was not computable (Fig. 2).

Influence of the SSRIs citalopram, fluvoxamine and paroxetine on DRL 72-s performance

The SSRIs citalopram, fluvoxamine and paroxetine all dose-dependently and monophasically decreased reinforcement rates, although this effect failed to reach statistical significance for fluvoxamine. With the exception of paroxetine at a dose of 30.0 mg/kg, for which response rates were significantly decreased, no significant changes were observed for this parameter. This profile of performance resulted in a significant decrease in efficiency for one dose (10.0 mg/kg) in each case. As for imipramine and desipramine, efficiency was not computable for paroxetine at the highest dose tested (Fig. 3).

Influence of the SNRIs venlafaxine and S33005 on DRL 72-s performance

Venlafaxine (2.5 mg/kg and 10.0 mg/kg) and S33005 (0.16, 2.5 and 10.0 mg/kg) did not significantly affect response rates, reinforcement rates or efficiency. Baseline data for reinforcements, responses and efficiency (reinforcements/responses) were, respectively, as follows:

- Venlafaxine, vehicle, 16±2, 63±3 and 0.27±0.03; 2.5 mg/kg, 16±3, 65±2 and 0.25±0.05 and 10.0 mg/kg, 14±2, 67±4 and 0.22±0.04. $n \geq 5$ per value

