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Review

Antidepressant treatment and rodent aggressive behaviour

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Abstract

This review examines two 'ethologically relevant' rodent models, the resident–intruder and social hierarchy paradigms, that are sensitive to chronic antidepressant treatment (including repeated electroconvulsive shock). These models of rodent social and agonistic behaviour demonstrate that acute and chronic treatment with antidepressant drugs (regardless of their acute pharmacological activity) induce diametrically opposite changes in rodent aggressive behaviour. The common ability of chronic antidepressant treatment to increase rodent aggression (which in turn results in increased hierarchical status in closed social groups) most likely reflects the increased assertiveness and associated externalization of emotions (indicative of increased extrapunitive aggression) expressed during recovery from depressive illness. Finally, findings that relate observed behavioural changes to underlying neurochemical changes are briefly reviewed in terms of adaptive mechanisms in the rodent central nervous system induced by antidepressants, and also with respect to suicide ideation and panicogenic responses observed in some patients at the onset of treatment with selective serotonin reuptake inhibitors for affective disorders.

Keywords: Animal model of depression; Chronic antidepressant treatment; Agonistic behaviour; Social hierarchy; Resident–intruder; Suicide ideation

Contents

1. Introduction

Animal models of depression are used for a variety of purposes: as screening tests to discover and develop novel antidepressant drug therapies; as simulations for investigating aspects of the neurobiology of depressive illness; and as experimental models within which the neuropharmacological mechanisms associated with antidepressant treatments, including the tricyclic antidepressant, selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), and monoamine

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oxidase (MAO) inhibitor drugs and electroconvulsive shock, may be investigated (Henn and McKinney, 1987; Jesberger and Richardson, 1986; McKinney, 1984; Willner, 1984, 1990; Willner and Mitchell, 2002). Whether any single animal model can fulfill all these diverse needs is questionable. The pessimistic view is that currently available animal models are only models of antidepressant activity (including electroconvulsive shock). If this is the case, they may prove adequate as both screening tests and as models to investigate neuropharmacological mechanisms associated with treatment, but their validity as simulations of the psychiatric condition is highly questionable.

The essential requirement for any antidepressant screening test is that it accurately predicts antidepressant activity. Ideally, it should also be cheap, robust, reliable and easy to use (Danysz et al., 1991; Willner, 1991) and should therefore be as simple as possible. Consequently, the majority of animal models used routinely as antidepressant screening tests rely on an acute response to drug treatment. The almost universal use by the pharmaceutical industry since the beginning of the 1970s of drug screening tests sensitive to acute or sub-acute drug treatment has resulted in the discovery of an array of antidepressant drugs all with pharmacological and therapeutic profiles qualitatively similar to that of the archetypal tricyclic antidepressant, imipramine, or MAO inhibitor, isoniazid. The success and consequent continued use of screening tests that rely on acute treatment has undoubtedly restricted the development of animal models with improved face and construct validity with respect to depressive illness, and has also largely been responsible for delaying the development of animal models in which antidepressants are active only following chronic administration. Such animal models are of no value in the drive to identify antidepressant drugs with a more rapid onset and have limited or minimal validity as simulations of depression (Willner, 1984; Willner and Mitchell, 2002). Consequently, the use of acute drug screening models has simply resulted in the identification of further 'me-too' compounds (novel compounds whose acute pharmacological profile is similar to those already available to the clinician), has provided no information on onset of clinical efficacy, has been of very limited use in furthering our knowledge of the mechanisms associated with the psychopathology of depressive illness or adaptive changes associated with the recovery process from depression, and has demonstrably failed to identify novel mechanisms and targets for future drug discovery.

However, the simplistic view that screening tests for antidepressant activity should necessarily rely on an acute response has changed during the last decade. The clinical requirement is now to identify rapid onset antidepressant treatments. Of necessity this approach involves the assessment of drug action associated with chronic/continuous drug treatment regimes and measuring an acute response is of little value, except to gain information regarding drug potency and thereby identify dose levels that may be used in subsequent chronic treatment studies. Appropriate screening tests to be used early during drug development should therefore have the ability to identify the time course of drug action associated with repeated treatment schedules.

The belief that clinical efficacy is dependent on chronic treatment has led to a considerable literature describing the effects of chronic antidepressant administration in normal animals, and numerous changes in pre- and/or post-synaptic receptor function have been reported, in a variety of systems. These studies are an essential first step towards establishing mechanisms of antidepressant action. However, the inability to determine which of the many effects of antidepressants are responsible for their therapeutic actions constitutes a fundamental limitation of this approach. The development of animal models that mimic, chronically, some aspects of the human disease state and which can be challenged with established or putative 'therapies', provides a powerful methodology for investigating these problems.

In contrast to the changing criteria for screening tests for antidepressant drugs, a simulation of depression aims to mimic aspects of the clinical situation. If a model is to be used to investigate antidepressant actions, a measurable, progressive, onset that is comparable to the clinical time course, is highly desirable. The importance of this feature is that only when a model allows detection of a gradual onset of action is it possible to detect a more rapid onset. The model should also respond differently (either in the direction of response or in response magnitude) to single and repeated (chronic/continuous) treatment regimes. One advantage of animal models which are able to identify novel therapies with a rapid, progressive, onset of action is that such animal models provide time-dependent behavioural markers of successful antidepressant treatment. These behavioural markers may then be used to identify concomitant changes in neurochemistry and neurotransmitter receptor-mediated function that may underpin the observed antidepressant-induced change in behaviour and so increase our understanding of the neurochemical mechanisms responsible for antidepressant action. The three models for which the clearest evidence for gradual onset of action exists are Chronic Mild Stress and two models based on the ethological analysis of rodent non-social, social and agonistic behaviour (the resident–intruder and social hierarchy tests) (see Willner and Mitchell, 2002). It is the latter two models that are the focus of this review.

2. Rodent non-social, social and agonistic behaviour

The ethological studies of Dixon and co-workers (Dixon et al., 1989) have shown that increased flight and impaired sociability are significant features of the non-verbal behaviour of patients with depressive illness. Clinical studies also indicate that such abnormal behavioural responses/reactions of patients with depressive illness to environmental and social stimulation are progressively modified during remission from the illness (Eisen, 1989; Khan et al., 1989; Oswald et al., 1972). Thus recovery from a depressive episode is associated with progressively reduced self-criticism and feelings of guilt (Priest et al., 1980) that lead to increased physical and/or verbal interaction with the environmental and social events

(Kaplan et al., 1961). The changes in human behaviour are argued to be a consequence of a positive change in the balance between extrapunitive and intropunitive aggression (Priest et al., 1980). Extrapunitive aggression is outwardly directed aggressive behaviour and constructive in nature (e.g. non-verbal and verbal communication, assertiveness, increased sociability) and should not be confused with externally directed violent aggression such as homicide, while intropunitive aggression is aggressive behaviour that is directed inwardly against oneself (e.g. guilt, remorse) the ultimate expression of which is suicide (including suicidal ideation, suicidal acts and completed suicide). The reversal of impaired sociability may therefore be an important index of the recovery process from depressive illness. In the preclinical arena the ability of antidepressant treatments to modify the behavioural responses of patients with depression has generally been ignored in the search for a definitive animal model of depressive illness. The resident–intruder paradigm provides a means to examine the ability of psychotropic drugs to modify the social and agonistic behaviour patterns of laboratory rodents. The term 'agonistic behaviour', first used by Scott (1958), refers to the spectrum of conflict related behaviours, including not only aggressive behaviours, but also the elements indicative of escape, defense and submission. The experimental paradigm relies exclusively on the concepts and techniques of ethological analysis of rodent behaviour since ethology provides a method of precise and quantitative assessment of natural patterns of animal behaviour. The experimental considerations and consequent design of the resident–intruder and social hierarchy paradigms have been described recently in detail (Mitchell and Redfern, 2005).

2.1. Resident–intruder paradigm

To profile fully the effect(s) of a compound on rodent non-social, social and agonistic behaviour, three experimental designs for the resident–intruder paradigm have been developed.

1) Acute treatment
2) Chronic treatment
3) Time-course

It is important to note that acute treatment studies with psychotropic drugs are an important precursor to subsequent chronic treatment studies since they provide invaluable information on drug potency and enable behaviourally active doses of compounds to be identified. In both acute and chronic treatment studies each group of animals are tested on four occasions only on a weekly cycle. Resident rats are isolated for three days prior to each test day and housed individually with food and water available ad libitum. At the start of each social encounter test the home cage containing the resident rat is positioned inside the recording cabinet (for details see Mitchell and Redfern, 1992a) for at least 30 min following which the intruder conspecific is introduced. The ensuing social encounter is recorded on videotape for 10 min under low-intensity (0.5–4 lx at the cage floor) red light illumination by a video camera positioned above the recording cabinet. At the end of each recording session both resident and intruder rats are returned to their respective group cages.

