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Rodent models of treatment-resistant depression

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Abstract

Major depression is a prevalent and debilitating disorder and a substantial proportion of patients fail to reach remission following standard antidepressant pharmacological treatment. Limited efficacy with currently available antidepressant drugs highlights the need to develop more effective medications for treatment resistant patients and emphasizes the importance of developing better preclinical models that focus on treatment resistant populations. This review discusses methods to adapt and refine rodent behavioral models that are predictive of antidepressant efficacy to identify populations that show reduced responsiveness or are resistant to traditional antidepressants. Methods include separating antidepressant responders from non-responders, administering treatments that render animals resistant to traditional pharmacological treatments, and identifying genetic models that show antidepressant resistance. This review also examines pharmacological and non-pharmacological treatments regimes that have been effective in refractory patients and how some of these approaches have been used to validate animal models of treatment-resistant depression. The goals in developing rodent models of treatment-resistant depression are to understand the neurobiological mechanisms involved in antidepressant resistance and to develop valid models to test novel therapies that would be effective in patients that do not respond to traditional monoaminergic antidepressants.

Keywords

Antidepressant; Treatment resistant depression; Animal model; Genetic; Behavior; Pharmacology

1. Introduction

Major depressive disorder is a considerable public health problem affecting approximately 16% of adults in the United States (Kessler et al., 2003) and is the fourth leading cause of disease burden worldwide (Ustun et al., 2004). The current standard of care for major

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depressive disorder is pharmacological treatments that modulate monoamines. First generation antidepressants, including monoamine oxidase inhibitors and tricyclic antidepressants (TCAs), were effective in treating depression but caused a wide range of side effects. Second generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and dopamine/norepinephrine reuptake inhibitors (Table 1), improved the side effect profile, but are still sub-optimal due to two major limitations. First, there is a delayed response between the start of treatment and the onset of beneficial effects, a lag that can often take several weeks; second, there is often an inadequate response to the pharmacological treatment, referred to as treatment resistance, with only approximately one third of patients achieving remission after treatment with a standard SSRI (Trivedi et al., 2006).

Treatment-resistant depression is generally defined as a failure to respond to two or more courses of antidepressant treatment (Souery et al., 2006). Treatment-resistant depression has been estimated to present an annual added societal cost $29–$48 billion, making the total societal costs of major depression in the United States $106–$118 billion per year (Mrazek et al., 2014). The largest study on treatment-resistant depression to date was the landmark STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) which investigated over 4000 patients with major depressive disorder in four phases of treatment. The first stage was treatment with citalopram and patients that were non-responders in stage 1 were assigned to treatments in stages 2–4 that included various monotherapies, combinations, or augmentations. Results indicated that only ~30% of patients showed remission after stage 1 treatment with citalopram (Trivedi et al., 2006) and remission rates were only 7–14% in patients still in the trial at the fourth stage (McGrath et al., 2006).

Most current rodent models of depression focus on antidepressant efficacy using behavioral tests that show robust responses to clinically prescribed antidepressant drugs. Ideally, an animal model of treatment-resistant depression should be validated by demonstrating that populations resistant to traditional antidepressants would respond to treatments shown to be effective in patients with treatment-resistant depression. One goal of developing rodent models of treatment-resistant depression is to better understand the neurobiological mechanisms that underlie refractory depression in humans. A second goal is to provide a framework for improved translation between preclinical research and clinical trials. For example, several compounds with novel mechanisms of action (e.g. neurokinin (NK) receptor NK_1, NK_2, NK_3 antagonists, corticotrophin releasing factor receptor 1 (CRF_1) antagonists, vasopressin receptor 1b (V_{1b}) antagonists) showed promise in traditional animal antidepressant models but failed to show consistent efficacy in the clinic (Belzung, 2014). It is unclear whether the clinical trials failed to detect the effect seen in animals, or if the animal models lacked appropriate validity. Preclinical models, with face, construct and predictive validity will allow a better understanding of the genetics and underlying neurobiology of treatment resistant depression and provide a translationally valid model for the development and testing of novel antidepressant therapeutics.

2. Traditional models of antidepressant efficacy

Most current behavioral models of antidepressant efficacy test mice after acute or chronic administration of traditional antidepressants (for an extensive discussion of rodent models used in depression research (see O'Leary and Cryan, 2013). The most popular models include the forced swim test (FST) (Lucki, 1997; Porsolt et al., 1977) and the tail suspension test (TST) (Steru et al., 1985) in which behavioral responses are seen following single or subchronic dosing. Acute effects of a wide range of antidepressants are also seen with the differential-reinforcement-of-low-rate (DRL-72) operant model (see O'Donnell et al., 2005 for a review). Models that more closely mimic the delay in antidepressant efficacy seen in humans are those in which rodents do not respond to acute or subchronic treatment, but respond only after chronic (several weeks) drug administration. Chronic behavioral models include novelty-suppressed feeding (Bodnoff et al., 1988), novelty-induced hypophagia (Dulawa and Hen, 2005), olfactory bulbectomy (Breuer et al., 2007), chronic mild stress (Willner, 1997, 2005), and chronic social defeat stress (Berton et al., 2006). Acute, chronic and subchronic antidepressant treatment have been reported to be effective in other models such as learned helplessness (see Pryce et al., 2012; Pryce et al., 2011 for a review).

Although the chronic treatment models more closely represent the delayed antidepressant response seen in humans, these tests do not adequately address antidepressant responses in treatment-resistant populations. More recently, issues regarding the predictive validity of traditional animal models for depression have called into question how well these models can translate to clinical efficacy (Belzung, 2014). Ideally, in an animal model of treatment-resistant depression, the resistant population would not respond to traditional treatments, but would show antidepressant-like responses to treatments effective in resistant patients.

3. Identifying treatment-resistance in rodents

Recently, investigators have started to focus on developing and understanding the mechanisms of antidepressant responsiveness and resistance in animal models (Levinstein and Samuels, 2014). Animal models of antidepressant resistance have used three basic approaches: (1) Separation of rodents into bimodal subpopulations that respond to or are resistant to traditional antidepressant treatments, which is often used following a behavioral stressor such as chronic mild stress (Jayatissa et al., 2006) or chronic social defeat (Der-Avakian et al., 2014); (2) Treatments that render rodents resistant to antidepressants (e.g. adrenocorticotropic hormone Kitamura et al., 2002 or inflammation Sukoff Rizzo et al., 2012); (3) Genetic models that show resistance to traditional antidepressant treatment (e.g. use of genetically modified mice Cryan and Mombereau, 2004). These models are discussed in detail below and are summarized in Table 2.

This review focuses on pharmacological antidepressant responsiveness in rodent models. Alterations in baseline behavior in the absence of antidepressant treatment will be discussed only in the context of interpreting antidepressant responses. In addition, pharmacological resistance will be discussed in the context of both general and antidepressant class-specific resistance (e.g. TCAs and SSRIs).

3.1. Separation into antidepressant responders and non-responders

3.1.1. Chronic mild stress—During chronic mild stress (also referred to as chronic unpredictable stress), rodents are exposed to a series of different stressors such as light and temperature changes, mild food or water deprivation, changes in cage mates, or exposure to soiled or tilted cages over a period of several weeks. The prolonged exposure to stressors produces changes in behavior such as reduced saccharin or sucrose intake, a proposed measure of anhedonia (Willner, 1997, 2005). Outbred Wistar rats exposed to chronic mild stress for 2 weeks showed reductions in sucrose preference compared to non-stressed controls. The rats were then administered escitalopram (5 mg/kg/day) for 4 weeks and a bimodal distribution of sucrose preference was observed. Half of the chronic mild stress-exposed rats showed a return to baseline levels (responders), whereas the other 50% showed no change (Jayatissa et al., 2006). Similar findings were reported for sertraline (Christensen et al., 2011). Additional analyses for biomarkers associated with antidepressant resistance showed that chronic escitalopram reversed a decrease in ventral hippocampal cell proliferation induced by chronic mild stress, but only in the rats that showed recovery of sucrose preference (Jayatissa et al., 2006). These results suggest that antidepressant resistance may be related to antidepressant actions on cell proliferation in the ventral hippocampus. Additional markers for escitalopram resistance in this model are lack of antidepressant modulation of dihydropyrimidinase-related protein-2 in the ventral hippocampus (Bisgaard et al., 2007) and an up-regulation of apoptotic pathway components (Bergstrom et al., 2007) in the treatment-resistant animals.

3.1.2. Chronic social defeat—Another stress procedure that has proven useful for identifying antidepressant non-responders is chronic social defeat in rodents. In this paradigm, intruders are forced into the territory of an aggressive resident which leads to aggressive interactions resulting in the intruder displaying defensive, subordinate behaviors. Repeated social defeat produces increased anhedonia, increased anxiety, and reduced social interaction and these behaviors present in a bimodal distribution of stress-susceptible and stress-resistant animals (Berton et al., 2006; Der-Avakian et al., 2014; Krishnan et al., 2007). In rats, chronic social defeat elevated brain reward thresholds as measured by intracranial self stimulation. Elevated intracranial self stimulation thresholds, reflecting decreased brain reward function, were sustained only in a subset of stress-susceptible rats. Of the susceptible cohort, approximately half returned to baseline intracranial self-stimulation levels following antidepressant treatment with fluoxetine or desipramine (Der-Avakian et al., 2014). In addition, the stress-susceptible rats with the highest intracranial self-stimulation thresholds showed the poorest antidepressant outcome, similar to clinical populations in which more severe anhedonia is a predictor of poorer antidepressant response (McMakin et al., 2012).

