REVIEW

Treatment-resistant depression: are animal models of depression fit for purpose?

Paul Willner[1] · Catherine Belzung[2,3]

Abstract

Background Resistance to antidepressant drug treatment remains a major health problem. Animal models of depression are efficient in detecting effective treatments but have done little to increase the reach of antidepressant drugs. This may be because most animal models of depression target the reversal of stress-induced behavioural change, whereas treatment-resistant depression is typically associated with risk factors that predispose to the precipitation of depressive episodes by relatively low levels of stress. Therefore, the search for treatments for resistant depression may require models that incorporate predisposing factors leading to heightened stress responsiveness.

Method Using a diathesis-stress framework, we review developmental, genetic and genomic models against four criteria: (i) increased sensitivity to stress precipitation of a depressive behavioural phenotype, (ii) resistance to chronic treatment with conventional antidepressants, (iii) a good response to novel modes of antidepressant treatment (e.g. ketamine; deep brain stimulation) that are reported to be effective in treatment-resistant depression and (iv) a parallel to a known clinical risk factor.

Results We identify 18 models that may have some potential. All require further validation. Currently, the most promising are the Wistar-Kyoto (WKY) and congenital learned helplessness (cLH) rat strains, the high anxiety behaviour (HAB) mouse strain and the CB1 receptor knockout and OCT2 null mutant mouse strains.

Conclusion Further development is needed to validate models of antidepressant resistance that are fit for purpose. The criteria used in this review may provide a helpful framework to guide research in this area.

Keywords Depression · Animal models · Antidepressant · Treatment resistance · Diathesis-stress model · Validation criteria

✉ Paul Willner
p.willner@swansea.ac.uk

1 Department of Psychology, Swansea University, Singleton Park, Swansea SA2 8PP, UK

2 INSERM 930, Tours, France

3 University Francois-Rabelais, Tours, France

Depression is one of the major causes of ill-health and economic burden worldwide, and the need to develop effective and efficient therapies has never been greater. However, after half a century of intensive research since antidepressant drugs were introduced into clinical practice, their efficacy remains stubbornly low, at around 70 % (compared with a no-treatment recovery rate of around 50 %); the onset of action remains stubbornly slow, at around 4–6 weeks; and with very few exceptions, drugs newly introduced into clinical practice have been 'me-too' variants of existing drugs: there has been almost no progress towards the identification of novel targets to improve these clinical parameters (Belzung 2014).

The past two decades have seen remarkable progress in understanding the nature of the abnormalities of information processing that characterise depression, the changes in neural activity that accompany those changes and the relationships between the psychopathology and pathophysiology of depression (Willner et al. 2013; Belzung et al. 2015). As part of this endeavour, research using animal models of depression has proven invaluable in the development of an understanding of the cellular and neuroanatomical changes underpinning these psychophysiological relationships and in establishing in detail the mechanism of action of antidepressant drugs

(Willner et al. 2013). This only increases the sense of frustration arising from the failure of such research to discover novel drugs to extend the reach of antidepressant therapy into the populations of patients who show little or no benefit. Animal models of depression have been of immense value in advancing an understanding of how antidepressants work and improving their side effect profile, and their continuing importance in these contexts is indisputable. However, the purpose of this paper is to explore a radical thesis: that in relation to the problem of treatment-resistant depression specifically (i.e. the situation in which antidepressants do not work), the animal models of depression in current use are not fit for purpose and a different approach is needed.

Animal models of depression

Animal models of psychiatric states may be defined as procedures applied to laboratory animals that engender behavioural changes which are intended to be homologous to aspects of psychiatric disorders, and can therefore be used as experimental tools to further the understanding of human psychopathology (Willner 2009). Animal models are developed for specific investigational purposes. The primary aim of early research was to elucidate psychological processes, but models are now used largely to address neurobiological issues, including the mechanisms of action of psychotherapeutic drugs; the neurotransmitter, neuroreceptor and intracellular changes underlying psychiatric states; the neuroanatomical basis of psychiatric states, and increasingly, questions about the role of specific genes; and of course, the evaluation of the potential psychotherapeutic value of novel pharmacological and non-pharmacological interventions.

According to this definition, animal models of psychopathology involve two elements: an input (a procedure used to elicit abnormal behaviour) and an output (a behavioural endpoint, often associated with biomarkers such as neuroendocrine changes, that is used to measure its effect). The inputs to the model may involve environmental manipulations (e.g. exposure to social or physical stressors, or training regimes), and/or alteration of the internal environment (e.g. by brain lesions or administration of psychotropic drugs), and/or identification of vulnerable individuals (by selective breeding or genomic methods). The behavioural endpoint represents a model of a process (or symptom) that is thought to be important in the disorder. Even if researchers often have the explicit intention to develop models of a pathology, the reality is that these models are typically limited in scope: they simulate specific aspects, reflected in the behavioural endpoint, rather than the entirety of the disorder. However, it may be found subsequently that further aspects of the disorder are also present. For example—as detailed below—the chronic mild stress (CMS) model of depression was developed around a specific

endpoint, a decreased intake of sweet fluids, reflecting an impairment of rewarded behaviour, but was subsequently shown to include a wide range of additional depression-relevant behavioural and physiological abnormalities.

Behavioural models are used in psychopharmacology for two distinct purposes: as simulations within which to study aspects of psychiatric states and as screening tests for the development of new treatments. Screening tests are subject to logistical considerations: for example, the test should be completed in the shortest possible time and ideally will respond to acute drug treatment. However, in a model of a psychiatric condition, these same features may be counter-indicated. Antidepressant drugs are clinically ineffective if administered acutely and are largely inert if administered to non-depressed people: therefore, a model of clinical antidepressant action should involve chronic drug treatment, administered within a context of abnormal behaviour rather than to 'normal' animals. Thus, a particular time course of antidepressant action and a particular level of behavioural sophistication may be desirable or undesirable features, depending upon the purpose for which a procedure is being used. Some of the procedures that are most frequently used in antidepressant research, such as the forced swim test (FST: Porsolt et al. 1977) and the tail suspension test (TST: Steru et al. 1985), involve acute drug treatment to 'normal' animals and should be thought of as screening tests for antidepressant-like activity rather than animal models of depression. They may, however, be employed as behavioural endpoints within animal models of depression, to measure the effect of environmental or physiological manipulations: the FST in particularly is frequently used in this manner.

The above definition of animal models of psychopathology emphasises that they aim to be homologous, rather than analogous, to aspects of psychiatric disorders: that is, to simulate essentially the same process across species rather than to implement a process that simply looks the same. (For example, a bird's wings are homologous to a mammal's limbs, but only analogous to a fly's wings.) It is this feature that provides their translational value. But to be useful for translational purposes, a model must be sufficiently valid, and an assessment of the validity of a model provides an indication of the degree of confidence that we can place in the hypotheses arising from its use. This involves an evaluation of strengths and weaknesses and areas of uncertainty, rather than a yes/no judgement. Several systems of evaluation have been proposed, which have the common feature that models are assessed on two or more independent dimensions. The most widely used method employs the three dimensions of predictive, face and construct validity: predictive validity means that performance in the test predicts performance in the condition being modelled (and vice versa); face validity means that there are phenomenological similarities between the two; and construct validity means that the model has a sound theoretical rationale

(Willner 1984). Some reviewers have advocated the primacy of one or other of these three dimensions (Geyer and Markou 2002; Weiss and Kilts 1998; Sarter and Bruno 2002); more complex frameworks have also been proposed (Belzung and Lemoine 2011). In relation to animal models of depression, predictive validity refers primarily to specific and selective responsiveness to (drug and non-drug) antidepressants; face validity is assessed by comparison to DSM (now DSM-V) symptom checklists, with particular reference to core symptoms of depression; and construct validity is based on an argument for similarity of psychological constructs, such as responsiveness to rewarding events, or if they are known, the underlying neurobiological mechanisms (Willner 1984).

Most animal models of depression are based on the induction of a depressive-like phenotype by stress, which, of course, plays a major clinical role in the onset of depression. Among these, the CMS model is the most extensively validated. Despite early concerns about the reliability of the CMS model, it is now very widely used: the initial report on this model (Willner et al. 1987) and a review of the first 10 years of CMS research (Willner 1997) have each been cited in excess of a thousand times, and the model has been a major player in the development of the current understanding of antidepressant drug action (Willner et al. 2013). In the CMS model, rats or mice are exposed chronically to a constant bombardment of unpredictable micro-stressors, resulting in the development of a plethora of behavioural changes, including decreased response to rewards, a behavioural correlate of the clinical core symptom of depression, anhedonia. Reward sensitivity is usually tracked by periodic (typically weekly) tests in which the animal is given access to a highly preferred sweet solution, or to a choice between a sweet solution and plain water. Consumption of or preference for the sweet reward decreases over weeks of exposure but can be restored to normal levels by chronic treatment with antidepressant drugs. This effect typically takes several weeks, paralleling the clinical situation. In addition to a decreased response to sweet rewards, animals subjected to CMS are generally anhedonic in other tests of rewarded behaviour, such as place preference conditioning or intracranial self-stimulation, and also show all of the other symptoms of depression that it is possible to model in animals, such as decreases in sexual, investigative and other motivated behaviours, decreased self-care, weight loss, disrupted sleep patterns and phase advance of the diurnal rhythm. Some studies have used decreased self-care (Surget et al. 2009, 2011) or increased immobility in the FST as alternative, non-hedonic, behavioural endpoints (Willner 2005). CMS also has extensive physiological and neurochemical parallels with depression (Hill et al. 2012). Reversal of CMS effects has been seen with representatives of all of the clinically used chemical families of antidepressant drug, but not with non-antidepressants of various kinds. Overall, therefore, the model has a high degree of construct, face and predictive validity (Willner

et al. 1987; Willner 1997, 2005). Occasionally, a pattern of behavioural and neurochemical changes has been reported that is opposite to what is usually observed. The basis for these anomalous effects has not been established, but they lead to a recommendation that behavioural validation of the model should always precede or accompany physiological investigations (Willner 2005).