In acute treatment studies resident rats are treated with drug or vehicle prior (typically 30–60 min) to each social encounter and returned to their respective home cage. In each study resident rats receive four treatments (drug-vehicle and three doses of drug) at weekly intervals and encounter each of the corresponding intruder conspecifics over the four test sessions. In chronic treatment studies resident rats are behaviourally tested on the first occasion without any treatment to provide a baseline behavioural profile, following which osmotic mini-pumps are implanted (usually subcutaneously). Social encounters are performed 7 and 14 days later, after which the mini-pumps are removed. The final social encounter is then performed 7 days after the cessation of drug treatment. Similarly, resident rats in chronic treatment studies encounter each of the corresponding intruder conspecifics over the four test sessions.

In the time-course studies, resident rats (initially 2 groups of 4 rats per group; each resident group with a corresponding intruder group) are subjected to eight social encounters. These animals are also isolated for three days prior to the first test day and housed individually with food and water available ad libitum, but remain isolated throughout the duration of the experiment. Again, resident rats are behaviourally tested on the first occasion without any treatment to provide a baseline behavioural profile, following which osmotic mini-pumps are implanted. Social encounters are then performed at daily intervals and arranged to ensure that each resident rat meets each of the corresponding 8 intruder conspecific rats over the test sessions. In this way the onset of drug-induced changes in rodent behaviour may be monitored during the first week of treatment.

During ethological analysis of rodent behaviour the occurrence of each behaviour or posture exhibited by the resident rats during each social encounter are identified and recorded during video playback. The scores for each behaviour/posture are

Table 1
Rodent ethogram

Motivational category	Behavioural element
Exploration	Locomotion, rearing
Investigation	Approach, follow, stretched attention, to–fro, walk round/circle/side, nose and investigate, sniff genitalia, tail rattle
Sexual	Mount*, attempt mount, lick penis
Aggression	Aggressive groom, aggressive posture, attack, bite, offensive sideways, offensive upright, pull, threat/thrust
Flight-submit	Defensive sideways, defensive upright, submit
Flight-escape	Attend, crouch, elevated crouch, flag and evade, retreat, under food hopper
Maintenance	Digging, drinking*, eating*, licking, scratching, head/body shake, washing

Summary of the various elements of rat behaviour, grouped according to motivational category, expressed by rats during social encounters. Adapted from Grant (1963).
*These behaviours are not recorded in resident–intruder studies described here. Full mating behaviour is not possible between male cohorts, while food and water are not available during each social encounter.

grouped according to their motivational category (see Table 1) for each animal and the total score for each category expressed as a percentage of the total number of behaviours observed for that animal. The data from the two groups of four resident rats are grouped and the mean and standard error of the mean are calculated for both the percentage values of each motivational category and the total number of behaviours/postures observed within each treatment group. In a typical 10-min social encounter resident rats will exhibit between 1200 and 1500 behavioural elements. Invariably resident rats exhibit high levels of investigatory behaviour (about 50–60% of all behaviours scored) directed at the intruder conspecific following introduction of the latter into the resident rat's home cage. In some cases such intense conspecific investigation leads to the expression of aggressive behaviour directed at the conspecific (about 5–8% of total behaviours) or flight behaviour (total flight behaviour equals about 15–20% of total behaviours scored). Flight behaviour in the rat may be subdivided into two flight pathways; flight submit and flight escape. In these studies the occurrence of flight escape behaviour invariably far exceeds flight submit behaviour (12–14 % c.f. 1–2%) and reflects the opportunity to flee afforded by the size of the cage in which the social encounter takes place. The remaining categories of behaviour (maintenance and sexual behaviour) occur very infrequently (about 1% of total behaviours scored in both cases).

2.1.1. Acute treatment

Compared to saline-treated controls, acute treatment of resident rats with increasing doses of venlafaxine, 5.54–49.85 mg/kg sc, induced a dose-related decrease in the aggressive behaviour of resident rats directed at the unfamiliar intruder conspecifics, concomitant with increased flight escape behaviour (Fig. 1).

None of the doses of venlafaxine examined significantly modified any other category of behaviour, including the total number of behavioural elements expressed by resident rats (see Fig. 2). The ability of venlafaxine to reduce aggressive behaviour and increase flight escape behaviour at doses devoid of effect on the total number of behaviours expressed during social encounters indicates that venlafaxine has a selective (i.e. non-sedative) effect on rodent agonistic behaviour. Indeed, an ability to reduce aggressive behaviour and invariably increase flight behaviour of resident rats in this paradigm following acute treatment is an ability shared by all pharmacologically disparate antidepressant compounds tested (Table 2), including examples of SSRIs, SNRIs, MAO inhibitors, tricyclic antidepressants and a typical antidepressant drugs such as mianserin and iprindole.

In contrast, almost without exception, psychotropic drugs with no recognized clinical efficacy in depressive illness either have no effect on rodent agonistic behaviour or only reduce aggressive behaviour at doses which cause marked reductions in

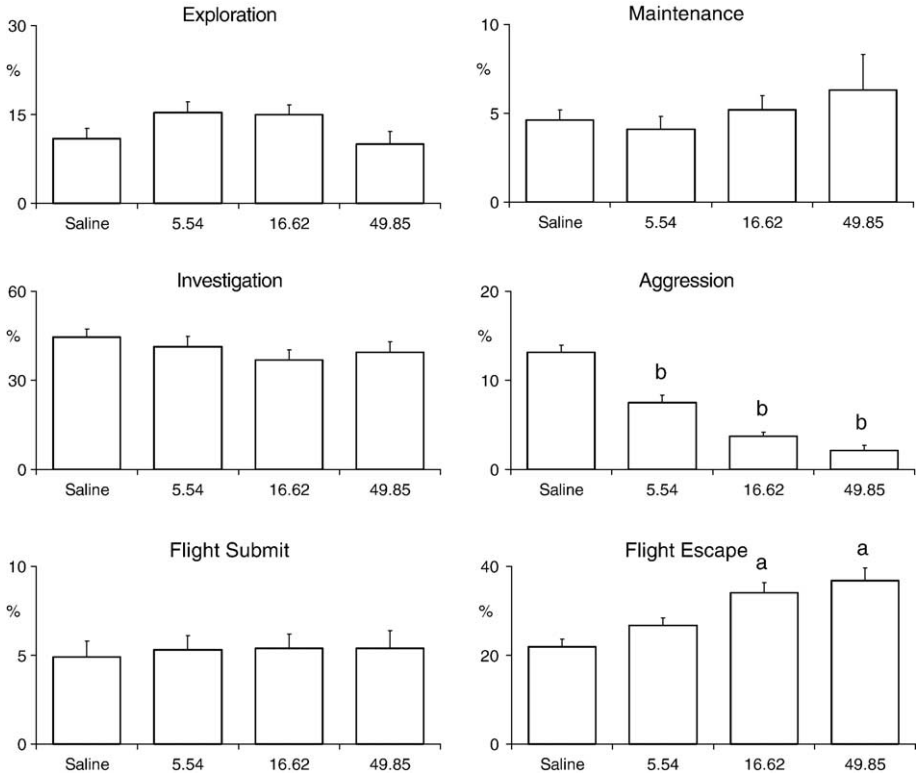

Fig. 1. Effect of 30 min pre-treatment with venlafaxine, 5.54–49.85 mg/kg sc, on the behavioural profile of resident rats compared to the effect of acute saline treatment expressed during social encounters with unknown intruder conspecifics. Individual elements of the behavioural repertoire were grouped according to motivational category (see Table 1) and expressed as a percentage of the total number of behavioural elements scored for each individual animal. The mean and S.E.M. of the percentage values for 8 resident rats were then calculated for each category of behaviour. Compared to saline-treatment, venlafaxine induced a dose-related reduction in aggressive behaviour concomitant with increased flight escape behaviour. *Post hoc* analysis (Dunnett's test); a $P<0.01$, b $P<0.001$ cf saline control rats. Re-drawn from Mitchell and Fletcher (1993).