3.1.3. Chronic corticosterone treatment—Treatment-resistant depression can also be modeled in rodents by inducing depressive-like states with chronic corticosterone administration and then separating antidepressant-resistant populations. Chronic administration of corticosterone increased anxietylike behavior in the majority of C57BL/6 mice in the novelty suppressed feeding, a conflict-based test in which food-restricted animals have the choice of consuming food in the center of a brightly lit arena or avoiding the center of the anxiogenic environment. Overall, chronic fluoxetine produced an

antidepressant-like response decreasing latency to feed. However, closer analyses revealed the corticosterone-treated mice show a bimodal response to chronic fluoxetine, with some not responding (Samuels et al., 2011). Comparisons of antidepressant responders and non-responders may identify genetic factors that mediate antidepressant resistance (Samuels et al., 2014).

One limitation to the approach of utilizing antidepressant non-responders is that the antidepressant resistant populations must identified by initial behavioral testing with traditional pharmacological treatments, prior to pharmacological validation with medications that are effective in treating treatment-resistant depression. This approach would require repeat testing in the behavioral models, some of which could be confounded by re-testing. However the dependent measures of sucrose preference in the chronic mild stress procedure and intracranial self-stimulation thresholds in the chronic social defeat, which involved repeated, within-subject testing, are both conducive to assessing antidepressant add-on or switch strategies.

3.2. Treatments that render rodents resistant to antidepressants

3.2.1. Adrenocorticotropic hormone (ACTH) model—Patients with major depressive disorder often exhibit a neuroendocrine dysfunction that is characterized by overactivity of the hypothalamic–pituitary–adrenal (HPA) axis. A high proportion of patients with depression have elevated levels of cortisol and show an exaggerated release of adrenocorticotropic hormone (ACTH) and cortisol in response to combined dexamethasone and corticotropin-releasing hormone treatment (dexamethasone/corticotropin-releasing hormone test) (Holsboer, 2000). HPA axis overactivity is often normalized after effective antidepressant treatment and some studies have suggested that failure of antidepressants to normalize the HPA axis may be a predictor of treatment resistance. For example, one study found that patients who still showed elevated cortisol in response to the dexamethasone/corticotropin-releasing hormone test after 2–3 weeks of antidepressant treatment showed poor clinical outcome at 5 weeks (Ising et al., 2007). Additional evidence that HPA axis dysregulation may be involved in some types of antidepressant resistance comes from studies in patients with Cushing's disease, a disorder characterized by chronic cortisol over production. Approximately 50% of patients with Cushing's disease have major depressive disorder and are poor responders to traditional antidepressant treatment (Pereira et al., 2010; Sonino et al., 1986).

Treatment-resistant depression has been successfully modeled in rodents by altering the HPA axis with chronic ACTH treatment. As initially described by Kitamura and colleagues (Kitamura et al., 2002), chronic administration of ACTH(1–24) for 3, 7, or 14 days (100 μg/day) in rats blocked the antidepressant-like effects of imipramine and desipramine, whereas rats that received chronic vehicle treatment showed the expected antidepressant-induced reduction in immobility in the FST. These findings have been replicated using imipramine in rats (Walker et al., 2013a) and mice (Caldarone and Brunner, 2009; Iwai et al., 2013). It is unclear if chronic ACTH produces resistance to SSRIs, but these results provide support for chronic ACTH treatment as a model of TCA resistance.

3.2.2. Induction of inflammation—There is increasing evidence that treatment-resistant depression may be linked to an increased immune response and over activation of the inflammatory system. Higher levels of pro-inflammatory cytokines such as interleukin 1 and interleukin 6 have been reported in the plasma of patients with treatment-resistant depression (Carvalho et al., 2013; Maes et al., 1997; O'Brien et al., 2007). Animal models demonstrate a connection between inflammatory response and antidepressant resistance. Fluoxetine was ineffective in the TST after central administration of interleukin 6 compared to vehicle-treated mice (Sukoff Rizzo et al., 2012). Furthermore, mice with endogenous overexpression of brain interleukin 6 ((MRL/MpJ-FasLPR/LPR (LPR mice)) showed both increased depressive-like behavior and antidepressant resistance (a reduced response to acute fluoxetine treatment in the TST and FST) when compared to the MRL control line (Sukoff Rizzo et al., 2012). In a rat model, lipopolysaccharide (LPS) was administered to mimic inflammation. LPS produces neuroinflammation and secretion of pro-inflammatory cytokines such as interleukin-1 beta, interleukin 6, and tumor necrosis factor alpha (Dantzer, 2009). Rats receiving LPS each day prior to receiving chronic mild stress showed an attenuated response to fluoxetine in the FST and novelty-suppressed feeding tests (Wang et al., 2011). Other studies, however, have not observed antidepressant resistance following LPS treatment. C57BL/6 mice treated chronically with LPS showed depressive-like behaviors as measured by decreased sucrose preference which was reversed following 3 weeks of fluoxetine treatment (Kubera et al., 2013). Antidepressant-like effects of fluoxetine and paroxetine have been reported in the TST following LPS in mice (Ohgi et al., 2013) and prenatal LPS increased depressive-like behavior in the FST in rats that was reversed by chronic fluoxetine (Lin and Wang, 2014). Further studies are needed to determine the specific conditions by which inflammation produces antidepressant-resistance in animal models.

3.2.3. Stress, diet, and environmental factors—Cardiovascular risk factors, such as diabetes, hypercholesterolemia, and hypertension predict a poor response to fluoxetine in depressed patients (Iosifescu et al., 2005). In mice, chronic mild stress treatment has been combined with administration of a high fat diet, known to induce hypercholesterolemia, to produce ant-idepressant-resistance. Mice were given either a regular or a high fat diet (45% fat), subjected chronic mild stress, and were treated with either vehicle or chronic fluoxetine (10 mg/kg, i.p.). Chronic mild stress induced depressive-like behaviors including coat state degradation, disturbances in grooming motivation, and decreased in motivation to obtain a palatable food reward. Fluoxetine reversed the depressive-like behaviors in mice fed the normal diet but had no effect on mice fed the high fat diet (Isingrini et al., 2010). In another study, after exposure to chronic stress, mice were administered fluoxetine in either a stressful environment, or an enriched environment. Mice administered fluoxetine in a stressful environment showed resistance to its antidepressant effects, displaying decreased saccharin preference in comparison to mice treated in the enriched environment (Branchi et al., 2013). These studies highlight the importance of environmental factors such as diet and enrichment on antidepressant responsiveness.

3.3. Genetic models

3.3.1. Mouse strain differences—Mouse inbred strains (which are ~99% genetically identical after 20 generations of brother–sister matings) could be utilized as tools to identify novel treatments to overcome antidepressant resistance. This approach involves identifying strains that show reduced sensitivity to traditional antidepressants and then determining whether treatments that are effective in treatment-resistant patients in the clinic would produce antidepressant-like responses in the rodent models. These inbred mouse strains could then be used to test novel treatments for treatment-resistant depression and also to map genes that mediate antidepressant resistance. Quantitative trait loci mapping, using recombinant inbred strains, F2 intercrosses, or backcrosses, could correlate associations between genetic markers and antidepressant sensitivity (Jacobson and Cryan, 2007).

Comparisons of antidepressant responsiveness have shown some mouse strains to be responsive to range of antidepressants across different tests, whereas the responses of other strains are less consistent (see Jacobson and Cryan, 2007 for a review). Variability in the data could be attributed to genetic differences between substrains or procedural variations. That some common strains show reduced sensitivity to some classes of antidepressants, in a reproducible manner across laboratories, highlights these strains as useful models to study genetic contributions to treatment-resistant depression.

The C57 mouse strain, one of the most commonly used strains for behavioral research, has shown reduced sensitivity to SSRIs in some behavioral assays for antidepressant efficacy: C57BL/6J mice were not responsive to acute (Castagne et al., 2009; Lucki et al., 2001) or chronic fluoxetine in the FST (Dulawa et al., 2004) or novelty-induced hypophagia test (Balu et al., 2009); acute fluvoxamine had no effect in C57BL/6Cr mice in the FST (Sugimoto et al., 2008); acute paroxetine had only moderate sensitivity in C57BL/6Cr mice in the FST compared to other strains (Sugimoto et al., 2011); and acute paroxetine was not effective in C57BL/6JRj in the FST at doses that did not affect locomotor activity (David et al., 2003). Although these studies suggest that C57BL/6 mice may show some resistance to SSRIs, other studies have reported sensitivity in C57BL/6J mice to citalopram in the TST (Crowley et al., 2005) and FST (Cervo et al., 2005). In addition, C57BL/6JRj mice were responsive to both paroxetine and citalopram in the TST (Ripoll et al., 2003).