In another frequently used procedure, the learned helplessness (LH) model, animals (originally, dogs; more typically rats or mice) are subjected to inescapable footshock and subsequently display an impairment in learning to escape when given the opportunity to do so (Maier and Seligman 1976). The learning impairment following inescapable shock, which is more evident the more difficult the learning task (for example, a chain of two responses rather than a single response), is interpreted as 'helplessness': the perception that escape is not possible (albeit that this interpretation has been questioned: Willner 1986). The procedure properly involves the use of a yoked control design, in which inescapably shocked animals receive the same shock regime as paired animals that are able to escape; the latter group shows no impairment relative to non-shocked animals. Many studies use a simpler (and less interpretable) procedure based on administration of inescapable shock and comparison of the performance of shocked and non-shocked animals. Animals subject to the learned helplessness procedure show many symptomatic parallels to major depression—so much so that it has been suggested that rodents subjected to uncontrollable shock could meet DSM diagnostic criteria (Weiss et al. 1982)! However, the learned helplessness paradigm is implemented in a variety of different ways in different laboratories, and the version of the paradigm giving rise to the broadest range of symptoms (Weiss et al. 1982) uses extremely high shock levels (4–6 ma) which are of doubtful relevance to depression. Furthermore, the effects of this regime largely dissipate within 2–3 days, and the effects of antidepressant treatment have not been studied using this procedure. Antidepressant effects have typically been studied using shocks of a considerably lower intensity (1.0–1.5 ma) which cause a far less pervasive pattern of behavioural impairment. For example, this procedure has not been reported to engender anhedonia; it does, however, cause some long-lasting physiological changes (e.g. Philbert et al. 2011). As with the CMS model, LH is reversed by a wide range of antidepressant drugs, with relatively few false positives or false negatives. There is some question as to whether LH is better considered as a model of depression or of post-traumatic stress disorder, which also responds to some degree to antidepressant treatment (Foa et al. 1992). Nevertheless, as with CMS, work using the LH model has made major contributions to the understanding of the neural systems underpinning antidepressant action (e.g. Maier and Watkins 2010).

An interesting hybrid model uses acute severe stress (shock) to elicit behavioural deficits then switches to chronic

mild stress to maintain them (Gambarana et al. 2001). This model, however, has been little used. Various other precipitants have been employed to elicit depression-relevant and antidepressant-reversible behavioural endpoints, including repeated social defeat (Chaouloff 2013), withdrawal of rewards (Huston et al. 2013) and withdrawal from chronic drug treatment (D'Souza and Markou 2010). Again, these procedures, while interesting and providing some neurobiological insights, have not been extensively validated or utilised to study mechanisms of antidepressant action.

Why animal models of depression may be of limited value for the development of treatments to overcome antidepressant resistance

Over the past two decades, research using the CMS and LH models (and others), and parallel clinical research, has established that stress precipitates depression primarily by damaging the hippocampus, leading to changes in the activity of a distributed neural system involving various midbrain and forebrain structures, with a particular focus in the ventromedial prefrontal cortex (vm-PFC), and that antidepressants work by repairing the damaged hippocampus, thus restoring the normal balance of activity within that circuitry (Willner et al. 2013). This mechanism—reversal of the neurotoxic effects of stress—represents a significant limitation to the scope of antidepressant action, because it assumes that stress-induced neurotoxicity is the problem that antidepressants need to overcome. However, there are many factors that are known to increase vulnerability to depression, meaning that the role of stress as a precipitant is correspondingly diminished: these include a clinical history of depression and a variety of genetic, personality or developmental risk factors. Significantly, heightened vulnerability to depression is associated with resistance to antidepressant drug treatment (Willne et al. 2014). Thus, although antidepressants provide an efficient means of reversing the neurotoxic effects of stress, they are much less effective in conditions where vulnerability to depression is elevated, the role of stress in precipitating depression is correspondingly lower, and as a result, the major substrate for antidepressant action (stress-induced neurotoxicity) is absent or minor.

In light of these findings, we have argued elsewhere that progress towards drug therapies for treatment-resistant depression may require a paradigm shift away from stress-based models of depression and towards models of vulnerability to depression (Willner et al. 2013, 2014). Indeed, the ideal models to investigate the potential reversal of risk factors may be models in which conventional antidepressants are ineffective.

Animal models of predisposition to depression

Risk factors (diatheses) for depression may present as 'silent' until activated by stress (e.g. a genetic risk factor that does not directly elicit depressive symptoms, or a tendency towards depressive thinking that is well controlled), as a sub-syndromal depressive condition (recognised as depressive personality disorder in DSM-III, which was retained for research purposes in DSM-IV, but has now been dropped from DSM-V), or as dysthymia (pervasive depressive disorder in DSM-V), a low-grade chronic condition that is difficult to distinguish symptomatically from a major depressive episode. Consequently, animal models of a depressive diathesis could appear either as essentially 'normal' animals that are more sensitive to a precipitant used to induce 'depressive' behaviour, or could present 'depressive' features in the absence of any specific experimental manipulation. In the latter case, from a modelling perspective, there is little to distinguish chronic low-grade depression from a major depressive episode other than severity and chronicity. In relation to predictive validity, chronic low-grade depressions are less responsive to drug treatment, but to the extent that they are treatable, they respond to the same range of antidepressant drugs as major depression. There is greater clinical use of dopaminergic antidepressants such as amisulpride in dysthymia, and a recent meta-analysis found that amisulpride was more effective than the SSRI fluoxetine (Kriston et al. 2014), but dopaminergic antidepressants are also effective in major depression, so this does not differentiate the two syndromes. In relation to face validity, some features, including anhedonia and vegetative symptoms, are perhaps less prominent in pervasive depressive disorder than in major depression, but the differential diagnosis is made entirely on the basis of duration of illness. There are also no significant differences in the theoretical understanding of chronic low-grade depression and major depression (construct validity). In a nutshell, there are no distinctive validity criteria for animal models of chronic low-grade depression as distinct from major depression (Willner and Mitchell 2002).

A diathesis-stress perspective

The situation is different, however, when we consider the problem of drug-resistant depression within a diathesis-stress perspective. As outlined above, antidepressant resistance arises, at least in part, from the occurrence of depression in high-risk individuals (Willne et al. 2014). Therefore, an appropriate model within which to investigate antidepressant-resistant depression is one in which a valid model of depression is implemented in the context of a valid model of a risk factor for depression. In this situation, two clear criteria should be satisfied. First, depression-like behaviour should be elicited

more readily in high-risk groups. As discussed above, this criterion may to some extent be automatically satisfied in relation to risk factors that by themselves elicit depressive-like features, but the features in question should be valid endpoints, such as hedonic measures. Second, and critically, the effectiveness of conventional antidepressants should be lower in high-risk than in low-risk groups. This is actually a less straightforward issue to investigate than might at first appear, because it requires a comparable pre-treatment behavioural baseline, which may be difficult to achieve if the high-risk group are more stress sensitive than the low-risk group.

We might tentatively propose a third criterion for models of antidepressant-resistant depression, that high-risk and low-risk groups should respond equally well to unconventional antidepressant treatments that act outside the hippocampus. The rationale for this proposal is that it is the action of antidepressants within the hippocampus that is responsible for the greater effectiveness of antidepressants in low-risk groups, where the effects of stress-induced neurotoxicity are more prominent. Thus treatments that bypass the hippocampus and act directly within other parts of the depression circuitry—in particular, the prefrontal cortex (PFC)—may not be limited in their action by a lesser involvement of stress in the precipitation of a depressive episode. For example, deep brain stimulation (DBS) of the vm-PFC has been reported to produce long-lasting antidepressant effects in treatment-resistant depressed patients (Mayberg 2009; Hamani et al. 2011; McGrath et al. 2014). A rapid reversal of CMS-induced anhedonia and other depression-related behaviours has also been demonstrated in rats following DBS of the vm-PFC (Hamani et al. 2012; Dournes et al. 2013; Veerakumar et al. 2014). For obvious reasons, DBS has not been used in antidepressant-responsive patients, but there is a reasonable expectation that it would be effective if implemented. Rapid improvements in antidepressant-refractory patients are also reported following single intravenous infusions of the NMDA receptor antagonist ketamine (Berman et al. 2000; Zarate et al. 2006; Diazgranados et al. 2010). These effects appear to be mediated by direct actions within the PFC, as ketamine has been shown to suppress activity in the rostral anterior cingulate cortex (Salvadore et al. 2009), a strong predictor of successful antidepressant treatment (Pizzagalli 2011), and this effect occurs too rapidly to be mediated through structural changes in the hippocampus. In the CMS model, a single injection of ketamine reversed not only the anhedonic and other behavioural deficits, but also the atrophy of dendritic spines in the PFC and the associated electrophysiological deficits (Li et al. 2010, 2011b; Duman et al. 2012). Ketamine has psychotomimetic effects, so again, for obvious reasons, it has not been tested in antidepressant-responsive patients.