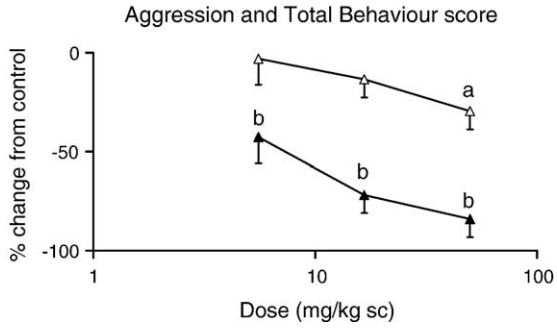

Fig. 2. Dose–response curves to acute treatment with venlafaxine on aggressive behaviour (closed triangles) and total behaviour score (open triangles) exhibited by resident rats during social encounters with unknown intruder conspecifics. Percentage change in aggression and total behaviour score calculated from the behavioural profile exhibited by resident rats treated with saline. *Post hoc* analysis (Dunnett's test); a $P<0.05$, b $P<0.001$ cf saline control rats. Re-drawn from Mitchell and Fletcher (1993).

total behaviour score (e.g. diazepam, haloperidol, phencyclidine, Table 2), indicative of motor impairment (i.e. sedation). It is therefore possible that an ability to selectively reduce aggressive behaviour following acute treatment may be related to a drug's antidepressant efficacy. This being so, then these data predict that amphetamine together with 5-HT_{1A} receptor agonists and partial agonists, e.g. 8-hydroxy-*n*,*n*-dipropyl aminotetralin (8-OH-DPAT) and gepirone, and the 5-HT_{2C} receptor agonist, e.g. *m*-chlorophenylpiperazine (*m*CPP), but not antagonists for these serotonin receptor subtypes (e.g. WAY-100635 and mesulergine, respectively) possess antidepressant activity. In addition, resident–intruder studies also suggest that the antidepressant efficacy of citalopram resides in the S(+)-enanatiomer (escitalopram, see Table 2) in agreement with other behavioural studies using the Chronic Mild Stress model (Mitchell and Hogg, 2001a; Sanchez et al., 2003). Some studies using the learned helplessness model of depression have suggested that antagonists of the octapeptide angiotensin II may possess antidepressant activity. In particular, it has been proposed that blockade of angiotensin AT_1 receptors by the selective antagonist losartan may have an antidepressant effect (Martin, 1994). Likewise, studies have shown that specific antagonists for subtypes of the cholecystokinin (CCK) receptor may possess antidepressant activity. For example, CCK_B receptor antagonists reduce immobility time in the murine forced swim test predictive of antidepressant activity (Hernando et al., 1994). In the resident–intruder paradigm, however, acute treatment with selective antagonists at angiotensin AT_1 receptors (losartan and ANA-756), angiotensin AT_2 receptors (PD-123177), CCK_A or CCK_B receptor antagonists (devazepide and L-365260, respectively) all failed to modify rodent agonistic behaviour at doses similar to those shown to induce antidepressant-like changes in behaviour in other models. The resident–intruder paradigm therefore predicts that these compounds will be devoid of antidepressant activity. However, such predictions are based on changes in rodent behaviour induced by acute drug treatment and should be treated with caution until the effect of chronic treatment with these compounds on rodent agonistic behaviour has been examined. Furthermore, a failure to respond appropriately to electroconvulsive shock would severely question the predictive validity of the model. Recent studies by our group (Mitchell et al., 2003) have shown that a single electroconvulsive shock markedly, and non-specifically, disrupts the behavioural profile of resident rats up to 4 h following treatment. It is therefore unlikely that changes in the behavioural profile of resident rats following acute psychotropic drug or single electroconvulsive shock treatment are directly related to their antidepressant activity. Indeed, such changes in rodent behaviour are most likely mechanistic and therefore reflect the acute pharmacological effects antidepressant drugs (but see Section 6).

Table 2
Effect of acute treatment with psychotropic drugs on aggression and total number of behaviours expressed by resident rats in the resident–intruder test

Drug class	Drug	ID_{50} values (mg/kg sc)	
		Aggression	Total behaviours
SSRIs	Citalopram[a]	1.28	>>1.0
	Escitalopram[b]	0.26	>>2.0
	R-(−)-citalopram[i]	>4.00	>4.00
	Fluoxetine[c]	0.90	>>3.1
	Paroxetine[a]	0.30	>>1.0
	Sertraline	1.91	>>10.0
SNRI	Venlafaxine[d]	6.89	>>49.9
	(±)-*O*-des-methyl venlafaxine (ODV)	12.74	>>30.0
	S(+)-ODV	8.39	>30.0
	R(−)-ODV	16.85	>>30.0
Tricyclic antidepressants	Clomipramine[c]	9.32	>>28.4
	Desipramine	1.21	>>7.98
MAO inhibitors	Phenelzine[c]	0.77	>>1.20
5-HT_{1A} receptor ligands	8-OH-DPAT[e]	0.027	>>0.03
	Gepirone[f]	1.72	3.39
	WAY-100635[e]	>>0.10	>>0.10
5-HT_{2C} receptor ligands	*m*CPP[g]	0.16	>0.90
	Mesulergine[g]	0.3 mg/kg = increased aggression	>>0.30
Atypical antidepressants	Iprindole[c]	1.59	>>2.6
	Mianserin[c]	0.31	>>0.8
Angiotensin II receptor antagonists	ANA-756 (AT_1)	>>10.0	>>10.0
	Losartan (AT_1)	>>10.0	>>10.0
	PD 123177 (AT_2)	>>10.0	>>10.0
CCK receptor antagonists	Devazepide (CCK_A)	>>1.0	>>1.0
	L-365260 (CCK_B)	>>1.0	>>1.0
Other psychotic compounds	Amphetamine[h]	0.1	>>1.0
	Diazepam[c]	2.49	>>2.6
	Haloperidol[c]	0.071	0.068
	Nisoxetine	6.65	>10.0
	Phencyclidine	0.61	1.0
	(±)-Pindolol	>20.0	>20.0
	S(−)-Pindolol	>>10.0	>>10.0

Values indicate the doses calculated to reduce aggressive behaviour and total behaviour score by 50% (ID_{50} doses, mg/kg sc). Where an ID_{50} value was not determined then the value indicates the highest dose tested. Antidepressant drugs invariably reduce aggression at doses lower than those required to reduce total behaviour score. Data on file unless otherwise indicated as follows; a Mitchell and Redfern (1997b), b, Mitchell and Hogg (2001a), c Mitchell and Redfern (1992a), d Mitchell and Fletcher (1993), e, Cobain et al. (1994b), f, Mitchell and Forster (1992), g Mitchell and Redfern (2000b), h Mitchell and Redfern (1997a), i, Mitchell et al. (2004).

The observed changes in resident rat behaviour following acute drug treatment are useful in two respects. First, such studies demonstrate that antidepressant drugs have a selective effect on rodent agonistic behaviour which is the primary criterion for identifying potential compounds of interest. Second, these studies allow behaviourally active doses of a compound to be identified which may then be used to examine the effects of chronic drug treatment on rodent behaviour.

2.1.2. Chronic treatment studies

In chronic treatment studies, drugs are invariably administered by sc-implanted osmotic minipump loaded with drug at a concentration calculated to administer the desired dose over 24 h for up to 14 days. In most cases the desired dose is defined as the minimal-effective dose determined in the acute treatment studies. Drug administration by osmotic minipump was chosen as the most appropriate mechanism of chronic drug delivery since this obviates the need for excessive handling of the resident rats and therefore reduces both handling-associated stress and the possibility of taming the subjects by repeated exposure to the experimenter which may modify the subject's behavioural profile during subsequent social encounters. Finally, delivering drugs over extended periods of time by this mechanism means that the amount of handling experienced by animals used in the acute treatment and chronic treatment resident–intruder paradigms are very similar, and results in very similar baseline behavioural profiles of the resident rats used in these two paradigms.

In contrast to the changes in rodent agonistic behaviour induced following acute treatment with antidepressant drugs, chronic treatment with these compounds increases aggressive behaviour concomitant with reduced flight behaviour. Fig. 3