The responses of C57 mice to TCAs have also been variable: C57BL/6JRj mice were not responsive to acute desipramine or imipramine in the FST (David et al., 2003); C57BL/6J mice did not respond to acute imipramine in the TST (Liu and Gershenfeld, 2001); chronic administration of desipramine and amitriptyline in C57BL/6J mice was ineffective in the LH assay (Shanks and Anisman, 1989); and chronic desipramine was inactive in the novelty-induced hypophagia test (Balu et al., 2009). In contrast, acute imipramine was effective in C57BL/6OlaHsd mice in the TST and FST (Bai et al., 2001); acute desipramine was active in C57BL/6J mice in the FST (Lucki et al., 2001); imipramine and desipramine were efficacious in C57BL/6JRj mice in the TST (Ripoll et al., 2003); and chronic amitriptyline, administered via drinking water, in were active in C57BL/6J mice in TST, FST, and learned helplessness (Caldarone et al., 2003).

Other inbred strains have variable responses to antidepressants. For example, BALB/cOLaHsd exhibit reduced sensitivity to the behavioral effects of chronic desipramine in the novelty-induced hypophagia test (O'Leary et al., 2013). The DBA/2 strain has shown variability in responses to SSRIs with several studies showing reductions in immobility in the TST with paroxetine and citalopram (Crowley et al., 2005; Ripoll et al., 2003) and fluoxetine in FST (Lucki et al., 2001; Lucki et al., 2001), while other studies reported no response with citalopram in the TST (Cervo et al., 2005) or FST (David et al., 2003) or paroxetine in the FST (David et al., 2003). Desipramine also produced varied responses in DBA mice with reports of both sensitivity in the FST (Lucki et al., 2001) and insensitivity in TST (Ripoll et al., 2003) and FST (David et al., 2003).

Some outbred lines have also shown reduced sensitivity to antidepressants. CD-1 mice were insensitive to acute administration of imipramine, amitriptyline and fluvoxamine in the TST (van der Heyden et al., 1987), and fluoxetine, fluvoxamine, and citalopram in the FST (Kobayashi et al., 2008; Lucki et al., 2001). Interestingly, CD-1 mice exhibited a strong reduction in marble burying behavior in response to fluvoxamine, fluoxetine, and citalopram (Kobayashi et al., 2008), demonstrating that the mice do not show a general insensitivity to SSRIs, but an insensitivity that is selective to antidepressant-efficacy tests. In addition, ICR mice did not respond to fluvoxamine in the FST (Sugimoto et al., 2008) and showed reduced sensitivity to paroxetine when compared to other strains (Sugimoto et al., 2011). ICR mice, however, did respond to desipramine in the FST (Sugimoto et al., 2008).

Use of recombinant inbred strains such as the BXD (derived from C57BL/6J and DBA/2J strains) would be useful to map genetic regions associated with antidepressant responsiveness. The BXD mice have been used to identify a cluster of genes associated with the serotonin transporter mRNA levels (Ye et al., 2014), a finding which could utilized to further examine antidepressant resistance in behavioral models of antidepressant sensitivity. A quantitative trait loci analysis on an F2 intercross of BALB/cJ and A/J inbred mice mapped three loci on chromosomes 7, 12, and 19 related to citalopram response in the TST (Crowley et al., 2006). An F2 intercross between the NMRI and 129S6 inbred strains identified quantitative trait loci on chromosomes 1, 4, and 5 for responsiveness to imipramine in the TST (Liu et al., 2007). Another quantitative trait loci analysis between an F2 cross of FVB/NJ and C57BL/6J (fluoxetine sensitive and insensitive strains, respectively) mice revealed a single nucleotide polymorphism of the mouse Zfp326 (rs6215396) gene that was associated with fluoxetine sensitivity in the mouse as well as in treatment response in patients with major depressive disorder (Liou et al., 2012).

These studies demonstrate that inbred mouse strains provide a valuable tool for beginning to identify genes that mediate antidepressant responsiveness. Use of both inbred and outbred antid-epressant-resistant mouse lines can also be useful to screen drugs with novel antidepressant mechanisms, but these tests should always be accompanied by an antidepressant responsive strain as a positive control to assure that assay conditions are optimized.

3.3.2. Selectively bred lines—Selectively bred lines are derived from selective breeding for a specific trait over several generations using genetically diverse/outbred rats or mice.

The hypothesis is that selection pressure will lead to an enrichment of genetic alleles that promote or prevent the behavior of interest, thereby allowing identification of the alleles that modulate the behavior. Often rodents may be selectively bred for one trait, such as high anxiety (Schmuckermair et al., 2013) or cholinergic sensitivity (Overstreet et al., 2005) but display clusters of symptoms or other disorders such as depressive-like characteristics. The effects of environmental manipulations can also be tested in selectively bred lines, providing an excellent tool to study gene/environment interactions.

A mouse line selectively bred for high anxiety-related behavior (HAB) also shows depressive-like behaviors including enhanced immobility behavior in the FST compared to a normal anxiety control line (NAB) (Schmuckermair et al., 2013). Male HAB mice are also insensitive to chronic administration of SSRIs in the FST. However, male HAB mice do respond to reboxetine and desipramine (Schmuckermair et al., 2013) and chronic fluoxetine decreased immobility in the FST in female HAB mice (Sah et al., 2012). These results suggest that male HAB mice may be a model of SSRI resistance.

The Flinders Sensitive Line of rats, selectively bred for increased cholinergic sensitivity, exhibits depressive-like behaviors, such as increased immobility in the FST, compared to the Flinders Resistant Line. Antidepressants responsiveness in the FST is more pronounced in Flinders Sensitive Line compared to Flinders Resistant Line rats, although this could be related to the lower baseline response in the Flinders Resistant Line rats (Overstreet et al., 2005).

Adverse early-life events in childhood increase susceptibility to major depressive disorder in adulthood and modulate treatment outcome (Keers and Uher, 2012). Maternal separation, used in rodent studies to model early life stress in humans (Millstein and Holmes, 2007), has been used in the Flinders Sensitive Line and Flinders Resistant Line rats to study gene × environment interactions. Maternal separation stress blocked effects of chronic escitalopram and nortriptyline in both the antidepressant responsive Flinders Sensitive Line rats and the less responsive Flinders Resistant Line rats (Piubelli et al., 2011a, 2011b). Proteomic analyses demonstrated that in Flinders Sensitive Line rats, escitalopram and nortriptyline modulated cytoskeleton proteins and carbohydrate metabolism, whereas in Flinders Resistant Line rats the antidepressants influenced intracellular transport mechanisms (Piubelli et al., 2011a, 2011b). The Flinders Sensitive Line are an interesting example of a gene × environment interaction in which stress can induce antidepressant resistance in a line that is, under normal conditions, hypersensitive to antidepressants, thus providing a promising model for treatment-resistant depression.

3.3.3. Single gene effects

3.3.3.1. Serotonergic system genes: Most prescribed antidepressants increase serotonin (5-HT) availability at the synapse through reuptake inhibition. Therefore, much focus has been placed on examining the neurobiology of serotonergic systems as a mechanism of treatment-resistant depression (Coplan et al., 2014). Genetic studies have supported the role of serotonergic systems in antidepressant resistance. For example, polymorphisms in the serotonin transporter gene promoter 5-HTTLPR and a single nucleotide polymorphism in the 5-HT_{1A} receptor (rs6295) in Asian populations were shown to predict antidepressant

response (Kato and Serretti, 2010). The 5-HT_{1A} receptor is predominantly expressed on presynaptic terminals in the dorsal raphe where it acts as an autoreceptor, controlling serotonergic tone through feedback inhibition. However, 5-HT_{1A} receptors are also expressed postsynaptically in several brain regions, including the hippocampus, where they act as heteroreceptors and are thought to be responsible for the therapeutic action of antidepressants (Savitz et al., 2009). The 5-HT_{1A} autoreceptors, on the other hand, are thought to delay antidepressant responses by exerting negative feedback in response to increased serotonin via acute inhibition of the serotonin transporter, and thus reducing serotonin availability at the postsynaptic receptors. As the 5-HT_{1A} autoreceptors desensitize following chronic antidepressant treatment, the inhibition is removed allowing greater activation of postsynaptic serotonin receptors (Celada et al., 2013).

3.3.3.1.1. Serotonin transporter: Knockout mice lacking the serotonin transporter showed no response to fluoxetine in the TST, but did respond to desipramine, which has a much higher affinity for the norepinephrine transporter. As might be expected, the response to imipramine, which has affinity for both the norepinephrine transporter and serotonin transporter, was partially attenuated (Holmes et al., 2002). Based on these findings, serotonin transporter knockout mice could be useful for screening novel antidepressants to treat SSRI-resistant populations.

3.3.3.1.2. Serotonin 5-HT_{1A} receptor: Responses to antidepressants in 5-HT_{1A} receptor knockout mice have been contradictory. In initial studies, 5-HT_{1A} knockout mice (129SvEvTac background) did not respond to chronic fluoxetine in the novelty-suppressed feeding test, and did not exhibit the expected increase in hippocampal neurogenesis (Santarelli et al., 2003). Subsequently, when tested on a BALB/cJ background, 5-HT_{1A} knockout mice did respond to chronic fluoxetine in the FST (Holick et al., 2008). The contribution of postsynaptic 5-HT_{1A} receptors, versus presynaptic 5-HT_{1A} autoreceptors, was investigated using conditional knockout mice in which just the presynaptic 5-HT_{1A} autoreceptors were manipulated (Richardson-Jones et al., 2010). Mice with lower levels of 5-HT_{1A} autoreceptors responded to fluoxetine in the novelty-suppressed feeding test, whereas mice with higher levels of autoreceptors, showed no response. These results suggest that higher levels of 5-HT_{1A} presynaptic autoreceptors could be an appropriate model for SSRI resistance. Similar findings have been observed in the clinic in which elevated density or activity of presynaptic 5-HT_{1A} autoreceptors was associated with mood disorders and poor treatment outcome (Stockmeier et al., 1998).

