Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 84 (2006) 436–452
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Animal models of depression in drug discovery: A historical perspective

Robert McArthur [a,*], Franco Borsini [b,1]

[a] McArthur and Associates GmbH, Ramsteinerstrasse 28, CH-4052 Basel, Switzerland
[b] Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina km 30,400-00040 Pomezia (Roma), Italy

Received 24 January 2006; received in revised form 31 May 2006; accepted 6 June 2006
Available online 14 July 2006

Abstract

Over the course of the last 50 years many models of major depressive disorder have been developed on the basis of theoretical aspects of this disorder. These models and procedures have been crucial in the discovery and development of clinically-effective drugs. Notwithstanding, there is presently great concern about the discrepancy between positive outcomes of new candidate drugs in animal models and apparent lack of efficacy in humans i.e., the predictive validity of animal models. Some reasons for this concern lie in the over-reliance in the face value of behavioural models, design of clinical trials, placebo responses, genetic variations in response to drugs, species differences in bioavailability and toxicology, and not least, disinterest of pharmaceutical sponsors to continue developing certain drugs. Present model development is focusing on endophenotypic aspects of behaviours rather than trying to model whole syndromes. This essay traces the origins and theoretical bases of our animal models of depression or depressed-like behaviours in humans and indicates how they have evolved from behavioural assays used to measure the potency and efficacy of potential candidate drugs to tools by which endophenotypes of depression may be identified and verified pharmacologically. A cautionary note is included though to indicate that the true predictive validity of our models will not be fully assessed until we can determine the attrition rate of molecules discovered from new drug targets translating into clinically-effective drugs.

Keywords: Animal; Models; Depression; Review; Stress; Anhedonia; Clinical trial; Placebo; Pharmacogenomics; Endophenotypes; Validity; Translational research

1. Introduction

There is presently great concern about the relevance and predictive validity of animal models of behavioural disorders (e.g., Duyk, 2003; Enserink, 1999; Matthews et al., 2005; Winsky and Brady, 2005). According to the FDA's (www.fda.gov/oc/initiatives/criticalpath/whitepaper.html) white paper on innovation or stagnation and prospects for 21st century drug discovery and development (Food and Drug Administration (U.S.A.), 2004), for example, there is a discrepancy between positive outcomes of candidate drugs in animal models followed by apparent lack of efficacy in humans i.e., the predictive validity of animal models. In order to put this concern into perspective, the intention of this essay is (1) to examine the development of animal models of depression, as they pertain to drug discovery, (2) to indicate reasons why there is an apparent discordance between animal and human results, (3) to show how the concept of animal models of behavioural syndromes has evolved to a phenotypical approach, and (4) to discuss ways in which the pharmaceutical industry, regulatory bodies and academics are working closer together to bring dialogue and congruence to animal and human testing of candidate drugs. This essay is not intended to be a comprehensive review of behavioural animal models. We will not discuss in detail, for example, the strengths and weaknesses of individual models or procedures, nor discuss occurrences of false positives or false negatives in each of these models as such reviews have already been published (e.g., O'Neill and Moore, 2003; Porsolt et al., 1991; Rupniak, 2003). The reader interested in more focused practical and theoretical reviews of animal models is invited to refer to the following for information (Boulton et al., 1991; Geyer and Markou, 1995, 2000; Nestler et al., 2002; Porsolt et al., 1993; Willner, 1984, 1991a; see also other contributions to Willner's, 1991b book "Behavioural models in psychopharmacology: theoretical, industrial and clinical perspectives").

* Corresponding author. Tel.: +41 61 3130767; fax: +41 61 3130768.
E-mail addresses: robert.mcarthur@rmcaa.org (R. McArthur), franco.borsini@sigma-tau.it (F. Borsini).
[1] Tel.: +39 06 91393325; fax: +39 06 91393988.

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.06.005

2. Origins of animal models of major depressive disorder

Animals are used in CNS drug discovery in an attempt to (1) reproduce aspects of the behavioural disorder that can be studied, (2) to use as a test bed for discovering novel pharmaceuticals that may treat the disorder and (3) as procedures through which new molecular targets can be identified for subsequent drug discovery and development. For example, a major depression episode is defined clinically according to the Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR. American Psychiatric Association, 1994) as a disorder where the subject demonstrates prolonged depressed mood and/or loss of all interest and pleasure (younger or adolescent subjects may present with abnormal irritability) in nearly all activities. These symptoms must interfere with the person's life significantly; meaning that they are present most of the day, nearly every day, for at least 2 weeks. In addition, the subject should present at least four of the following symptoms during the same 2 week depressed period: appetite or weight disturbance; sleep disturbance; activity disturbances—either agitation or slowing down; abnormal fatigue or loss of energy; abnormal self-reproach or inappropriate guilt; abnormal poor concentration or indecisiveness; suicidal ideation or suicide. The subject, however, should not present a mood-incongruent psychosis, nor should these symptoms be due to physical illness, alcohol, medication, drugs of abuse, or to normal bereavement. Finally, the subject should not have had a previous manic, mixed, or a hypomanic episode. Recurrence is variable, but some 60% of patients may be expected to experience further episodes and progress to major depressive disorder (American Psychiatric Association, 1994).

Early attempts to model major depression sought to simulate the phenomenology described above (e.g., McKinney and Bunney, 1969). However, it must be kept in mind that DSM-IV TR provides *diagnostic criteria* based on changes in behaviour and by simply placing labels on the abnormal behaviours does not imply etiology (see discussions by Gottesman and Gould (2003) or Matthews et al. (2005) on this issue). One of the fundamental problems with modelling behavioural disorders has been the attempts to simulate changes in behaviour without really knowing the cause or causes of such abnormalities. Furthermore, it would be impossible to try and simulate all the changes in behaviour in an animal. Indeed, the initial and traditional pharmacological models of "depression" used in drug discovery were based loosely on behaviours resembling human depression but mostly on changes in behaviour induced by specific neurochemical manipulations.

It is a truism that clinically effective medicinals for behavioural disorders were discovered initially through serendipity. In the case of depression, the standard tricyclic antidepressant (TCA) imipramine (Tofranil®), which is a reuptake inhibitor of monoamines such as noradrenaline and serotonin, was initially proposed as a hypnotic tranquilizer to calm schizophrenic patients (c.f., Kuhn, 1999). Similarly, the prototypical monoamine oxidase inhibitor (MAOI) iproniazid (Marsilid®) or the diamino oxidase inhibitor isoniazid were initially anti-tubercular drugs (c.f., Kline, 1958; Lurie, 1999; for readers interested in the early discoveries of standard treatments of behavioural disorders and the history of psychopharmacology, the interviews conducted by Healy, 1996, 1999, 2000 are an excellent resource). In both cases, careful clinical observation indicated that (1) imipramine could improve mood in schizophrenics without being very effective on the positive symptoms of schizophrenia and (2) tubercular patients receiving isoniazid or iproniazid reported improved mood. These observations then led to more focused clinical trials that helped establish these compounds as clinical standards. Conversely, reserpine, which depletes these monoamines as well as dopamine, was reported to induce depression in humans who were taking this drug for the treatment of hypertension. These results, among others, helped to formulate the biogenic theory of depression (Schildkraut, 1965), which postulates that depression is associated with central monoaminergic dysfunction.

3. Neurochemical models of depression

The 1960s was a period during which neurochemical models of depression were being proposed and refined. The antagonism of the pharmacological effects of reserpine was the first model of abnormal monoaminergic function in depression where antidepressants were differentiated from other psychoactive drugs (Askew, 1963; Costa et al., 1960; Garattini et al., 1962; McGrath and Ketteler, 1963; Metys and Metysova, 1967). In addition to reserpine, other agents with different relative monoamine-depleting specificity such as tetrabenazine, Ro-4-1284, parachloramphetamine and 6-hydroxydopamine were also used (Colpaert et al., 1975; Pawlowski, 1988; Sulser et al., 1964; Von Voigtlander and Losey, 1976). Physiological effects of reserpine such as ptosis, hypomotility, diarrhoea, bradycardia and hypothermia are readily observed of which hypothermia is most readily antagonized by TCA and MAOI antidepressants (Askew, 1963; Bourin et al., 1983; Colpaert et al., 1975; Spencer, 1967).

In keeping with the theory that antidepressants could ameliorate monoaminergic dysfunction, some researchers investigated the interactions between reuptake inhibitors with other indirect or direct monoaminergic receptor agonists. For example, antidepressants were found to potentiate the stimulant effects of amphetamine on motor activity and body temperature (DeGraaf et al., 1985; Halliwell et al., 1964; Morpurgo and Theobald, 1965; Silvestrini, 1982; Valzelli et al., 1967b; Van Riezen, 1972). The syndrome of piloerection, hypermotility, irritability and aggression induced by the catecholamine precursor levodopa is potentiated by antidepressants (Everett, 1967; Silvestrini, 1982; Van Riezen, 1972).

The 1970s saw further refinements in neurochemical models of depression; in particular investigating the relative contribution of one monoamine system over another to depression. For example, it was observed that the dopaminergic receptor agonist apomorphine induces hypothermia stereotyped behaviours and vertical climbing in mice. Depending upon the dose of apomorphine, neuroleptics can be differentiated from some

antidepressants. Stereotyped behaviours and climbing, but not hypothermia induced by low (1.0 mg/kg) dose of apomorphine are blocked by neuroleptics. On the other hand, the hypothermia induced by high doses (16 mg/kg) of apomorphine, but not stereotyped behaviours and climbing are antagonized by tricyclic antidepressants as well as the atypical antidepressants nomifensine and viloxazine, but not by trazodone or monoamine oxidase inhibitors (Maj et al., 1974; Maj, 1980; Przegalinski et al., 1979; Puech et al., 1978, 1981).

Likewise, the role of the noradrenergic system in mediating antidepressant activity has been studied using compounds such as yohimbine and clonidine as pharmacological tools. Yohimbine is an α_2 adrenoceptor antagonist that enhances noradrenaline release. This compound increases heart rate and pressure in mice leading eventually to death. These effects are potentiated by a wide range of antidepressant drugs such as the TCAs, MAOIs and serotonin reuptake inhibitors (SSRI) (DeGraaf et al., 1985; Lapin, 1980; Malick, 1981; Quinton, 1963). On the other hand, the hypothermia induced by the noradrenaline α_2 receptor agonist clonidine can be antagonised by antidepressants (Von Voigtlander et al., 1978). Parachloroamphetamine has relative specificity for the serotonergic system. Von Voigtlander et al. (1978) as well as Pawlowski (1988) demonstrated that the serotonin depletion and hyperthermia induced by parachloramphetamine was reversed by antidepressants. Nagayama et al. (1980) proposed a model based upon the antagonism of 5-hydroxytryoptophan-induced behavioural depression. However, the clinically active antidepressant fluoxetine was found to potentiate these behaviours rather than ameliorate them (Shopsin et al., 1981).

Neurochemical models were also used to investigate receptors thought to be involved in the ethiopathology of depression and is thought to be a state marker of the disorder (c.f., Leonard, 2000). Changes in β-adrenergic receptor number and sensitivity, for example, have been associated with depression and suicide. It was found that chronic treatment with TCAs could reduce the number of β-adrenergic receptors (Banerjee et al., 1977; Clements-Jewery, 1978; Enna and Duman, 1983; Ferris and Beaman, 1983; Gandolfi et al., 1984; Kinnier et al., 1980; Peroutka and Snyder, 1980; Sarai et al., 1978; Schechter and Chance, 1979; Sellinger-Barnette et al., 1980). However, treatment with atypical antidepressants such as maprotiline, mianserine, zimelidine, nomifensine and buproprion, failed or gave equivocal results on this parameter (Clements-Jewery, 1978; Garcha et al., 1985; Hall et al., 1984; Mishra et al., 1980; Pandey et al., 1985; Sellinger-Barnette et al., 1980).

It was clear that such behavioural assays or "gut baths" would be very efficient in screening for improved enhancers of monoaminergic function, but were unlikely to discover new chemical entities with novel mechanisms of action. Thus, the 1960 and 70s was also a period that saw the development of non-mechanistic based models of depression, that is, models that were not dependent upon the induction of specific neurochemical alterations reversible by specific pharmacological manipulations. Consequently model development concentrated on the replication of some of the changes in behaviour thought to be core to the disorder. Stress and the physiological modifications induced by stress are thought to be a significant risk factor for to the development of depression (as well as other behavioural disorders e.g., de Kloet et al., 2005a,b; Hammen, 2005; Kessler, 1997; Nemeroff and Vale, 2005), and most of these models focused on the phenomenology of behavioural changes induced by stress due to social or environmental manipulations.