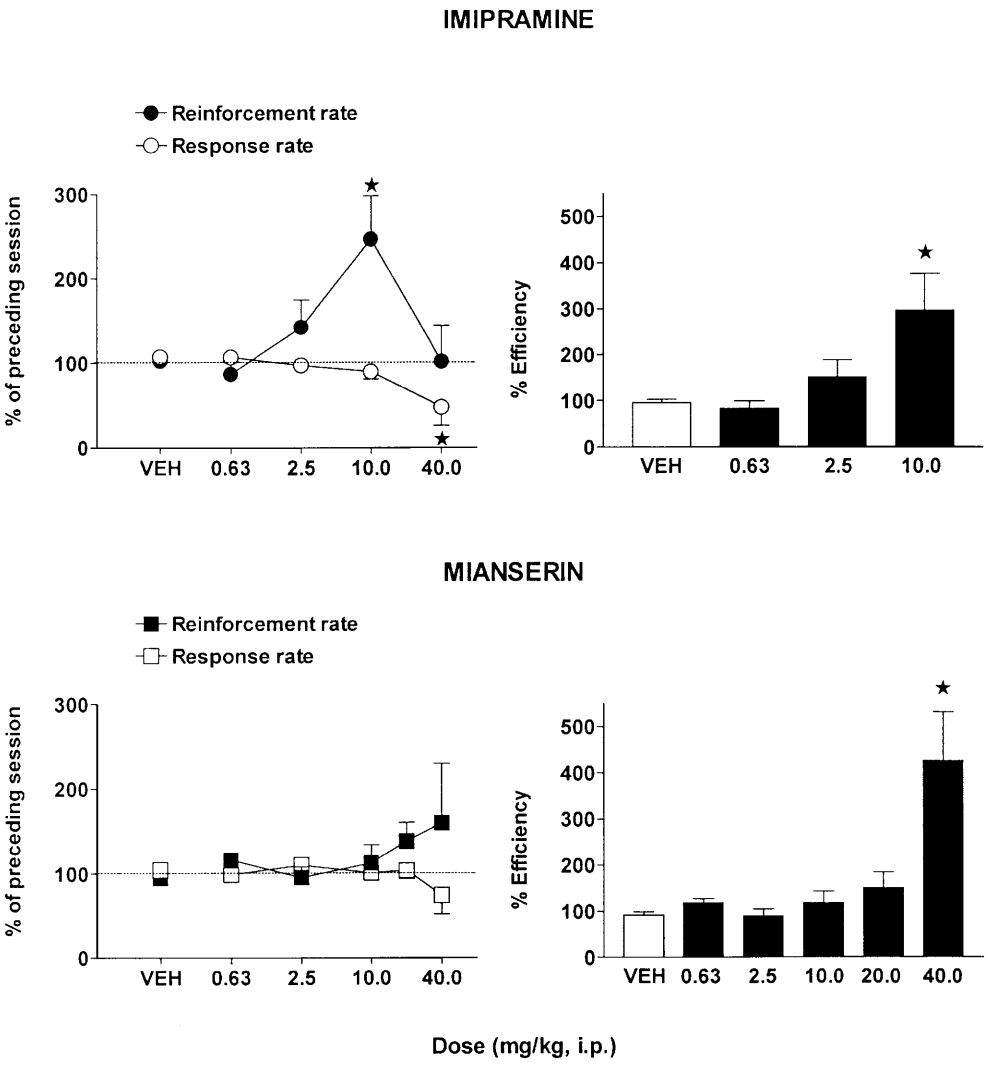

Fig. 1 Effects of the antidepressant agents imipramine and mianserin on differential reinforcement of low-rate (DRL) 72-s performance. Drug or vehicle (*VEH*) were administered 30 min prior to testing. Data are mean±SEM of percentage of preceding training session, which was defined as 100%. Baseline data for reinforcements, responses and efficiency (reinforcements/responses) are, respectively, as follows: Imipramine, veh, 13±2, 72±5 and 0.20±0.03; 0.63 mg/kg, 10±2, 76±8 and 0.14±0.04; 2.5 mg/kg, 12±2, 77±11 and 0.19±0.06; 10.0 mg/kg, 9±2, 78±8 and 0.13±0.03 and 40.0 mg/kg, 11±2, 66±5 and 0.17±0.04. Mianserin, veh, 11±2, 79±6 and 0.16±0.04; 0.63 mg/kg, 10±2, 69±3 and 0.15±0.04; 2.5 mg/kg, 12±2, 65±5 and 0.19±0.04; 10.0 mg/kg, 15±3, 65±4 and 0.24±0.06 and 40.0 mg/kg, 13±3, 64±3 and 0.22±0.06. $n \geq 5$ per value. ANOVA as follows. Imipramine, reinforcements, $F_{4,34}=5.2$, $P<0.01$, responses, $F_{4,34}=8.0$, $P<0.001$ and efficiency, $F_{3,30}=6.8$, $P<0.01$. Mianserin, reinforcements, $F_{5,35}=1.0$, $P>0.05$, responses, $F_{5,35}=1.5$, $P>0.05$ and efficiency, $F_{5,35}=4.0$, $P<0.01$. *Asterisks* indicate significance of differences to vehicle values in Dunnett's test following ANOVA. *$P<0.05$

  - ANOVA as follows: venlafaxine, reinforcements, $F_{2,20}=1.4$, $P>0.05$, responses, $F_{2,20}=1.9$, $P>0.05$ and efficiency, $F_{2,20}=1.4$, $P>0.05$
- S33005, vehicle, 16±1, 64±2 and 0.26±0.03; 0.16 mg/kg, 12±4, 68±5 and 0.21±0.08; 2.5 mg/kg, 11±2, 71±5 and 0.17±0.05 and 10.0 mg/kg, 17±2, 65±4 and 0.28±0.06. $n \geq 5$ per value
  - ANOVA as follows: S33005, reinforcements, $F_{3,26}=0.3$, $P>0.05$, responses, $F_{3,26}=1.0$, $P>0.05$ and efficiency, $F_{3,26}=0.5$, $P>0.05$

Influence of the DARIs bupropion and GBR12935 on DRL 72-s performance

Bupropion (0.16, 2.5 and 10.0 mg/kg) and GBR12935 (0.63, 2.5 and 10.0 mg/kg) did not significantly affect response rates, reinforcement rates or efficiency. Baseline data for reinforcements, responses and efficiency (reinforcements/responses) were, respectively, as follows:

- Bupropion, vehicle, 13±2, 70±5 and 0.21±0.04; 0.16 mg/kg, 9±2, 70±4 and 0.14±0.03; 2.5 mg/kg, 16±3, 66±5 and 0.26±0.07 and 10.0 mg/kg, 10±2, 75±5 and 0.14±0.03. $n \geq 5$ per value
  - ANOVA as follows: bupropion, reinforcements, $F_{3,26}=0.01$, $P>0.05$, responses, $F_{3,26}=1.9$, $P>0.05$ and efficiency, $F_{3,26}=0.02$, $P>0.05$
- GBR12935, vehicle, 10±2, 80±7 and 0.15±0.04; 0.63 mg/kg, 12±2, 66±4 and 0.19±0.04; 2.5 mg/kg, 14±2, 63±3 and 0.23±0.04 and 10.0 mg/kg, 11±1, 67±4 and 0.18±0.04. $n \geq 5$ per value
  - ANOVA as follows: GBR12935, reinforcements, $F_{3,32}=0.3$, $P>0.05$, responses, $F_{3,32}=2.3$, $P>0.05$ and efficiency, $F_{3,32}=0.8$, $P>0.05$

Influence of imipramine and mianserin relative to NARIs, SSRIs and SNRIs on frontocortical levels of 5-HT, NE and DA

Imipramine and mianserin elicited a pronounced elevation in levels of NE and DA in the frontal cortex of freely moving rats, whereas they exerted comparatively little influence on levels of 5-HT quantified in the same dialysate samples. Desipramine and reboxetine likewise