3.3.3.1.3. Serotonin 5-HT_{1B} receptor and p11: Serotonin 5-HT_{1B} receptors are located throughout the brain on presynaptic serotonin terminals, where they function as inhibitory autoreceptors, and on postsynaptic terminal of non-serotonergic neurons, where they act as heteroreceptors to control the release of other neurotransmitters such as acetylcholine, glutamate, dopamine, norepinephrine, and γ-aminobutyric acid (GABA) (see Hoyer et al., 2002). The antidepressant responses of 5-HT_{1B} receptor knockout mice are mixed. Both increased sensitivity (fluoxetine and desipramine) (Mayorga et al., 2001) and resistance (Trillat et al., 1998) have been reported.

p11, a protein that binds to 5-HT_{1B} receptors and regulates receptor cell surface localization and downstream G-protein regulated and extracellular signal-regulated kinases signaling, has been implicated in depression and the therapeutic response to antidepressants (Svenningsson et al., 2013). In mice, p11 and 5-HT_{1B} receptors are co-localized in many cell types in the cortex, hippocampus and striatum (Egeland et al., 2011; Warner-Schmidt et al., 2009). Levels of p11 are reduced in neurons of the frontal cortex, nucleus accumbens and hippocampus of depressed individuals as well as in the H/Rouen mouse model of depression, which displays a helpless phenotype in the TST (Svenningsson et al., 2006). As expected, p11 levels are upregulated by antidepressant treatment in mice (Svenningsson et al., 2006).

p11 knockout mice exhibit reduced density of 5-HT_{1B} receptors at the cell surface and reduced behavioral and neurogenic responses to antidepressants (Egeland et al., 2010; Svenningsson et al., 2006; Warner-Schmidt et al., 2010). In addition, mice with a cortical specific knockout of p11 showed a reduced response to fluoxetine in the novelty-suppressed feeding and TST (Schmidt et al., 2012) and knockout mice lacking SMARCA3, a signaling molecule downstream of p11, do not respond to fluoxetine (novelty-suppressed feeding and neurogenic response) or citalopram (sucrose preference test) (Oh et al., 2013). In contrast, mice with a knockout of p11 in specific cell types (cholinergic interneurons in the nucleus accumbens as well as dopamine D_1, dopamine D_2, and adenosine A_{2A} striatal neurons) retain responsiveness to citalopram in the TST (Warner-Schmidt et al., 2012), demonstrating anatomical and cell type distinction in the effects of p11 on antidepressant responsiveness. p11 levels may be a predictor of antidepressant response in depressed patients. Early reduction in p11 levels in white blood cells was associated with a positive response to citalopram in patients with major depressive disorder (Svenningsson et al., 2014). Although a correlation between good antidepressant response and low levels of p11 would not be predicted by the animal studies, p11 knockout mice are a promising model to study antidepressant resistance resulting from dysregulated neurotransmission exerted via 5-HT_{1B} receptors.

3.3.3.2. Noradrenergic system genes: TCA and norepinephrine reuptake inhibitor antidepressants act by binding to the norepinephrine transporter to increase norepinephrine in the synapse and activate noradrenergic receptors, and can also act by direct activation of noradrenergic receptors or via actions on ion channels (Cottingham and Wang, 2012; Su et al., 2007). Two common single nucleotide polymorphisms of the norepinephrine transporter gene have been studied in relation to antidepressant responsiveness. The T allele of the norepinephrine transporter T-182C polymorphism was associated with a better antidepressant response, whereas the A/A genotype of the norepinephrine transporter G1287A polymorphism was associated with a slower onset of therapeutic response to milnacipran (Yoshida et al., 2004). These finding were supported by another study that found the A/A and G/A genotypes of the norepinephrine transporter G1287A polymorphism were associated with poorer responsiveness to nortriptyline, but not fluoxetine (Kim et al., 2006).

Mouse studies have confirmed the role of the norepinephrine transporter, as well as other noradrenergic-related genes, in the behavioral responses to antidepressants. Knockout mice

lacking the norepinephrine transporter do not respond to acute treatment to the norepinephrine reuptake inhibitor antidepressants desipramine and reboxetine in the TST. Although the norepinephrine transporter knockout mice show a reduced immobility time in the FST and TST compared to wild type mice, it is unlikely that the norepinephrine reuptake inhibitor insensitivity can be attributed to the altered baseline because citalopram, which does not have affinity for norepinephrine transporter, reduced immobility in the norepinephrine transporter knockout mice (Dziedzicka-Wasylewska et al., 2006). The enzyme dopamine beta hydroxylase is required for the synthesis of norepinephrine and mice that lack dopamine beta hydroxylase do not respond to a wide range of antidepressants including monoamine oxidase inhibitors, norepinephrine reuptake inhibitors, TCAs, and several SSRIS (fluoxetine, paroxetine, and sertraline (but not citalopram)) (Cryan et al., 2004).

Organic cation transporter 2 is a member of the polyspecific organic cation transporter family that is involved in monoamine clearance. Knockout mice with genetic deletion of organic cation transporter 2 show reduced brain concentrations of norepinephrine and serotonin under basal conditions and reduced clearance after treatment with venlafaxine. Although organic cation transporter 2 knockout mice showed enhanced sensitivity to acute antidepressant treatment, organic cation transporter 2 knockout mice were insensitive to chronic venlafaxine treatment after induction of a depressive-like state with chronic corticosterone treatment (Bacq et al., 2012). As venlafaxine inhibits both norepinephrine and serotonin reuptake, these results suggest that that organic cation transporter 2 deficiency could model insensitivity to noradrenergic and/or serotonergic antidepressants.

Dysregulation of adrenergic α2 receptors has been associated with depressive disorders (Cottingham and Wang, 2012). Adrenergic α_{2A} receptor knockout mice show reduced immobility in the FST and insensitivity to imipramine, although the decreased imipramine sensitivity could be related to the alterations in baseline immobility (Schramm et al., 2001).

There are limitations in utilizing mice with single gene alterations in monoaminergic systems, because these single gene effects may not fully model the complexity of treatment-resistant depression in depressed patients. However, the noradrenergic and serotonergic mutant mice are useful models to identify antidepressant drugs that work via novel mechanisms that bypass the serotonergic and noradrenergic pathways.

3.3.3.3. Cholinergic system genes: The cholinergic hypothesis of depression postulates that depression may be due to an overactivity or hypersensitivity of the cholinergic system over the adrenergic system (Janowsky et al., 1972; van Enkhuizen et al., 2014). Several investigators have suggested decreasing acetylcholine neurotransmission, through muscarinic or nicotinic acetylcholine receptor blockade, may be an effective novel treatment for depression and that traditional antidepressants may act in part via acetylcholine receptor antagonism (Drevets et al., 2013; Jaffe et al., 2013; Mineur and Picciotto, 2010; Shytle et al., 2002). Clinical support for this hypothesis comes from studies showing that the muscarinic antagonist scopolamine produced rapid antidepressant responses in depressed patients (Drevets and Furey, 2010; Furey and Drevets, 2006) as well as treatment-resistant patients (Ellis et al., 2014). Similarly, the nicotinic acetylcholine receptor antagonist

dexmecamylamine (TC-5214) showed promise in early clinical trials as an effective add-on to traditional antidepressants in treatment-resistant patients, but failed to show efficacy in a large Phase III trial (Vieta et al., 2014).

Mouse models support a role for nicotinic acetylcholine receptors in antidepressant responsiveness. Nicotinic acetylcholine receptors are ligand-gated ion channels composed of five subunits. In the mammalian brain, homomeric receptors are comprised of α7 subunits and heteromeric receptors generally contain two α (α2–α6) and three β (β2–β4) subunits. Receptors that contain the β2 subunit are widely distributed throughout the brain, with very high levels in the thalamus, whereas those containing the β4 subunit are more restricted with high levels in the interpeduncular nucleus and medial habenula. (α7 receptors are also widely distributed with high levels in the cortex and hippocampus (see Picciotto et al., 2000). Knockout mice lacking the β2 subunit of the nicotinic acetylcholine receptor are resistant to the antidepressant behavioral (FST, TST, and learned helplessness) and neurogenic effects of amitriptyline seen in wild type mice (Caldarone et al, 2004). β2 and α7 nicotinic acetylcholine receptor knockout mice also do not show the antidepressant-like effects of the nicotinic acetylcholine receptor antagonist mecamylamine (Rabenstein et al, 2006). β2 nicotinic acetylcholine receptor knockout mice are insensitive to the antidepressant-like effects of the nicotinic acetylcholine receptor partial agonist/desensitizer sazetidine-A (Caldarone et al, 2011). Knockout mice lacking the β4 subunit of the nicotinic acetylcholine receptor showed the expected antidepressant-like response to acute bupropion (Radhakrishnan et al, 2013), an antidepressant that has been proposed to work via nicotinic acetylcholine receptor antagonism as well dopamine transporter/norepinephrine transporter inhibition (Shytle et al, 2002). However, the chronic antidepressant-like effects of bupropion in the FST, which were seen in female wild type mice, were blunted in the β4 knockouts (Radhakrishnan et al, 2013). Muscarinic receptor knockout mice (M_1–M_5) did not show reduced responsiveness to imipramine, in the FST, although only one dose of imipramine was tested (Witkin et al, 2014).