4. Ethological models of depression based on social stress (*separation, prolonged isolation, social hierarchy*)

The separation of infant monkeys from their mothers was one of the earliest models of the effects of social and environmental stress on depression. Infant monkeys react to this separation initially by protesting and finally with behaviours resembling despair (Hinde et al., 1966; Hrdina et al., 1979; Jensen and Tolman, 1962; Kaufman and Rosenblum, 1967; McKinney and Bunney, 1969; Seay et al., 1962). Similar effects are observed following maternal separation in other animal species (e.g., Panksepp et al., 1978). The maternal separation model has evolved considerably in the hands of investigators such as Meaney and his colleagues. Brief periods of separation of a pup from its dam can induce endocrine responses related to stress such as increased corticotrophin-releasing factor and decreased glucocorticoids in various brain areas (c.f., Francis et al., 1999). These changes, however, are not limited to depressed-like behaviours, but to other behavioural disturbances related to stress. In chicks, for example, it was reported that the protest phase of maternal separation was reduced by anxiolytics, while the despair phase was attenuated by antidepressants (Lehr, 1989). Furthermore, not only does an early-life experience such as separation affect the offspring, but can also have consequences on parent–child relationships and future generations (Meaney, 2001).

Prolonged social isolation was found to uncover muricidal activity in rats (Horovitz et al., 1965, 1966; Kostowski et al., 1984; Sofia, 1969a,b; Valzelli and Garattini, 1976; Valzelli et al., 1981) and aggression in mice (Sofia, 1969a; Valzelli et al., 1967a,b). While aggression, particularly towards mice, might not be considered a core abnormality in depression, nevertheless, forms of irritability and aggression in adolescents may be, and these behaviours can be reduced by antidepressants (DeGraaf et al., 1985; Horovitz et al., 1965, 1966; Simler et al., 1982; Sofia, 1969a,b; Valzelli et al., 1967a; Valzelli and Garattini, 1976; Vogel and Haubrich, 1973). Social isolation also induces hyperactivity in rats (Einon et al., 1975; Sahakian et al., 1975, 1977; Willner, 1981, 1984), which could be related to the disturbances in activity described in DSM-IV TR. This hyperactivity was found to be reduced by some antidepressants (Garzon et al., 1979; Garzon and Del Rio, 1981).

Stress can be induced not only by social isolation and separation, but also by competition within a social milieu. A model of depression based on social hierarchy and subordination was proposed by Malatynska and Kostowski (1984). Pair-housed rats are forced to eat within a limited time, which means that the dominant of the pair alone managed to eat a sufficient amount of food. Repeated treatment with an antidepressant

helps the submissive animal to become more assertive and compete longer for food. Mitchell and Redfern (1992) established triads of dominant, sub-dominant and submissive rats when they were housed 3 to a cage. Similarly to the results shown by Malatynska and Kostowski, antidepressants helped the submissive rats become more assertive. Subsequently, this model was adapted to mice (Malatynska et al., 2005) and primates. Fuchs (2005) describes his work with male tree shrews that are placed together and establish a dominant–subordinate relationship. The shrews are subsequently housed in visual and olfactory contact with each other. The subordinate tree shrew shows dramatic behavioural, physiological changes such as reduction in feeding and body weight, neglect of grooming and hypoactivity as well as neuroendocrine changes such as increases in cortisol levels or decrements in testosterone. These changes are antagonized by clomipramine and tianeptine (Czeh et al., 2001; Fuchs et al., 1996).

Another animal model of isolation and consequent social interaction is the resident–intruder paradigm, in which a rat is placed in the home cage (intruder) of one that has been isolated (resident). The number and type of social interactions between the resident and intruder rat are scored. Resident rats will typically show increased exploration of the intruder, aggression and flight from the intruder rat (c.f., Mitchell, 2005). Aggression is reduced by antidepressants such as TCAs, SSRIs and MAOIs as flights from the intruder rat are increased. On the other hand, chronic treatment with antidepressants will increase rather than decrease aggressive behaviour, which is sensitive to antidepressants. Aggression in the resident rat is also increased by repeated electroconvulsive shock (Mitchell et al., 2003).

The resident–intruder paradigm was used by Strekalova et al. (2004) to define aggressive, submissive and neutral mice on the basis of their social interactions. The submissive and aggressive mice were then subjected to various forms of stressors (exposure to a rat, restraint stress and tail suspension) until a decreased preference for a sucrose solution over water was established in the majority of mice. This reduction in response for palatable solutions is considered a measure of the anhedonia, or reduced capacity to derive pleasure in depressed humans, and is an important behavioural read out in present model development (see discussion below). At baseline all mice had a similar sucrose preference. Following the 4 week period of stress, all of the submissive mice were anhedonic as opposed to less than 40% of the aggressive ones. Anhedonia-like behaviour was also related to the latency to float and the duration of immobility in the forced swimming test (FST).

Another variant of the resident–intruder paradigm has been proposed in which rats are deliberately placed in the home cage of heavier, more aggressive rats. The intruder rat is consequently attacked and defeated (Koolhaas et al., 1990). The intruder rat can be returned to the aggressor's cage for repeated social defeats, or can either be put in lose proximity to the aggressor or even in the vacant home cage of the aggressor to reinforce this negative experience. There is a number of individual differences in degree of response to this treatment procedure, however, the causes of which have been identified as fighting back, or resisting defeat, housing conditions after the defeat. Interestingly, it appears that the effects of social defeat is magnified in previously aggressive rats that have subsequently been subjected to social defeat (c.f., Buwalda et al., 2005 for a thorough review of the paradigm and its consequences). The social defeat experience produces long-lasting behavioural, neurological and neuroendocrinological changes reminiscent of human major depressive disorder such as dexamethasone suppression (Buwalda et al., 1999), impaired 5-HT_{1A} functionality (Korte et al., 1995) and anhedonic-like behaviours (Von Frijtag et al., 2000). The reduced sucrose intake was reversed by imipramine (Von Frijtag et al., 2002), while Berton et al. (1999), demonstrated that fluoxetine reversed social defeat-induced hypophagia in Lewis rats. This paradigm is being used to examine the role of social stress on physiological indices of stress and subsequent behavioural disorders. For example, Bohus et al. (1993) indicated that social defeat can produce equivalent suppression of the humoral immune responses to sheep red blood cell antigen as electrical foot shock. Furthermore, mitogen-induced lymphocyte proliferation is facilitated by social defeat and can lead to an increased $T_{suppressor/cytotoxic}$ ratio. This works illustrates the use of animal models with high face and construct validity to explore putative endophenotypes of behavioural disorders (see discussion on modelling endophenotypes below).

5. Ethological models of depression, based on environmental stress (*learned helplessness, forced swimming test/tail suspension, chronic stress*)

The learned helplessness model was proposed and developed during the 1960–1970s. A presumed state of depression is induced in animals by exposing them to aversive stimuli like shock under circumstances in which they cannot control or predict the onset or duration these stimuli. This procedure results in long-lasting deficits in the motivation and ability to escape in subsequent trials where escape is possible, and show behavioural alterations such as vocalizations and passivity (Anisman et al., 1979; Overmier and Seligman, 1967; Seligman and Beagly, 1975; Seligman et al., 1975; Sherman et al., 1979, 1982); as well as alterations in sleep–wake patterns (Adrien et al., 1991). Pharmacological treatment with antidepressants such as imipramine reduces these behavioural changes (Besson et al., 1999; Leshner et al., 1979; Petty and Sherman, 1980; Sherman et al., 1982). This procedure has been refined by Henn and his colleagues (e.g., Vollmayr and Henn, 2001), who have described a genetic component to the procedure in that congenital learned helpless rats respond less for a sucrose solution, i.e., were anhedonic (Vollmayr et al., 2004).

The forced swimming test, also called behavioural despair or the Porsolt test was first proposed as a simpler variation of the learned helplessness test, and is probably the most widely used screening test of antidepressant potential of novel compounds (c.f., Cryan and Holmes, 2005; Hunter et al., 2000; Nestler et al., 2002). Animals are forced to swim in a confined space. They become immobile following a phase of extensive swimming and climbing (Porsolt et al., 1977a,b). Tricyclic and atypical antidepressants reduce the immobility time when the rat is

replaced in the water cylinder 24 h following the initial experience (Borsini et al., 1981; Cooper et al., 1980; DeGraaf et al., 1985; Martorana and Nitz, 1979; Porsolt et al., 1977a,b, 1978). A single test session without a pre swim session is usually carried out in mice. The FST test has a variant in the tail-suspension test (TST) in which mice are suspended by their tail and both the duration of immobility as well as the force of the movements is measured in this test (Stéru et al., 1985). Contrary to the FST (see below) SSRIs are active in this test (e.g., Perrault et al., 1992).

FST was originally validated by using the total immobility time (Borsini and Meli, 1988; Porsolt et al., 1977a). SSRIs are generally inactive and do not alter the total immobility time (Borsini, 1995). Subsequently, Lucki and his colleagues modified the observation parameters to include the frequency of immobility episodes as well as the type of activity such as swimming and climbing shown by the rat as it tries to escape from the cylinder. This refinement of the FST has helped to differentiate antidepressant drugs that work primarily through a noradrenergic mechanism of action or through serotonin (Detke et al., 1995). This procedure is also sensitive to the effects of acute or chronic administration of antidepressants (Detke et al., 1997), as well as detecting potential antidepressant activity of non-monoaminergic compounds (c.f., Cryan et al., 2005a; Slattery et al., 2005; Tezval et al., 2004).

Under circumstances other than natural disasters and war, humans are not normally exposed to brief but intense stress. Rather, people are more likely to be subjected to periods of stress that wax and wane during their lifetime. Some people are less resilient to these stresses, and can be vulnerable to mild but prolonged stress (Hammen, 2005; Kessler, 1997). A stress model of depression seeking to simulate this environmental condition was initially proposed and developed by Katz and his colleagues who subjected rats to various stressors, such as electrical shock, immersion in cold water, reversal of light/dark cycle, fast, isolation, tail pinch, being shaken, moved from cage to cage over a period of 3 weeks. Following this induction period the rats were exposed to high intensity light and sound that provoked a reduced hypermotility in the stressed animal when compared to non-stressed animals (c.f., Katz, 1981; Katz et al., 1981). Furthermore, chronically stressed animals reduced their intake of a palatable saccharine solution (Katz, 1982) suggesting that they were impaired in their capacity to derive pleasure from this solution, i.e., anhedonic (see further discussion of this concept below). Tricyclic and atypical antidepressants electroshock and some MAOIs attenuated stress-induced behavioural changes (Katz, 1981, 1982; Katz and Baldiraghi, 1982; Katz and Sibel, 1982). Variations to extreme stress procedures have been proposed. For example, rats have been forced to run in a running wheel. Those animals, which survived after being forced to run in a running wheel, exhibit low level of motility, which can be ameliorated by imipramine (Hatotani et al., 1982).

The chronic stress model was further developed by Willner and his colleagues (c.f., Willner, 1997) whereby rodents are subjected to similar but milder stressors to those used by Katz. Initially the behavioural read-out variable indicative of anhedonia in this chronic mild stress (CMS) model was sucrose or saccharine intake (Muscat et al., 1992; Papp et al., 1991). However, this has been considered by some to be too variable and other indices of anhedonia-like behaviour have been proposed (e.g., Anisman and Matheson, 2005; Barr and Phillips, 1998; Hagan and Hatcher, 1997; Moreau, 1997; Nestler et al., 2002). For example, existing behavioural differences in a supposedly homogeneous group of animals may contribute to the variability of a subsequent measure. As described above, Strekalova et al. (2004) first identified submissive and aggressive animals using the resident–intruder procedure and then showed how these behavioural characteristics could subsequently change hedonic responses in the CMS model. Subsequently, other dependent measures such as changes in feeding and body weight (e.g., Griebel et al., 2002), response rates for access to sweetened solutions (e.g., Vollmayr et al., 2004), or rates of electrical self-stimulation have been proposed (Moreau et al., 1992).