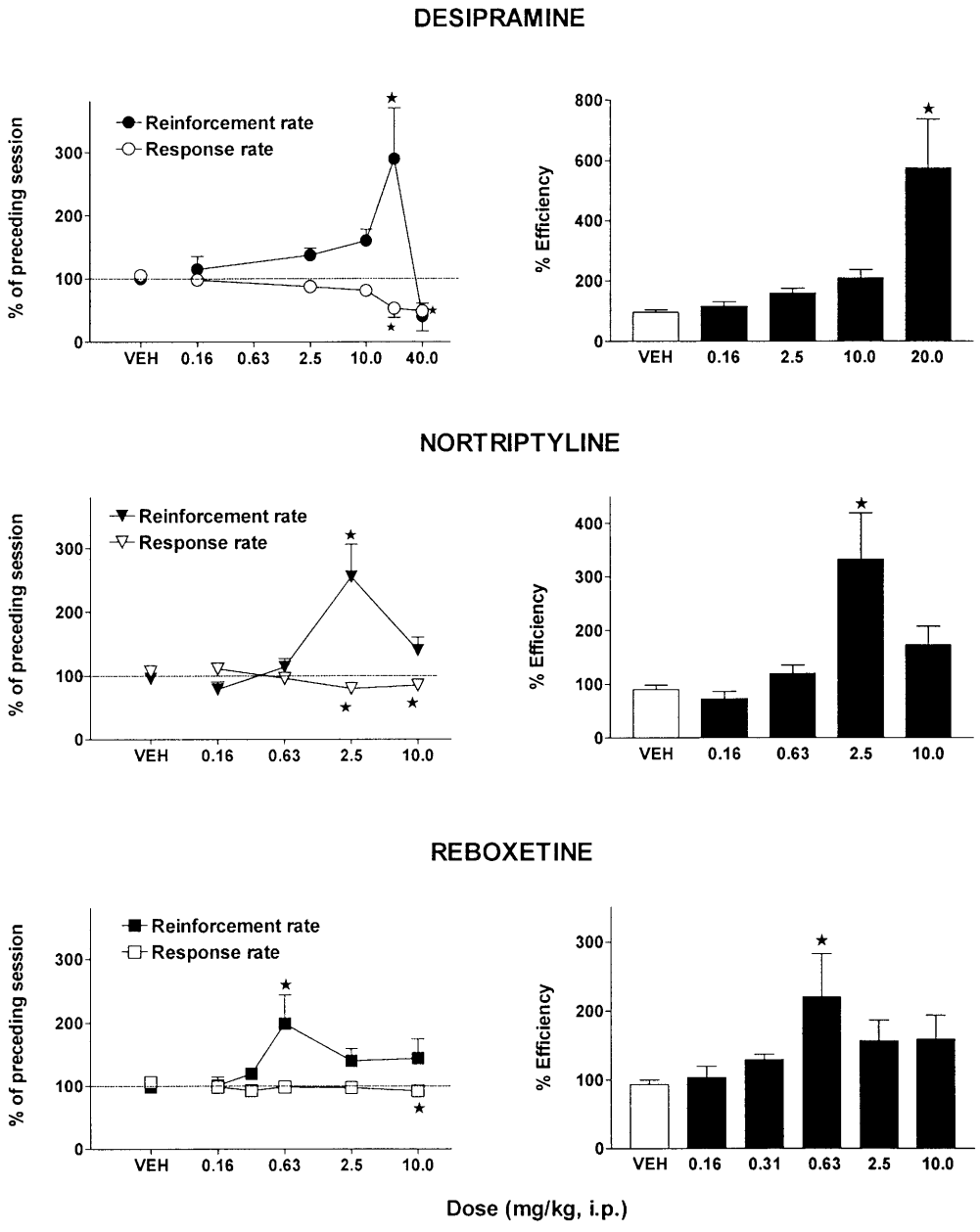

Fig. 2 Effects of the norepinephrine reuptake inhibitors (NARIs) desipramine, nortriptyline and reboxetine on differential reinforcement of low-rate (DRL) 72-s performance. Drug or vehicle (*VEH*) were administered 30 min prior to testing. Data are mean±SEM of percentage of preceding training session, which was defined as 100%. Baseline data for reinforcements, responses and efficiency (reinforcements/responses) are, respectively, as follows: Desipramine, veh, 15±2, 65±3 and 0.25±0.03; 0.16 mg/kg, 19±3, 58±3 and 0.33±0.07; 2.5 mg/kg, 16±1, 69±3 and 0.23±0.02; 10.0 mg/kg, 14±1, 67±2 and 0.22±0.03; 20.0 mg/kg, 9±2, 69±4 and 0.14±0.04 and 40.0 mg/kg, 19±4, 58±8 and 0.37±0.11. Nortriptyline, veh, 11±1, 71±3 and 0.18±0.03; 0.16 mg/kg, 15±5, 70±7 and 0.25±0.11; 0.63 mg/kg, 12±3, 66±4 and 0.20±0.05; 2.5 mg/kg, 6±1, 84±6 and 0.08±0.01 and 10.0 mg/kg, 13±4, 71±7 and 0.22±0.10. Reboxetine, veh, 13±1, 73±4 and 0.20±0.03, 0.16 mg/kg, 13±3, 73±11 and 0.23±0.08; 0.31 mg/kg, 17±4, 68±9 and 0.31±0.10; 0.63 mg/kg, 10±3, 71±4 and 0.17±0.06; 2.5 mg/kg, 12±2, 69±3 and 0.18±0.03 and 10.0 mg/kg, 15±2, 66±3 and 0.24±0.04. $n \geq 5$ per value. ANOVA as follows: Desipramine, reinforcements, $F_{5,43}=4.7$, $P<0.01$, responses, $F_{5,43}=5.4$, $P<0.001$ and efficiency, $F_{4,39}=12.0$, $P<0.001$. Nortriptyline, reinforcements, $F_{4,33}=8.6$, $P<0.001$, responses, $F_{4,33}=9.8$, $P<0.001$ and efficiency, $F_{4,33}=8.4$, $P<0.001$. Reboxetine, reinforcements, $F_{5,57}=2.6$, $P<0.05$, responses, $F_{5,57}=2.8$, $P<0.05$ and efficiency, $F_{5,57}=2.5$, $P<0.05$. *Asterisks* indicate significance of differences to vehicle values in Dunnett's test following ANOVA. *$P<0.05$