3.3.3.4. Brain derived neurotrophic factor: The “neurotrophic hypothesis of depression” states that stress decreases expression of brain derived neurotrophic factor (BDNF) in brain structures that regulate mood and depression and the decreased levels of BDNF are thought to contribute to hippocampal atrophy seen in depressed patients. Chronic antidepressants are hypothesized to exert therapeutic actions by reversing the hippocampal neuronal atrophy and cell loss (Duman and Monteggia, 2006). Chronic antidepressant treatment can increase adult neurogenesis in the hippocampus in rodents (Malberg et al, 2000) and postmortem studies in humans demonstrated that depressed patients on medication at the time of death show elevated levels of cell birth in the hippocampus (Boldrini et al, 2012). Decreased BDNF mRNA levels have been associated with treatment-resistant depression (Hong et al, 2014) and high serum BDNF levels were associated with improved treatment outcomes in depressed patients (Mikoteit et al, 2014).

In agreement with the clinical studies, alterations in BDNF levels change behavioral responses to antidepressants in mice. Heterozygous BDNF null mice showed resistance to chronic imipramine in the TST and resident intruder test and following chronic mild stress (Ibarguen-Vargas et al, 2009) and to acute imipramine in the FST (Saarelainen et al, 2003).

BDNF conditional knockouts, with loss of BDNF restricted to the hippocampus and cortex, showed no response to desipramine in the FST (Monteggia et al, 2004, 2007). Furthermore, viral-mediated gene knockdown of BDNF in the dentate gyrus of the hippocampus was sufficient to block the actions of desipramine and citalopram in the FST (Adachi et al, 2008). Thus both clinical data and mouse models suggest reduced hippocampal BDNF is a promising model of treatment-resistant depression.

3.3.3.5. Regulator of G protein signaling 4: Downstream of modulating synaptic monoamine levels, alterations in signal transduction molecules may also result in treatment resistance. For example, Regulator of G protein Signaling 4 (RGS4) is a potent modulator of monoamine receptor function, which controls the signaling amplitude and termination of these receptors by modulating the time Gα and Gβγ subunits are available to their effectors (Stratinaki et al, 2013; Terzi et al, 2009). Specifically, RGS4 binds to activated Gα subunits and accelerates their GTPase activity, but may also influence signal transduction by preventing effector activation by Gα subunits. A recent study (Stratinaki et al, 2013) revealed that constitutive inactivation of RGS4, or conditional inactivation of RGS4 in the mouse nucleus accumbens, robustly reduced sensitivity to desipramine, fluoxetine and reboxetine in the FST. Prevention of RGS4 action also reduced responses to chronic desipramine in the novelty-suppressed feeding test. Notably, increasing RGS4 activity via viral-mediated overexpression of RGS4 in the nucleus accumbens, enhanced responses to desipramine. In post mortem human brain, RGS4 expression in the nucleus accumbens was not altered by major depressive disorder, but was increased threefold by chronic treatment with monoamine targeting antidepressants, although it is not know whether patients were responsive or resistant to antidepressant treatment. Interestingly, constitutive RGS4 knockout mice, as well as mice with viral-mediated knockdown of RGS4 in the prefrontal cortex, show a facilitated response to ketamine and the delta opioid receptor agonist SNC80 in the FST (Stratinaki et al, 2013), providing support for the idea that monoamine resistance can be bypassed with drugs acting via novel mechanisms. Although one study found no genetic associations between the RGS4 rs951436 polymorphism and risk of treatment resistant depression and ECT treatment outcome (Huuhka et al, 2008), some studies have reported associations between RGS4 polymorphisms and schizophrenia (Talkowski et al, 2006) as well as treatment outcome in response to risperidone (Lane et al, 2008). Identification of loss of function RGS4 polymorphisms in humans could be used to predict treatment resistance in depressed patients and such polymorphisms may also increase responsiveness to atypical antidepressants.

3.4. Pharmacological treatments

One of the biggest challenges in modeling treatment-resistant depression in animals is validation to demonstrate that treatments shown to be effective in treatment-resistant patients can reverse depressive-like behaviors in animals that do not respond to classical antidepressants. Efforts to validate rodent models of treatment resistant depression have utilized both pharmacological and non-pharmacological approaches. The current therapies for treatment resistant depression, including both the United States Food and Drug Administration (FDA) approved and experimental treatments, are discussed below in relation to treatment-resistant depression animal models.

3.4.1. Antipsychotic augmentation—Augmentation strategies for treatment-resistant depression refer to the addition of a drug, which is not a standard antidepressant, to ongoing antidepressant treatment. This strategy, which is commonly employed by clinicians treating patients with treatment-resistant depression, attempts to augment standard monoamine antidepressant treatment by adding drugs with additional pharmacological mechanisms. The FDA has approved several atypical antipsychotics as add-ons to ongoing antidepressant treatment for treatment-resistant depression. These include quetiapine, aripiprazole, olanzapine and a combination drug that contains olanzapine and fluoxetine (Symbyax). Overall, findings on augmentation with atypical antipsychotics have been positive (Carvalho et al, 2014; Kato and Chang, 2013).

Animal studies have confirmed the role of antipsychotics in augmenting antidepressant activity. The precise mechanism of quetiapine is unknown, but serotonin 5-HT_{2A} and dopamine D_2 receptor antagonism may contribute to its therapeutic actions (Saller and Salama, 1993). In addition, the active metabolite of quetiapine, *N*-desalkylquetiapine, is a potent inhibitor of the norepinephrine transporter and a partial agonist of the serotonin 5-HT_{1A} receptor (Jensen et al., 2008). One study that used chronic mild stress to induce depressive-like behaviors found that, in the 20–30% of the rats resistant to fluoxetine treatment across antidepressant tests, quetiapine add-on therapy improved responses (Wang et al., 2013).

Aripiprazole is partial agonist at dopamine D_2 and D_3 receptors, and serotonin 5-HT_{1A} receptors and an antagonist at serotonin 5-HT_{2A} receptors (Burris et al., 2002; Shapiro et al., 2003). In Swiss mice, aripiprazole potentiated subthreshold doses of paroxetine, citalopram, venlafaxine and milnacipran in the FST but not desipramine and bupropion (Bourin et al., 2009). In contrast in ICR mice, aripiprazole potentiated the effects of the fluoxetine in the TST (Kamei et al., 2008), thus highlighting the importance of mouse genetic background in antidepressant responsiveness.

Olanzapine has a broad binding profile acting as an antagonist at dopamine (D_1–D_5), serotonin (5-HT_{2A}, 5-HT_{2C}), adrenergic $\alpha 1$, histamine H_1, and muscarinic $M_{1–5}$ receptors (Bymaster et al., 1996a, 1996b; Schotte et al., 1996; Zhang and Bymaster, 1999). In rats, the combination of olanzapine and fluoxetine produced robust, sustained increases of extracellular levels of dopamine and norepinephrine in the prefrontal cortex that was greater than either drug given alone (Zhang et al., 2000). Combinations of olanzapine and fluoxetine in rats also produces changes related to energy metabolism (Agostinho et al., 2011a, 2009), increased brain levels of neurotrophin-3 (NT-3) (Agostinho et al., 2011b), and produced increases in intracellular survival pathways (Reus et al., 2012). However, it is not known whether these changes translate into improved efficacy of fluoxetine in treatment-resistant depression models.

3.4.2. Lithium augmentation—Adjunctive administration of lithium is a common strategy for treating treatment-resistant depression. A meta-analysis of more than 30 open-label trials and 10 placebo controlled trials showed substantial efficacy of lithium augmentation (Bauer et al., 2014). The efficacy of lithium has also been confirmed in rodent models of treatment-resistant depression. The mouse strain BALB/cOLaHsd exhibits

reduced sensitivity to the behavioral effects of chronic desipramine in the novelty-induced hypophagia test, whereas chronic treatment with lithium plus desipramine, but neither drug alone, induced antidepressant-like behavior and hippocampal neurogenesis (O'Leary et al., 2013). In addition, C57BL/6J and DBA2/strains, which show variable responses to traditional antidepressants (Jacobson and Cryan, 2007), exhibit an antidepressant-like response in the TST and FST to chronic (3 weeks) lithium (Can et al., 2011). In the ACTH rat model of treatment resistant depression, treatment with both lithium and imipramine, but neither drug alone, produced antidepressant-like effects in the FST (Kitamura et al., 2002). In addition, co-administration of imipramine and lithium for 14 days blocked the loss of hippocampal cell proliferation (but not cell survival) that resulted from chronic treatment with ACTH (Kitamura et al., 2011). These results support the use of BALB/cOLaHsd, C57BL/6J and DBA/2J mice, as well as ATCH-treated rats, as appropriate models for testing novel antidepressant therapeutic treatments.

3.4.3. Ketamine—Ketamine is a high-affinity non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Evidence from clinical and preclinical studies has implicated the glutamatergic system in the pathophysiology of major depressive disorder and the mechanism of action of antidepressant treatments (Sanacora et al., 2008; Skolnick et al., 2009). Berman and colleagues (Berman et al., 2000) initially reported that a single subanesthetic dose of ketamine had rapid antidepressant effects in patients with major depressive disorder. This finding has been replicated in several studies with both single and repeated ketamine administration, although patients generally relapsed within several weeks of the first infusion (reviewed in Naughton et al., 2014; Niciu et al., 2014). A recent active placebo controlled trial demonstrated fast-acting, but transient effects of ketamine in treatment-resistant depression patients (Murrough et al., 2013).