Animal models of heightened vulnerability and antidepressant resistance

We will now consider some animal models of predisposition to depression in relation to specific risk factors that are known to be associated with an increased proclivity to depression and resistance to antidepressant treatment (Willne et al. 2014). In each case, we consider the extent to which the model can be said to meet the first two of the criteria we have outlined: increased sensitivity to stress in a valid animal model of depression and insensitivity of those effects to conventional antidepressant treatment. The third criterion, a good response to unconventional antidepressants that appear effective in treatment-resistant depression, is barely discussed for the simple reason that with three exceptions (the Wistar-Kyoto (WKY) and congenital learned helplessness (cLH) rat and high anxiety behaviour (HAB) mouse strains), the effectiveness of unconventional treatments for resistant depression has not been examined in any of the other models under consideration.

The models that we discuss all involve the application of stress to animals with a biological background that can be considered depression-related (Harro 2012); that is, they include both a putative risk factor and a proximal stressor. Not reviewed here in detail are procedures advanced as models of predisposition to depression—many of which, as discussed above, display a depressive-like phenotype—for which tests have not been conducted to confirm that they do actually involve heightened vulnerability. (This exclusion would apply, for example, to a genetically manipulated mouse for which the FST represents the extent of its behavioural evaluation.) We also do not discuss procedures that result in an antidepressant-like phenotype or that confer resilience to stress, because these models do not provide a test-bed for research on treatment-resistant depression.

History of depression

One of the most powerful risk factors for depression is a previous history of depressive episodes. Each episode of depression increases the probability of a further episode (American Psychiatric Association 2000; Solomon et al. 2000), and with each successive episode, the severity of stress needed to precipitate the episode decreases (Kendler et al. 2000; Dienes et al. 2006; Stroud et al. 2008; Morris et al. 2010; Slavich et al. 2011). Recurrent depressions are also more resistant to pharmacotherapy than first-episode depressions (O'Reardon et al. 2007; Souery et al. 2007; Kaymaz et al. 2008; Rush et al. 2011). However, this reflects a specific failure of antidepressant drug treatment: the efficacy of cognitive therapy for depression is maintained across repeated episodes (Leykin et al. 2007), which presumably reflects the fact that psychotherapy engages the PFC directly and differently from

antidepressant drugs (Kennedy et al. 2007; Mayberg 2009; Clark and Beck 2010; Hamani et al. 2011).

We are aware of only a single study that has modelled a history of depression by repeated stress induction. Isingrini et al. (2010) subjected BALB/c mice to two 7-week periods of CMS separated by a 6-week interval. Using a relatively mild CMS procedure, a wider range of behavioural impairments was seen after the second, relative to the first, period of CMS exposure, indicating an increase in stress sensitivity. In animals maintained on a normal diet, chronic treatment with fluoxetine decreased all of the behavioural impairments. However, in mice fed a high-fat diet (modelling the vascular risk for depression: Camus et al. 2004), mice treated with fluoxetine showed no behavioural impairment after the first CMS period, but fluoxetine was without effect following the second CMS exposure. Thus, the study demonstrated increased stress sensitivity in previously stressed animals, and antidepressant resistance was induced by an interaction between a high-fat diet and a history of repeated stress exposure.

Early life stress

Developmental factors, such as multiple loss events or childhood adversity (Souery et al. 1999), are also associated with both vulnerability to depression and antidepressant treatment resistance. The developmental factor that has been most studied is childhood maltreatment. A recent meta-analysis reported that adults who had been abused as children had a greatly elevated risk of developing recurrent or persistent depression, as well as a substantial increase in rates of failure to respond to pharmacotherapy (Nanni et al. 2012). As with a history of depression, the elevated level of risk involves an increased sensitivity to stress rather than an increased exposure to stressors (Kendler et al. 2004; Harkness et al. 2006; Shapero et al. 2014), and adults who were abused as children were normally responsive to psychotherapeutic interventions, again indicating a specific resistance to antidepressant drug treatment (Nanni et al. 2012).

There are many and diverse animal models of early stress, including several paradigms involving interference with mother-pup interactions by periods of separation and variations in the quality of maternal care or the postnatal environment; there is also considerable variation in the comparison group used (Pryce et al. 2005). None of these manipulations in themselves produces a reliable depression-like phenotype in mice or rats (Millstein and Holmes 2007; Schmidt et al. 2011); in particular, there is little if any evidence that rats subjected to these early manipulations are anhedonic (Pryce et al. 2005). However, as discussed above, for present purposes, the major issue is whether any of these procedures produce an increase in stress precipitation of depression-relevant behaviours in later life. Again, there is little evidence that early life stress increases responsiveness to stress in adulthood; indeed,

resilience to adult stress is often reported (Schmidt et al. 2011). In one study, separation of Sprague-Dawley rat pups from their mothers, for 15 min daily between postnatal days 2 and 14, led to an increase in anhedonia and other depression-relevant behaviours, hypothalamic-pituitary-adrenal (HPA) activity and gene expression in vm-PFC, following repeated restraint stress, but the response to antidepressant treatment was not studied (Uchida et al. 2010). However, in another study, early deprivation was reported to increase the acquisition of LH by adult rats of the Fischer strain (but not by Wistar rats), but the effect was reversed by chronic fluoxetine treatment, suggesting that this will not lead to a model for antidepressant resistance (Rüedi-Bettschen et al. 2004). A third study reported that naturalistically occurring poor maternal care led to an increased anhedonic response to CMS in outbred Wistar rats; the response to antidepressant treatment was not examined (Henningsen et al. 2012). However, there is evidence that greater adult emotionality between mouse strains may to some extent reflect differences in early maternal care (Calatayud and Belzung 2001), and this is not associated with resistance to antidepressant treatments (Ibarguen-Vargas et al. 2009). Overall, these data do not give confidence that work with combined early-life and late stress models will significantly improve the research environment for the development of treatments for antidepressant-resistant depression.

An important limitation of rodent studies of early-life stress is that the early post-natal period in rodents corresponds to the pre-natal period of brain development in humans, which casts doubt on the validity of early manipulations as models of childhood adversity. A closer parallel is provided by a model in which stress is applied to 'juvenile' rats in the post-weaning to pre-pubertal stage. Juvenile exposure to stressors, such as predator scent or a 3-day varied stress regime (forced swim, elevated platform and restraint), leads to increased emotional reactivity in adulthood, with around a third of subjects showing LH and other depression-related abnormalities, while the other two thirds exhibited anxiety-related behaviour (Tsoory and Richter-Levin 2006; Tsoory et al. 2007; Horovitz et al. 2012). Antidepressants have not been tested in this model.

Genetic factors

Depression has a strong familial component. For example, whereas women with a low genetic risk for depression showed the typical pattern of high stress exposure before a first episode of depression and a gradual decrease in the extent of stress exposure before subsequent episodes, in women with a family history of depression and a depressed co-twin, the first episode of depression was precipitated by very low levels of stress, and this did not change across episodes (Kendler et al. 2001a). These familial effects could reflect a shared environment, but are typically assumed to reflect genetic influences, and as discussed below, several genes have been

identified that are associated with both predisposition to depression and resistance to antidepressant treatment.

Many transgenic mice have been designed to assess the effects of antidepressant drugs. Some of them are completely unrelated to depression. For example, the P-gp knockout mouse (abcb1a mouse, Uhr et al. 2000, 2003; Uhr and Grauer 2003; Karlsson et al. 2013) is a model targeting drug penetration across the blood-brain barrier, such that in the knockout mice, effects of drugs were prevented if they were Pg-p substrates, but not otherwise—so unlike other SSRIs, the effects of fluoxetine were unaffected. Due to the fact that Pg-P is a multidrug resistance protein completely unspecific to depression, no data have been published regarding the stress sensitivity of this model, so it is not possible to assess its validity in relation to our first criterion. However, this does parallel clinical data showing an association between a polymorphism of the *ABCB1* gene and antidepressant response (Uhr et al. 2008).

As monoaminergic drugs are classically used in the treatment of depression, the contribution of the monoaminergic system to their effects has been extensively investigated. For example, PCPA, which blocks serotonin synthesis, suppressed the effects of subchronic treatment with fluoxetine and imipramine, but not those of noradrenergic compounds such as reboxetine or desipramine (O'Leary et al. 2007). In TPH2 (−/−) mice, the enzyme that enables serotonin synthesis in the brain is absent. While the knockout mice did not respond to SSRIs, their sensitivity to stress in the CMS and LH models was unchanged (Angoa-Pérez et al. 2014), so this model does not meet our first criterion.