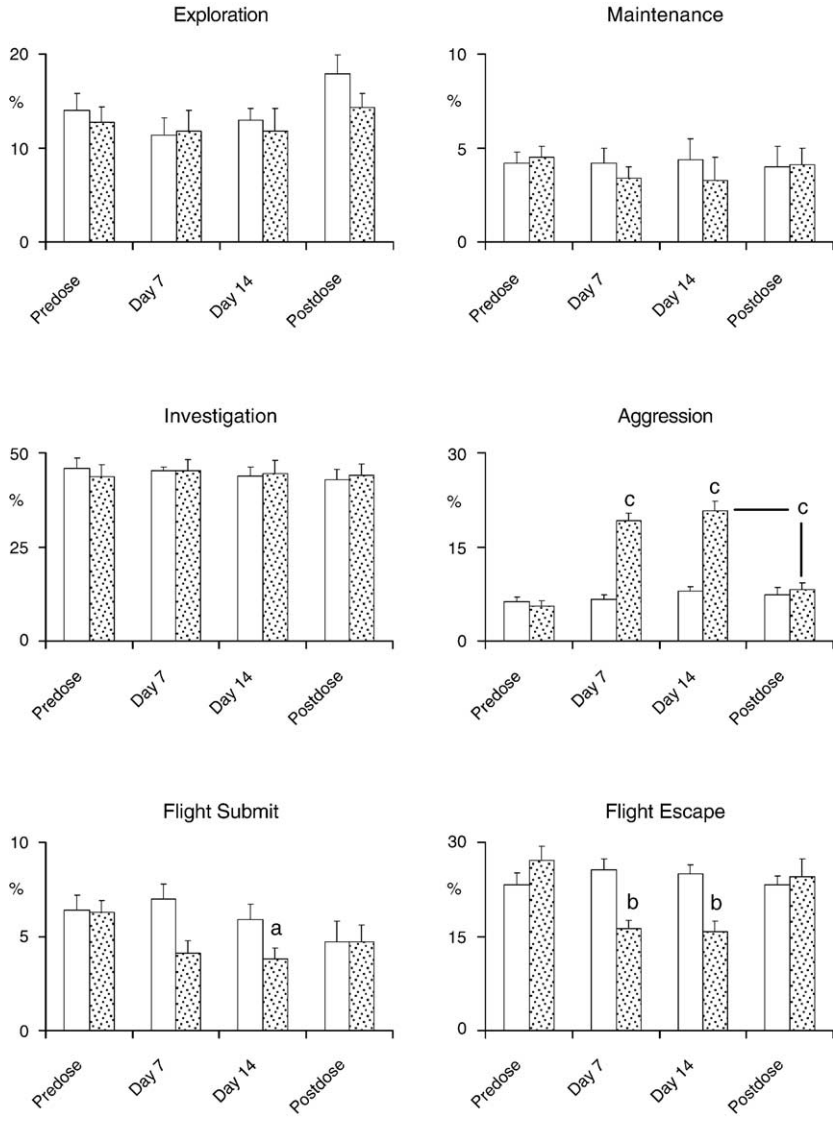

Fig. 3. Effect of chronic treatment via sc-implanted osmotic minipump with saline (open columns) or venlafaxine (5.54 mg/kg/day; stippled columns) on the behavioural profile of resident rats expressed during social encounters with unknown intruder conspecifics. Saline-treated resident rats exhibited no change in their behavioural profile throughout the study. In contrast, venlafaxine-treated resident rats exhibited increased aggressive behaviour, concomitant with reduced flight behaviour after 7 and 14 days of treatment. Following the cessation of treatment the behavioural profiles returned to predose levels. *Post hoc* analysis (1-way ANOVA); a $P<0.05$, b $P<0.01$, c $P<0.001$ c.f. predose level of behaviour except where indicated. Re-drawn from Mitchell and Fletcher (1993).

compares the behavioural profiles of two groups of resident rats during chronic treatment with saline and venlafaxine (5.54 mg/kg/day sc via osmotic minipump), respectively. Throughout the experiment saline-treated resident rats maintained a constant behaviour profile. However, compared to the respective baseline levels of each motivational category and also to the saline-treated resident rats at each time point, resident rats treated with venlafaxine exhibited increased aggressive behaviour concomitant with reduced flight submit and flight escape behaviour at both 7 and 14 days of treatment. No other significant changes in any category of behaviour were observed, including the total number of behavioural elements observed (data not shown). Chronic treatment with venlafaxine therefore induces diametrically opposite changes in the behavioural profile of resident rats compared to when this compared is administered acutely. Furthermore, an ability to increase the aggressive behaviour of resident rats is a common effect on behaviour observed during chronic treatment with antidepressant drugs regardless of the pharmacological action of these chemically disparate compounds (see Table 3) (Cobain et al., 1994a,b; Mitchell and Fletcher, 1993, 1994; Mitchell and Forster, 1992; Mitchell and Hogg, 2001a,b; Mitchell and Redfern, 1992a, 1997a,b, 2000b; Willner et al., 1981).

Interestingly, electroconvulsive shock (which disrupted behaviour for up to 4 h following a single shock) similarly increased aggressive behaviour when single shocks were administered every other day throughout the experiment (Mitchell et al., 2003). This observation supports the argument that an animal model predictive for antidepressant activity should show a positive response to repeated electroconvulsive shock (Willner and Mitchell, 2002). In contrast, amphetamine (which selectively reduced aggressive behaviour after a single dose predictive of antidepressant activity, see Table 2) failed to increase aggression during the period of chronic treatment. Indeed, amphetamine, 1.0 mg/kg/day, induced behavioural changes characteristic of social withdrawal; a phenomenon more closely associated with the negative symptomatology of psychosis.

Compounds which failed to modify the aggressive behaviour of resident rats following acute treatment similarly failed to modify behaviour during chronic treatment (e.g. the selective 5-HT_{1A} receptor antagonist WAY-100635). Overall, these observations are consistent with the view that aggression is the only type of social and agonistic behaviour exhibited by rats that is consistently increased following chronic treatment with antidepressants (File and Tucker, 1986). Interestingly, and in contrast to the rat studies, the aggressive behaviour of male mice

Table 3
Effect of chronic treatment with psychotropic drugs on rodent aggression and flight behaviour expressed by resident rats in the resident–intruder test

Drug class	Drug	Dose (mg/kg sc)	Aggressive behaviour	Flight behaviour	Onset (days)
SSRIs	Citalopram[a]	1.0	Increased	Decreased	4
	Escitalopram[b]	0.5	Increased	Decreased	1
	Fluoxetine[c,d]	0.34	Increased	Decreased	5
		1.02	Increased	Decreased	3
		3.09	Increased	Decreased	3
	Paroxetine[a,d]	0.33	Increased	Decreased	5
SNRI	Venlafaxine[d,e]	5.54	Increased	Decreased	2
Tricyclic antidepressants	Clomipramine[c]	3.15	Increased	Decreased	<7
	Desipramine	0.88	Increased	Decreased	<7
MAO inhibitors	Phenelzine[c]	0.14	Increased	Decreased	<7
5-HT_{1A} receptor ligands	8-OH-DPAT[f]	0.003	Increased	Decreased	<7
	Gepirone[f,g]	1.0	Increased	Decreased	<7
	WAY-100635[f]	0.1	No change	No change	
5-HT_{2C} receptor ligands	*m*CPP[h]	0.1	Increased	Decreased	<7
Atypical antidepressants	Iprindole[c]	0.85	Increased	Decreased	<7
	Mianserin[c]	0.08	Increased	Decreased	<7
Other psychotic compounds	Amphetamine[i]	0.11	No change	Increased	
		1.0	Decreased	Increased	
	R-(−)-citalopram[j]	2.0	No change	No change	
	Diazepam[c]	0.94	No change	No change	
	Haloperidol[c]	0.04	Decreased	Increased	
	Nisoxetine	3.3	No change	Decreased	
	Phencyclidine	0.1	No change	No change	
		1.0	Decreased	Increased	
	S(−)-Pindolol	3.3	No change	No change	
Non-drug treatment	Electroconvulsive shock[k]	1 shock on alternate days	Increased	Decreased	<7

Dose values indicate the daily doses administered to the resident rats, by osmotic mini pump, and were based on doses previously shown to modify rodent behaviour when given acutely (see text for details and Table 2). Antidepressant drugs invariably increase aggression during chronic administration by at least day 7 of treatment (indicated as <7 time for onset). Onset values indicate the minimum number of treatment days required to induce significantly elevated aggressive behaviour compared to vehicle-treated controls. Data on file unless otherwise indicated as follows; a Mitchell and Redfern (1997b), b Mitchell and Hogg (2001b), c Mitchell and Redfern (1992a), d Mitchell and Redfern (1997c), e Mitchell and Fletcher (1993), f Cobain et al. (1994a), g Mitchell and Forster (1992), h Mitchell and Redfern (2000b), i Mitchell and Redfern (1997a), j Mitchell et al. (2004), k Mitchell et al. (2003).

in resident–intruder studies is particularly sensitive to anxiolytic, rather than antidepressant, drug activity (e.g. (Lumley et al., 2000). The reason for this species difference in responses to antidepressant and anxiolytic drugs most likely resides in the functional differences in aggressive behaviour between rats and mice. Mice will violently defend their territory while rats live in social colonies where excessively violent behaviour is detrimental to the social group.

By programming daily dyadic encounters, the resident–intruder paradigm can also be used to compare the rate of onset of antidepressant-induced increases in aggression between antidepressant treatments (Table 3) and to assess the ability of potential adjuvant treatment to accelerate antidepressant-related changes in rodent behaviour. Fig. 4 compares the aggressive behaviour of three groups of rats during 7 days chronic treatment with saline, venlafaxine (5.54 mg/kg sc) and fluoxetine (0.34 mg/kg/day sc). While the aggressive behaviour expressed by saline-treated animals remains essentially constant throughout the duration of the experiment, both venlafaxine- and fluoxetine-treated resident rats exhibit increased aggression by days 2 and 5 of treatment, respectively. Interestingly, the doses of venlafaxine and fluoxetine used in this study were the minimal-effective doses on rodent behaviour when administered acutely, and both are slightly less than their respective ID_{50} values on rodent aggression (compare Tables 2 and 3).