Ketamine's antidepressant properties have been demonstrated in several animal models of antidepressant efficacy (reviewed in Browne and Lucki, 2013) as well as in some treatment-resistant depression models. In BDNF heterozygous null mice, where imipramine had no effect in the FST, ketamine produced a robust antidepressant-like response at 50 mg/kg (Lindholm et al., 2012). In contrast, conditional BDNF knockout mice (with loss specific to the hippocampus and cortex), did not respond to ketamine in the FST (Autry et al., 2011). Thus a partial reduction of BDNF (BDNF heterozygous knockout mice) is sufficient to disrupt the response to monoamine-based antidepressants but maintain responsiveness to glutamatergic antidepressants, whereas a more severe reduction in BDNF in certain brain regions will abolish the behavioral response to all types of antidepressants. In the inflammatory/LPS model of treatment resistant depression, a low dose of ketamine administered immediately before LPS in C57BL/6J mice abolished the development of LPS induced depressive-like behavior in the sucrose preference test and FST (Walker et al., 2013b). In addition, RGS4 knockout mice, which exhibit reduced sensitivity to traditional antidepressants, show a facilitated response to ketamine in the FST (Stratinaki et al., 2013).

These studies provide excellent examples showing that reduced monamine sensitivity can be bypassed using a novel, fast acting antidepressant that has shown efficacy in treatment resistant patients. More selective NMDA antagonists that lack the dissociative side effects of ketamine are being pursued for treatment resistant depression. Antagonists to the NR2B

subunit of the NMDA receptor such as MK-0657 (Ibrahim et al., 2012) and CP-101,606 (Preskorn et al., 2008) have shown promising results in treating treatment resistant depression patients.

3.4.4. Dopamine augmentation—Addition of a dopaminergic component to serotonin and noradrenergic reuptake inhibitors has been hypothesized to produce better efficacy and fewer side effects than SSRIs, serotonin/nor-epinephrine reuptake inhibitors, or norepinephrine reuptake inhibitors alone. A hypodopaminergic state is thought to produce anhedonia and drugs that increase dopaminergic activity in the mesolimbic dopamine system may reverse the anhedonia associated with depression (Dunlop and Nemeroff, 2007; Nestler and Carlezon, 2006). There is evidence to support the hypothesis that targeting dopaminergic system may be helpful in improving response rates in treatment-resistant patients; the combination of the dopamine/norepinephrine reuptake inhibitor bupropion and either an SSRI or a serotonin/norepinephrine reuptake inhibitor was shown to boost antidepressant response in the clinic (Zisook et al., 2006); the dopamine D_2/D_3 agonist pramipexole is a potentially efficacious treatment strategy in patients that do not respond to standard antidepressant therapies (Cusin et al., 2013); and the wake promoting agent modafinil has also shown some effectiveness in treatment resistant depression patients that report fatigue and sleepiness (Fava et al., 2007). The wake promoting effects of modafinil are thought to work via binding to the dopamine and norepinephrine transporters, thereby affecting dopaminergic and adrenergic signaling (Wisor, 2013). Support for this comes from a study showing modafinil behaves like bupropion, fully substituting for cocaine in a drug discrimination assay in rats (Paterson et al., 2010).

Animal studies suggest that dopaminergic modulation may be effective in treating treatment-resistant depression. In the rat ACTH model of treatment-resistant depression, dopamine in the prefrontal cortex was significantly depleted (Walker et al., 2013a). Treatment with pramipexole (Kitagawa et al., 2009) or bupropion (Kitamura et al., 2010) produced antidepressant-like effect in the FST in ACTH treated rats. Serotonin, norepinephrine, and dopamine reuptake inhibitors, or triple reuptake inhibitors, are a new class of antidepressant in development for major depressive disorder. Amitifadine (DOV 21,947), and its racemate DOV 216,303 are the best studied triple reuptake inhibitors in both animal models and the clinic (Skolnick et al., 2006, 2003; Tran et al., 2012). DOV 216,303 has antidepressant-like effects in the FST and TST in mice (Caldarone et al., 2010; Skolnick et al., 2006) and the olfactory bulb-ectomy model of depression in rats (Breuer et al., 2008), although the antidepressant-like effects of DOV 216,303 in the olfactory bulbectomy rat model were not observed when drug levels in plasma and brain were not detectable (Prins et al., 2011). In mice as well as olfactory bulbectomized rats, DOV 216,303 increased levels of serotonin, norepinephrine and dopamine in the prefrontal cortex (Caldarone et al., 2010; Prins et al., 2010). DOV 216, 303 also induced long-lasting enhancement of brain reward activity in the rats as measured by reduced intracranial self-stimulation reward thresholds (Prins et al., 2012).

In the inflammatory treatment-resistant depression model, peripheral administration of LPS can produce anhedonia, as measured by increased intracranial self-stimulation thresholds (van Heesch et al., 2013). In mice, LPS increased extracellular levels of monoamine

metabolites (5-hydroxyindoleacetic acid (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)) in the nucleus accumbens and medial prefrontal cortex and pretreatment with DOV 216,303 prevented the LPS-induced DOPAC and HVA formation in the nucleus accumbens (van Heesch et al., 2014). These results suggest that LPS leads to increased dopamine transporter activity, removal of dopamine from the synaptic cleft, and increased dopamine metabolism in the nucleus accumbens, which may be responsible for the LPS-induced anhedonia.

Although drugs that facilitate dopamine neurotransmission may hold a promise as effective medications in the clinic to treat, results from a recent clinical call into question the potential efficacy of triple reuptake inhibitors as efficacious medications in resistant patients. The triple reuptake inhibitor amitifadine was found to be ineffective when tested a Phase IIb/IIIa trial (TRIADE) in patients who failed to respond to one course of first-line antidepressants (Euthymics, 2013). However, it is possible that higher doses of amitifadine, or other triple reuptake inhibitors that are currently in development (Quesseveur and Guiard, 2013), could be effective in future trials.

3.5. Non-pharmacological treatments

There are several non-pharmacological interventions for treatment-resistant depression including electroconvulsive therapy, vagus nerve stimulation, repetitive transcranial magnetic stimulation, and deep brain stimulation (see Cusin and Dougherty, 2012; Shelton et al., 2010 for reviews). Electroconvulsive therapy is widely used and clinical effects are well established in treatment-resistant depression. Vagus nerve stimulation was approved by the FDA in 1997 as adjunctive therapy after four prior treatment failures and repetitive transcranial magnetic stimulation was FDA approved in 2008 for major depressive disorder in patients who have not responded to a single antidepressant medication in the current episode. However, the efficacy of vagus nerve stimulation and repetitive transcranial magnetic stimulation are less well established than electroconvulsive therapy. Deep brain stimulation is an experimental treatment but has shown efficacy in small treatment-resistant patient trials. Deep brain stimulation in brain regions such as the subcallosal cingulate gyrus (Lozano et al., 2012; Mayberg et al., 2005) and ventral striatum/nucleus accumbens (Bewernick et al., 2010; Bewernick et al., 2012) offer promise for treatment in antidepressant resistant populations.

Electroconvulsive therapy has been studied in animal models of treatment-resistant depression. Electroconvulsive stimuli administered for 6 or 14 days produced antidepressant-like effects in the FST and increased BDNF protein levels in the hippocampus of ACTH treated-imipramine resistant rats (Li et al., 2006), effects that persisted 6–7 days following treatment (Li et al., 2007). Reduced hippocampal cell proliferation, induced by chronic ACTH, was also restored by electroconvulsive stimuli treatment (Kuwatsuka et al., 2013). These studies suggest that electroconvulsive stimuli may work by triggering hippocampal cell proliferation via increases in hippocampal BDNF.

Deep brain stimulation has also been studied in treatment-resistant depression mouse models. In one study, chronic mild stress exposed mice that were fluoxetine-resistant mice, were exposed to repeated deep brain stimulation of the cingulate cortex. Stimulation restored

several behaviors, including motivated behavior, anxiety-related behavior, and locomotor responses (Dournes et al., 2013). In another study, repeated, but not single, deep brain stimulation of the nucleus accumbens induced robust antidepressant and anxiolytic-like responses in SSRI-resistant HAB mice (FST, TST, novelty suppressed feeding) and enhanced hippocampal neurogenesis (Schmuckermair et al., 2013). These finding demonstrate that electroconvulsive stimuli and deep brain stimulation can produce antidepressant-like effects in treatment-resistant depression rodent models and provide framework for testing non-pharmacological treatments that are effective in treatment-resistant patients in the clinic.

4. Conclusions and future directions

In the development of rodent models of depression, investigators have typically relied on pharmacological validation by determining if classical antidepressants can reverse a stress-induced behavioral change in normal animals. This may have led to underreporting of models that do not respond to classical antidepressants. Utilizing animal models that do not respond to classical antidepressants, but are responsive to drugs that have shown efficacy in refractory patients in the clinic, may offer an improved framework to test new pharmacological therapies for treatment-resistant depression.