In humans, the most studied of the monoaminergic genes is a functional polymorphism in the promoter region of the serotonin transporter gene, 5-HTTLPR, which has been reported to moderate the effects of stressful life events on depression. In the absence of stress, all genetic subtypes have the same low risk of depression, but as the frequency of stressful events increases, the risk of depression is greatly elevated in individuals homozygous for the short allele of the 5-HTTLPR gene relative to individuals homozygous for the long allele, with heterozygotes showing an intermediate level of risk (Caspi et al. 2003, 2010; Uher and McGuffin 2008; Karg et al. 2011). The parallel finding is that individuals homozygous for the short allele of the 5-HTTLPR gene are less responsive to antidepressant treatment than individuals homozygous for the long allele, with heterozygotes showing an intermediate response (Serretti et al. 2007; Zobel and Maier 2010; Licinio and Wong 2011).

Similar results have been found in primates, as the short allele of the 5-HTTLPR gene increased the neuroendocrine response to separation stress in infant macaques (Barr et al. 2004), increased sensitivity to social stress in adult rhesus monkeys (Jarrell et al. 2008), and was also associated with a decreased hormonal response to acute administration of the

SSRI citalopram (Michopoulos et al. 2011). These results suggest that polymorphisms of the 5-HTTLPR gene may have similar effects on stress sensitivity and antidepressant responsiveness in humans and non-human primates. Similarly, in mice, the serotonin transporter knockout mouse may fulfil at least the two first validity criteria as a model of antidepressant resistance. These mutant mice display both heightened vulnerability to stress (Hariri and Holmes 2006; Muller et al. 2011) and an absence of effects of acute SSRIs (Holmes, et al. 2002). To our knowledge, the behavioural effects of chronic SSRIs have not been assessed after genetic deletion of the serotonin transporter. However, the effects of chronic duloxetine, a mixed 5-HT-NA uptake inhibitor, on brain-derived neurotrophic factor (BDNF) levels in the hippocampus and the frontal cortex were maintained in this model (Calabrese et al. 2010), suggesting that antidepressant resistance may be specific to SSRIs.

Others studies have investigated the effects of ablation of different 5-HT receptors. Mice bearing mutations of both 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors show increased emotionality, but they still respond to chronic SSRIs (Guilloux et al. 2011). However, the effects of SSRIs but not of imipramine were abolished in 5-HT$_{1A}$ knockout mice (Santarelli et al. 2003). Interestingly, the mutants displayed increased anxiety (Ramboz et al. 1998; Heisler et al. 1998; Parks et al. 1998; Zhuang et al. 1999) and decreased depressive-like behaviour (Ramboz et al. 1998; Heisler et al. 1998; Parks et al. 1998), alongside increased physiological responses to acute and chronic stress (Patti et al. 2002; Carnevali et al. 2014). If we consider that the critical factor is stress sensitivity, rather than behaviour in depressive behaviour bioassays, this mutant fulfils the first two criteria as a model of antidepressant resistance, albeit that resistance would be restricted to SSRIs. This parallels clinical findings showing an association of a polymorphism of the 5-HT$_{1A}$ receptor with antidepressant resistance (Kato and Serretti 2010). In 5-HT$_{1B}$ knockout mice, the effects of acute but not of chronic SSRIs were prevented (Trillat et al. 1998; Mayorga et al. 2001) so this would not be considered a model of antidepressant resistance. However, a recent study reported that these mice displayed increased stress-induced autonomic and locomotor responses and no response to chronic fluvoxamine, suggesting that this model may merit further study (Vinkers et al. 2011). Genetic mutants studied in relation to other serotoninergic-receptor genes include mice with a deletion of the 5-HT$_{2B}$ receptor, which showed resistance to chronic fluoxetine and paroxetine (Diaz et al. 2012) but were not tested for stress sensitivity, and mice with a deletion of the 5-HT$_{2C}$ gene, which showed potentiation of the effects of acute fluoxetine in a bioassay (Cremers et al. 2004) but were not studied further to our knowledge. Studies on the 5-HT$_4$ receptor null mutant showed that ablation of this receptor attenuated the response to stress-induced hypophagia (Compan et al. 2004), while repeated

administration of citalopram produced a total inhibition of 5-HT firing in the knockouts, and only a partial inhibition in wild-type mice (Conductier et al. 2006): both results suggest that this might rather be a model of decreased antidepressant resistance. A final target related to serotoninergic neurotransmission is p11 (which recruits 5-HT1B receptors to the cell membrane) and its target SMARCA3. Ablation of p11 abolished the effects of chronic imipramine in the open field and induced increased thigmotaxis (suggesting heightened anxiety behaviour) (Svenningsson et al. 2006), while ablation of SMARCA3 suppressed the effect of chronic escitalopram on stress-induced anhedonia (Oh et al. 2013). However, ablation of SMARCA3 did not modify sucrose consumption after chronic stress (or the effects of acute escitalopram in the tail suspension test) (Oh et al. 2013). Overall, while there may be some interesting leads, none of the 5-HT receptor mutant mouse models stand out as clearly relevant to treatment-resistant depression.

The effects of targeted modifications of the noradrenergic system have also been investigated. For example, ablation of the gene encoding dopamine beta-hydroxylase (DBH), which converts dopamine into noradrenaline and adrenaline, prevented the antidepressant-like effects of noradrenergic drugs, such as desipramine or reboxetine, but it also abolished the action of drugs acting on other monoaminergic targets such as pargyline, bupropion and the SSRIs fluoxetine, sertraline and paroxetine, though strangely the effects of citalopram remained unchanged (Cryan et al. 2001, 2004). Further, the ablation of DBH increases sensitivity to restraint stress (Kvetnanský et al. 2008), albeit that depression-relevant behaviours have not been tested. Therefore, this mutant may satisfy two criteria as a model of antidepressant drug resistance. However, the antidepressant studies involved acute drug treatment in the FST: further studies using chronic drug treatment and a more valid behavioural model are needed.

Another interesting monoamine-related genetic model is the OCT2 (Organic Cation Transporter 2) null mutant mouse. OCT2 is involved in the clearance of noradrenaline and serotonin so the mutant mice display decreased levels of serotonin and noradrenaline, associated with increased anxiety and immobility in the FST (Bacq et al. 2012). Interestingly, the effects of acute selective noradrenaline or serotonin transporter blockers were increased in bioassays, but the effects of chronic venlafaxine in the chronic corticosterone model were decreased (Bacq et al. 2012). Subsequently, these mice were shown to exhibit an increased sensitivity to behavioural effects of CMS (Couroussé et al. 2014). Therefore, this model does appear to fulfil two criteria as a genetic model of antidepressant resistance (increased stress sensitivity and no response to chronic antidepressant treatment).

Other neurotransmitter-related mutants that have been investigated in relation to stress include mutants of the glutamatergic system. Effects reported include increased sensitivity

to chronic stress or defeat stress for vGLUT1+/− mice (Garcia-Garcia et al. 2009; Venzala et al. 2012) and greater LH for mice with a GSK3 mutation inhibiting GSK3 phosphorylation (Polter et al. 2010). However, the effects of chronic antidepressants have not been assessed in these models. The endocannabinoid (eCB) system is a neuromodulatory system in which post-synaptic cannabinoids suppress presynaptic transmitter release from GABAergic and glutamatergic axon terminals via CB1 receptors. Clinical data have shown that both predisposition to depression and resistance to antidepressant treatment are linked to polymorphisms of genes coding for the CB1 receptor (Domschke et al. 2008; Juhasz et al. 2009). Endocannabinoids are metabolised by fatty acid amide hydroxylase (FAAH), and mice with deletion of the FAAH gene show resistance to chronic stress (Hill et al. 2013). Conversely, increased CMS-induced anhedonia has been observed in CB1 receptor knockout mice (Martin et al. 2002; Valverde and Torrens 2012). Further, sensitivity to subchronic (three injections) administration of desipramine or paroxetine was slightly altered in these mice (Steiner et al. 2008), suggesting the possibility of antidepressant resistance.

As antidepressant resistance in humans is associated with dysregulation of the HPA axis, (Belzung and Billette De Villemeur 2010), other studies have investigated modifications of genes encoding components of the stress axis. Various mutants of glucocorticoid receptors (GR) have been described, including models of loss of GR and models of increased GR. The models of loss include GR+/− mice, which exhibit a partial loss of GR in the whole body; GR^NesCre mice, which have GR loss restricted to the entire brain, neurons and glial cells during adulthood; FBGRKO mice which display GR loss in forebrain neurons during adulthood; GR^CaMKCre mice, which exhibit GR loss in neurons in brain and cells in the pituitary during development (at P6); Sim1Cre-GRe3D mice, which exhibit GR loss primarily in PVN neurons during adulthood; and GR^POMCCre mice, which show GR loss in the anterior pituitary cells throughout life. GR+/− mice display increased stress responsivity in the LH model (Ridder et al. 2005). Stress coping behaviour is increased in GR^NesCre and GR^POMCCre mice while the opposite is found in FBGRKO mice (depending upon the genetic background), while no effect is detected in GR^CaMKCre and Sim1Cre-GRe3D mice. Further, the GR^NesCre and Sim1Cre-GRe3D mice show increased corticosterone levels after stress (Laryea et al. 2015). Additional models include loss of GR in dorsal raphe neurons (DRNGRKO), associated with increased stress coping behaviour (Vincent and Jacobson 2014), or loss of GR in DA neurons, which induces some resilience when GR have been inactivated in DA-innervated postsynaptic neurons, but not when they have been inactivated on presynaptic DA neurons (Barik et al. 2013). To our knowledge, out of all of the mutants so far mentioned, the effects of antidepressant treatments have only been investigated in the FBGRKO mice, revealing

normal responses to acute or chronic antidepressants (Boyle et al. 2005; Vincent et al. 2013). Additionally, viral-induced knockdown of GR in the prefrontal cortex had no effect on corticosterone or behaviour in the FST but increased sensitivity to chronic imipramine (Hussain and Jacobson 2015). Mutants with increased GR function include mice overexpressing GR throughout the brain (so-called YGR mice because overexpression is achieved by a yeast artificial chromosome). Interestingly, they exhibit a hormonal and the behavioural resistance to immobilisation stress and are also more resistant to the development of LH (Ridder et al. 2005). To our knowledge, antidepressant sensitivity has not been tested in these mice.