Even though the doses used in this latter study are therefore near-equipotent the time-course data suggest that venlafaxine is able to increase rodent aggression more rapidly than fluoxetine. Further studies have shown that paroxetine (0.33 mg/kg/day sc), citalopram (1.0) and escitalopram (0.5) increase the aggressive behaviour of resident rats by days 5, 4 and 1, respectively (Table 3), indicating that different antidepressant drugs (at equi-potent doses when given acutely) have different rates of onset during chronic treatment. However, it is possible that the rate of onset is a function of dose. In a further time-course experiment, the rate of onset of three doses of fluoxetine (0.34, 1.02 and 3.09 mg/kg/day sc) was compared. The results of this study (see Mitchell and Redfern, 2005) show that while fluoxetine, 0.34 mg/kg/day, increased aggression by day 5 (consistent with the earlier study) the two higher doses of fluoxetine both increased aggression by day 3. These data clearly indicate that while a more rapid response to fluoxetine may be obtained by increasing the dose form 0.34 to 1.02 mg/kg/day, this effect cannot be further reduced to less than 3 days irrespective of dose.

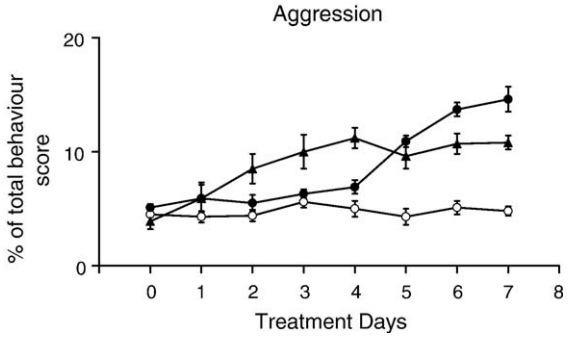

Fig. 4. Effect of chronic treatment via sc-implanted osmotic minipump with saline (open circles), venlafaxine (5.54 mg/kg/day/day; black triangles) or fluoxetine (0.34 mg/kg/day sc; black circles) on the aggressive behaviour of resident rats expressed during daily social encounters with unknown intruder conspecifics. Saline-treated resident rats exhibited no change in the level of aggression throughout the study (repeated measures ANOVA; $F(7,49)=0.84$, $P>0.05$). In contrast, venlafaxine- and fluoxetine-treated resident rats exhibited increased aggressive behaviour [$Fs(7,49)\geq 9.25$, $P<0.001$ in both cases] from days 2 and 5 of treatment, respectively. Re-drawn from Mitchell and Redfern (1997c).

2.2. Social hierarchy paradigm

Observations of the social behaviour of grouped rats throughout their light–dark cycle indicate that intense levels of social and agonistic behaviour, involving all group members to an equal extent, routinely occur at the onset of the dark phase and appear to indicate a fixed pattern of behaviour that enable the re-establishment of the hierarchical structure. Such behaviour precedes any grooming or consummatory behaviour and may be analyzed using ethological techniques. In these studies (Mitchell and Redfern, 1992b) male Wistar rats were housed in triads (i.e. $n=3$). Each social interaction between the grouped rats during the initial 30 min of the dark-phase was carefully monitored and the 'winner' and 'loser' of each social interaction recorded. The 'loser' was identified as the rat which adopted the final posture(s) of either the Flight Submit or Flight Escape behavioural pathways (i.e. *Submit* posture, or *Flag and Evade* or *Retreat*, respectively; see Table 1) in response to the aggressive posturing of a cage partner (which was therefore identified as the 'winner'). In some instances the social interaction was terminated by the loser exhibiting FLIGHT ESCAPE behaviour prior to any *Approach* by a more dominant cage partner. In these situations the result of the social encounter was recorded provided the winner and loser could be clearly identified. Interactions where no winner or loser could be unequivocally identified were ignored. The relative success level attained by each group member during social encounters was then calculated by expressing the total number of wins as a percentage of the total number of encounters in which that animal was involved. The highest success value indicates the dominant animal, the next highest the subdominant animal, and the lowest success value indicates the subordinate.

Early studies showed that administration of either clomipramine or mianserin for two weeks (at the same doses which increased the aggressive behaviour of resident rats in the resident–intruder paradigm; see Table 3) to the subdominant animal resulted in an increase in that subject's rank position at the expense of the level of dominance enjoyed by the dominant group member (Mitchell and Redfern, 1992b). The increase in the social position of the antidepressant-treated subdominant rat is likely to be related to increased assertiveness expressed during social encounters. An attractive feature of this model is that daily assessment of social structure allows the time-course of antidepressant-induced elevation of social position to be determined. Recent studies have demonstrated that while subdominant rats chronically treated with saline (via osmotic minipump) maintain their level of success during social

encounters with cage partners indicating constancy of social position, subdominant rats treated with clomipramine or venlafaxine, at doses which increase aggressive behaviour in the resident-intruder paradigm (see Table 3), exhibited increased social position from days 5 and 2, respectively (Mitchell and Redfern, 2005) at the expense of the level of dominance enjoyed by the dominant rats. Interestingly, venlafaxine-treated subdominant rats achieved full dominance over their cage partners while clomipramine-treated subdominant rats achieved parity of social position with their previously dominant cage partners. Following the cessation of venlafaxine or clomipramine treatment the treated rats reverted back towards their original subdominant level.

Importantly, the time course of the response to venlafaxine in these experiments corresponds closely to that in the resident–intruder paradigm. It can therefore be suggested that whatever adaptive changes in neurotransmitter receptor-mediated function that underpin the antidepressant-induced increases in assertive behaviour observed in the resident–intruder paradigm are also responsible for the ability of antidepressant drugs to increase the social position of subdominant rats in the social hierarchy test.

3. Acceleration of antidepressant-induced increases in rodent aggression

The delay in onset of antidepressant-induced changes in the behaviour of resident rats suggests that adaptive changes in neurotransmitter function are responsible for the behavioural changes induced by chronic antidepressant treatment, including repeated electroconvulsive shock. The different rates of onset observed for different antidepressant drugs suggest that these adaptive mechanisms may be invoked at different rates (Table 3). It is generally accepted that while the delayed onset of clinical efficacy with tricyclic antidepressant, SSRI and SNRI antidepressant drugs is difficult to equate with the acute pharmacological effects of these compounds, the inhibition of 5-HT and/or norepinephrine reuptake must play an important role in initiating such adaptive mechanisms. Evidence suggests that somatodendritic 5-HT_{1A} receptors located on the cell body of serotonergic neurons in the midbrain raphé nuclei have an inhibitory influence over the activity of central serotonergic neurons. Acute inhibition of 5-HT reuptake results in a local increase in extracellular 5-HT that activates the somatodendritic 5-HT_{1A} autoreceptors, in turn reducing the firing rate of midbrain raphé neurons (e.g. see Gartside et al., 1995). In consequence, acute treatment with antidepressant drugs may produce only transient increases in 5-HT levels in terminal fields. Elevated 5-HT levels in terminal regions necessary to invoke adaptive changes in central neurotransmitter receptor-mediated function that lead to antidepressant activity may depend on recovery of the normal firing rate of central serotonergic neurons once the somatodendritic 5-HT_{1A} autoreceptors in the midbrain raphé nuclei down regulate. Following this line of argument it would be predicted that elevated 5-HT levels in terminal regions may be achieved more rapidly during the course of treatment by the combination of an SSRI with a 5-HT_{1A} receptor antagonist (Artigas, 1993; Blier and De Montigny, 1994). To test this thesis a number of studies using the resident–intruder model were performed examining acute and chronic treatment with fluoxetine given alone and in combination with the selective 5-HT_{1A} receptor antagonist, WAY-100635. In these studies acute pretreatment with WAY-100635, 0.1 mg/kg sc, significantly potentiated the reduction in aggression induced by acute treatment with fluoxetine, 0.34 mg/kg sc (Mitchell and Redfern, 1997c). Furthermore, in chronic treatment studies, resident rats treated with fluoxetine (0.34 mg/kg/day sc by osmotic minipump) alone exhibited increased aggression from day 5, while co-administration of fluoxetine with WAY-100635 (0.1 mg/kg/day) significantly increased the aggression exhibited by resident rats by day 2 (Mitchell and Redfern, 1997c). As far as we are aware these were the first published studies to demonstrate the 'proof of concept' of the ability of a selective 5-HT_{1A} receptor antagonist (WAY-100635) to accelerate time-dependent changes in a behavioural model induced by an antidepressant drug (Mitchell and Redfern, 1997c). Results from another recent study demonstrated that the antidepressant-like effects of acute and chronic treatment with escitalopram (the active moiety of citalopram) are severely hindered by *R*(−)-citalopram, both in terms of response magnitude and, in chronic treatment studies, rate of onset (Mitchell et al., 2004). Thus, in addition to its ability to profile the preclinical antidepressant-like efficacy of psychotropic drugs *per se* (with respect to both drug dosage and rate of onset of appropriate changes in behaviour), the resident–intruder paradigm also has the ability to identify the potential utility of adjuvant treatment to existing antidepressant therapies with respect to accelerating drug-induced changes in agonistic behaviour.