induced a marked increase in dialysis levels of NE and DA in contrast to those of 5-HT. In distinction, citalopram, paroxetine and fluvoxamine all evoked a pronounced augmentation in extracellular levels of 5-HT, whereas levels of NE and DA were much less markedly affected, with the exception of NE levels in the case of fluvoxamine. In distinction to the above drugs, both venlafaxine and S33005 resulted in a pronounced elevation in dialysis levels of 5-HT, NE and DA in each case (Table 2).

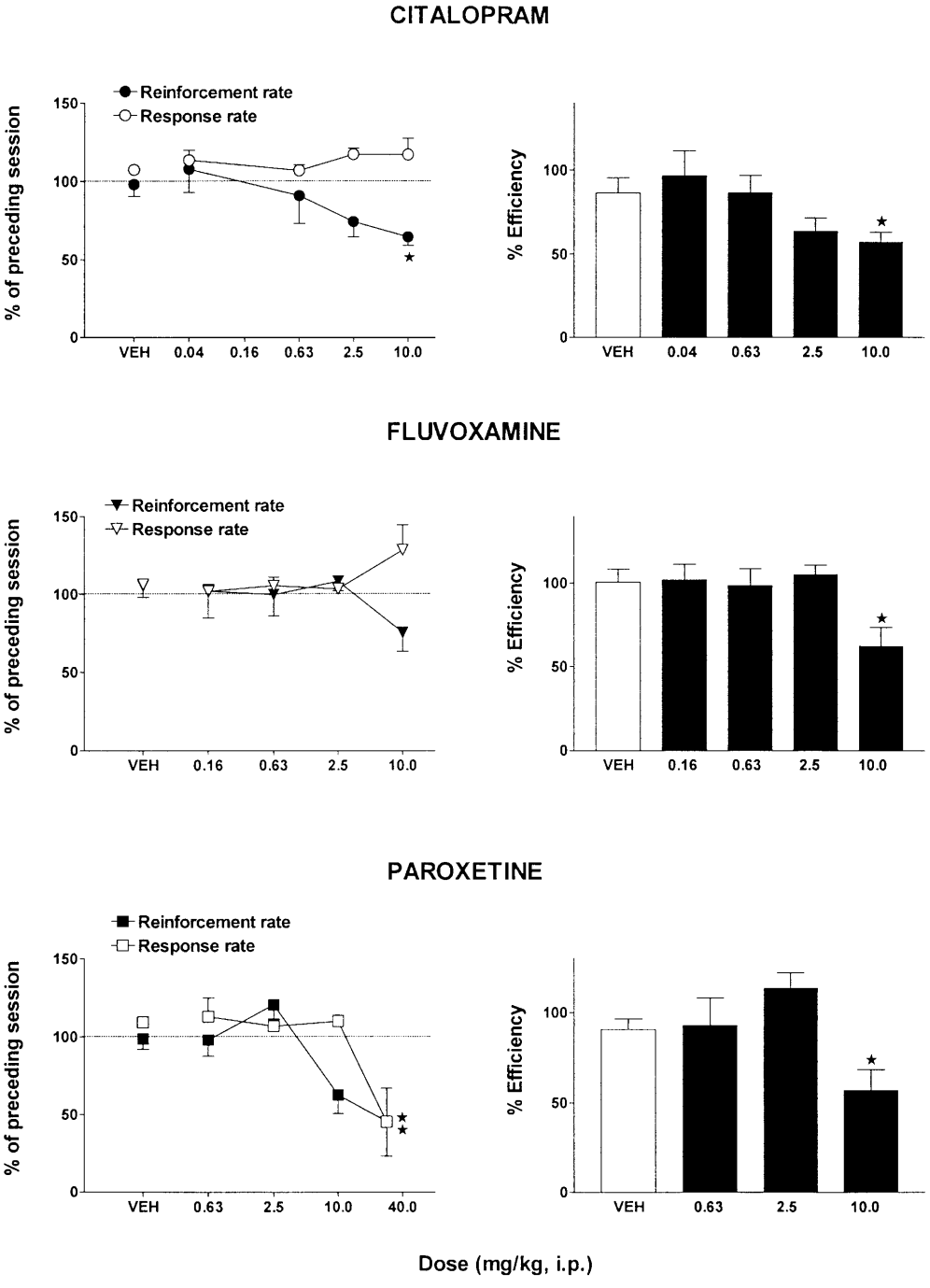

Fig. 3 Effects of the serotonin reuptake inhibitors (SSRIs) citalopram, fluvoxamine and paroxetine on differential reinforcement of low-rate (DRL) 72-s performance. Drug or vehicle (*VEH*) were administered 30 min prior to testing. Data are mean±SEM of percentage of preceding training session which was defined as 100%. Baseline data for reinforcements, responses and efficiency (reinforcements/responses) are, respectively, as follows: Citalopram, veh, 13±2, 71±5 and 0.22±0.03; 0.04 mg/kg, 9±2, 71±7 and 0.14±0.04; 0.63 mg/kg, 12±3, 72±6 and 0.18±0.05; 2.5 mg/kg, 10±2, 77±10 and 0.14±0.04 and 10.0 mg/kg, 17±1, 66±5 and 0.27±0.02. Fluvoxamine, veh, 13±2, 68±3 and 0.22±0.03; 0.16 mg/kg, 11±2, 67±4 and 0.17±0.05; 0.63 mg/kg, 14±3, 64±5 and 0.24±0.08; 2.5 mg/kg, 9±2, 79±8 and 0.12±0.04 and 10.0 mg/kg, 12±2, 68±4 and 0.19±0.04. Paroxetine, veh, 14±2, 66±3 and 0.24±0.03; 0.63 mg/kg, 16±5, 67±10 and 0.30±0.11; 2.5 mg/kg, 9±2, 71±2 and 0.12±0.03; 10.0 mg/kg, 18±2, 62±5 and 0.30±0.06 and 30.0 mg/kg, 17±3, 63±6 and 0.31±0.07. $n \geq 5$ per value. ANOVA as follows: Citalopram, reinforcements, $F_{4,33}=2.7$, $P<0.05$, responses, $F_{4,33}=0.9$, $P>0.05$ and efficiency, $F_{4,33}=2.9$, $P<0.05$. Fluvoxamine, reinforcements, $F_{4,35}=1.2$, $P>0.05$, responses, $F_{4,35}=2.2$, $P>0.05$ and efficiency, $F_{4,35}=2.8$, $P<0.05$. Paroxetine, reinforcements, $F_{4,34}=5.3$, $P<0.01$, responses, $F_{4,34}=8.2$, $P<0.001$ and efficiency, $F_{3,29}=4.9$, $P<0.01$. *Asterisks* indicate significance of differences to vehicle values in Dunnett's test following ANOVA. *$P<0.05$