6. Olfactory bulbectomy

The ethological models and the conditions used to induce altered behaviours and the behaviours themselves described above have an intuitive similarity with conditions that are associated with human depressed behaviours, i.e., high face validity (see Table 1). The olfactory bulbectomy model of depression (Cairncross et al., 1978), on the other hand has little apparent face validity. It is difficult to understand exactly how lesions of the olfactory bulbs of rats could be related to

Table 1
Criteria of validity of animal models of behavioural disorders following definitions established by Geyer and Markou (1995)

Type of validity	Definition
Face	The phenomenological similarity between the behaviour exhibited by the animal model and the specific symptoms of the human condition. This is mainly an intuitive criterion of the "reasonableness" of the model, but is neither necessary nor sufficient to establish the model.
Etiological	This concept of etiological validity is closely related to the causes of the disorder in humans. When etiology can be established, the model becomes extremely useful. Unfortunately, the causes of behavioural disorders are seldom known. Therefore, this validity is limited to hypothesis regarding possible etiology.
Construct	Construct validity is closely related to the pathology and symptomatology of the disorder, and the accuracy with which changes in the model organism reflects that in the human. For example, close correspondence of changes in neurochemical or endocrinological parameters in depressed subjects and in the model systems used study depression endow the model with increasing construct validity.
Predictive	The ability to predict changes in the human subject based upon changes in the model. This requires constant reality checking with clinical measures to make sure that the changes in the model correspond to those in the human. In terms of drug development, the special condition of predictive validity is usually determined through pharmacological validation that refers to clinically effective drugs showing activity in the test or model (pharmacological isomorphism).

depression until one considers the importance of pheromone detection in the psychosocial milieu of the rodent (c.f., Leonard and Tuite, 1981; Shepherd, 2006), and the subsequent consequences of olfactory bulb ablation on the rodent limbic system and function of the amygdala. For example, bulbectomy results in dysregulation of the limbic–hypothalamic axis, increased sensitivity to stress, alterations in immune function, abnormal sleep patterns, agitation, weight loss and changes in hedonic behaviour; changes that are also seen in depressed patients (c.f., Kelly et al., 1997; Richardson, 1991; Song and Leonard, 2005). The most salient behavioural change following olfactory bulbectomy is increased exploration and hyperactivity in an open field arena that can be attenuated after repeated administration with antidepressants (Broekkamp et al., 1980; Cairncross et al., 1978; 1979; Noreika et al., 1981).

7. Operant response models

One of the core symptoms of major depressive episodes is the lack of pleasure which suggests an altered reward system. Consequently, a number of investigators exploited operant response procedures that are maintained by reinforcement as test beds for evaluating antidepressant potential of novel compounds. An animal can be trained to respond to a lever for a reward such as water, food or sweetened solutions. The simplest "schedule of reinforcement" is one where the animal is required to press the lever once for a reward. Other, more complex schedules are then imposed such as progressive ratio where after being trained on a certain number of single responses, the animal is then required to respond, twice, four times, etc. for the same reward. Progressive ratio schedules are used frequently in motivational studies (refer to handbooks such as Davey, 1987 for more thorough discussions of operant responding and schedules of reinforcement).

Suicide is a common feature of major depression and it can be considered an impulsive act. The differential low rate reinforcement (DRL) schedule of operant responding is a procedure by which impulsivity and inhibitory control can be tested, and is probably the best known operant procedure used to assess antidepressant potential of novel drugs (c.f., O'Donnell et al., 2005). In this procedure, rats are required to withhold a lever response until a pre-selected time interval since the last reinforcement has elapsed. This interval is usually around 72 s (DRL-72). If the rat responds before this interval has elapsed, the timer is re-set and no reward is given (McGuire and Seiden, 1980; O'Donnel and Seiden, 1982; Seiden et al., 1985). This schedule of reinforcement has been found to be sensitive to a wide range of antidepressant drugs including the TCAs, MAOIs, SSRIs and the more recently developed dopaminergic and noradrenergic reuptake inhibitors. Rats become more efficient at DRL responding following administration of these drugs by reducing their response rates and subsequently increasing the rate at which they are reinforced (O'Donnell et al., 2005).

8. Natural genetic models of depression

Major depressive episodes and other depressions have a strong genetic basis that interacts with the environment (c.f., Lesch, 2004; McGuffin and Katz, 1989; Sullivan et al., 2000). Certain rodent strains have been found to exhibit depression-like characteristics. Probably the best know natural genetic model of depression is the Flinders rat strain developed by Overstreet and his colleagues (Overstreet, 1993; Overstreet et al., 2005). This strain shows abnormal responses to stress, changes in REM sleep and circadian rhythms and changes in locomotor activity; particularly in the forced swim test. These abnormalities are responsive to TCAs as well as SSRIs. This strain is also reported to show decreased operant responding for water when it has to respond on a progressive ratio schedule (Russell et al., 1982). The Wistar Kyoto rats have also been suggested to have behavioural and endocrinological similarities to depressed humans (Solberg et al., 2001) and be responsive to antidepressant drugs (e.g., Lopez-Rubalcava and Lucki, 2000).

9. Other tests and models proposed

We have briefly discussed the major models and procedures that have been developed since the 1960s. However, others have been proposed, but either these have not been further developed, or they have been developed for other indications. For the sake of completeness we list these briefly below.

9.1. Electrical kindling

There is a long history relating convulsions with depression. Electroconvulsive shock was one of the first and most widely used treatments for depression before the discovery of imipramine or iproniazid (c.f., Brady, 1999), and is still in use today for intractable depression (c.f., Andrade and Kurinji, 2002). Electroshock can also reverse the behavioural effects in animal models such as learned helplessness (Sherman et al., 1982), FST (Porsolt et al., 1978), TST (Teste et al., 1990), CMS (Moreau et al., 1995), or the resident–intruder paradigm (Mitchell et al., 2003). Kindling is a model of seizures and complex partial seizures wherein daily low-intensity electrical brain stimulation will sensitize certain brain areas such as the amygdala to the point where seizures will be spontaneously elicited (c.f., Kupferberg, 2001). Investigators such as Babington and Wedeking (1973), Maj (1980) or Stach et al. (1980) were interested in studying whether antidepressants could interfere with this sensitization phenomenon. This test was found to be unselective for detecting antidepressant activity (Willner, 1984).

On the other hand, kindling and sensitization have been shown to be useful concepts to explain the recurrent and progressive nature of various affective disorders. Post (1992), for example, indicated how a first episode of an affective disorder is frequently related to a major psychosocial stressor, and not with subsequent episodes. It has been suggested that patients having undergone such a psychological trauma were rendered more vulnerable and predisposed to subsequent

episodes; this vulnerability being a consequence of changes in gene expression, structure and memory function. The "kindling" concept has been very influential in the past decade, although its basic tenets are now being questioned. Monroe and Harkness (2005), for example, indicated that it is still not clear whether more frequent minor stresses are capable precipitating recurrent episodes, or whether these can be precipitated independently by any less frequent major or minor stressful event. They suggest that more longitudinal clinical studies are necessary to determine whether affected individuals are rendered more sensitive and vulnerable by a major stressful life event or not. In practice, however, kindling has been shown to be a useful model for bipolar disorder; a condition that is being successfully treated with anticonvulsant drugs (De Leon, 2001; Ketter et al., 2003).

9.2. Chemical convulsants

Tricyclic antidepressants such as imipramine and amitriptyline have equivocal effects on electroshock or chemically-induced seizures. Some investigators such as Fink and Swinyard (1960) suggested that an anticonvulsant effect was characteristic of the chemical class. On the other hand, other investigators such as Barron et al. (1965) reported that imipramine potentiated rather than inhibited picrotoxin-induced convulsions. This potentiating effect of imipramine on picrotoxin-induced convulsions was confirmed by Cowan and Harry (1974). Furthermore, similar potentiating effects were observed with nialamide (MAOI), tranylcypromine (MAOI), desmethylimipramine and viloxazine (noradrenergic uptake inhibitor). These results prompted them to propose this test as a functional screen for antidepressants. Roszkowski et al. (1976), however, indicated that the effects of tricyclic antidepressants, at least, have a complex effect upon the type of convulsants and seizure. Thus, both imipramine and amitriptyline antagonize maximal tonic convulsions induced by electroshock or pentylenetetrazole with a potency equivalent to standard anticonvulsants such as phenobarbital, diazepam and hydantoin. However, imipramine and amitriptyline both potentiated minimal clonic seizures and death induced by pentylenetetrazole. Moreover, this effect is specific to the convulsants used; imipramine either did not change or lowered the incidence of maximal electroshock-induced clonic seizures or face-twitches.

9.3. Circadian rhythms and phase-shift

Altered sleep patterns and circadian rhythms play a major role in mood disorders and on antidepressant drugs (Adrien, 2002; Bunney and Bunney, 2000; Rusak, 2000; Wirz-Justice, 2003; but see Benca et al., 1992 for a discussion of specificity of changes in sleep parameters associated with mood disorders). For example, antidepressants increase the readjustment of motor activity after reversal of the light/dark cycle (Baltzer and Weiskrantz, 1973; Goodwin et al., 1982). A related model was later advanced, based on REM sleep in animals (Scherschlicht et al., 1982). However, no relation was apparent between the ability of antidepressants to suppress REM sleep and their clinical potency (Willner, 1984). Solberg and colleagues have combined the effects of CMS and exercise as a model of studying altered circadian rhythms and depression. Mice that are subjected to stress and allowed access to a running wheel show depressed-like behaviours including anhedonia and increased immobility in the FST. Exercise through the availability of a running wheel ameliorated the effects of CMS (Solberg et al., 1999).

10. Present directions: genetic approaches to modelling depressed-like behavioural endophenotypes

Up to the past decade, animal models concentrated on the induction of depressed-like behaviours such as helplessness, despair or anhedonia through procedures that are intuitively felt to induce depression in humans. On the whole, these models have had high face validity, and are felt to be "reasonable". Furthermore, these models have been shown to reproduce molecular, biochemical and physiological changes seen in depressed humans, thus endowing them with good construct validity (see Table 1 for definitions of validity in animal models and refer to Geyer and Markou, 1995, 2000 or Willner, 1984, 1991a; Willner and Mitchell, 2002 for comprehensive discussions of concepts of validity). The causes of behavioural disorders like depression are still very poorly understood and the etiological validity of the models is hypothetical. One of the reasons for our limited understanding of the causes of the depressions is that this is a complex disorder, which is difficult, if not impossible to model in its entirety, and consequently endophenotypic approaches are being pursued. An endophenotype is defined as a heritable characteristic of the illness that is present in affected individual and family members regardless of whether the disorder is active or not (Gottesman and Gould, 2003). Anhedonia is considered a candidate behavioural endophenotype of depression (Hasler et al., 2004), as well as other psychiatric disorders such as schizophrenia (c.f., Le Pen et al., 2002; Schurhoff et al., 2003).

The procedures developed previously to model depressed-like behaviours in animals have subsequently become very important tools in identifying and defining behavioural endophenotypes. FST and TST are not models of the complex behavioural disorder of depression per se, but rather procedures that are capable of producing changes in behaviour that may be exacerbated by conditions associated with depression, and are sensitive to treatments effective in ameliorating depression in the clinic. This behaviour of immobility bears some resemblance to, but is not identical to fatigue and loss of energy described in DSM-IV TR. These procedures in particular have being used to induce depressed-like behaviours in rodents for subsequent genetic analysis leading to new molecular targets (Crowley and Lucki, 2005; Cryan et al., 2005b). Similarly, the ability of learned helplessness (Vollmayr and Henn, 2001; Vollmayr et al., 2004) to characterise specific behavioural abnormalities such as anhedonia, reduced activity, passivity and impaired cognition, which are other putative endophenotypes of depression, suggests its use as a procedure useful in the

identification of candidate genes of this disorder (see discussion below, Crowley and Lucki, 2005). Other procedures such as olfactory bulbectomy and CMS and the natural genetic models described above are also being used to define behavioural endophenotypes (c.f., Cryan and Mombereau, 2004). For example, both the Flinders and Wistar Kyoto rats have been shown to have altered sleep patterns (Dugovic et al., 2000; Shiromani et al., 1988). The Wistar Kyoto rat also has impaired responses to alterations in light–dark cycle (Solberg et al., 2001). On the other hand, olfactory bulbectomy also alters sleep patterns (Sakurada et al., 1976). These changes indicate that these rats and procedure may be used to model the putative endophenotype of disturbed sleep in depression and other behavioural disorders (c.f., Benca et al., 1992; Boivin, 2000).

10.1. Genetic techniques and behavioural analyses

The advent of genetically modified mice in the past decade has radically altered the use of animal models of behavioural disorders. Random mutations are being induced by chemical mutagens such as *N*-ethyl-*N*-nitrosourea (ENU) in rodents to alter their genetic makeup (Brown and Nolan, 1998; Justice et al., 1999). The resulting general phenotypes are evaluated through behavioural testing batteries while specific behavioural phenotypes are subsequently confirmed using the very procedures developed as animal models of behavioural disorders including depression (e.g., Blanchard et al., 2003; Crawley, 1999; Hunter et al., 2000; Rogers et al., 1997). Identification of the *Clock* gene through ENU-induced mutations (Vitaterna et al., 1994), for example, has directed research into the influence of this gene on the etiology of depression (Bunney and Bunney, 2000; Desan et al., 2000).