4. Mechanism of action of antidepressant-induced increases in rodent aggression

Acute pharmacological challenge tests are useful to determine whether changes in neurotransmitter receptor-mediated function are associated with chronic antidepressant (including electroconvulsive shock) treatment. In these studies specific behaviours are induced in rats by acute treatment with selective ligands for a neurotransmitter receptor subtype. Comparison of the behavioural responses between control- and antidepressant-treated groups of subjects can then be used in an attempt to reveal differences from the expected behavioural response that may reflect changes in the function of the neurotransmitter receptor-mediated system under investigation. Such studies, however, are only of value if appropriate and valid chronic treatment schedules are used. A number of pharmacological challenge tests have been performed during chronic drug treatment schedules at various times appropriate to the onset of behavioural markers specific for antidepressant activity as identified by the resident–intruder paradigm (i.e. increased aggressive behaviour). In these studies (Mitchell and Redfern, 2000a) activity at 5-HT_{2C} receptors was measured in terms of hypolocomotion induced by acute challenge with *m*CPP. Chronic treatment with venlafaxine (5.54 mg/kg/day sc by

osmotic minipump) reduced *m*CPP-induced hypolocomotion after 2 days. In contrast treatment with fluoxetine and paroxetine (0.34 and 0.33 mg/kg/day sc, respectively, by osmotic minipump) did not produce a significant reduction in *m*CPP-induced hypolocomotion until day 9 (see Table 4). In contrast, all three antidepressant drugs failed to modify 5-HT_{2A} receptor-mediated head shake behaviour induced by 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) by day 7 of treatment. Furthermore, venlafaxine potentiated the 5-HT_{1A} receptor-mediated hypothermia induced by acute challenge with 8-OH-DPAT from day 5 of treatment. Thus chronic treatment with venlafaxine, administered at a daily dose which induces behavioural changes indicative of antidepressant activity, evokes a sequence of adaptive changes in the functional sensitivity of two of the three serotonin receptor subtypes examined. Of these, reduced sensitivity of 5-HT_{2C} receptors, as measured by *m*CPP-induced hypolocomotion, most closely follows the development of venlafaxine-induced increases in aggressive behaviour (see Fig. 5).

The same studies (Mitchell and Redfern, 2000a) also showed that repeated electroconvulsive shock, administered on alternate days, nearly abolished 5-HT_{2C} receptor-mediated function from day 3 (24 h following a second shock), while, interestingly, 5-HT_{2A} receptor-mediated function was unaffected until 24 h after a fourth shock (day 7) whereupon an increase in head shake response to DOI was observed. The similarity of the temporal sequence of adaptive changes in 5-HT_{2A} and 5-HT_{2C} receptor-mediated function induced by repeated electroconvulsive shock and chronic venlafaxine treatment clearly suggest that reduced 5-HT_{2C} receptor-mediated function is a prime candidate as a possible adaptive mechanism that underpins the increase in assertive behaviour induced by chronic antidepressant treatment. Such an explanation would also explain the increased aggressive behaviour observed following acute treatment with the 5-HT_{2C} receptor antagonist, mesulergine (see Table 2).

Table 4
Temporal relationship between antidepressant-induced increase in rodent aggression and changes in 5-HT receptor-mediated function

	Change in aggression[a]	5-HT_{1A} (8-OH-DPAT)[b]	5-HT_{2A} (DOI)[b]	5-HT_{2C} (*m*CPP)[b]
Electroconvulsive shock[c]	Increase established by Day 7	No effect Day 7	No effect Day 5 Increased on Day 7	No effect Day 1 Reduced on Day 3
Venlafaxine	Increased from Day 2	Increased on Day 5	No effect Day 7	Reduced on Day 2
Fluoxetine	Increased from Day 5	No effect Day 5 No effect Day 7	No effect Day 7	Reduced on Day 9
Paroxetine	Increased from Day 5	No effect Day 5 No effect Day 7	No effect Day 7	No effect Day 2 Reduced on Day 9

This table compares the time for onset of antidepressant-induced increased rodent aggression (resident–intruder test) against changes observed in the behavioural or physiological responses to stimulation of 5-HT receptor subtypes. 5-HT_{1A} receptor function was assessed by monitoring 8-OH-DPAT-induced hypothermia, 5-HT_{2A} receptor function was assessed by measuring DOI-induced head shake behaviour, and 5-HT_{2C} receptor function was assessed by measuring *m*CPP-induced hypolocomotion (see text for further details). The time course for antidepressant-induced increased aggression most closely follows the reduction in 5-HT_{2C} receptor-mediated function. References cited; a, drug aggression data from Mitchell and Redfern (1997c); b, 5-HT receptor function data from Mitchell and Redfern (2000a); c, electroconvulsive shock data from Mitchell et al. (2003).

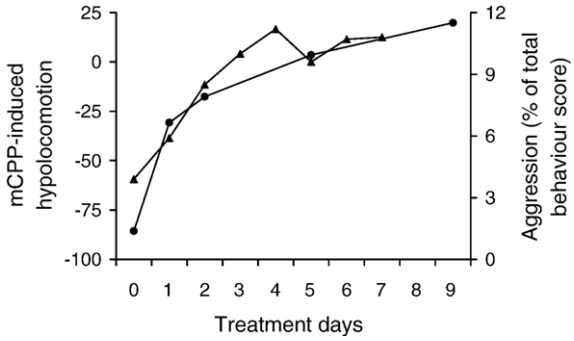

Fig. 5. Comparison between the time-courses of venlafaxine-induced increased aggression and reduced 5-HT_{2C} receptor-mediated function. Left *y*-axis indicates percentage reduction in locomotor activity induced by acute challenge of venlafaxine-treated rats with *m*CPP (2.5 mg/kg sc). Right *y*-axis indicates aggressive behaviour exhibited by resident rats (expressed as a percentage of total behavioural elements observed). Venlafaxine, 5.54 mg/kg/day sc administered by osmotic minipump. *m*CPP data re-drawn from Mitchell and Redfern (2000a). Aggression data re-drawn from Mitchell and Redfern (1997c).

5. Relationship between antidepressant-induced changes in rodent and human behaviour

The diagnosis of depressive illness relies almost exclusively on both observation of behaviour and interpersonal relations, and on reported feelings and beliefs of the patient. Consequently, modeling depressive illness is inherently difficult if not impossible (see Willner and Mitchell, 2002). Even commonly used animal models of proven utility can rarely claim more than face and/or predictive validity. Clinical experience has shown that only rarely do antidepressants induce clinical improvement within the first two weeks of treatment. Assuming that the time lag for clinical efficacy is a real phenomenon, there is certainly some debate about whether this relates to the underlying disease state or to the mechanism(s) of action of currently available treatments. Traditionally, however, it has been a major consideration in the design of antidepressant drug screening tests that they respond to acute or subacute drug administration. A direct consequence of this approach is that such tests are incapable, by virtue of their design, of responding to the major current challenge of discovering new antidepressants that have a shorter onset of action. In contrast, animal models sensitive to chronic antidepressant treatment (including electroconvulsive shock) do have the capacity to detect a rapidly acting novel antidepressant treatment. Most pharmaceutical companies now accept this view and have abandoned the high-throughput random screening approach in favour of the development of a small number of compounds specifically designed to meet predetermined pharmacological criteria. Consequently,

behavioural screening methods now have their rightful place within the development phase of drug discovery.

The focus of this review has been to describe the effect of antidepressant drugs on the non-social, social and agonistic behaviour rats in two ethologically relevant animal models of antidepressant activity; the resident–intruder and social hierarchy paradigms. The resident–intruder paradigm coupled with ethological analysis of the resulting non-social, social and agonistic behaviour quite clearly shows that antidepressant drugs have very specific effects on rodent behaviour that are dependant on the duration of drug treatment. Thus, while acute treatment with antidepressant drugs selectively reduces aggressive behaviour, chronic treatment increases aggression. In both cases such changes in aggressive behaviour are associated with reciprocal changes in flight behaviour. The ability of chronic antidepressant treatment to increase aggression in rats, as observed in the resident–intruder paradigm, is a measure of increased assertiveness in this species. This may reflect the increased assertiveness and associated externalization of emotions expressed during recovery from depressive illness in the clinic. Such increased assertive/aggressive behaviour is consistent with the effects of such treatment in the social hierarchy model. However, it must be acknowledged that the face validity of both the resident–intruder and social hierarchy models is slightly reduced by the fact that these tests use normal animals, whereas non-depressed people do not respond to antidepressant treatment.

Of particular interest is the time course of response to chronic antidepressant treatment in both models. The importance of this feature should not be underestimated since only when a model shows a gradual response that reflects a drug's gradual onset of action is it possible to detect a more rapid onset. In this respect the resident–intruder and social hierarchy paradigms can legitimately claim improved face and predictive validity, since the increase in aggressive behaviour during chronic treatment observed in these models can be seen as reflecting the increased assertiveness and drive in patients when the symptoms of endogenous depression begin to lift. Equally important is the observation that these behavioural effects are seen at clinically relevant doses that do not produce other, potentially confounding effects on behaviour. It is not, however, possible to claim construct validity for these models because at the molecular and neurochemical level the underlying causes of depressive illness remain unknown.