Influence of drugs tested in the DRL 72-s model on spontaneous locomotion and food intake

All drugs provoked a reduction in food intake, which attained statistical significance for mianserin, desipramine, citalopram and paroxetine. Spontaneous locomotor activity was also reduced by all drugs, with statistical significance seen for mianserin, desipramine and paroxetine (Table 3).

Discussion

Neurochemical profiles of drugs evaluated

Though imipramine possessed only marginally higher affinity at native rat NE relative to 5-HT transporters, it more markedly elevated dialysate levels of NE versus 5-HT in the frontal cortex (Table 2). This possibly reflects [as discussed in detail by Millan et al. (2001b)] the involvement of specific isoforms of transporters in the control of extracellular levels of 5-HT and NE in the

Table 3 Influence of antidepressant agents on food intake and spontaneous locomotion at doses affecting efficiency in the differential reinforcement of low-rate (DRL) 72-s study. *↓ or ↑* decrease or increase, respectively, *% Efficiency* % reinforcement rate/response rate versus preceding training session, *% Spont Loc* % change in spontaneous locomotion in rats versus control (vehicle) values which were defined as 0% (these were 49±6 locomotion counts for nortriptyline and fluvoxamine, 77±7 for paroxetine, and 63±9 for the other compounds), *% Food intake* % change in food intake in 24-h food-deprived rats versus control (vehicle) values which were defined as 0% (these were 6±1 g for all compounds). *n*=5 per value

Drug	Dose (mg/kg, i.p.)	% Efficiency	% Food intake ±SEM	% Spont Loc ±SEM
Imipramine	10.0	↑	–39±20	–40±22
Mianserin	40.0	↑	–55±7*	–73±7*
Desipramine	20.0	↑	–89±23*	–94±3*
Nortriptyline	2.5	↑	–32±10	–28±20
Reboxetine	0.63	↑	–36±16	–24±14
Citalopram	10.0	↓	–55±10*	–21±21
Fluvoxamine	10.0	↓	–42±12	–21±25
Paroxetine	10.0	↓	–77±9*	–62±12*