The opposite profile was found in transgenic mice with GR overexpression in forebrain (GRov), which showed increased environmental reactivity and vulnerability to stress-induced cognitive deficits (Hebda-Bauer et al. 2010). GRov mice also showed evidence of impaired negative feedback inhibition of the HPA axis (Wei et al. 2007). However, as these mice are supersensitive to antidepressants (Wei et al. 2004), they cannot be considered a model of antidepressant resistance. Finally, mice overexpressing mineralocorticoid receptors (MR) in the forebrain exhibited decreased anxiety behaviour and corticosterone release in response to restraint stress (Rozeboom et al. 2007). So far, therefore, there is no evidence that direct manipulations of GR or MR produces a model of antidepressant resistance, though for most models the relevant experiments have not yet been conducted. A related target is the FK506 binding protein 51 (FKBP51), which is a regulator of the GR via its action on the chaperone Hsp90. Knockouts for FKBP51 have been generated that do display resistance both to the behavioural and physiological effects of chronic paroxetine while if anything being less sensitive to stress (Gassen et al. 2014).

In people, several studies have shown that genetic polymorphisms in the *CRFR1* gene modulate the influence of exposure to childhood abuse on adult depression (Bradley et al. 2008; Ressler et al. 2010; Polanczyk et al. 2009; Kranzler et al. 2011; Grabe et al. 2010). In mice, two haplotypes of the *CRFR1* gene have been described that are associated with single nucleotide polymorphisms on regulatory regions of the gene identical to the ones found in humans (Labermaier et al. 2014). The risk haplotype (TT homozygotes) is associated with higher sensitivity to chronic stress in adolescence, when compared to mice from the CC genotype (Labermaier et al. 2014), and this pattern is reversed by CRFR1 antagonists. However, the effects of more classical antidepressants have not yet been assessed in this mutant. Other CRH-related mutants include conventional CRF-overexpressing mice (Stenzel-Poore et al. 1994; van Gaalen et al. 2002), mice with CRH overexpression in neurons (Dirks et al. 2001; Groenink et al. 2002), CRFR1 knockout mice (Smith et al. 1998; Timpl et al. 1998), mice with transient perinatal forebrain CRF

overexpression (Kolber et al. 2010), mice with conditional forebrain-restricted inactivation of CRFR1 (Muller et al. 2003), mice with CRH overexpression in the pituitary and mice with deficient CRF2 receptors (Bale et al. 2000, 2002). With the exception of the mice overexpressing CRF in the pituitary (Dedic et al. 2012), all other mutants exhibit increased anxiety like-behaviour but were not assessed for stress vulnerability. Interestingly, mice deficient in CRFR2 receptors are hypersensitive to stress exposure and display increased stress-induced corticosterone levels and increased anxiety-like behaviour (Bale et al. 2000, 2002). Unfortunately, to our knowledge, none of the CRF mutants has been tested in relation to antidepressant resistance. Finally, due to the synergistic effects of vasopressin with CRF in the control of the HPA axis, the phenotype of the V1b knockout has also been investigated. In these mice, release of ACTH and corticosterone following acute stress was attenuated (see Koshimizu et al. 2012), as were corticosterone levels after acute fluoxetine or desipramine (Stewart et al. 2008). Further, V1b knockout mice show decreased ACTH after chronic restraint (Lolait et al. 2007), which suggests increased stress sensitivity. However, to our knowledge, the effects of chronic antidepressants have not been assessed in this model. In conclusion, none of the HPA-related mutants (GR/MR/CRH/vasopressin) fulfils both the criteria of increased stress sensitivity and that of resistance to chronic antidepressants.

Other players in antidepressant resistance are transcription factors and their targets, for example, the transcription factor deltafosB and its targets GluA2 (an AMPA receptor subunit) and CaMKII. Overexpression of DeltaFos within the nucleus accumbens (achieved either using bitransgenic mice or by viral injection) promotes resilience to chronic social defeat, whereas increased expression of deltaJun in the same area has the opposite effects (Nestler 2015). Viral-mediated overexpression of GluA2 in the same structure also induced resilience to social defeat (Nestler 2015). The effects of chronic fluoxetine were abolished in mice with a viral-induced overexpression of deltafosB or CaMKII within the accumbens (Nestler 2015). However, in this model, antidepressant resistance is not associated with increased stress sensitivity.

Considering that BDNF mediates the chronic effects of monoaminergic antidepressants (D'Sa and Duman 2002), polymorphisms modifying the expression of BDNF could alter the therapeutic action of antidepressants. In human studies, two meta-analyses (Kato and Serretti 2010; Zou et al. 2010) reported a better response to antidepressants in Met allele carriers, while conversely, the val/val genotype was linked to resistance to chronic treatment with escitalopram (El-Hage et al. 2015). These findings have been translated to rodents, but with findings opposite to those predicted: BDNF (met/met) mice exhibit increased anxiety behaviour and a decreased response to long-term fluoxetine (3 weeks) (Chen et al. 2006). However, sensitivity to chronic stress has not been assessed in

these mice. Interestingly, BDNF+/− mice exhibited normal effects of acute antidepressants (Saarelainen et al. 2003) and a normal response to CMS, but the effects of chronic imipramine in CMS mice were dampened (Ibarguen-Vargas et al. 2009), suggesting antidepressant resistance. These mice performed normally in various depression-related tests, other than an increase in LH that was attributable to a decrease in pain sensitivity (MacQueen et al. 2001). BDNF is known to function differently in different brain areas, and deletion of BDNF restricted to the dentate gyrus was found to attenuate the effects of subchronic injections of desipramine or citalopram in the FST (Adachi et al. 2008), but again, the effects of chronic stress were not assessed. Finally, some studies have explored the involvement of the target of BDNF, the TrkB receptor. First it was shown that TrkB ablation suppressed the effects of acute imipramine and fluoxetine in the FST (Saarelainen et al. 2003), and ablation of TrkB in hippocampal neural stem cells (but not in mature neurons of the dentate gyrus) suppressed the antidepressant-like effects of chronic (21 days) fluoxetine or imipramine. Unfortunately, the effects of chronic stress were again not assessed. Overall, these data suggest that there might be some potential for region-specific BDNF-related mutants, but research is at a very early stage.

Two final genetic models are not directly related to synaptic transmission or transduction. Aquaporins (AQPs) are water channel proteins involved in regulating water homeostasis, AQP4b being the predominant form in the brain where it is expressed in adult neural stem cells as well as in astrocytes. In the AQP4 knockout mouse, the antidepressant and anxiolytic effects of chronic fluoxetine were prevented, as were the fluoxetine-induced enhancement of adult hippocampal neurogenesis and the hippocampal CREB phosphorylation. However, mutants and wild-type mice were similar in their behavioural responses to CMS (Kong et al. 2009). Finally, mice with a genetic deletion of macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine expressed in the brain, particularly in hippocampal stem cells and proliferating cells, show increased immobility in the FST and decreased adult hippocampal neurogenesis, as well as resistance to the ability of chronic (14 days) fluoxetine to increase hippocampal neurogenesis (Conboy et al. 2011). Although the sensitivity of these mice to chronic stress has not been assessed and resistance to the behavioural effects of chronic antidepressants have not been tested, the observed phenotype suggests that this model could potentially fulfil our criteria for antidepressant resistance.

Personality factors

Much of the influence of both genetics and early traumatic events on depressive symptomatology is mediated through the personality factor of neuroticism (Kendler and Gardner 2011), which is one of the strongest risk factors for depression (Enns and Cox 1997; Christensen and Kessing 2006; Kendler and Myers 2010). Early-onset depression, in particular (first episode before the age of 30), is characterised by a higher level of neuroticism and a higher prevalence of comorbid personality disorders (Bukh et al. 2011). Neuroticism is also well established as a factor associated with resistance to antidepressant treatment (Souery et al. 1999; Bock et al. 2010).