The fact that chronic antidepressant treatment increases aggressive behaviour appears at first sight to be incompatible with the use of SSRIs in the clinical treatment of impulsive aggression (Coccaro and Kavoussi, 1997; Evenden, 1999; Fava and Rosenbaum, 1993). This apparent paradox is most likely clinical, rather than an experimental, since antidepressants both increase aggression in submissive depressed individuals (manifest as a reversal of intropunitive aggression and/or impaired sociability: see Dixon et al., 1989; Kaplan et al., 1961; Priest et al., 1980) and decrease pathological aggression (e.g. Hollander, 1999; Vartiainen et al., 1995). A resolution of this paradox is that antidepressant treatment increases assertiveness, thereby increasing low levels of social dominance while at the same time decreasing high levels of physical aggression. The clinical requirement for chronic treatment regimes has produced a large literature describing the effects of chronic antidepressant treatment in normal animals and reporting numerous changes in pre- and/or post-synaptic receptor function in a variety of neurotransmitter systems. These studies are pivotal in establishing mechanisms of antidepressant action. However, it is important to recognize that the specific mechanisms that underpin antidepressant efficacy may only be elucidated by using treatment schedules determined in animal models that induce behavioural markers specifically related to antidepressant action. Indeed, the inability to identify which of the many effects of antidepressants described in the literature are responsible for their therapeutic action is a fundamental limitation of this approach, and most likely reflects experimental naivety and the use of inappropriate treatment schedules borne from inadequate scientific rigour. The development of animal models sensitive to chronic antidepressant drug treatment, in which a change of state is induced and maintained for a prolonged period of time, provides a powerful model for investigating these issues. It may be, therefore, that examination of neurochemical changes accompanying the measured behavioural changes observed in the resident–intruder paradigm will, by extrapolation, throw some light on the underlying causes of clinical depression. The evidence from pharmacological-challenge studies accumulated thus far clearly indicates that a reduction in 5-HT_{2C} receptor-mediated function may be a key adaptive change in the serotonergic system associated with antidepressant efficacy. Whether this directly initiates antidepressant activity or occurs in response to other, as yet unidentified, changes remains to be seen.

5.1. Suicide and antidepressant drugs

Unipolar depressive illness affects about 2.63% of the British adult population at any one time (Singleton et al., 2001). The characteristics of this debilitating psychiatric illness include depressed mood, hopelessness, helplessness, guilt, sadness, low self-esteem, self-harm and suicide (APA, 1994). Current data indicate that up to 15% of patients suffering from depressive illness eventually commit suicide (Davies et al., 2001). The National Institute for Clinical Excellence (NICE) guidelines recommend treating moderate to severe depression with antidepressant drugs (NICE, 2004). Over the last few years, however, the SSRIs have attracted a number of adverse claims relating to increased suicide ideation, homicidal behaviour, drug dependence and even addiction (Healy, 2000, 2002, 2003; Healy et al., 1999; Medawar, 1997). This has led to confusion in the public domain in the United Kingdom, fuelled by media hype, since suicidal ideation, suicide attempts, successful or otherwise, and self-harm are precisely the extreme symptoms of depressive illness that these drugs are supposed to reduce. Evidence from recent review studies, however, has not established a clear relationship between SSRIs and suicide. For example, Fergusson et al. (2005) concluded that patients treated with SSRIs showed a two-fold increase in the odds ratio of fatal and non-fatal suicide attempts compared to placebo or other

non-tricyclic antidepressant therapies. Importantly, however, no increase in risk of fatal suicide was identified between SSRIs and placebo, nor in the overall suicide rate for patients treated with SSRIs or tricyclic antidepressants. In comparison, Gunnell et al. (2005) found that SSRIs marginally increased the risk of self-harm, but not for completed suicide, compared to placebo. Finally, a review by Martinez et al. (2005) concluded that patients treated with SSRIs were not at increased risk of suicide or self-harm compared to patients treated with tricyclic antidepressants. However, evidence from children and adolescents (aged 18 or less) treated with SSRIs suggested a slightly higher risk of self-harm. It is important to note that any increased risk of suicide attempts, suicide ideation or self-harm associated with antidepressant drugs is generally observed during the early phase of treatment (Cipriani et al., 2005). If there is a relationship between SSRIs and suicide then this is neither unexpected, nor is it limited to the SSRIs, but most likely includes all antidepressant drugs and electroconvulsive therapy (Nutt, 2003), particularly those drugs that inhibit monoamine reuptake. The ability of tricyclic antidepressants, SSRIs, and most likely SNRIs also, to cause agitation and activation (characterized by insomnia, anxiety, restlessness) (Cooper, 1988; Nutt, 2003) at the onset of treatment has long been recognized. It has been argued (Nutt, 2003) that if during the recovery from depressive illness the characteristic anergia (loss of energy) and retardation start to subside before other symptoms start to resolve then patients become 'energized'. The result is a dangerous period during initial treatment since these acute responses to antidepressant treatment are perceived by patients as a worsening of depression, thereby increasing the risk of suicide. The tricyclic antidepressants are extremely toxic in overdose and before the advent of the SSRIs and SNRIs the tricyclic antidepressants were often used as agents to complete suicide (Henry, 1997). In comparison, the SSRIs are safer in overdose (Markowitz, 2001) and thus other, more violent, methods of completing are now more likely to be used (Jick et al., 1995). Changes in methods used to attempt or complete suicide or perform acts of self-harm over the last 40 years or so therefore probably reflect changes in drug therapy.

An alternative explanation to the energizing theory for increased suicide ideation during treatment is clearly predicted from preclinical studies using the resident–intruder paradigm. Current data obtained from resident–intruder and social hierarchy studies indicate that chronic treatment with antidepressants (including electroconvulsive shock) increase the assertive behaviour of rodents. Such changes in behaviour most likely reflect the increased assertiveness and associated externalization of emotions (indicative of increased extrapunitive aggression) expressed during recovery from depressive illness. Thus, while hostility levels and intropunitiveness are high in depressive illness, recovery from a depressive episode is associated with progressively reduced self-criticism and feelings of guilt (Priest et al., 1980) that lead to increased physical and/or verbal interaction with the environmental and social events (Kaplan et al., 1961). The changes in human behaviour that occur during recovery from depression are therefore the consequence of a positive change in the balance between extrapunitive and intropunitive aggression (Priest et al., 1980). In contrast, acute treatment with antidepressant drugs selectively reduces rodent aggressive behaviour indicative of reduced assertiveness. If the ability of antidepressant drugs to increase rodent aggression, and hence assertiveness, during chronic treatment of rodents accurately reflects the increased assertiveness in depressed patients during recovery from depression, it follows that the reduction in rodent aggression/assertiveness observed immediately following acute antidepressant treatment equally predicts that antidepressant drugs should intensify depressive illness during the first few days or so of treatment prior to the later, delayed, stages of recovery.

So how may antidepressant-induced changes in the behaviour of rodents and depressed patients be explained in terms of drug-induced changes in serotonin function?

Microdialysis studies have shown that inhibition of 5-HT reuptake following acute treatment with SSRIs increases the level of extracellular 5-HT in sub-cortical areas of rodent brain (Dreshfield et al., 1996; Gartside et al., 1995; Hjorth, 1993, 1996; Invernizzi et al., 1992, 1996; Romero et al., 1996, but see Hjorth and Auerbach, 1996). Importantly, any SSRI-induced increase in extracellular 5-HT in terminal regions is generally transient compared to the more profound changes in dorsal raphé (Adell and Artigas, 1991; Gartside et al., 1995; Invernizzi et al., 1992). Electrophysiological studies have shown that acute systemic treatment with SSRIs reduces the firing rate of ascending serotonergic neurones emanating from both the dorsal and median raphé (Chaput et al., 1986; Gartside et al., 1995; Hajos et al., 1995) which may be reversed by treatment with selective 5-HT_{1A} receptor antagonists (Gartside et al., 1995; Hajos et al., 1995). These studies indicate that SSRIs block the serotonin reuptake carrier present in the cell bodies of ascending 5-HT neurones (Hrdina et al., 1990). The elevated levels of locally released 5-HT in the raphé nuclei then activate a 5-HT_{1A} receptor-mediated negative feedback mechanism which results in a reduction in the firing rate of serotonergic neurones and a consequent decrease in serotonin synthesis and release in the nerve terminal (Carlsson and Lindqvist, 1978; Fornal and Jacobs, 1988).