*$P<0.05$; significance of differences to vehicle values in unpaired *t*-test

frontal cortex. Further, as discussed by Millan et al. (2000b), the similar influence of imipramine on DA and NE levels reflects the important role of NE transporters in the clearance of DA from the synaptic cleft in this structure. For mianserin and the NARIs desipramine and reboxetine, the prominent influence on NE (and DA) versus 5-HT levels (Table 2) reflects their preference for NE versus 5-HT transporters. However, the preferential increase in levels of 5-HT versus NE (and DA) for the SSRIs citalopram, paroxetine and fluvoxamine (Table 2) corresponds to their more potent actions at 5-HT than NE transporters (Frazer 1997; Tatsumi et al. 1997; Millan et al. 2000b, 2001b). Interestingly, confirming a recent study employing the s.c. route (Millan et al. 2001b), S33005 and venlafaxine displayed an intermediate profile in enhancing levels of 5-HT as well as NE (and DA) (Table 2). The significance of this observation, which corresponds to their SNRI profiles in diverse behavioural models (Millan et al. 2001a, 2001b), is evoked below.

Improvement of efficiency by imipramine and mianserin: pharmacological validation

The present data corroborate numerous studies employing a water reward (McGuire and Seiden 1980a, 1980b; O'Donnell and Seiden 1983; Howard and Pollard 1984; Olivier et al. 1993), and two studies employing a food reward (Sanger 1988; Van Hest et al. 1992), in demonstrating that the DRL 72-s procedure is responsive to the tricyclic imipramine. The increase of efficiency elicited by the "atypical" agent mianserin is similarly in line with work with water-rewarded DRL 72-s models (O'Donnell and Seiden 1983; Marek et al. 1989b; Hand et al. 1991; Jackson et al. 1995; Jones et al. 1998) and is of significance since mianserin was inactive in a DRL 60-s model with food reward (Sanger 1988).

Actions of NARIs: implication of adrenergic mechanisms

Both imipramine, by inhibition of NE reuptake, and mianserin, by blockade of α_2-ARs and 5-HT_{2C} receptors (Millan et al. 2000b), elevate extracellular levels of NE (Table 2) suggesting that adrenergic mechanisms might be involved in their actions. The potential significance of NE is indicated by the increase in efficiency elicited by the NARIs desipramine and nortriptyline, in analogy to previous studies employing either water (O'Donnell and Seiden 1983; Wong et al. 2000) or food (Britton and Koob 1989; Bright et al. 1997) reward. These drugs do not exclusively interact with NE transporters, so it is of importance that the highly selective NARI, reboxetine, similarly increased efficiency. This finding corroborates the report of Wong et al. (2000), who employed a water-rewarded DRL 72-s protocol.

Psychological substrates of the increase in efficiency elicited by NARIs in both food-rewarded (present study) and water-rewarded (O'Donnell and Seiden 1983; Wong et al. 2000) DRL 72-s models, as well as delayed-reinforcement protocols (Bizot et al. 1988) remain to be further elucidated. Nevertheless, inasmuch as such experimental procedures reflect the capacity to wait (Introduction), it is of pertinence that adrenergic mechanisms were recently implicated in the control of impulsive behaviour in rats (Evenden 1999). The role of multiple ARs in drug performance in the DRL 72-s procedure will require examination in future studies. α_1-ARs are unlikely to be implicated since imipramine, desipramine and nortriptyline possess antagonist properties at these sites (Marek et al. 1989b; Tatsumi et al. 1997; Millan et al. 2000b). Similarly, α_2-ARs are unlikely to be involved since mianserin is a potent antagonist at α_2-ARs. However, β_1 and/or β_2 ARs may be of importance in as much as $\beta_{1/2}$- and β_2-AR agonists increased reinforcement rates and decreased response rates in a DRL 72-s model (Bizot et al. 1988; O'Donnell 1990, 1993; O'Donnell et al. 1994), while the action of desipramine was attenuated by the β_1-AR antagonist metoprolol (Seiden et al. 1988). Studies with selective antagonists would be of interest to perform with the NARI reboxetine.

Irrespective of the underlying receptorial and "psychological" mechanisms, the reproducible actions of NARIs in DRL 72-s procedures complements observations of their activity in diverse experimental models predictive of antidepressant properties (Detke et al. 1995; Wong et al. 2000; Dekeyne et al. 2001; Millan et al. 2001b) and their clinical utility in the management of depressive states (Frazer 1997; Massana et al. 1999; Schatzberg 2000).

Actions of SSRIs: decrease in efficiency

In contrast to NARIs, all SSRIs decreased efficiency, including citalopram, the most selective SSRI known

(Popik 1999), which has not, to date, been examined in this experimental procedure. This reduction reflected a variable influence on response rates but a consistent reduction in reinforcement rates. Though there are exceptions (Jones et al. 1998; Wong et al. 2000), and individual SSRIs do not display identical profiles (Sokolowski and Seiden 1999), previous studies of SSRIs have reported a consistent increase in reinforcement rates which may or may not be accompanied by a decrease in response rates (Van Hest et al. 1992; Olivier et al. 1993; Bright et al. 1997; Jones et al. 1998).