In this review, we discussed a diversity of models for treatment-resistant depression. These models included selecting populations of antidepressant non-responders; inducing treatment resistance through stress hormone treatment or induction of inflammation; and a range of genetic models including inbred strains, selectively bred lines, and single gene mutants of a variety of mechanisms. This diversity in animal models may be required to reflect the heterogeneity of depression in human populations and allow development of specific treatments for different subtypes of depression. Major depression symptom-based subtypes have been reported to predict depression persistence and severity (van Loo et al., 2014) and patients may require individualized care to adequately treat depressive symptoms. Understanding the biological mechanisms that underlie treatment resistance, will aid in the development of novel, non-monoamine based antidepressants that can be used to treat heterogeneous populations of treatment-resistant patients.

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References

Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry. 2008; 63:642–649. [PubMed: 17981266]

Agostinho FR, Reus GZ, Stringari RB, Ribeiro KF, Ferraro AK, Benedet J, Rochi N, Scaini G, Streck EL, Quevedo J. Treatment with olanzapine, fluoxetine and olanzapine/fluoxetine alters citrate synthase activity in rat brain. Neurosci Lett. 2011a; 487:278–281. [PubMed: 20971158]

Agostinho FR, Reus GZ, Stringari RB, Ribeiro KF, Pfaffenseller B, Stertz L, Panizzutti BS, Kapczinski F, Quevedo J. Olanzapine plus fluoxetine treatment increases Nt-3 protein levels in the rat prefrontal cortex. Neurosci Lett. 2011b; 497:99–103. [PubMed: 21545827]

Agostinho FR, Scaini G, Ferreira GK, Jeremias IC, Reus GZ, Rezin GT, Castro AA, Zugno AI, Quevedo J, Streck EL. Effects of olanzapine, fluoxetine and olanzapine/fluoxetine on creatine kinase activity in rat brain. Brain Res Bull. 2009; 80:337–340. [PubMed: 19748553]

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011; 475:91–95. [PubMed: 21677641]

Bacq A, Balasse L, Biala G, Guiard B, Gardier AM, Schinkel A, Louis F, Vialou V, Martres MP, Chevarin C, Hamon M, Giros B, Gautron S. Organic cation transporter 2 controls brain norepinephrine and serotonin clearance and antidepressant response. Mol Psychiatry. 2012; 17:926–939. [PubMed: 21769100]

Bai F, Li X, Clay M, Lindstrom T, Skolnick P. Intra- and interstrain differences in models of "behavioral despair". Pharmacol Biochem Behav. 2001; 70:187–192. [PubMed: 11701187]

Balu DT, Hodes GE, Anderson BT, Lucki I. Enhanced sensitivity of the MRL/MpJ mouse to the neuroplastic and behavioral effects of chronic antidepressant treatments. Neuropsychopharmacology. 2009; 34:1764–1773. [PubMed: 19177066]

Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. Role of lithium augmentation in the management of major depressive disorder. CNS Drugs. 2014; 28:331–342. [PubMed: 24590663]

Belzung C. Innovative drugs to treat depression: did animal models fail to be predictive or did clinical trials fail to detect effects? Neuropsychopharmacology. 2014; 39:1041–1051. [PubMed: 24345817]

Bergstrom A, Jayatissa MN, Thykjaer T, Wiborg O. Molecular pathways associated with stress resilience and drug resistance in the chronic mild stress rat model of depression: a gene expression study. J Mol Neurosci. 2007; 33:201–215. [PubMed: 17917079]

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47:351–354. [PubMed: 10686270]

Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science. 2006; 311:864–868. [PubMed: 16469931]

Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010; 67:110–116. [PubMed: 19914605]

Bewernick BH, Kayser S, Sturm V, Schlaepfer TE. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. Neuropsychopharmacology. 2012; 37:1975–1985. [PubMed: 22473055]

Bisgaard CF, Jayatissa MN, Enghild JJ, Sanchez C, Artemychyn R, Wiborg O. Proteomic investigation of the ventral rat hippocampus links DRP-2 to escitalopram treatment resistance and SNAP to stress resilience in the chronic mild stress model of depression. J Mol Neurosci. 2007; 32:132–144. [PubMed: 17873297]

Bodnoff SR, Suranyi-Cadotte B, Aitken DH, Quirion R, Meaney MJ. The effects of chronic antidepressant treatment in an animal model of anxiety. Psychopharmacology (Berl). 1988; 95:298–302. [PubMed: 3137614]

Boldrini M, Hen R, Underwood MD, Rosoklija GB, Dwork AJ, Mann JJ, Arango V. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. Biol Psychiatry. 2012; 72:562–571. [PubMed: 22652019]

Bourin M, Chenu F, Prica C, Hascoet M. Augmentation effect of combination therapy of aripiprazole and antidepressants on forced swimming test in mice. Psychopharmacology (Berl). 2009; 206:97–107. [PubMed: 19517098]

Branchi I, Santarelli S, Capoccia S, Poggini S, D'Andrea I, Cirulli F, Alleva E. Antidepressant treatment outcome depends on the quality of the living environment: a pre-clinical investigation in mice. PLoS One. 2013; 8:e62226. [PubMed: 23653679]

Breuer ME, Chan JS, Oosting RS, Groenink L, Korte SM, Campbell U, Schreiber R, Hanania T, Snoeren EM, Waldinger M, Olivier B. The triple monoaminergic reuptake inhibitor DOV 216,303 has antidepressant effects in the rat olfactory bulbectomy model and lacks sexual side effects. Eur Neuropsychopharmacol. 2008; 18:908–916. [PubMed: 18789657]

Breuer ME, Groenink L, Oosting RS, Westenberg HG, Olivier B. Long-term behavioral changes after cessation of chronic antidepressant treatment in olfactory bulbectomized rats. Biol Psychiatry. 2007; 61:990–995. [PubMed: 17141743]

Browne CA, Lucki I. Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. Front Pharmacol. 2013; 4:161. [PubMed: 24409146]

Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002; 302:381–389. [PubMed: 12065741]

Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology. 1996a; 14:87–96. [PubMed: 8822531]

Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl). 1996b; 124:87–94. [PubMed: 8935803]

Caldarone B, Brunner D. Preclinical testing in mice for treatment resistant depression. Front Neurosci. 2009; 3:264–265.

Caldarone BJ, Harrist A, Cleary MA, Beech RD, King SL, Picciotto MR. High-affinity nicotinic acetylcholine receptors are required for antidepressant effects of amitriptyline on behavior and hippocampal cell proliferation. Biol Psychiatry. 2004; 56:657–664. [PubMed: 15522249]

Caldarone BJ, Karthigeyan K, Harrist A, Hunsberger JG, Wittmack E, King SL, Jatlow P, Picciotto MR. Sex differences in response to oral amitriptyline in three animal models of depression in C57BL/6J mice. Psychopharmacology (Berl). 2003; 170:94–101. [PubMed: 12879206]

Caldarone BJ, Paterson NE, Zhou J, Brunner D, Kozikowski AP, Westphal KG, Korte-Bouws GA, Prins J, Korte SM, Olivier B, Ghavami A. The novel triple reuptake inhibitor JZAD-IV-22 exhibits an antidepressant pharmacological profile without locomotor stimulant or sensitization properties. J Pharmacol Exp Ther. 2010; 335:762–770. [PubMed: 20864506]

Caldarone BJ, Wang D, Paterson NE, Manzano M, Fedolak A, Cavino K, Kwan M, Hanania T, Chellappan SK, Kozikowski AP, Olivier B, Picciotto MR, Ghavami A. Dissociation between duration of action in the forced swim test in mice and nicotinic acetylcholine receptor occupancy with sazetidine, varenicline, and 5-I-A85380. Psychopharmacology (Berl). 2011; 217:199–210. [PubMed: 21487659]

Can A, Blackwell RA, Piantadosi SC, Dao DT, O'Donnell KC, Gould TD. Antidepressant-like responses to lithium in genetically diverse mouse strains. Genes Brain Behav. 2011; 10:434–443. [PubMed: 21306560]

Carvalho AF, Berk M, Hyphantis TN, McIntyre RS. The integrative management of treatment-resistant depression: a comprehensive review and perspectives. Psychother Psychosom. 2014; 83:70–88. [PubMed: 24458008]

Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Juruena MF, Markopoulou K, Cleare AJ, Pariante CM. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. J Affect Disord. 2013; 148:136–140. [PubMed: 23200297]

Castagne V, Porsolt RD, Moser P. Use of latency to immobility improves detection of antidepressant-like activity in the behavioral despair test in the mouse. Eur J Pharmacol. 2009; 616:128–133. [PubMed: 19549518]

Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs. 2013; 27:703–716. [PubMed: 23757185]

Cervo L, Canetta A, Calcagno E, Burbassi S, Sacchetti G, Caccia S, Fracasso C, Albani D, Forloni G, Invernizzi RW. Genotype-dependent activity of tryptophan hydroxylase-2 determines the response to citalopram in a mouse model of depression. J Neurosci. 2005; 25:8165–8172. [PubMed: 16148224]

Christensen T, Bisgaard CF, Wiborg O. Biomarkers of anhedonic-like behavior, antidepressant drug refraction, and stress resilience in a rat model of depression. Neuroscience. 2011; 196:66–79. [PubMed: 21889970]

Coplan JD, Gopinath S, Abdallah CG, Berry BR. A neurobiological hypothesis of treatment-resistant depression—mechanisms for selective serotonin reuptake inhibitor non-efficacy. Front Behav Neurosci. 2014; 8:189. [PubMed: 24904340]