There have been numerous attempts to model the personality risk for depression by selective breeding of animals with depressive characteristics, high levels of emotionality or dysfunctions of the stress axis. Roman low avoidance (RLA) and fawn hooded (FH) are two 'classic' high-emotionality rat strains. The RLA rat strain was selectively bred for poor avoidance in the shuttle box paradigm, while their high-avoidance (RHA) counterparts were selectively bred for their good performance in that task. RLA rats show behaviour characteristic of heightened emotionality in several tests, including increased immobility in the FST (Steimer and Driscoll 2003). However, RLA and RHA rats react similarly to social defeat (Meerlo et al. 1997), and in the FST RLA rats show a greater response to acute or chronic antidepressant treatment (Piras et al. 2014). FH rats exhibit hyperactivity of the HPA axis, a characteristic of depressive illness, increased ethanol intake and preference and increased immobility in the FST (Rezvani et al. 2002), though this has not always been observed (e.g. Lahmame et al. 1996). Again, these abnormalities are corrected by antidepressant treatment (Rezvani et al. 2002). These findings suggest that the RLA and FH strains are likely to prove of limited relevance to treatment-resistant depression.

One of the most studied 'depressive' rat strains is the Flinders sensitive line (FSL), which was originally bred for cholinergic supersensitivity, and subsequently shown to display a range of physiological and behavioural features characteristic of depression, including dysregulation of serotonergic neurotransmission, increased rapid eye movement (REM) sleep and elevated immobility in the FST (Overstreet and Wegener 2013). Significantly, the FSL rat does not show abnormal responses to rewards under baseline conditions (Pucilowski et al. 1993; Matthews et al. 1996) but does show increased anhedonia when subjected to CMS (Pucilowski et al. 1993). However, in comparison to the Flinders resistant line (FRL) control strain, the FSL rat is much more responsive to antidepressant reduction of immobility in the FST (Overstreet and Wegener 2013). While antidepressant studies have not been conducted in FSL rats subjected to CMS, these results suggest that the FSL rat also does not show promise in relation to treatment-resistant depression.

More promising are Wistar-Kyoto rats, which were originally bred as a normotensive control strain for the spontaneously hypertensive (SHR) rat strain, but were later found to display physiological and behavioural features suggestive of

heightened emotionality, including increased immobility in the FST (Nam et al. 2014) and, of greater relevance, enhanced physiological responses to repeated stress (Morilak et al. 2005) and an increased propensity to develop LH (Belujon and Grace 2014). Strain differences in antidepressant responses have not been studied in relation to LH, but WKY rats have been shown repeatedly to be less responsive to antidepressants in the FST, with some studies reporting a specific sub-sensitivity to serotonergic antidepressants (López-Rubalcava and Lucki 2000) and others reporting a more general effect (Lahmame et al. 1997). WKY rats are also sub-sensitive to suppression of REM sleep by both noradrenergic and serotonergic antidepressants, despite showing a higher baseline of REM sleep (Ivarsson et al. 2005). Interestingly, LH was reversed by ketamine in WKY rats (Belujon and Grace 2014). There was no comparison with the control strains in this study; however, WKY rats were more responsive than outbred Wistar rats to ketamine reversal of immobility in the FST (Tizabi et al. 2012). These findings suggest that WKY rats go some way to satisfying all three of our criteria for a model of antidepressant treatment resistance.

Another interesting procedure is the congenital learned helplessness (cLH) strain. cLH rats, and their counterpart congenital non-LH controls, were bred by selecting for individuals that developed the most and least severe LH when tested with mild levels of shock that induce LH in only some of the subjects. After many generations, cLH animals were produced that fail to escape even without prior stress exposure (Vollmayr and Henn 2001). They are also anhedonic in several different behavioural tests (Vollmayr et al. 2004; Sanchis-Segura et al. 2005; Shumake et al. 2005; Shabel et al. 2014). Importantly, unlike LH, which is readily reversed by antidepressant treatment, cLH animals are said to be resistant to antidepressant reversal of their helpless behaviour (Sartorius et al. 2007; F. Henn, personal communication; B. Vollmayr, personal communication). However, an antidepressant effect in cLH rats was found with a high dose of the MAO-B inhibitor deprenyl, which preferentially protects DA rather than NA or 5-HT. Deprenyl has also been reported to be effective in treatment-resistant depression (Sunderland et al. 1994); uniquely, the effect in cLH rats required experience of repeated test trials, suggesting some form of learning process that has not been described for any other antidepressant (Schulz et al. 2010). Neuroimaging studies of cLH rats have shown metabolic and functional connectivity changes very similar to those observed in major depression (Shumake et al. 2000; Shumake and Gonzalez-Lima 2003; Gass et al. 2014). In particular, cLH rats show increased metabolism in the subgenual region of the cingulate cortex and in the lateral habenula, which are regions in which antidepressant effects of DBS have been reported in depressed patients (Sartorius et al. 2010; Hamani et al. 2011). Correspondingly, DBS or pharmacological inhibition of the lateral habenula has been found to restore

normal escape behaviour in cLH rats (Li et al. 2011a; Winter et al. 2011). Thus, the cLH rat may also meet all three criteria for a model of antidepressant treatment resistance. Phenomenologically, the cLH rat could be considered as a model of the depressive personality, which is associated with both vulnerability to depression (Kwon et al. 2000; Ono et al. 2002) and resistance to antidepressant treatment (Hirschfeld et al. 1998; Souery et al. 2007; Takahashi et al. 2013).

Mice selectively bred for high anxiety behaviour (HAB mice) display reduced hippocampal neurogenesis and increased immobility in the FST. They are usually compared to mice displaying normal anxiety behaviour (NAB mice). A first study reported that chronic fluoxetine was able to alleviate the depressive-like features in HAB mice but had no effects on the anxiety behaviours and on hippocampal neurogenesis (Sah et al. 2012), while a second study from the same group reported that HAB mice responded normally to chronic noradrenergic drugs such as reboxetine or desipramine but were resistant to the effects of chronic SSRIs including fluoxetine, paroxetine and citalopram (Schmuckermair et al. 2013). However, HAB mice did respond to repeated DBS of the nucleus accumbens (Schmuckermair et al. 2013). In these selected lines, the effects of environmental enrichment have been assessed in HAB and the effects of CMS in NAB, with the objective of rescuing the differences, but CMS has not been assessed in HAB mice; also the main depression-relevant behavioural measures were the FST and TST. Nevertheless, there is a hint that HAB mice might also be able to meet all three criteria for a model of treatment-resistant depression. A HAB rat has also been described, which, compared with its low anxiety behaviour (LAB) counterpart, and like the HAB mouse, also shows increased immobility in the FST. However, unlike the HAB mouse, this effect in rats, along with associated neurochemical changes, was reversed by chronic paroxetine treatment (Keck et al. 2003, 2005).

Another set of mouse models is based on HPA reactivity. A bidirectional breeding strategy selecting mice according to differences in corticosterone secretion after stress produced the high (HR), intermediate (IR) and low (LR) reactivity mouse lines (Touma et al. 2008). HR mice display a hyperactive coping style (decreased floating in the FST), while LR mice show the opposite pattern (Touma et al. 2008, 2009; Knapman et al. 2010; Mattos et al. 2013). These opposite patterns are sometimes presented as models of the melancholic subtype of depression (HR mice) and of atypical depression (LR mice). Interestingly, chronic fluoxetine was able to reverse the phenotype of HR mice, which is consistent with the efficacy of antidepressants in melancholic depression, but it aggravated the depressive-like phenotype of the LR mice, which is consistent with the observation that atypical depression responds poorly to antidepressants (Surget et al. 2012). However, the LR mouse, while showing enhanced immobility in the FST and being resistant to fluoxetine, is sub-

sensitive to stress (as its name indicates). This inconsistency merits further investigation.

A different strategy is to select sub-groups from a general population. When using chronic social defeat to differentiate stress-susceptible and stress-resistant rats, a greater anhedonic response (stress-induced reward threshold elevation) is associated with poor antidepressant-like effects of fluoxetine or desipramine (Der-Avakian et al. 2014), which suggests that the susceptible population can be considered as a model in which increased stress sensitivity is associated with antidepressant resistance. But applying the same strategy to mice, those selected for higher social avoidance after chronic social defeat showed good behavioural and neurochemical responses to chronic fluoxetine (Cao et al. 2010): so this strategy cannot be used to model antidepressant resistance in mice. However, in another mouse model, mice were selected on the basis of dexamethasone suppression after 2 weeks of CMS (low suppression (LS) indicating a higher stress response). These two sub-populations did not differ behaviourally after 9 weeks of stress but did exhibit differences in the response to chronic fluoxetine, the LS mice displaying partial antidepressant resistance (Khemissi et al. 2014).

Female sex

Depression is 1.5–3 times more common among women compared with men. However, although men and women tend to experience, and be affected by, different types of stressful life events, there is no overall difference in either frequency of exposure to stressful life events or sensitivity to their pathogenic effect (Kendler et al. 2001b). Moreover, the increased vulnerability among women is not accompanied by resistance to antidepressant treatment. Indeed, women have been reported to respond significantly better than men to SSRIs, though not to tricyclic antidepressants, possibly as a result of interactions between gonadal hormones and the 5-HT system (Khan et al. 2005). Furthermore, non-depressed women do not express a variety of physiological changes that are typically associated with other risk factors for depression (Willne et al. 2014).