Forward genetic techniques such as ENU make no a priori assumptions regarding the role of putative genes on behaviour as the effects of point mutations on behaviour are evaluated after random mutagenesis. On the other hand, reverse genetic techniques such as the use of transgenic mice are used specifically to evaluate the role of candidate genes on the behavioural changes induced or measured by animal models (Boutrel et al., 1999, 2002; Takahashi et al., 1994; Tarantino and Bucan, 2000). Indeed, each molecular target generates its own genetically mouse strain. Consequently, this past decade has seen an explosion in the use of genetically-modified mice not only to understand the molecular bases of behavioural disorders such as depression, but also in validating molecular drug targets (c.f., Tamminga et al., 2002). Recent examples of combining genetic, pharmacological and behavioural techniques to validate drug targets include $GABA_{B(1)}$ receptor antagonists (Cryan and Kaupmann, 2005; Mombereau et al., 2004), or corticotropin-releasing factor antagonists (Bale and Vale, 2003; Ducottet et al., 2003; Griebel et al., 2002; Keck et al., 2005; Overstreet and Griebel, 2004). While it is beyond the scope of this essay to review the use and utility of each of these strains for understanding depression and developing novel pharmaceuticals; the interested reader is directed to Cryan and Mombereau (2004) or Cryan and Holmes (2005) for recent and comprehensive reviews.

Another reverse genetic technique is the use of quantitative trait locus (QTL) analyses to identify candidate genes related to the risk of manifesting a behavioural disorder, and to help define patient populations responsive to one or another antidepressant treatment. Lucki and his colleagues, for example, have been employing the FST and the TST successfully in their analyses (Crowley and Lucki, 2005; Cryan et al., 2005a,b; Nestler et al., 2002; but see Roubertoux and Le Roy-Duflos, 2001 for a discussion regarding the limitations of QTL in behavioural disorders). Lucki and colleagues have recently published two very interesting reports of their work identifying (1) strain differences in mice responding to the SSRI citalopram (Crowley et al., 2005) and (2) the application of QTL to identify genes that could underlie this differential response (Crowley et al., 2006). One of the caveats of behavioural testing of mice; especially mutant mice, is the need to be aware of the background strains from which such mice have generated as differential responses to the same task are strain-dependent (e.g., Bai et al., 2001; Crawley et al., 1997; Crawley, 2000; Cryan and Holmes, 2005). For QTL mapping, however, these divergent responses are used to an advantage in order to provide the genetic variability that will later be used to correlate with phenotypic variability in the analysis (Crowley and Lucki, 2005).

In a recent clinical trial (Trivedi et al., 2006), close to 3000 depressed subjects were recruited for a 12-week trial with citalopram. At the end of this trial only 30% achieved full remission, and it took higher final doses of citalopram for a longer duration than what is normally given in clinical practice to achieve this. These results underline the importance of pharmacogenomic responses to given pharmacological treatment of behavioural disorders (Licinio and Wong, 2001; Serretti and Artioli, 2004a,b), and highlight the importance of using animal models to try and identify genes associated with these variable responses. Crowley et al. (2006) recent QTL analysis of the responses of mice in the TST to citalopram is therefore a very opportune and germane example how animal models of depression are moving beyond the "gut bath" approach to drug discovery.

10.2. Modelling endophenotypes: anhedonia

Intracranial electrical self-stimulation (ICSS) is a widely used technique to measure the effects of reward in rodents. This procedure was originally described by Olds and Milner in 1954. They noted that rats with electrodes chronically implanted in the septum will repeatedly press a lever for electrical stimulation. Further work by Hoebel and Teitelbaum (1962) indicated that electrical stimulation of the lateral hypothalamic area was related to the drive to feed, and that the rates of self-stimulation or feeding are inversely related i.e., feeding can reduces self-stimulation rates while hunger increases the rate. These early studies established the use of electrical and/or chemical methods by which insights into the limbic system of motivation and reward could be tapped (c.f., Miller, 1958), and have subsequently

become tools not only of normal behaviour, but also of behavioural disorders such as addiction and substance abuse (c. f., Koob et al., 1998; Markou and Koob, 1992).

Rates of electrical self-stimulation are a very sensitive readout for models of anhedonia-like behaviour in depression. However, by itself ICSS has variable sensitivity to antidepressants alone. Wauquier (1980), for example, reported that acute antidepressant treatment prolonged lever pressing for reward in a progressive ratio schedule in normal rats. Binks et al. (1979), on the other hand, observed that neither imipramine nor protriptyline modified the rates of ICSS in rats. Fibiger and Phillips (1981) indicated that 2 weeks desipramine treatment was needed to observe a significant shift in the rate current-intensity function of ICSS responding. Nevertheless, Hall et al. (1990) reported that acute administration of desipramine reduced ICSS reward using a rate–frequency method in rats implanted in the lateral hypothalamus. Chronic administration of desipramine, however, had no significant effect on ICSS reward. The authors suggest that differences in paradigms may account for this discrepancy and that the best use of ICSS is not in normal animals, but rather in animals that have been subjected to a manipulation inductive of a depressed-like state. For example, ICSS is reduced in animals after amphetamine withdrawal or lesions of internal capsule. Antidepressants ameliorate these reductions (Kokkinidis et al., 1980; Cornfeldt et al., 1982). These results, and others (e.g., Epping-Jordan et al., 1998), have prompted the proposal of psychostimulant withdrawal as a model of depressed-like behaviours (Barr et al., 2002).

The use of sucrose intake as a behavioural readout of anhedonia in the CMS test has already been discussed above. Moreau et al. (1992) examined the effects of inducing anhedonia-like behaviour through CMS by using rates of ICSS from electrodes implanted in the ventral tegmental area. CMS will increase the rates of ICSS throughout the stressful period and return to control levels once CMS is terminated. Concomitant administration of DMI prevents this increase in the rate of ICSS. However, Barr and Phillips (1998) demonstrated that while rats subjected to CMS reduced their intake of sucrose solution, their motivation to work for this solution was unchanged. The authors indicate that there is dissociation between the psychological constructs of wanting (motivation to respond) and liking (hedonic reaction to a reinforcing solution), which may have different neural substrates. Intra strain variability is sufficient to make either sucrose intake or ICSS measures difficult to replicate. Furthermore, the considerable individual variability in rate and frequency responses to ICSS makes even this readout difficult to use as a method for detecting novel drug treatments for depression (Nielsen et al., 2000).

11. So why aren't we producing new antidepressants?

As we indicated at the beginning of this essay, our primary intention was to remind us of the animal models of depression that have been already developed since the early 1960s and their use in drug discovery, and to indicate how they have evolved. It is clear that there is no lack of available models; each of them having been conceived and developed on the basis of very clear rationales. The original neurochemical models have tried to recapitulate (a) the mechanisms of action of pharmaceuticals effective in the treatment of some, but not all the depressions (please refer to the discussions by Kuhn, 1999; Lurie, 1999 on how some depressions are refractory to even standard drugs like imipramine); and (b) changes in brain function as a consequence/cause of depression. On the other hand, the more ethological models have tried to recapitulate the environmental and social factors that could induce depression in humans. All of these models are valid in so far that they have stood the test of time and, within their limitations, achieve what they have set out to do. Furthermore, all of these models have been validated pharmacologically (clinical standards are shown to be active) at one time or another. Thus, throughout this essay we have simply indicated that antidepressant drugs are active in a particular model or procedure, usually referring generally to the TCAs, MAOIs and SSRIs, without specifying them. We have not done so as this information is readily available to the interested reader (op. cit.), and was not the intention of this essay to review animal models of behavioural disorders intensively.

Notwithstanding the robustness, reliability and reproducibility of the models discussed in this essay, the concern expressed by the FDA's white paper on innovation and stagnation begs the question of why the predictive validity of our present animal models is called into question? Perhaps the very reasonableness or intuitive validity of behavioural models has been both a boon and bane for CNS drug discovery. Too often non-behaviourally trained colleagues and managers are "sold" on the idea of the depressed, anxious or memory-impaired animal. This over-reliance on the face validity of animal models may have tremendous reassuring power when an experimental compound is shown to be active, but equally well may serve to stop or hinder further development on a compound if it has failed to do so. More so, if a compound does manage to reach clinical testing, but does not show activity in humans, very serious doubts are generated on the use of animal models as a whole. This concern, especially from many directors of research and development in pharmaceutical companies is not new. Lasagna (1999), for example, describes how a Merck director in the early 1950s asserted that he had no confidence in the animal models used to predict potential therapeutic efficacy of CNS compounds, and that the "proof of the pudding" was to be found in randomized clinical trials. This is an attitude still often expressed within the pharmaceutical industry, and an attitude perhaps best countered by Crawley's important and germane admonition not to anthropomorphize animal behaviour too much (Crawley, 2000).

Showing activity in one or more animal models of depression is not a guarantee that a given compound will reach the market as a clinically effective antidepressant, but it is usually a sine qua non for that compound to be considered a clinical candidate. Once having done so, moreover, the compound is faced with a series of challenges that greatly reduces its chances of reaching the market as an effective pharmaceutical. According to Eli Lilly, out of 12,000 molecules

originally synthesized and screened, only 4 will reach clinical trials and hopefully 1 will reach the market (summarised by Palmer and Stephenson, 2005). Among the reasons for this high attrition are species differences in bioavailabity (pharmacokinetics/dynamics) and metabolism, as well as toxicological issues (c.f., Amer and Morris, 2004; Palmer and Stephenson, 2005; Winsky and Brady, 2005). Even when these challenges have been overcome the compound must not only show efficacy in clinical trials during the various phases of clinical development, but also juggle for attention and resources within the pharmaceutical company sponsoring its development. It is not uncommon for compounds to be dropped, not for lack of clinical efficacy, but because of shifts in priority by the sponsoring company. Some of these compounds may be reintroduced through the licensing process, or simply allowed to disappear.

Assuming, however, that the compound has been very carefully and successfully tested in a series of models of antidepressant potential, has an acceptable absorption, distribution, metabolism and excretion profile, does not show unacceptable toxicity and enjoys the support of the sponsoring company, efficacy–or the lack thereof–may still conspire to kill the compound. Some of these reasons are due to patient heterogeneity. This could be due to differences in diagnosis or sub-types of depressions (the interested reader is invited to refer to Matthews et al., 2005 or to Kuhn's, 1999, p. 103 interview for an interesting account of the specificity of imipramine's antidepressant effect for "vital depression" rather than "depression with melancholic delusions"), spontaneous remission and responses to a placebo treatment, or to genetically-influenced responses to antidepressant drugs. Notwithstanding Lasagna's apocryphal Merck director's faith in randomized clinical trials (Lasagna, 1999), the design of these trials is presently being challenged. Matthews et al. (2005), for example, point out the discrepancy between results in antidepressant clinical trials and "real world antidepressant effectiveness". While clinical trials are short-term (12 weeks or less) there are very little data available on the effects of long-term antidepressant treatment on chronic or treatment resistant. In an attempt to align clinical trials with the "real world", initiatives such as the STAR∗D study are being encouraged (Insel, 2006; Trivedi et al., 2006), which allow adjustment of doses according to specific measurement-based criteria including self rating; in other words, adjusting the treatment for individual patients.

12. Are we measuring the same thing in animal models of depression that is being measured in groups of depressed patients in clinical trials?

Animal models of depression rate the efficacy of a potential or clinically effective antidepressant on changes in behaviour or physiology, while clinical trials base their estimate of efficacy on changes in rating scales such as the HAM-D with efficacy being considered significant if a change of 50% or more is achieved (e.g., Faries et al., 2000). This rate of change is influenced by at least 2 major factors, which may account for the suspension of a considerable number of CNS drugs from development. One of these factors is the "placebo response" within every clinical trial. It is estimated that 30% of subjects enrolled in clinical trials for depression respond to the placebo condition (Brown et al., 1988; see also Kirsch and Sapirstein, 1998; Kirsch et al., 2002). This placebo response is variable and can dilute the significance of change due to the potential antidepressant within a particular clinical trial and not in others. It has been suggested, considering the high placebo response and spontaneous recovery rate (e.g., Posternak and Miller, 2001) that we may be underestimating the true number and potency of potential antidepressant drugs that have not made it past clinical testing (Matthews et al., 2005; Rupniak, 2003). Although it is conceptually difficult to imagine testing for a placebo response in animals, recent studies have indicated that the placebo effect can be detected by brain imaging and may implicate reward mechanisms and immune-mediated disorders (c.f., de la Fuente-Fernandez et al., 2002), both of which can be measured in both humans and animals (e.g., Ader and Cohen, 1982; Benedetti et al., 2005; Mayberg et al., 2002).

A second major factor to consider is the variable response to pharmacological treatment. This is a very real problem. It is estimated that some 60–70% of patients treated will fail to show full remission to either pharmacological or psychosocial antidepressant treatment (Insel, 2006), which until recently has not been addressed by standard clinical trial design or by preclinical animal studies. Genetically-determined factors can have a huge influence on the individual response to a drug (Adam et al., 2000; Licinio and Wong, 2001). The importance of polymorphisms of the serotonin transporter can not only influence the response to SSRIs such as citalopram, but also to the level of dosage necessary for a clinical response (Glatt and Reus, 2003; Serretti and Artioli, 2004a; Weizman and Weizman, 2000). Serotonin is not the only monoamine associated with depression (Glatt and Reus, 2003), and associations of major depression with polymorphisms of the noradrenaline or dopamine transporters are also being established (Frisch et al., 1999; Owen et al., 1999; Ryu et al., 2004). Pharmacogenomic studies in animals combining QTL techniques and pharmacology (Crowley et al., 2006) represent an important step in the development of animal models of behavioural disorders. Nevertheless, while advances in combining forward and reverse genetic techniques with pharmacology (e.g., Mombereau et al., 2004; Nielsen, 2006) hold great promise for identifying and validating new drug targets, and hopefully discovering and developing new drugs more quickly and efficiently (Berton and Nestler, 2006), we must still await the results of clinical registration of these new drugs with non-aminergic mechanisms of action to determine at least the predictive validity of these tests and models.