The ability of the present protocol to distinguish SSRIs from NARIs is of particular interest since clinical studies have suggested that actions of SSRIs may differ to those of NARIs in depressed patients (Dubini et al. 1997; Healy and McMonagle 1997; Massana et al. 1999; Eriksson 2000; Schatzberg 2000). Further, only few experimental models of antidepressant properties have succeeded in differentiating SSRIs and NARIs (Detke et al. 1995; Dekeyne et al. 2001; Millan et al. 2001a). Nevertheless, it is important to address the question as to why SSRIs were ineffective.

First, the decrease in reinforcement rates may reflect the use of food as the reward inasmuch as SSRIs inhibit appetite (Currie et al. 1998; Leibowitz and Alexander 1998; Bray and Greenway 1999; Carek and Dickerson 1999). Indeed, all SSRIs suppressed food intake in food-deprived animals (Table 3). However, this explanation seems unlikely. (1) In previous studies employing food reward, an increase in efficiency was seen with SSRIs (Van Hest et al. 1992; Bright et al. 1997; Jones et al. 1998). (2) NARIs also suppress appetite (Gehlert et al. 1998; Bray and Greenway 1999; Carek and Dickerson 1999; Rowland et al. 2000) and reduced food intake to a magnitude similar to SSRIs despite a significant increase in reinforcement rates. (3) In previous studies of serotonergic agents in models of delayed reinforcement employing food reward, a clear dissociation of the modulation of feeding behaviour relative to performance was demonstrated (Richards et al. 1993; Bizot et al. 1999). Nevertheless, it may be of relevance that, in the present study, water was available during both sessions of training and testing.

Second, SSRIs may perturb motor function, resulting in non-specific reductions of reinforcement rates. Indeed, fluvoxamine, citalopram and paroxetine exerted a mild inhibitory influence on spontaneous locomotion of rats. However, similar decreases in spontaneous locomotion were observed for other drugs at doses that enhanced efficiency. Further, SSRIs did not consistently decrease response rates that would be expected if they exerted a generalised perturbation of motor behaviour.

Third, baseline performances were highly stable throughout the testing period and absolute response rate and reinforcement rate were similar to those observed by others (Seiden et al. 1985; Jones et al. 1998; Sokolowski and Seiden 1999). Nevertheless, subtle procedural differences between the present and previous studies may be of pertinence to the inactivity of SSRIs. Although animals were, as usual, submitted to a fixed ratio 1 then to a DRL 18-s, and finally to the DRL 72-s schedule (Seiden et al. 1985), as proposed by other authors (Bright et al. 1997), they also underwent overnight, 8-h training sessions with the DRL 72-s schedule in order to accelerate training. Additional differences (Seiden et al. 1985; Sokolowski and Seiden 1999) comprise the treatment-to-test interval (30 min herein versus 1 h for i.p. administrations), the strain of rat employed (Wistar versus Sprague-Dawley) and the frequency of testing (once a week, followed by two resting days, versus twice a week). An extensive parametric analysis would be necessary to determine the precise significance of these variables.

Finally, an enhancement of serotonergic transmission may be not crucial for activity in the DRL 72-s model. (1) The 5-HT releaser fenfluramine did not enhance efficiency in a DRL 72-s procedure (Richards et al. 1993). (2) 5-HT_2 receptor antagonists and 5-HT_{1A} receptor agonists are associated with activity in the DRL 72-s procedure (Marek et al. 1989a; Van Hest et al. 1992; Richards et al. 1994; Borsini et al. 1997; Jolly et al. 1999; Cousins et al. 2000; but see Martin et al. 1998). Now, 5-HT_{1A} agonists, by activating autoreceptors, suppress serotonergic transmission, whereas, in common with 5-HT_2 antagonists, they reinforce (disinhibit) corticolimbic adrenergic transmission (Millan et al. 2000b). That is, in common with other antidepressants active in the DRL 72-s procedure, such as tricyclics and mianserin, they increase extracellular levels of NE. (3) At high doses active in DRL 72-s models (Sokolowski and Seiden 1999), SSRIs increase dialysate levels of NE in the frontal cortex (Millan et al. 2000b). (4) Even in rats lacking serotonergic pathways, the precursor, 5-hydroxytryptophane, was effective in a DRL 72-s model (Jolly et al. 1999). However, this viewpoint may be too extreme inasmuch as depletion of 5-HT elicits a pattern of behaviour opposite to SSRIs in DRL 72-s models, including a diminution in reinforcement rates (Wogar et al. 1993; Fletcher 1995; Jolly et al. 1999). Further, under these conditions, 5-HT_{1A} agonists are still active, indicative of actions at post-synaptic 5-HT_{1A} receptors (Bizot et al. 1988; Fletcher 1995; Jolly et al. 1999).