Attention is frequently drawn to the anomaly of depression being more prevalent in women, whereas females are rarely tested in animal models of depression. However, in the learned helplessness and CMS models, female rats are actually less likely than males to develop depressive behaviours (Dalla et al. 2010; Franceschelli et al. 2014). Therefore, female sex is not associated with increased stress responsiveness in either people or rodents. So while it remains a matter of some importance to understand the basis for the sex difference in the incidence of depression (cf. Hyde et al. 2008; Siddaway et al. 2015), an increase in the use of females in animal models

would be unlikely to lead to marked progress towards a solution to the problem of treatment-resistant depression.

Evaluation of the models

Table 1 summarises the models that, from the literature reviewed, may be of value for the study of treatment-resistant depression. For each model listed, the table summarises the position in relation to the three criteria discussed (increased stress responsiveness; decreased response to chronically administered conventional antidepressants; good response to novel antidepressant modalities) and the fourth, implicit, criterion of whether the model corresponds to a known clinical risk factor. To maintain readability, the table does not include references to support the statements made: all of the information in the table is taken from the earlier text. We have included in Table 1 studies for which there is partial information about how they meet the criteria we have considered, including some models for which this is as yet no information about antidepressant responsiveness. (Empty cells in the table indicate that those questions have not yet been asked.) We have not included many models discussed in the text that failed to display antidepressant resistance when tested.

The three models that stand out as most likely to prove informative are the WKY and cLH rat strains and the HAB mouse, which relate to neurotic (WKY, HAB) or depressive (cLH) personality features. In addition to increased stress responsivity and resistance to classic antidepressants, these three models have also been shown to respond to the novel antidepressant modalities that are claimed to be effective in treatment-resistant depression, ketamine (WKY) and DBS (cLH and HAB). Nevertheless, in all three cases, the evidence is patchy. For WKY, we currently lack evidence of resistance to chronic antidepressant treatment, and the evidence of antidepressant resistance in cLH is unpublished. HAB data are based on behaviour in the FST, which is also the case for the ketamine response in WKY. And DBS was applied to lateral habenula (cLH) or nucleus accumbens (HAB), but while clinical antidepressant effects have been reported for DBS of both of these structures, DBS of the anterior cingulate cortex, the major focus of clinical interest, has not yet been reported in these animal models.

The second section of the table includes four models related to specific human risk factors that show some evidence of heightened stress sensitivity and antidepressant resistance, but again, with significant limitations. Mice were more sensitive to a second bout of CMS and were antidepressant resistant, but this was only seen in animals fed a high-fat diet, which suggests that the relevance of this model may be limited to vascular depression. 5-HT transporter and $5-HT_{1A}$ knockout mice are resistant to SSRIs (perhaps unsurprisingly) but appear to respond normally to non-serotonergic antidepressants; additionally, the $5-HT_{1A}$

Table 1 Evaluation of animal models of treatment-resistant depression

Model	Species	Human counterpart	Evidence of increased stress responsivity	Resistance to chronic administration of classic antidepressants	Good response to novel antidepressants
Human counterpart and some evidence on all three criteria					
Wistar-Kyoto	Rat	Neuroticism	Increased LH	Subsensitive to acute ADs	Good response to ketamine (FST)
Congenital LH	Rat	Depressive personality	Increased LH and anhedonic	Said to be AD resistant: evidence not published	Responds to deprenyl (learning?); good response to DBS of lHb
HAB	Mouse	Neuroticism	Increased immobility in FST	Insensitivity to chronic ADs (SSRIs only)	Good response to DBS of NAc
Human counterpart and some evidence on the first two criteria					
Prior CMS	Mouse	History of depression	Increased response to CMS	AD resistance if fed a high-fat diet	
5-HT transporter KO	Mouse	5-HTTLPR polymorphism	Heightened LH	SSRI specific (?) AD resistance	
5-HT$_{1A}$ receptor KO	Mouse	5-HT$_{1A}$ receptor polymorphism	Increased physiological but decreased depressive-like behavioural response	SSRI-specific AD resistance	
CB1 KO	Mouse	CB1 receptor polymorphism	Increased response to CMS	Small decrease in response to 3-day AD administration	
Some evidence on the first two criteria but no human counterpart					
5-HT$_{1B}$ KO	Mouse		Increased locomotor response to acute stress	Insensitivity to chronic SSRI (evidence inconsistent)	
DBH KO	Mouse		Increased responses to restraint stress	Insensitivity to acute AD treatment (FST) including most SSRIs	
OCT2 null mutant	Mouse		Increased response to CMS	Increased acute AD response but insensitivity to chronic venlafaxine	
Merits further study					
Juvenile stress	Rat	Childhood adversity	Increased LH in 1/3 of subjects; heightened anxiety in others		
vGLUT+/−	Mouse		Increased sensitivity to chronic or defeat stress		
GSK3 mutant	Mouse		Heightened LH		
FKBP1 KO	Mouse		Responses to stress unchanged or decreased	Decreased sensitivity to acute AD and chronic paroxetine	
CRHR1 TT haplotype	Mouse	CHRFR1 receptor polymorphism	Increased HPA sensitivity to chronic stress in adolescence		Good response to a CRF1 antagonist
5-HT$_{2B}$ KO	Mouse			Insensitivity to anxiolytic effect of chronic SSRIs	
P11 KO	Mouse			Insensitivity to anxiolytic effect of chronic imipramine	
MIF KO	Mouse		Increased immobility in FST	Resistance to FXT effect on HPC neurogenesis	
Low dexamethasone suppression	Rat	HPA dysregulation	Similar responses to CMS in high and low suppressors	Decreased sensitivity to fluoxetine	

knockout does not display a depressive-like behavioural phenotype. Perhaps the most promising of this group is the CB1 knockout mouse, but currently, the evidence of antidepressant resistance only extends as far as 3 days of treatment.

The third section of the table lists three mutant mouse strains where the weight of behavioural evidence is comparable to those listed above, but there is no evidence from human studies for a role of the genes targeted, and again, the evidence is limited. 5-HT$_{1B}$ and DBH knockout mice show increased stress responsiveness, but in both cases, depression-relevant behavioural endpoints have not been tested. For DBH knockout mice, antidepressant resistance has been demonstrated for many antidepressants, including some (but not all) SSRIs, but only for acute administration; chronic drug administration has been used with 5-HT$_{1A}$ knockouts, but the results are inconsistent across studies. The most promising model in this group is the OCT2 null mutant mouse, which shows a range of heightened stress responses, including responses to CMS, and despite showing increased responses to acute antidepressant treatment, was found to be insensitive to chronic administration of the 5-HT/NA uptake inhibitor venlafaxine. Further evidence is needed of the effects of chronic treatment with a wider range of antidepressants to validate this model.

The final group of models listed in the table can be said to merit further study, insofar as there is in each case some intriguing evidence that falls well short of a convincing picture. Juvenile (unlike neonatal) stress causes heightened emotional responsiveness in adult rats, which in around a third of subjects is expressed as a depression-like phenotype. Similar depression-relevant responses to stress are seen in vGlut+/− and GSK3 mutant mice. However, in none of these models has the response to antidepressants been examined. Outbred mice carrying the TT haplotype of the CRHR1 gene also showed an increased neuroendocrine response to chronic stress, which was normalised by treatment with a CRF1 antagonist. There is also a paucity of behavioural data for 5-HT$_{2B}$ and p11 knockout mice. For these two strains, neither their stress sensitivity nor their drug responsiveness in depression-related tests has been assessed, but they are both reported to be sub-sensitive to anxiolytic effects of chronic antidepressant treatment: further work in more directly depression-related behavioural models is needed. The MIF knockout mouse has been reported to show both an increased stress response—but only in the FST—and antidepressant sub-sensitivity—but only for a neurochemical effect. Finally, rats selected as low dexamethasone suppressors showed some evidence of decreased sensitivity to fluoxetine, but their greater HPA activity was not accompanied by heightened sensitivity to the behavioural effects of CMS. The one model in this group for which drug resistance in a depression-related test has been reported is the FKBP1 knockout mouse, which was less resistant to acute amitriptyline and to acute or chronic paroxetine in the FST and on various neurochemical measures, but does not show an increased response to stress.

Evaluation of the criteria

Resistance to antidepressant treatment

It goes without saying that resistance to antidepressant treatment is an essential criterion for a model of treatment-resistant depression. However, some aspects of this criterion should be mentioned. First, it is also essential that resistance is demonstrated for chronic, not only acute, antidepressant treatment. This is not yet the case for several of the models listed in Table 1, including the Wistar-Kyoto rat which heads the list. Second, it may be possible to predict treatment resistance on the basis of the other criteria that we have considered, as indicated by the presence towards the bottom of Table 1 of several models in which antidepressants have not yet been tested. Third, because antidepressants are effective in both depression and anxiety, if the focus of interest is on treatment-resistant depression, then the model should involve depression-relevant rather than anxiety-relevant behavioural endpoints. As shown towards the foot of Table 1, this is not universally the case. Fourth, we note that for some of the models listed (e.g. the HAB mouse and some of the knockout mouse strains), treatment resistance extends only to serotonergic antidepressants. This highlights the importance of testing a wide range of antidepressants before concluding that treatment resistance has been demonstrated: for some of the models listed in Table 1, the range is narrow and further evidence is needed.