In contrast, long-term treatment with SSRIs is associated with a progressive recovery in serotonergic firing rate (Chaput et al., 1986), with concomitant desensitisation of somatodendritic 5-HT_{1A} autoreceptors, terminal 5-$HT_{1B/1D}$ autoreceptors (Blier et al., 1990) and the 5-HT reuptake process (Pineyro et al., 1994). The attenuation of the feedback inhibition of serotonergic firing eventually results in a sustained elevation of basal release of 5-HT in the terminal regions of serotonergic neurons (Bel and Artigas, 1993) leading to changes that may underpin the neurochemical mechanisms responsible for antidepressant action. Importantly, microdialysis studies suggest that acute treatment with drugs which possess antagonist activity at central 5-HT_{1A} receptors markedly potentiate the transient SSRI-induced elevation of extracellular 5-HT in terminal regions (Dreshfield et al., 1996; Fuller et al., 1996; Gartside et al., 1995; Hjorth, 1993; Invernizzi et al., 1992, 1996; Romero et al., 1996). Thus acute treatment with a combination of an SSRI and a 5-HT_{1A} receptor antagonist and chronic SSRI

treatment alone similarly increase basal 5-HT levels in terminal fields.

Functional studies described earlier indicate that chronic treatment with SSRI/SNRI (administered at doses which increase rodent aggression) reduces 5-HT_{2C} receptor-mediated neurotransmission earlier during treatment before any change in either 5-HT_{1A} or 5-HT_{2A} receptor-mediated neurotransmission (see Section 4). Indeed, venlafaxine-induced increased aggression and reduced 5-HT_{2C} receptor-mediated neurotransmission follow an almost identical time course (see Fig. 5) suggesting that reduced 5-HT_{2C} receptor-mediated neurotransmission is a prime candidate responsible for inducing this change in rodent agonistic behaviour. Furthermore, reduced 5-HT_{2C} receptor-mediated neurotransmission may also be achieved by acute treatment with a selective 5-HT_{2C} receptor antagonist; in the resident–intruder paradigm acute treatment with the 5-HT_{2C} receptor antagonist, mesulergine, increases the assertive behaviour of resident rats (Table 2) in a manner similar to chronic antidepressant treatment. If changes in 5-HT_{2C} receptor-mediated neurotransmission mediate the behavioural effects of chronic treatment with SSRIs and SNRIs, then it is highly probable that the same serotonin receptor subtype mediates the behavioural changes observed following acute treatment with these compounds. Thus, while the transient increase in 5-HT levels induced by acute treatment with tricyclic antidepressants, SSRIs and SNRIs most probably leads to increased 5-HT receptor stimulation in general, it is the increased 5-HT_{2C} receptor stimulation that mediates the reduction in rodent aggressive/assertive behaviour; indeed, acute treatment with the 5-HT_{2C} receptor agonist, *m*CPP, reduces the assertive behaviour of resident rats (Table 2) in a manner similar to acute antidepressant treatment, while chronic treatment with *m*CPP increases assertive behaviour (Table 3) similar to chronic treatment with antidepressant drugs.

Clearly, the preclinical evidence implicates the 5-HT_{2C} receptor in mediating the effects of acute and chronic antidepressant treatment on rodent aggressive/assertive behaviour. It is therefore possible that changes in the functional level of this subtype of the serotonin receptor mediate the clinical effects of antidepressant drugs. For example, in clinical studies acute challenge with *m*CPP may cause activation, panic and anxiety (Kahn et al., 1988; Klein et al., 1991) similar to that found during the initial treatment phase with SSRIs (Kahn and Wetzler, 1991), effects most probably due to increased stimulation of the 5-HT_{2C} receptor. Interestingly, there is a strong association between panic disorder and suicide attempts, while patients with pure panic disorder (i.e. without comorbidity with other psychiatric disorders) show similar suicide rates to patients with major depression (Johnson et al., 1990). Furthermore, depressed patients with comorbid anxiety generally have lower mood compared to depression alone, are more likely to have panic attacks and also have a higher risk of suicide (Fawcett, 1990; Tylee, 1999; Tylee et al., 1999; Wunderlich et al., 1998). Examples of both tricyclic antidepressants and SSRIs have shown efficacy in the treatment of anxiety disorders, including panic disorder (Fahy et al., 1992; Modigh et al., 1992; Nutt, 2000). During the initial phase of treatment with tricyclic antidepressants patients often experience 'jitteriness' with a worsening of their anxiety symptoms. As treatment continues into the chronic phase so the anxiety symptoms subside. The time-course of these behavioural changes during treatment of anxiety disorders with tricyclic antidepressants and SSRIs are remarkably similar to those changes seen in depressive illness, suggesting that similar mechanisms may be responsible. In agreement with this view and with the preclinical functional studies described above, neuroendocrine and hyperthermic responses to acute *m*CPP challenge in human volunteers are blunted during long-term paroxetine treatment (Quested et al., 1977), indicative of reduced 5-HT_{2C} receptor-mediated function as a consequence of chronic SSRI treatment.

5.2. A simple explanatory model

Inhibition of monoamine reuptake that occurs within minutes following acute treatment with tricyclic antidepressants, SSRIs or SNRIs evokes a transient increase in synaptic and extracellular levels of the monoamine neurotransmitters, 5-HT and for the tricyclic antidepressants and SNRIs, to a lesser extent, norepinephrine. The increased availability of 5-HT in terminal regions results in increased stimulation of postsynaptic 5-HT_{2C} receptors (among others) which, in the rat, leads to reduced aggression/assertiveness. In the clinic, the transient increase in serotonin levels at the start of antidepressant treatment similarly increases stimulation of serotonin receptors leading to increased 5-HT_{2C} receptor-mediated panic and 5-HT_{2A} receptor-mediated anxiety in susceptible patients. These effects are perceived by patients as 'restlessness', 'agitation', 'jitters' and an exacerbation of their symptomatology leading to increased suicide ideation, suicide attempts and self-harm. These effects are not always experienced with the older tricyclic antidepressants since they are effectively masked by the daytime sedation associated with acetylcholine-muscarinic and histamine receptor antagonism, while the non-sedative SSRIs and SNRIs are more likely to evoke active behaviours associated with self-harm and suicide.

The transient increase in serotonin levels in terminal regions gradually subsides over the following few hours because of activation of the somatodendritic 5-HT_{1A} receptor-mediated negative feedback mechanism reducing the firing rate of serotonin neurons with the subsequent reduction in serotonin release. Over the subsequent days/weeks of treatment, the sustained elevation of serotonin levels in the cell body region of serotonin neurons leads to down-regulation of somatodendritic 5-HT_{1A} receptors. This results in a gradual diminution in the effectiveness of the negative feedback mechanism, thereby allowing the firing rate of serotonin neurons to recover to a level that may even exceed the pretreatment baseline firing rate. This effect, together with continued inhibition of the serotonin reuptake system, results in maintained elevated levels of serotonin in terminal regions that eventually evoke adaptive changes in the functional level of monoamine receptors. In the resident–intruder model the antidepressant-induced increase in aggression/assertiveness is most likely

mediated by reduced function of the 5-HT_{2C} receptor. Further adaptive changes in the function of other serotonin receptor subtypes may occur later. The similarity between antidepressant-induced changes in rodent behaviour and during the recovery from depressive illness suggests that down-regulation of 5-HT_{2C} receptor function may also be involved in the successful treatment of depressive illness. This simple model is also in agreement with the Deakin and Graeff model of affective disorders (Deakin and Graeff, 1991; Graeff et al., 1996). Thus, reduced 5-HT_{2C} receptor-mediated function leads to reduced behaviours associated with panic and anxiety, while inreased 5-HT_{1A} receptor-mediated function increases coping strategies in the advent of aversive events.

6. Concluding remarks

The resident–intruder and social hierarchy paradigms provide two ethologically relevant animal models by which the effects of acute and chronic treatment with antidepressant drugs on rodent non-social, social and agonistic behaviour may be examined. In particular, the ability of chronic antidepressant treatment to increase rodent aggressive behaviour is indicative of increased assertive behaviour in this species and mirrors similar changes in behaviour observed during the recovery from depressive illness; such changes in rodent behaviour are therefore highly predictive of antidepressant efficacy. The ability of chronic antidepressant treatment to increase rodent aggressive/assertive behaviour is most likely associated with reduced 5-HT_{2C} receptor-mediated function. In contrast, acute antidepressant drug treatment selectively reduces rodent aggression/assertiveness. In earlier publications (e.g. Mitchell and Fletcher, 1993; Mitchell and Redfern, 1992a, 1997c) this change in behaviour has been argued to be also predictive of antidepressant efficacy; however current data suggests that this behavioural change may be more predictive of suicide ideation, suicide attempts and self-harm mediated, possibly, by increased stimulation of central 5-HT_{2C} receptors. The realization that activation of the somatodendritic 5-HT_{1A} receptor-mediated negative feedback mechanism may delay the onset of antidepressant action has led to the search for new antidepressant compounds that possess serotonin reuptake inhibitory properties combined with antagonist activity at central 5-HT_{1A} receptors. The resident–intruder paradigm predicts that while such compounds may indeed achieve a rapid onset of antidepressant action (see Mitchell and Redfern, 1997c), their ability to elevate 5-HT levels significantly and early during treatment suggests that patients are likely to exhibit increased risk of self-harm, suicide ideation and suicide attempts during this initial phase of treatment.

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