Thus, the present data accentuate the importance of adrenergic mechanisms in the DRL 72-s procedure, as well as the need for additional mechanistic studies of their implication. Further study is required to establish the reasons underlying the intriguing lack of activity of SSRIs in the present model relative to previous studies.

Lack of influence of SNRIs on efficiency

Venlafaxine displays robust effects in virtually all preclinical models predictive of antidepressant properties, is active in experimental protocols of impulsive behaviour (Schweizer et al. 1997; Redrobe et al. 1998; Millan et al. 2001a) and generalises to discriminative stimuli elicited by the NARI reboxetine and the SSRI citalopram (Millan et al. 2001a; Dekeyne et al. 2001). Its lack of activity in

the present DRL 72-s procedure was, therefore, surprising. However, its lack of efficacy in the DRL 72-s protocol was underlined by use of a further SNRI, S33005, which shows a similar (though more potent) functional profile (Millan et al. 2001a, 2001b). Inasmuch as NARIs and SSRIs exerted an opposite increase and decrease in efficiency, the lack of activity of SNRIs may simply reflect "cancellation" of these opposing actions. It might be argued that this explanation is unsatisfactory since it does not account for the increase in efficiency acquired with imipramine, which also interacts both with 5-HT and NE transporters. However, imipramine shows a mild preference for the latter versus the former, whereas both venlafaxine and S33005 show superior affinity for rat 5-HT relative to NE reuptake sites (Tatsumi et al. 1997; Millan et al. 2001b). Further, this contention is strongly underpinned by dialysis analyses performed in parallel with the DRL 72-s studies. Thus, imipramine mimicked mianserin and the NARIs desipramine and reboxetine in preferentially elevating extracellular levels of NE versus 5-HT. However, while SSRIs preferentially increased levels of 5-HT and disrupted DRL 72-s performance, venlafaxine and S33005 showed an intermediate effect in the dialysis studies in augmenting levels of both 5-HT and NE: this corresponds to their "intermediate" profile relative to SSRIs and NARIs in the DRL 72-s procedure. This hypothesis of opposing actions of venlafaxine and S33005 at 5-HT versus NE transporters may apply exclusively to the present procedure. Thus, it would be of importance to evaluate their effects in other models of capacity to wait in which SSRIs are effective – including water-rewarded DRL 72-s procedures – prior to any definitive conclusions.

Lack of influence of DARIs on efficiency

At a high dose (60 mg/kg, i.p.), bupropion, which displays a modest preference for DA versus NE and 5-HT reuptake sites (Table 1), did not modify reinforcement rates in a water-rewarded DRL 72-s procedure, whereas it elevated response rates (Seiden et al. 1985). This pattern of performance is comparable to psychostimulants and presumably reflects potentiation of mesolimbic dopaminergic transmission (Britton and Koob 1989; Li et al. 1989; Jackson et al. 1995; Sabol et al. 1995; Millan et al. 2000b). Herein, over an extensive dose range that increases extracellular levels of DA in the nucleus accumbens and frontal cortex (Millan et al. 2000b), bupropion likewise failed to affect reinforcement rates or efficiency and tended to enhance response rates at the highest dose. These data are supported by the parallel observation that GBR12935, a highly selective DARI, likewise failed to display an antidepressant profile over a dose range that markedly elevates dialysate levels of DA (Millan et al. 2000b). It may be concluded that selective inhibition of DA reuptake is ineffective in this DRL 72-s procedure. Both buproprion and GBR12935 also enhance NE levels in dialysate levels of frontal cortex due to the role of NE transporters in this structure on the reuptake of DA (Millan et al. 2000b). This appears to contradict the argument that adrenergic mechanisms are of importance for efficacy in DRL 72-s procedures. However, it is possible that increases in NE levels in brain regions other than the frontal cortex underlie the actions of NARIs.

Summary and conclusions

In conclusion, the present study constitutes a systematic and comparative evaluation of the influence of diverse classes of antidepressant agent in a food-rewarded DRL 72-s procedure. The data demonstrate robust and consistent increases in efficiency with NARIs, in analogy to imipramine and mianserin, which share their ability to enhance adrenergic transmission. In contrast, SSRIs are ineffective under the present conditions, for reasons that require clarification. Irrespective of the explanation, the present data add to an accumulating body of evidence, including clinical observations, that the functional actions of NARIs can be differentiated from those of SSRIs. The lack of activity of the SNRIs venlafaxine and S33005 probably reflects their predominant interaction with 5-HT relative to NE reuptake sites. Finally, inhibition of DA reuptake is not effective in this DRL 72-s procedure. In conclusion, the present data support the importance of adrenergic mechanisms in the control of behaviour under conditions of delayed responding. Further, they underpin the interest of DRL 72-s models for the characterisation of antidepressant agents and suggest that variants of this experimental procedure may provide additional insights into their functional profiles of activity.

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