Fifth, and perhaps most important, the demonstration that a model is insensitive to chronic antidepressant treatment, while necessary, may not be sufficient to infer with confidence that the model will be a useful experimental tool. The working assumption behind efforts to develop novel treatments is that antidepressant effects are achieved at a site downstream from the site of action of conventional treatments. Specifically, there is extensive evidence that while many antidepressants act primarily within the hippocampus, their antidepressant effects result from consequent actions in the prefrontal cortex (Willner et al. 2013, 2014). The general proposition, that the brain contains alternative sites of antidepressant action distinct from those at which conventional antidepressants act, is supported by the efficacy of novel treatment modalities such as DBS. At the present stage of scientific development, a model that proved resistant to both conventional and novel antidepressants would not be helpful. For most of the models listed in Table 1, the extent of treatment resistance is unknown.

Table 2 Clinical definitions of treatment-resistant depression

	Definition	Reference(s)
1	Failure of two sequential treatments with antidepressants	Nierenberg and Amsterdam (1990), Rush et al. (2003)
2	Stage 1: resistance to 1 adequate treatment Stage 2: failure of two adequate treatments from two different pharmacological classes Stage 3: resistance to two different classes and to one tricyclic Stage 4: resistance to two different classes and to tricyclics and to MAOIs Stage 5: as stage 4, plus resistant to ECT	5 level classification: Thase and Rush (1997)
3	Level 1: resistance to one treatment Level 2: resistance to two treatments from different classes Level 3: resistance to 5 treatments	3-level scale: Souery et al. (1999)
4	Non response to each adequate trial with an antidepressant generates a point on a resistance scale. If after a strategy to optimise the dose/duration/combination no response is still observed, the overall score increases by 5 points for each trial. Failure to obtain remission after ECT increases the overall score by a further 3 points.	The Massachusetts General Hospital classification: Petersen et al. (2005)
5	Level 1: resistance to citalopram Level 2: still resistant following a switch to buproprion, sertraline, venlafaxine or cognitive therapy, or augmentation with an add-on (buproprion, buspirone or cognitive therapy) Level 3: still resistant following a switch to mirtrazapine or nortriptyline, or augmentation with another drug (lithium, triiodothyronine, sertraline or venlafaxine) Level 4: resistant to tranylcypromine or mirtazepine combined with venlafaxine	The STAR*D trial: Trivedi et al. (2006), Rush et al. (2006)

Finally, we should also mention that different clinical criteria have been proposed to define antidepressant treatment resistance (Table 2). These definitions have the common feature that patients are not considered treatment resistant until they have failed to respond to adequate therapy with at least two or more sequential treatments. According to these definitions, no animal model can be considered as an animal model of antidepressant treatment resistance because sequential application of different treatments has never been used as a strategy to counteract depression-related behaviours in animals.

Response to novel antidepressants

The recent clinical and preclinical studies of antidepressant and antidepressant-like responses to ketamine and DBS provide proof of principle that antidepressant resistance can be overcome. However, as shown in Table 1, the preclinical evidence is limited to only three models (the WKY and cLH rat) and the HAB mouse. And in two of these models (WKY and HAB), the FST was used as the behavioural endpoint, which is problematic because the FST has limitations, not least, a limited pharmacological specificity. Furthermore, as far as we are aware, DBS has not yet been applied in these particular models to the anterior cingulate cortex, the area most frequently targeted in clinical and preclinical studies. (DBS of the cingulate cortex did, however, reverse a behavioural effect of CMS in a sub-group of mice identified empirically as resistant to chronic fluoxetine (Dournes et al. 2013)). Clearly, more work is needed to establish the effectiveness of DBS of the anterior cingulate cortex in models of treatment resistance, to extend studies with ketamine and DBS to more relevant behavioural

endpoints, and to examine the effects of these novel treatment modalities in a wider range of models, particularly those listed in the second section of Table 1. We note also that the optogenetic method can be used to generate depressive-like behaviours and to investigate the mechanisms underlying remission. Repeated stimulation of glutamatergic neurons from the anterior cingulate cortex is sufficient to elicit depressive-like behaviours (Barthas et al. 2015), while photoactivation of the vmPFC (Covington et al. 2010), of the projections from vmPFC to the DRN (Challis et al. 2014) or of the projections from VTA to mPFC (Friedman et al. 2014) all restore depressive behaviours elicited by social defeat. This procedure may be helpful in refining the targets for DBS.

In addition to ketamine and DBS, transcranial magnetic stimulation (TMS) applied to the left dl-PFC is another treatment that is known to be effective in treatment-resistant depression, either as monotherapy or as an add-on to ineffective antidepressant treatment (Solvason et al. 2014; Liu et al. 2014). However, while TMS is also effective in reversing behavioural and neurochemical abnormalities in animal models of depression (e.g. Keck et al. 2001; Feng et al. 2012; Kim et al. 2014; Wang et al. 2014), to our knowledge, TMS has not yet been tested in any of the models listed in Table 1 that are of interest in relation to treatment-resistant depression.

Increased stress responsivity

Our proposal to include increased stress responsivity as a useful criterion for models of antidepressant resistance is perhaps the most controversial of the four criteria we have proposed. This proposal derives from the evidence

that conventional antidepressants act primarily by reversing stress-induced neurotoxicity and are less effective in remediating components of depression that reflect long-standing predispositions that are present before the onset of current or recent stress (Willner et al. 2013, 2014). We have summarised here the evidence that such predispositions, associated with resistance to antidepressant treatment, can be identified clinically in relation to history of depression, early life stress, genetic factors and personality factors, and that in relation to each of these diatheses, animal models can also be identified in which increased stress sensitivity is associated with a decreased response to antidepressant treatment.

Obviously, increased responsiveness to stress could have many meanings. For some of the models listed in Table 1 as meeting this criterion (e.g. the WKY or cLH rat and the CB1 KO and OCT2 null mutant mouse), the procedure within which animals display hypersensitive to stress is one that is considered, on conventional criteria, to have good validity as a model of depression (CMS or LH). Other models have used a weaker behavioural endpoint, the FST (e.g. HAB mouse), or physiological endpoints (e.g. CRH1 TT haplotype mouse), and in one model (the 5-HT$_1$ KO mouse), physiological and behavioural responses to stress are discrepant. Clearly, the more valid the depression model, the greater the confidence that an exaggerated response in the model will provide a useful model for studying antidepressant resistance. The use of CMS, LH or other models with some validity for depression (e.g. repeated defeat) is therefore to be encouraged.

While the clinical relationship between a predisposition to depression and antidepressant resistance provides a productive basis for finding a similar relationship between stress hypersensitivity and antidepressant resistance in animal models, it is apparent that there are also models of antidepressant resistance that do not involve hypersensitivity to stress (e.g. the FKBP1 KO mouse and the low dexamethasone suppression rat). The utility of these models remains to be determined (as, indeed, is the case for the majority of the models reviewed). There are also some known causes of antidepressant resistance that we have described as 'theoretically trivial' (Willner et al. 2013), including, for example, pharmacokinetic factors such as polymorphisms of liver cytochrome 450 enzymes or failure to penetrate the blood-brain barrier (El-Hage et al. 2013), which, if modelled in animals, would likely not be associated with increased stress sensitivity. And as we have pointed out, the greater propensity to depression in women relative to men is not associated with antidepressant resistance. This means that there are exceptions to the relationship between hypersensitivity to stress and antidepressant resistance in both directions. Therefore, increased stress sensitivity should be considered a potentially useful criterion when assessing animal models of drug resistance, but one that is far from absolute.

Human counterpart

There is substantial variability in the extent to which the predisposing factors known to be associated with antidepressant resistance have been modelled. Only a single study (Isingrini et al. 2010), with limited results, has attempted to model the effect of a history of depression. Perhaps more surprisingly, studies of early stress have generally failed to observe either hypersensitivity to adult stress or antidepressant resistance. This may reflect the different course of development of rodents and humans, since juvenile stress does produce a depressive-like phenotype in a proportion of adult rats, though antidepressants have not yet been tested in this model. By contrast, several of the genetic factors found to be associated with an increased risk of depression and antidepressant resistance are paralleled by similar effects in genetically modified mice (Table 1). There are also many genomic models listed in Table 1 for which there is no known human counterpart, and their relevance remains to be established. However, we are not aware of the converse situation, of genetic factors associated with increased clinical risk for depression and antidepressant resistance for which the corresponding genomic manipulation fails to model the risks. This is not the case for genetic models: we have discussed a number of 'emotional' or 'depressive' strains that fail to show reliable evidence of antidepressant resistance (e.g. the RLA, FH or FSL rat strains). However, three strains, the WKY and cLH rats and the HAB mouse, do show some evidence of heightened responses to stress associated with antidepressant resistance but a good response to ketamine and/or DBS. These are the front-runners in the present analysis. However, it will be apparent that the parallels between the behaviour of these strains and 'neurotic' or 'depressive' personality traits are very imprecise.

Conclusions

In conclusion, we have identified 18 models that may have some potential in relation to antidepressant resistance. All require further validation, and in most cases, this need is extensive. Currently, the most promising models are the CMS or LH procedures applied to the WKY and cLH rat strains, the HAB mouse strain and the CB1 knockout and OCT2 null mutant genetically modified mouse strains. Further development is needed to validate models of antidepressant resistance that are fit for purpose. The criteria used in this review may provide a helpful framework to guide research in this area.

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