13. Where do we go from here?

There is a pressing need for academic researchers and industrial preclinical and clinical researchers to work together, to identify the relevant endophenotypes of chronic depression and develop appropriate models and tests. There is also a pressing need for clinical trial design to go beyond the HAM-D and to include more endpoints relevant to the behavioural and

physiological measures done in animal models so that better estimates of causality may be tested. Furthermore, in order to evaluate the true predictive validity of our animal models and their use in CNS drug discovery, it is incumbent upon pharmaceutical companies to publish, or at least make public, the results of their clinical trials. Given the concern and significant expense of the attrition rate of candidate drugs in development, the sharing of such information to improve the cross-evaluation of efficacy would be a boon to the pharmaceutical industry. Without this essential information it is difficult to relate efficacy determined by activity in animal tests to efficacy, or lack of it, in humans. Public disclosure initiatives from various pharmaceutical companies posting their clinical trial results on the Web (e.g., http://ctr.gsk.co.uk/medicinelist.asp; http://www.organon.com/clinical_trials/Clinical_Trial_Registry/index.asp; http://www.novartisclinicaltrials.com/clinicaltrialrepository/public/login.jsp) are clear indications that the pharmaceutical industry is responding to this need.

The current emphasis on translational research promises to be an important development in achieving preclinical and clinical congruence of results (e.g., Hurko and Ryan, 2005). Although these are early days yet, some procedures used in animal research can be used in humans. Hughes et al.s' (1985) use of progressive ratios for monetary reward in depressed patients, for example, can be related to the use of this schedule of reinforcement for more basic rewards in animals. On the other hand, Pizzagalli et al. (2005) applied signal detection analysis (c.f., Frey and Colliver, 1973) of DRL responses for monetary reward in college students that had subsequently been assessed as being high or low on self-report depression scales. Within this non-clinical sample, subjects with higher self-reported depressive symptoms showed a blunted response to reinforcing stimuli. While other putative endophenotypes are being evaluated (c.f., Hasler et al., 2004; Cryan and Holmes, 2005), further experimental medicine studies are crucial not only for early clinical validation of new molecular targets, but for guiding preclinical studies in animals as well.

Finally, the apparent lack of predictive validity of animal models of depression or depressed-like behaviours in humans is not only a concern of the pharmaceutical industry, but involves academic and industrial researchers and governmental bodies as well. Initiatives such as the strong collaborations between academia, governmental bodies and the pharmaceutical industry (e.g., Winsky and Brady, 2005; Nestler et al., 2002; Sachs et al., 2003; Schneider et al., 2001; Tamminga et al., 2002; Trivedi et al., 2006; MATRICS initiative http://www.matrics.ucla.edu/) indicate that concerted efforts are presently in place to address this issue.

14. Conclusions

1) We must be aware that notwithstanding the emphasis and enthusiasm with which genetic analysis of behavioural disorders such as depression is presently being done, we are engaging very much in a tautological exercise. Models of depressed-like behaviours have been developed over the past 30 years based initially on criteria of high face validity. Construct validity has been established in varying degrees for many of these models, but at the end they remain models of a disorder (s) whose etiology is very poorly understood. One must be cautious not to mistake genetically-modified mice, for example, as a "depressed" mouse, but rather as a mouse with molecular defects that shows behavioural characteristics that may reasonably be associated with depression in humans.
2) Given this caveat, it would be best to concentrate on a few animal models with high face and construct validity, which are capable of inducing behavioural changes that can reasonably approximate candidate endophenotypes of depression.
3) Considering the injunction that "good genetics needs good phenotypes" (Hasler et al., 2004; Lander, 1988; Tarantino and Bucan, 2000), one should aim to characterise behavioural responses on the basis of their simplicity robustness and reproducibility. The use of behavioural procedures and measures such as sucrose intake and selection, rates of ICSS and changes in sleep–wake patterns, or even immobility in the FST and TST, should be done with caution as these can be very much influenced by procedure.
4) The human response to environmental or social stress is variable. In contrast, animals are requested to respond homogenously to various social or environmental stressors. Strategies to identify more vulnerable subjects in the various animal models such as those described by Crowley and Lucki (2005), Henn and Vollmayr (2005) or Strekalova et al. (2004), and to use this differential vulnerability as a factor for discovering candidate genes of depression should be encouraged.
5) A greater emphasis should be placed on preclinical and clinical research interaction. Translational research offers the best opportunity to align human and animal responses not only to a drug, but also to conditions inducing a depressed-like state.
6) Changes in the present design of clinical trials are to be encouraged. A reduction of 50% in the HAM-D scale may be necessary to register a drug as antidepressant, but this criterion is subject to great variability due to placebo and pharmacogenetic responses may not give candidate drugs a chance to show their true potential.

References

Adam GI, Reneland R, Andersson M, Risinger C, Nilsson M, Lewander T. Pharmacogenomics to predict drug response. Pharmacogenomics 2000;1:5– 14.

Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science 1982;215:1534–6.

Adrien J. Neurobiological bases for the relation between sleep and depression. Sleep Med Rev 2002;6:341–51.

Adrien J, Dugovic C, Martin P. Sleep–wakefulness patterns in the helpless rat. Physiol Behav 1991;49:257–62.

Amer RE, Morris ID. Trends in early drug safety. Drug News Perspect 2004;17:143–8.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth edition text revision. Washington (DC): American Psychiatric Press; 1994.

Andrade C, Kurinji S. Continuation and maintenance ECT: a review of recent research. J ECT 2002;18:149–58.
Anisman H, Matheson K. Stress, depression, and anhedonia: caveats concerning animal models. Neurosci Biobehav Rev 2005;29:525–46.
Anisman H, Remington G, Skalr LS. Effects of inescapable shock on subsequent escape performance: catecholaminergic and cholinergic mediation of response initiation and maintenance. Psychopharmacology 1979;61: 107–24.
Askew BM. A simple screening procedure for imipramine-like antidepressant agents. Life Sci 1963;10:725–30.
Babington RG, Wedeking P. The pharmacology of seizures induced by sensitization with low intensity brain stimulation. Pharmacol Biochem Behav 1973;1:461–7.
Bai F, Li X, Clay M, Lindstrom T, Skolnick P. Intra- and interstrain differences in models of "behavioural despair". Pharmacol Biochem Behav 2001;70: 187–92.
Bale TL, Vale WW. Increased depression-like behaviours in corticotropin-releasing factor receptor-2-deficient mice: sexually dichotomous responses. J Neurosci 2003;23:5295–301.
Baltzer V, Weiskrantz L. Antidepressant agents and reversal of diurnal activity cycles in the rats. Biol Psychiatry 1973;10:199–209.
Banerjee SP, Kung LS, Riggi SJ, Chanda SK. Development of beta-adrenergic receptor subsensitivity by antidepressants. Nature 1977;268:455–6.
Barr AM, Phillips AG. Chronic mild stress has no effect on responding by rats for sucrose under a progressive ratio schedule. Physiol Behav 1998;64: 591–7.
Barr AM, Markou A, Phillips AG. A 'crash' course on psychostimulant withdrawal as a model of depression. Trends Pharmacol Sci 2002;23: 475–82.
Barron DI, Hall GH, Natoff IL, Vallance DK. Pharmacological properties of 3-dimethylamino-2-methyl-1-phenyl-1-*o*-tolylpropanol (SK and F 70463-A). J Pharm Pharmacol 1965;17:509–16.
Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 1992;49:651–68.
Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J-K. Neurobiological Mechanisms of the Placebo Effect. J Neurosci 2005;25:10390–402.
Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 2006;7:137–51.
Berton O, Durand M, Aguerre S, Mormede P, Chaouloff F. Behavioral, neuroendocrine and serotonergic consequences of single social defeat and repeated fluoxetine pretreatment in the Lewis rat strain. Neuroscience 1999; 92:327–41.
Besson A, Privat AM, Eschalier A, Fialip J. Dopaminergic and opioidergic mediations of tricyclic antidepressants in the learned helplessness paradigm. Pharmacol Biochem Behav 1999;64:541–8.
Binks SM, Murchie JK, Greenwood DT. A reward-reduction model of depression using self stimulating rats: an appraisal. Pharmacol Biochem Behav 1979;10:441–3.
Blanchard DC, Griebel G, Blanchard RJ. The Mouse Defence Test Battery: pharmacological and behavioural assays for anxiety and panic. Eur J Pharmacol 2003;463:97–116.
Bohus B, Koolhaas JM, Heijnen CJ, deBoer O. Immunological responses to social stress: dependence on social environment and coping abilities. Neuropsychobiology 1993;28:95–9.
Boivin DB. Influence of sleep–wake and circadian rhythm disturbances in psychiatric disorders. J Psychiatry Neurosci 2000;25:446–58.
Borsini F. Role of the serotonergic system in the forced swimming test. Neurosci Biobehav Rev 1995;19:377–95.
Borsini F, Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity? Psychopharmacology 1988;94:147–60.
Borsini F, Bendotti C, Velkov V, Rech R, Samanin R. Immobility test: effects of 5-hydroxytryptaminergic drugs and role of catecholamines in the activity of some antidepressants. J Pharm Pharmacol 1981;33:33–7.
Boulton AA, Baker GB, Martin-Iverson MT, editors. Animal models in psychiatry. II: Neuromethods 19. Clifton, New Jersey: The Humana Press; 1991.
Bourin M, Poncelet M, Chermat R, Simon P. The value of the reserpine test in psychopharmacology. Arzneim-Forsh/Drug Res 1983;33:1173–6.
Boutrel B, Franc B, Hen R, Hamon M, Adrien J. Key role of 5-HT1B receptors in the regulation of paradoxical sleep as evidenced in 5-HT1B knock-out mice. J Neurosci 1999;19:3204–12.
Boutrel B, Monaca C, Hen R, Hamon M, Adrien J. Involvement of 5-HT1A receptors in homeostatic and stress-induced adaptive regulations of paradoxical sleep: studies in 5-HT1A knock-out mice. J Neurosci 2002; 22:4686–92.
Brady J. The evolution of behavioural pharmacology. In: Healy D, editor. The psychopharmacologists. II: Interviews by Dr David Healey. London: Arnold; 1999. p. 71–91.
Broekkamp CL, Garrigou D, Lloyd KG. Serotonin-mimetic and antidepressant drugs on passive avoidance learning by olfactory bulbectomized rats. Pharmacol Biochem Behav 1980;13:643–6.
Brown SD, Nolan PM. Mouse mutagenesis-systematic studies of mammalian gene function. Hum Mol Genet 1998;7:1627–33.
Brown WA, Dornseif BE, Wernicke JF. Placebo response in depression: a search for predictors. Psychiatry Res 1988;26:259–64.
Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. Neuropsychopharmacology 2000;22:335–45.
Buwalda B, de Boer SF, Schmidt ED, Felszeghy K, Nyakas C, Sgoifo A, et al. (Jul) Long-lasting deficient dexamethasone suppression of hypothalamic–pituitary–adrenocortical activation following peripheral CRF challenge in socially defeated rats. J Neuroendocrinol 1999;11:513–20.
Buwalda B, Kole MH, Veenema AH, Huininga M, de Boer SF, Korte SM, et al. Long-term effects of social stress on brain and behavior: a focus on hippocampal functioning. Neurosci Biobehav Rev 2005;29:83–97.
Cairncross KD, Cox B, Forster C, Wren AF. A new model for the detection of antidepressants drugs: olfactory bulbectomy in the rats comparing to the existing models. J Pharmacol Methods 1978;1:131–43.
Cairncross KD, Cox B, Forster C, Wren AF. Olfactory projection systems, drugs and behaviour: a review. Psychoneuroendocrinology 1979;4:253–72.
Clements-Jewery S. The development of cortical beta-adrenoceptor subsensitivity in the rat by chronic treatment with trazodone, doxepin and mianserine. Neuropharmacology 1978;17:779–81.
Colpaert FC, Lenaerts FM, Niemegeers CJE, Janssen PA. A critical study on RO-4-1284 antagonism in mice. Arch Int Pharmacodyn 1975;215:40–90.
Cooper BR, Hester TJ, Maxwell RA. Behavioural and biochemical effects of antidepressant bupropion (Wellbutrin): evidence for selective blockade of dopamine uptake in vivo. J Pharmacol Exp Ther 1980;215:127–34.
Cornfeldt M, Fisher B, Fielding S. Rat internal capsule lesion: a new test for detecting antidepressant. Fed Proc 1982;41:1066.
Costa E, Garattini S, Valzelli L. Interactions between reserpine, chlorpromazine, and imipramine. Experentia 1960;16:461–3.
Cowan A, Harry EJ. Potentiation of picrotoxin-induced convulsions in mice by antidepressants. Specificity of the effect. Br J Pharmacol 1974;52:432P.
Crawley JN. Behavioural phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioural tests. Brain Res 1999;835:18–26.
Crawley JN. What's wrong with my mouse? Behavioural phenotyping of transgenic and knockout mice. New York: Wiley-Liss; 2000.
Crawley JN, Belknap JK, Collins A, Crabbe JC, Frankel W, Henderson N, et al. Behavioural phenotypes of inbred mouse strains: implications and recommendations for molecular studies. Psychopharmacology 1997;132: 107–24.
Crowley JJ, Lucki I. Opportunities to discover genes regulating depression and antidepressant response from rodent behavioural genetics. Curr Pharm Des 2005;11:157–69.
Crowley JJ, Blendy JA, Lucki I. Strain-dependent antidepressant-like effects of citalopram in the mouse tail suspension test. Psychopharmacology 2005; 183:257–64.
Crowley JJ, Brodkin ES, Blendy JA, Berrettini WH, Lucki I. Pharmacogenomic evaluation of the antidepressant citalopram in the mouse tail suspension test. Neuropsychopharmacology 2006, doi:10.1038/sj.npp.2006.1301065.
Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. Nat Rev Drug Discov 2005;4:775–90.
Cryan JF, Kaupmann K. Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. Trends Pharmacol Sci 2005;26:36–43.

Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behaviour in genetically modified mice. Mol Psychiatry 2004;9:326–57.

Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioural effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev 2005a;29:547–69.

Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 2005b;29:571–625.

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 2001;98:12796–801.

Davey G. Animal learning and conditioning. London: Macmillan Education Ltd; 1987.

De Graaf JS, van Riezen H, Berendsen HHG, van Delft AML. A set of behavioural tests predicting antidepressant activity. Drug Dev Res 1985; 5:291–301.

deKloet ER, Sibug RM, Helmerhorst FM, Schmidt M. Stress, genes and the mechanism of programming the brain for later life. Neurosci Biobehav Rev 2005a;29:271–81.

de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci 2005b;6:463–75.

de la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002;1:85–91.

De Leon OA. Antiepileptic drugs for the acute and maintenance treatment of bipolar disorder. Harv Rev Psychiatry 2001;9:209–22.

Desan PH, Oren DA, Malison R, Price LH, Rosenbaum J, Smoller J. Genetic polymorphism at the CLOCK gene locus and major depression. Am J Med Genet 2000;96:418–21.

Detke MJ, Rickels M, Lucki I. Active behaviours in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 1995;121:66–72.

Detke MJ, Johnson J, Lucki I. Acute and chronic antidepressant drug treatment in the rat forced swimming test model of depression. Exp Clin Psychopharmacol 1997;5:107–12.

Ducottet C, Griebel G, Belzung C. Effects of the selective nonpeptide corticotropin-releasing factor receptor 1 antagonist antalarmin in the chronic mild stress model of depression in mice. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:625–31.

Dugovic C, Solberg LC, Redei E, VanReeth O, Turek FW. Sleep in the Wistar–Kyoto rat, a putative genetic animal model for depression. NeuroReport 2000;11:627–31.

Duyk G. Attrition and translation. Science 2003;302:603–5.

Einon DF, Morgan MJ, Sahakian BJ. The development of intersession habituation and emergence in social reared and isolated rats. Dev Psychol 1975;8(4):553–9.

Enna SJ, Duman RS. Beta-adrenergic receptor regulation and antidepressants: the influence of adrenocorticotropin. J Neural Transm 1983;57:297–307.

Enserink M. Can the placebo be the cure? Science 1999;284:238–40.

Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 1998;393:76–9.

Everett GM. Dopa response potentiation test and its use in screening for antidepressant drugs. In: Garattini S, Dukes MNH, editors. Antidepressant drugs. Amsterdam: Excerpta Medica Foundation; 1967. p. 164–7.

Faries D, Herrera J, Rayamajhi J, DeBrota D, Demitrack M, Potter WZ. The responsiveness of the Hamilton Depression Rating Scale. J Psychiatr Res 2000;34:3–10.

Ferris RM, Beaman OJ. Bupropion: a new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic beta-adrenergic, serotonergic (5-HT2), alpha 2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 1983;22:1257–67.

Fibiger HC, Phillips AG. Increased intracranial self-stimulation in rats after long-term administration of desipramine. Science 1981;214:683–5.

Fink GB, Swinyard EA. Effects of psychopharmacologic agents on experimentally-induced seizures in mice. J Am Pharm Assoc 1960;49:510–3.

Food and Drug Administration (U.S.A.). Innovation or stagnation: challenge and opportunity on the critical path to new medical products. Washington (DC): U.S. Department of Health and Human Services, Food and Drug Administration; 2004.

Francis DD, Champagne FA, Liu D, Meaney MJ. Maternal care, gene expression, and the development of individual differences in stress reactivity. Ann N Y Acad Sci 1999;896:66–84.

Frey PW, Colliver JA. Sensitivity and responsivity measures for discrimination learning. Learn Motiv 1973;4:327–42.

Frisch A, Postilnick D, Rockah R, Michaelovsky E, Postilnick S, Birman E, et al. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. Mol Psychiatry 1999;4: 389–92.

Fuchs E. Social stress in tree shrews as an animal model of depression: an example of a behavioural model of a CNS disorder. CNS Spectr 2005; 10:182–90.

Fuchs E, Kramer M, Hermes B, Netter P, Hiemke C. Psychosocial stress in tree shrews: clomipramine counteracts behavioral and endocrine changes. Pharmacol Biochem Behav 1996;54:219–28.

Gandolfi O, Barbaccia ML, Costa E. The (−)-deprenyl actions on beta-adrenergic receptors require the integrity of brain serotonergic axon terminals. Eur J Pharmacol 1984;100:233–7.

Garattini S, Giachetti A, Jori A, Pieri L, Balzelli L. Effect of imipramine. Amitriptyline and their monomethyl derivatives on reserpine activity. J Pharm Pharmacol 1962;14:509–14.

Garcha G, Smokcum RWJ, Stephenson JD, Weeramanthri TB. Effects of some atypical antidepressants on beta-adrenoceptor binding and adenylate cyclase activity in the rat forebrain. Eur J Pharmacol 1985;108:1–7.

Garzon J, Del Rio J. Hyperactivity induced in rats by long-term isolation: further studies on a new animal model for detection of antidepressants. Eur J Pharmacol 1981;74:287–94.

Garzon J, Fuentes JA, Del Rio J. Antidepressants selectively antagonize the hyperactivity induced in rats by long-term isolation. Eur J Pharmacol 1979; 59:293–6.

Geyer MA, Markou A. Animal models of psychiatric disorders. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995. p. 787–98.

Geyer MA, Markou A. The role of preclinical models in the development of psychotropic drugs. In: Davis KL, Charney JT, Nemroff C, editors. Neuropsychopharmacology: the fifth generation of progress. New York: American College of Neuropsychopharmacology; 2000. p. 446–56.

Glatt CE, Reus VI. Pharmacogenetics of monoamine transporters. Pharmacogenomics 2003;4:583–96.

Goodwin FK, Wirz-Justice A, Wehr TA. Evidence that pathophysiology of depression and the mechanism of action of antidepressant drugs both involve alterations in circadian rhythms. In: Costa E, Racagni G, editors. Typical and atypical antidepressants: clinical practice, vol. 32. New York: Raven Press; 1982. p. 1–11.

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636–45.

Griebel G, Simiand J, Steinberg R, Jung M, Gully D, Roger P, et al. 4-(2-Chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-*N*-(2-propynyl)-1, 3-thiazol-2-amine hydrochloride (SSR125543A), a potent and selective corticotrophin-releasing factor(1) receptor antagonist. II: Characterization in rodent models of stress-related disorders. J Pharmacol Exp Ther 2002;301:333–45.

Hagan JJ, Hatcher JP. Revised CMS model. Psychopharmacology 1997;134: 354–356.

Hall H, Ross SB, Sallmark. Effect of destruction of central noradrenergic and serotonergic nerve terminals by systemic neurotoxins on the long-term effects of antidepressants on beta-adrenoceptors and 5-HT2 binding sites in the rat cerebral cortex. J Neural Transm 1984;59:9–23.

Hall FS, Stellar JR, Kelley AE. Acute and chronic desipramine treatment effects on rewarding electrical stimulation of the lateral hypothalamus. Pharmacol Biochem Behav 1990;37:277–81.

Halliwell G, Quinton RM, Williams DE. A comparison of imipramine, chlorpromazine and related drugs in various tests involving autonomic functions and antagonism of reserpine. Br J Pharmacol Chemother 1964; 23:330–50.

Hammen C. Stress and depression. Annu Rev Clin Psychol 2005;1:293–319.

Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29:1765–81.
Hatotani N, Nomura J, Kitayama I. Changes of brain monoamines in the animal model for depression. In: Langer SZ, Takahashi R, Segawa T, Briley M, editors. New vistas in depression. New York: Pergamon Press; 1982. p. 65–72.
Healy D, (Ed.). The psychopharmacologists. I: Interviews by Dr David Healy. London: Altman, Chapman and Hall;1996.
Healy D, editor. The psychopharmacologists. II: Interviews by Dr David Healy. London: Arnold; 1999.
Healy D, editor. The psychopharmacologists. III: Interviews by Dr David Healy. London: Arnold; 2000.
Henn FA, Vollmayr B. Stress models of depression: forming genetically vulnerable strains. Neurosci Biobehav Rev 2005;29:799–804.
Hinde RA, Spencer-Booth Y, Bruce M. Effects of 6-day maternal deprivation on rhesus monkey infants. Nature 1966;210:1021–3.
Hoebel BG, Teitelbaum P. Hypothalamic control of feeding and self-stimulation. Science 1962;135:375–7.
Horovitz ZP, Ragozzino PW, Leaf RC. Selective block of rat mouse-killing by antidepressants. Life Sci 1965;4:1909–12.
Horovitz ZD, Piala JJ, High JP, Burke JC, Leaf RC. Effects of drugs on the mouse-killing (muricide) test and its relationship to amygdaloid function. Int J Neuropharmacol 1966;5:405–11.
Hrdina P, von Kulmiz P, Stretch R. Pharmacological modification of experimental depression in infant macaques. Psychopharmacology 1979; 64:89–93.
Hughes JR, Pleasants CN, Pickens RW. Measurement of reinforcement in depression: a pilot study. J Behav Ther Exp Psychiatry 1985;16:231–6.
Hunter AJ, Nolan PM, Brown SDM. Towards new models of disease and physiology in the neurosciences: the role of induced and naturally occurring mutations. Hum Mol Genet 2000;9:893–900.
Hurko O, Ryan JL. Translational Research in Central Nervous System Drug Discovery. NeuroRx 2005;2:671–82.
Insel TR. Beyond efficacy: the STAR*D trial. Am J Psychiatry 2006;163:5–7.
Jensen GD, Tolman CW. Mother–infant relationship in the monkey, *Macaca nemestrina*: the effect of brief separation and mother–infant specificity. J Comp Physiol Psychol 1962;55:131–6.
Justice MJ, Noveroske JK, Weber JS, Zheng B, Bradley A. Mouse ENU mutagenesis. Hum Mol Genet 1999;8:1955–63.
Katz RJ. Animal model of depression: effects of electroconvulsive shock therapy. Neurosci Biochem Rev 1981;5:273–7.
Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol Biochem Behav 1982;6:965–8.
Katz RJ, Baldiraghi G. A further parametric study of imipramine in an animal model of depression. Pharmacol Biochem Behav 1982;16:969–72.
Katz RJ, Sibel M. Animal model of depression: tests of three structurally and pharmacologically novel antidepressant compounds. Pharmacol Biochem Behav 1982;16:973–7.
Katz RJ, Roth KA, Carroll BJ. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neurosci Biochem Rev 1981;5:247–51.
Kaufman IC, Rosenblum LA. Depression in infant monkeys separated from their mothers. Science 1967;155:1030–1.
Keck ME, Ohl F, Holsboer F, Muller MB. Listening to mutant mice: a spotlight on the role of CRF/CRF receptor systems in affective disorders. Neurosci Biobehav Rev 2005;29:867–89.
Kelly JP, Wrynn AS, Leonard BE. The olfactory bulbectomized rat as a model of depression: an update. Pharmacol Ther 1997;74:299–316.
Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol 1997;48:191–214.
Ketter TA, Manji HK, Post RM. Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. J Clin Psychopharmacol 2003;23: 484–495.
Kinnier WJ, Chuang DM, Costa E. Down regulation of dihydroalprenolol and imipramine binding sites in brain of rats repeatedly treated with imipramine. Eur J Pharmacol 1980;67:289–94.
Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. Prev Treat 1998;1:1–13.
Kirsch I, Moore TJ, Scoboria A, Nicholls SS. The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat 2005;5:1–23.
Kline NS. Clinical experience with iproniazid (marsilid). J Clin Exp Psychopathol 1958;19:72–8.
Kokkinidis L, Zacharcko RM, Predy PA. Post-amphetamine depression of self-stimulation responding from the substantia nigra: reversal by tricyclic antidepressants. Pharmacol Biochem Behav 1980;13:379–83.
Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. Neuron 1998; 21:467–76.
Koolhaas JM, Herman PM, Kemperman C, Bohus B, Van den Hoofdakker RH, Beerma DHG. Single social defeat in male rats induces a gradual but long-lasting behavioural change: a model of depression? Neurosci Res Commun 1990;7:35–41.
Korte SM, Buwalda B, Meijer O, De Kloet ER, Bohus B. Socially defeated male rats display a blunted adrenocortical response to a low dose of 8-OH-DPAT. Eur J Pharmacol 1995;272:45–50.
Kostowski W, Valzelli L, Kozak W, Bernasconi. Activity of desipramine, fluoxetine and nomifensine on spontaneous and *p*-CPA-induced muricidal aggression. Pharmacol Res Commun 1984;16:265–71.
Kuhn R. From imipramine to levoprotiline: the discovery of antidepressants. In: Healey D, editor. The psychopharmacologists. II: Interviews by Dr David Healey. London: Arnold; 1999. p. 93–118.
Kupferberg H. Animal models used in the screening of antiepileptic drugs. Epilepsia 2001;42(Suppl. 4):7–12.
Lander ES. Splitting schizophrenia. Nature 1988;336:105–6.
Lapin IP. Adrenergic nonspecific potentiation of yohimbine toxicity in mice by antidepressants and related drugs and antiyohimbine action of antiadrenergic and serotonergic drugs. Psychopharmacology 1980;70:179–81.
Lasagna L. Back to the future: evaluation and drug development. 1948–1998. In: Healy D, editor. The psychopharmacologists. II: Interviews by Dr David Healey. London: Arnold; 1999. p. 135–65.
Lehr E. Distress call reactivation in isolated chicks: a behavioural indicator with high selectivity for antidepressants. Psychopharmacology 1989;97: 145–6.
Leonard BE. Clinical implications of mechanisms of action of antidepressants. Adv Psychiatric Treat 2000;6:178–86.
Leonard BE, Tuite M. Anatomical, physiological and behavioural aspects of olfactory bulbectomy in the rat. Int Rev Neurobiol 1981;22:251–86.
Le Pen G, Gaudet L, Mortas P, Mory R, Moreau JL. Deficits in reward sensitivity in a neurodevelopmental rat model of schizophrenia. Psychopharmacology 2002;161:434–41.
Lesch KP. Gene–environment interaction and the genetics of depression. J Psychiatry Neurosci 2004;29:174–84.
Leshner AI, Remler H, Biegon A, Samuel D. Effects of desmethylimipramine (DMI) on learned helplessness. Psychopharmacology 1979;66:207–13.
Licinio J, Wong ML. The pharmacogenomics of depression. Pharmacogenomics J 2001;1:175–7.
Lopez-Rubalcava C, Lucki I. Strain differences in the behavioural effects of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology 2000;22:191–9.
Lurie M. The enigma of isoniazid. In: Healey D, editor. The psychopharmacologists. II: Interviews by Dr David Healey. London: Arnold; 1999. p. 119–34.
Maj J. Studies on the action of antidepressant drugs of second generation. Pol J Pharmacol Pharm 1980;32:437–49.
Maj J, Pawlowski L, Wiszniowska G. The effect of tricyclic antidepressants on apomorphine-induced hypothermia in the mouse. Pol J Pharmacol Pharm 1974;26:329–36.
Malatynska E, Kostowski W. The effect of antidepressant drugs on dominance behaviour in rats competing for food. Pol J Pharmacol Pharm 1984;36: 531–540.
Malatynska E, Rapp R, Harrawood D, Tunnicliff G. Submissive behaviour as a test for antidepressant drug activity. Pharmacol Biochem Behav 2005;83: 306–313.
Malick JB. Yohimbine potentation as a predictor of antidepressant action. In: Enna SJ, Malick JB, Richelson E, editors. Antidepressants: neurochemical, behavioural and clinical perspectives. New York: Raven Press; 1981. p. 441–5.

Markou A, Koob GF. Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations. Physiol Behav 1992;51:111–9.

Martorana PA, Nitz RE. The new antidepressant pirlindole. Arzneim-Forsh/ Drug Res 1979;29:946–9.

Matthews K, Christmas D, Swan J, Sorrell E. Animal models of depression: navigating through the clinical fog. Neurosci Biobehav Rev 2005;29: 503–513.

Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002; 159:728–37.

McGrath WR, Ketteler HJ. Potentation of the anti-reserpine effects of dihydroxyphenylalanine by antidepressants and stimulants. Nature 1963; 199:917–8.

McGuffin P, Katz R. The genetics of depression and manic–depressive disorder. Br J Psychiatry 1989;155:294–304.

McGuire PS, Seiden L. Differential effects of imipramine in rats as a function of DRL schedule value. Pharmacol Biochem Behav 1980;13: 691–4.

McKinney Jr WT, Bunney Jr WE. Animal model of depression. I: Review of evidence: implications for research. Arch Gen Psychiatry 1969;21: 240–8.

Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci 2001; 24:1161–92.

Metys J, Metysova J. Relationship between antireserpine and central cholinolytic effects of imipramine-like antidepressants. In: Garattini S, Dukes MNH, editors. Antidepressant drugs. Amsterdam: Excerpta Medica Foundation; 1967. p. 255–65.

Miller NE. Central stimulation and other new approaches to motivation and reward. Am Psychol 1958;13:100–8.

Mishra R, Janowsky A, Sulser F. Action of mianserin and zimelidine on the norepinephrine receptor coupled adenylate cyclase system in brain: subsensitivity without reduction in beta-adrenergic receptor binding. Neuropharmacology 1980;19:983–7.

Mitchell PJ. Antidepressant treatment and rodent aggressive behaviour. Eur J Pharmacol 2005;526:147–62.

Mitchell PJ, Redfern PH. Chronic treatment with clomipramine and mianserin increases the hierarchical position of subdominant rats housed in triads. Behav Pharmacol 1992;3:239–47.

Mitchell PJ, Fairhall SJ, Fletcher A, Redfern PH. Effects of single and repeated electroconvulsive shock on the social and agonistic behaviour of resident rats. Neuropharmacology 2003;44:911–25.

Mombereau C, Kaupmann K, Froestl W, Sansig G, Van Der Putten H, Cryan JF. Genetic and pharmacological evidence of a role for GABA(B) receptors in the modulation of anxiety- and antidepressant-like behavior. Neuropsychopharmacology 2004;29:1050–62.

Monroe SM, Harkness KL. Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol Rev 2005;112:417–45.

Moreau JL. Reliable monitoring of hedonic deficits in the chronic mild stress model of depression. Psychopharmacology 1997;134:357–8.

Moreau JL, Jenck F, Martin JR, Mortas P, Haefely WE. Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behaviour in rats. Eur Neuropsychopharmacol 1992;2:43–9.

Moreau JL, Scherschlicht R, Jenck F, Martin JR. Chronic mild stress-induced anhedonia model of depression; sleep abnormalities and curative effects of electroshock treatment. Behav Pharmacol 1995;6:682–7.

Morpurgo C, Theobald W. Influence of imipramine-like compounds and chlorpromazine on the reserpine–hypothermia in mice and the amphetamine–hyperthermia in rats. Med Pharmacol Exp Int J Exp Med 1965;2: 226–232.

Muscat P, Papp M, Willner P. Reversal of stress-induced anhaedonia by the atypical antidepressants, fluoxetine and maprotiline. Psychopharmacology 1992;109:433–8.

Nagayama H, Hintgen JN, Aprison MH. Pre- and postsynaptic serotonergic manipulations in an animal model of depression. Pharmacol Biochem Behav 1980;15:575–9.

Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. J Clin Psychiatry 2005;66(Suppl. 7):5–13.

Nestler EJ, Gould E, Manji H, Buncan M, Duman RS, Greshenfeld HK, et al. Preclinical models: status of basic research in depression. Biol Psychiatry 2002;52:503–28.

Nielsen DM. Corticotropin-releasing factor type-1 receptor antagonists: the next class of antidepressants? Life Sci 2006;78:909–19.

Nielsen CK, Arnt J, Sanchez C. Intracranial self-stimulation and sucrose intake differ as hedonic measures following chronic mild stress: interstrain and interindividual differences. Behav Brain Res 2000;107:21–33.

Noreika L, Pastor G, Liebman J. Delayed emergence of antidepressant efficacy following withdrawal in olfactory bulbectomized rats. Pharmacol Biochem Behav 1981;15:393–8.

O'Donnel JM, Seiden LS. Effects of monoamine oxidase inhibitors on performance during differential reinforcement of low response rats. Psychopharmacology 1982;86:55–60.

O'Donnell JM, Marek GJ, Seiden LS. Antidepressant effects assessed using behaviour maintained under a differential-reinforcement-of-low-rate (DRL) operant schedule. Neurosci Biobehav Rev 2005;29:785–98.

Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 1954; 47:419–27.

O'Neill MF, Moore NA. Animal models of depression: are there any. Hum Psychopharmacol Clin Exp 2003;18:239–54.

Overmier JB, Seligman ME. Effects of inescapable shock upon subsequent escape and avoidance responding. J Comp Physiol Psychol 1967;63: 28–33.

Overstreet DH. The Flinders sensitive line rats: a genetic animal model of depression. Neurosci Biobehav Rev 1993;17:51–68.

Overstreet DH, Griebel G. Antidepressant-like effects of CRF1 receptor antagonist SSR125543 in an animal model of depression. Eur J Pharmacol 2004;497:49–53.

Overstreet DH, Friedman E, Mathe AA, Yadid G. The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev 2005;29:739–59.

Owen D, Du L, Bakish D, Lapierre YD, Hrdina PD. Norepinephrine transporter gene polymorphism is not associated with susceptibility to major depression. Psychiatry Res 1999;87:1–5.

Palmer AM, Stephenson FA. CNS drug discovery: challenges and solutions. Drug News Perspect 2005;18:51–7.

Pandey GN, Sudershan P, Davis JM. Beta adrenergic receptor function in depression and the effect of antidepressant drugs. Acta Pharmacol Toxicol 1985;56(Suppl. 1):66–79.

Panksepp J, Vilberg T, Bean NJ, Coy DH, Kastin AJ. Reduction of distress vocalization in chicks by opiate-like peptides. Brain Res Bull 1978;3: 663–667.

Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. Psychopharmacology 1991;104:255–9.

Pawlowski L. Effects of the membrane-active antidepressant drugs, selective 5-HT or NA uptake inhibitors, on *p*-chloramphetamine (PCA)-induced hyperthermia in heat-adapted rats. In: Briley M, Fillion G, editors. New concepts in depression. New York: MacMillan Press; 1988. p. 204–10.

Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. Science 1980;210:88–90.

Perrault G, Morel E, Zivkovic B, Sanger DJ. Activity of litoxetine and other serotonin uptake inhibitors in the tail suspension test in mice. Pharmacol Biochem Behav 1992;42:45–7.

Petty F, Sherman AD. Reversal of learned helplessness by imipramine. Commun Psychopharmacol 1980;3:371–3.

Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry 2005; 57:319–27.

Porsolt RD, LePichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatment. Nature 1977a;266:730–2.

Porsolt RD, Bertin A, Jalfre. Behavioural despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn 1977b;229:327–36.

Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural depression in rats a new model sensitive to antidepressant treatments. Eur J Pharmacol 1978; 47:379–91.

Porsolt RD, Lenègre A, McArthur RA. Pharmacological models of depression. In: Olivier B, Slangen J, Mos J, editors. Animal models in psychopharmacology. Basel: Birkhauser Verlag; 1991. p. 137–59.

Porsolt RD, McArthur RA, Lenègre A. Psychotropic screening procedures. In: van Haaren F, editor. Methods in behavioural pharmacology. Amsterdam: Elsevier BV; 1993. p. 23–51.

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010.

Posternak MA, Miller I. Untreated short-term course of major depression: a meta-analysis of outcomes from studies using wait-list control groups. J Affect Disord 2001;66:139–46.

Przegalinski E, Bigajaska K, Siwanowicz J. The effect of some new antidepressants on apomorphine-induced hypothermia in mice. J Pharm Pharmacol 1979;31:560–1.

Puech AJ, Frances H, Simon P. Imipramine antagonism of apomorphine-induced hypothermia: a non-dopaminergic interaction. Eur J Pharmacol 1978;47:125–7.

Puech AJ, Chermat R, Poncelet M, Doare, Simon P. Antagonism of hypothermia and behavioural response to apomorphine: a simple, rapid and discriminating test for screening antidepressants and neuroleptics. Psychopharmacology 1981;75:84–91.

Quinton RM. The increase in the toxicity of yohimbine induced by imipramine and other drugs in mice. Br J Pharmacol Chemother 1963;21:51–66.

Richardson JS. The olfactory bulbectomized rat as a model of major depressive disorder. In: Boulton AA, Baker GB, Martin-Iverson MT, editors. Animal models in psychiatry. II: Neuromethods 19. Clifton, New Jersey: The Humana Press; 1991. p. 61–79.

Rogers DC, Fisher EM, Brown SD, Peters J, Hunter AJ, Martin JE. Behavioural and functional analysis of mouse phenotype: SHIRPA, a proposed protocol for comprehensive phenotype assessment. Mamm Genome 1997;8:711–3.

Roszkowski AP, Schuler ME, Schultz R. Augmentation of pentylenetetrazole induced seizures by tricyclic antidepressants. Mater Med Pol 1976;8:141–5.

Roubertoux P, Le Roy-Duflos I. Quantitative trait locus mapping: fishing strategy or replicable results? Behav Genet 2001;31:141–8.

Rupniak NMJ. Animal models of depression: challenges from drug development. Behav Pharmacol 2003;14:385–90.

Rusak B. Chronobiology and mood disorders: background and introduction. J Psychiatry Neurosci 2000;25:443–5.

Russell RW, Overstreet DH, Messenger M, Helps SC. Selective breeding for sensitivity to DFP: generalization of effects beyond criterion variables. Pharmacol Biochem Behav 1982;17:885–91.

Ryu SH, Lee SH, Lee HJ, Cha JH, Ham BJ, Han CS, et al. Association between norepinephrine transporter gene polymorphism and major depression. Neuropsychobiology 2004;49:174–7.

Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003;53:1028–42.

Sahakian BJ, Robbins TW, Morgan MJ, Iversen SD. The effects of psychomotor stimulants on stereotypy and locomotor activity in social deprived and control rats. Brain Res 1975;84:195–205.

Sahakian BJ, Robbins TW, Iversen SD. The effects of isolation rearing on exploration in the rat. Anim Learn Behav 1977;5:193–8.

Sakurada T, Shima K, Tadano T, Sakurada S, Kitara K. Sleep wakefulness rhythms in the olfactory bulb lesioned rat. Jpn J Pharmacol 1976;26:606–10.

Sarai K, Frazer A, Brunswick D, Mendels J. Desmethylimipramine-induced decrease in beta-adrenergic receptor binding in rat cerebral cortex. Biochem Pharmacol 1978;27:2179–81.

Schechter MD, Chance WT. Non-specificity of "behavioural despair" as an animal model of depression. Eur J Pharmacol 1979;60:139–42.

Scherschlicht R, Polc P, Schneeberger J, Steiner M, Haefely W. Selective suppression of rapid eye movement sleep (REMS) in cats by typical and atypical antidepressants. Adv Biochem Psychopharmacol 1982;31:359–64.

Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509–22.

Schneider LS, Tariot PN, Lyketsos CG, Dagerman KS, Davis KL, Davis S, et al. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE):Alzheimer disease trial methodology. Am J Geriatr Psychiatry 2001;9:346–60.

Schurhoff F, Szoke A, Bellivier F, Turcas C, Villemur M, Tignol J. Anhedonia in schizophrenia: a distinct familial subtype? Schizophr Res 2003;61:59–66.

Seay B, Hansen E, Harlow HF. Mother–infant separation in monkeys. J Child Psychol Psychiatry 1962;3:3–32.

Seiden LS, Dahms JL, Shaughnessy RA. Behavioural screen for antidepressants: the effect of drugs and electroconvulsive shock on performance under a differential-reinforcement-of-low-rat schedule. Psychopharmacology 1985;86:55–60.

Seligman ME, Beagly G. Learned helplessness in the rat. J Comp Physiol Psychol 1975;88:534–41.

Seligman ME, Rossellini RA, Kozak MJ. Learned helplessness in the rat: reversibility, time course and immunization. J Comp Physiol Psychol 1975;88:542–7.

Sellinger-Barnette MM, Mendels J, Frazer A. The effect of psychoactive drugs on beta-adrenergic receptor binding sites in rat brain. Neuropharmacology 1980;19:447–54.

Serretti A, Artioli P. From molecular biology to pharmacogenetics: a review of the literature on antidepressant treatment and suggestions of possible candidate genes. Psychopharmacology 2004a;174:490–503.

Serretti A, Artioli P. The pharmacogenomics of selective serotonin reuptake inhibitors. Pharmacogenomics J 2004b;4:233–44.

Sherman AD, Allers GL, Petty F, Henn FA. A neuropharmacologically-relevant animal model of depression. Neuropharmacology 1979;18:891–3.

Shepherd GM. Behaviour: smells, brains and hormones. Nature 2006;439:149–51.

Sherman AD, Sacquitne JL, Petty F. Specificity of the learned helplessness model of depression. Pharmacol Biochem Behav 1982;16:449–54.

Shiromani PJ, Overstreet D, Levy D, Goodrich CA, Campbell SS, Gillin JC. Increased REM sleep in rats selectively bred for cholinergic hyperactivity. Neuropsychopharmacology 1988;1:27–33.

Shopsin B, Cassano GB, Conti L. An overview of new "second generation" antidepressant compounds: research and treatment implications. In: Enna SJ, Malick JB, Richelson E, editors. Antidepressants: neurochemical, behavioural and clinical perspectives. New York: Raven Press; 1981. p. 219–51.

Silvestrini B. Trazodone—A new type of antidepressant: a discussion of pharmacological data and their clinical implications. In: Costa E, Racagni G, editors. Typical and atypical antidepressants: molecular mechanism, vol. 32. New York: Raven Press; 1982. p. 327–32.

Simler S, Puglisi-Allegra S, Mandel P. Gamma-aminobutyric acid in brain areas of isolated aggressive or non-aggressive inbred strains of mice. Pharmacol Biochem Behav 1982;16:57–61.

Slattery DA, Desrayaud S, Cryan JF. GABAB receptor antagonist-mediated antidepressant-like behavior is serotonin-dependent. J Pharmacol Exp Ther 2005;312:290–6.

Sofia RD. Effects of centrally active drugs on four models of experimentally-induced aggression in rodents. Life Sci 1969a;8:705–16.

Sofia RD. Structural relationship and potency of agents which selectively block mouse killing (muricide) behaviour in rats. Life Sci 1969b;8:1201–10.

Solberg LC, Horton TH, Turek FW. Circadian rhythms and depression: effects of exercise in an animal model. Am J Physiol Regul Integr Comp Physiol 1999;276:R152–61.

Solberg LC, Olson SL, Turek FW, Redei E. Altered hormone levels and circadian rhythm of activity in the WKY rat, a putative animal model of depression. Am J Physiol Regul Integr Comp Physiol 2001;281:R786–94.

Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev 2005;29:627–47.

Spencer PSJ. Antagonism of hypothermia in the mouse by antidepressants. In: Garattini S, Dukes MNH, editors. Antidepressant drugs. Amsterdam: Excerpta Medica Foundation; 1967. p. 194–204.

Stach R, Lazarova MB, Kacz D. The effects of antidepressant drugs on the seizures kindled from the rabbit amygdala. Pol J Pharmacol Pharm 1980;32:505–12.

Stéru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 1985;85:367–70.

Strekalova T, Spanagel R, Bartsch D, Henn FA, Gass P. Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. Neuropsychopharmacology 2004;29:2007–11.

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157:1552–62.

Sulser F, Bickel MH, Brodie BB. The action of desmethylimipramine in counteracting sedation and cholinergic effects of reserpine-like drugs. J Pharmacol Exp Ther 1964;144:321–30.

Takahashi JS, Pinto LH, Vitaterna MH. Forward and reverse genetic approaches to behaviour in the mouse. Science 1994;264:1724–33.

Tamminga CA, Nemeroff CB, Blakely RA, Brady L, Carter CS, Davis KL, et al. Developing novel treatments for mood disorders: accelerating discovery. Biol Psychiatry 2002;52:589–609.

Tarantino L, Bucan M. Dissection of behaviour and psychiatric disorders using the mouse as a model. Hum Mol Genet 2000;9:953–65.

Teste JF, Martin I, Rinjard P. Electrotherapy in mice: dopaminergic and noradrenergic effects in the Tail Suspension Test. Fundam Clin Pharmacol 1990;4:39–47.

Tezval H, Jahn O, Todorovic C, Sasse A, Eckart K, Spiess J, et al. Cortagine, a specific agonist of corticotropin-releasing factor receptor subtype 1, is anxiogenic and antidepressive in the mouse model. Proc Natl Acad Sci U S A 2004;101:9468–73.

Trivedi M, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40.

Valzelli L, Garattini S. Psychoactive drug effects on behavioural changes induced by prolonged socio-environmental deprivation in rats. Psychol Med 1976;6:271–6.

Valzelli L, Giacalone E, Garattini S. Pharmacological control of aggressive behaviour in mice. Eur J Pharmacol 1967a;2:144–6.

Valzelli L, Consolo S, Morpurgo C. Influence of imipramine-like drugs on the metabolism of amphetamine. In: Garattini S, Dukes MNH, editors. Antidepressant drugs. Amsterdam: Excerpta Medica Foundation; 1967b. p. 61–9.

Valzelli L, Bernasconi S, D'Alessandro M. Effect of tryptophan administration on spontaneous and P-CPA-induced muricidal aggression in laboratory rats. Pharmacol Res Commun 1981;13:891–7.

Van Riezen H. Different central effects of the 5-HT antagonists mianserine and cyproheptadine. Arch Int Pharmacodyn Ther 1972;198:256–69.

Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, et al. Mutagenesis and mapping of a mouse gene. *Clock*, essential for circadian behavior. Science 1994;264:719–25.

Vogel JR, Haubrich DR. Chronic administration of electroconvulsive shock effects on mouse-killing activity and brain monoamines in rats. Physiol Behav 1973;11:725–8.

Vollmayr B, Henn FA. Learned helplessness in the rat: improvements in validity and reliability. Brain Res Brain Res Protoc 2001;8:1–7.

Vollmayr B, Bachteler D, Vengeliene V, Gass P, Spanagel R, Henn F. Rats with congenital learned helplessness respond less to sucrose but show no deficit in activity or learning. Behav Brain Res 2004;150:217–21.

Von Frijtag JC, Reijmers LG, Van der Harst JE, Leus IE, Van den Bos R, Spruijt BM. Defeat followed by individual housing results in long-term impaired reward- and cognition-related behaviours in rats. Behav Brain Res 2000; 117:137–46.

Von Frijtag JC, Van den Bos R, Spruijt BM. Imipramine restores the long-term impairment of appetitive behavior in socially stressed rats. Psychopharmacology 2002;162:232–8.

Von Voigtlander PF, Losey EG. On the use of selective neurotoxic amine analogs to measure the blockade of norepinephrine and 5-hydroxytryptamine uptake systems by antidepressants. Res Commun Chem Pathol Pharmacol 1976;13:389–400.

Von Voigtlander PF, Triezenberg HJ, Losey EG. Interactions between clonidine and antidepressant drugs: a method for identifying antidepressant-like agents. Neuropharmacology 1978;17:375–81.

Wauquier A. The influence of psychoactive drugs on brain self-stimulation in rats. In: Wauquier A, Rolls ER, editors. Brain stimulation reward. Amsterdam: North Holland; 1980. p. 123–71.

Weizman A, Weizman R. Serotonin transporter polymorphism and response to SSRIs in major depression and relevance to anxiety disorders and substance abuse. Pharmacogenomics 2000;1:335–41.

Willner P. Isolation-induced fighting in rats. Pharmacol Biochem Behav 1981;14:475–9.

Willner P. The validity of animal models of depression. Psychopharmacology 1984;83:1–16.

Willner P. Animal models of depression. In: Willner P, editor. Behavioural models in psychopharmacology: theoretical, industrial and clinical perspectives. Cambridge: Cambridge University Press; 1991a. p. 91–125.

Willner P, editor. Behavioural models in psychopharmacology: theoretical, industrial and clinical perspectives. Cambridge: Cambridge University Press; 1991b.

Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 1997;134:319–29.

Willner P, Mitchell PJ. The validity of animal models of predisposition to depression. Behav Pharmacol 2002;13:169–88.

Winsky L, Brady L. Perspective on the status of preclinical models for psychiatric disorders. Drug Discov Today: Disease Models 2005;2:279–83.

Wirz-Justice A. Chronobiology and mood disorders. Dialogues Clin Neurosci 2003;5:315–27.