Cottingham C, Wang Q. alpha2 adrenergic receptor dysregulation in depressive disorders: implications for the neurobiology of depression and antidepressant therapy. Neurosci Biobehav Rev. 2012; 36:2214–2225. [PubMed: 22910678]

Crowley JJ, Blendy JA, Lucki I. Strain-dependent antidepressant-like effects of citalopram in the mouse tail suspension test. Psychopharmacology (Berl). 2005; 183:257–264. [PubMed: 16220334]

Crowley JJ, Brodkin ES, Blendy JA, Berrettini WH, Lucki I. Pharmacogenomic evaluation of the antidepressant citalopram in the mouse tail suspension test. Neuropsychopharmacology. 2006; 31:2433–2442. [PubMed: 16554742]

Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. Mol Psychiatry. 2004; 9:326–357. [PubMed: 14743184]

Cryan JF, O'Leary OF, Jin SH, Friedland JC, Ouyang M, Hirsch BR, Page ME, Dalvi A, Thomas SA, Lucki I. Norepinephrine-deficient mice lack responses to antidepressant drugs, including selective serotonin reuptake inhibitors. Proc Natl Acad Sci USA. 2004; 101:8186–8191. [PubMed: 15148402]

Cusin C, Dougherty DD. Somatic therapies for treatment-resistant depression: ECT, TMS, VNS, DBS. Biol Mood Anxiety Disord. 2012; 2:14. [PubMed: 22901565]

Cusin C, Iovieno N, Iosifescu DV, Nierenberg AA, Fava M, Rush AJ, Perlis RH. A randomized, double-blind, placebo-controlled trial of pramipexole augmentation in treatment-resistant major depressive disorder. J Clin Psychiatry. 2013; 74:e636–641. [PubMed: 23945458]

Dantzer R. Cytokine, sickness behavior, and depression. Immunol Allergy Clin North Am. 2009; 29:247–264. [PubMed: 19389580]

David DJ, Renard CE, Jolliet P, Hascoet M, Bourin M. Antidepressant-like effects in various mice strains in the forced swimming test. Psychopharmacology (Berl). 2003; 166:373–382. [PubMed: 12601501]

Der-Avakian A, Mazei-Robison MS, Kesby JP, Nestler EJ, Markou A. Enduring deficits in brain reward function after chronic social defeat in rats: susceptibility, resilience, and antidepressant response. Biol Psychiatry. 2014

Dournes C, Beeske S, Belzung C, Griebel G. Deep brain stimulation in treatment-resistant depression in mice: comparison with the CRF1 antagonist, SSR125543. Prog Neuropsychopharmacol Biol Psychiatry. 2013; 40:213–220. [PubMed: 23367508]

Drevets WC, Furey ML. Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. Biol Psychiatry. 2010; 67:432–438. [PubMed: 20074703]

Drevets WC, Zarate CA Jr, Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. Biol Psychiatry. 2013; 73:1156–1163. [PubMed: 23200525]

Dulawa SC, Hen R. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. Neurosci Biobehav Rev. 2005; 29:771–783. [PubMed: 15890403]

Dulawa SC, Holick KA, Gundersen B, Hen R. Effects of chronic fluoxetine in animal models of anxiety and depression. Neuropsychopharmacology. 2004; 29:1321–1330. [PubMed: 15085085]

Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006; 59:1116–1127. [PubMed: 16631126]

Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry. 2007; 64:327–337. [PubMed: 17339521]

Dziedzicka-Wasylewska M, Faron-Gorecka A, Kusmider M, Drozdowska E, Rogoz Z, Siwanowicz J, Caron MG, Bonisch H. Effect of antidepressant drugs in mice lacking the norepinephrine transporter. Neuropsychopharmacology. 2006; 31:2424–2432. [PubMed: 16554743]

Egeland M, Warner-Schmidt J, Greengard P, Svenningsson P. Neurogenic effects of fluoxetine are attenuated in p11 (S100A10) knockout mice. Biol Psychiatry. 2010; 67:1048–1056. [PubMed: 20227680]

Egeland M, Warner-Schmidt J, Greengard P, Svenningsson P. Co-expression of serotonin 5-HT(1B) and 5-HT(4) receptors in p11 containing cells in cerebral cortex, hippocampus, caudate-putamen and cerebellum. Neuropharmacology. 2011; 61:442–450. [PubMed: 21300076]

Ellis JS, Zarate CA Jr, Luckenbaugh DA, Furey ML. Antidepressant treatment history as a predictor of response to scopolamine: clinical implications. J Affect Disord. 2014; 162:39–42. [PubMed: 24767003]

Euthymics. 2013. (http://euthymics.com/wp-content/uploads/2013/05/FINAL_Euthymics_TRIADE_Results_052913.pdf)

Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry. 2007; 19:153–159. [PubMed: 17729016]

Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Arch Gen Psychiatry. 2006; 63:1121–1129. [PubMed: 17015814]

Holick KA, Lee DC, Hen R, Dulawa SC. Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology. 2008; 33:406–417. [PubMed: 17429410]

Holmes A, Yang RJ, Murphy DL, Crawley JN. Evaluation of antidepressant-related behavioral responses in mice lacking the serotonin transporter. Neuropsychopharmacology. 2002; 27:914–923. [PubMed: 12464448]

Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 2000; 23:477–501. [PubMed: 11027914]

Hong W, Fan J, Yuan C, Zhang C, Hu Y, Peng D, Wang Y, Huang J, Li Z, Yu S, Liu X, Wu Z, Chen J, Yi Z, Xu L, Fang Y. Significantly decreased mRNA levels of BDNF and MEK1 genes in treatment-resistant depression. Neuroreport. 2014

Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav. 2002; 71:533–554. [PubMed: 11888546]

Huuhka K, Kampman O, Anttila S, Huuhka M, Rontu R, Mattila KM, Hurme M, Lehtimaki T, Leinonen E. RGS4 polymorphism and response to electroconvulsive therapy in major depressive disorder. Neurosci Lett. 2008; 437:25–28. [PubMed: 18434012]

Ibarguen-Vargas Y, Surget A, Vourc'h P, Leman S, Andres CR, Gardier AM, Belzung C. Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress. Behav Brain Res. 2009; 202:245–251. [PubMed: 19463708]

Ibrahim L, Diaz Granados N, Jolkovsky L, Brutsche N, Luckenbaugh DA, Herring WJ, Potter WZ, Zarate CA Jr. A Randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. J Clin Psychopharmacol. 2012; 32:551–557. [PubMed: 22722512]

Iosifescu DV, Clementi-Craven N, Fraguas R, Papakostas GI, Petersen T, Alpert JE, Nierenberg AA, Fava M. Cardiovascular risk factors may moderate pharmacological treatment effects in major depressive disorder. Psychosom Med. 2005; 67:703–706. [PubMed: 16204427]

Ising M, Horstmann S, Kloiber S, Lucae S, Binder EB, Kern N, Kunzel HE, Pfennig A, Uhr M, Holsboer F. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression—a potential biomarker? Biol Psychiatry. 2007; 62:47–54. [PubMed: 17123470]

Isingrini E, Camus V, Le Guisquet AM, Pingaud M, Devers S, Belzung C. Association between repeated unpredictable chronic mild stress (UCMS) procedures with a high fat diet: a model of fluoxetine resistance in mice. PLoS One. 2010; 5:e10404. [PubMed: 20436931]

Iwai T, Ohnuki T, Sasaki-Hamada S, Saitoh A, Sugiyama A, Oka J. Glucagon-like peptide-2 but not imipramine exhibits antidepressant-like effects in ACTH-treated mice. Behav Brain Res. 2013; 243:153–157. [PubMed: 23333402]

Jacobson LH, Cryan JF. Feeling strained? Influence of genetic background on depression-related behavior in mice: a review. Behav Genet. 2007; 37:171–213. [PubMed: 17029009]

Jaffe RJ, Novakovic V, Peselow ED. Scopolamine as an antidepressant: a systematic review. Clin Neuropharmacol. 2013; 36:24–26. [PubMed: 23334071]

Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. Lancet. 1972; 2:632–635. [PubMed: 4116781]

Jayatissa MN, Bisgaard C, Tingstrom A, Papp M, Wiborg O. Hippocampal cytogenesis correlates to escitalopram-mediated recovery in a chronic mild stress rat model of depression. Neuropsychopharmacology. 2006; 31:2395–2404. [PubMed: 16482085]

Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB, Roth BL. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. Neuropsychopharmacology. 2008; 33:2303–2312. [PubMed: 18059438]

Kamei J, Miyata S, Sunohara T, Kamei A, Shimada M, Ohsawa M. Potentiation of the antidepressant-like effect of fluoxetine by aripiprazole in the mouse tail suspension test. J Pharmacol Sci. 2008; 108:381–384. [PubMed: 18987428]

Kato M, Chang CM. Augmentation treatments with second-generation antipsychotics to antidepressants in treatment-resistant depression. CNS Drugs. 2013; 27(Suppl 1):S11–19. [PubMed: 23709358]

Kato M, Serretti A. Review and meta-analysis of antidepressant pharma-cogenetic findings in major depressive disorder. Mol Psychiatry. 2010; 15:473–500. [PubMed: 18982004]

Keers R, Uher R. Gene-environment interaction in major depression and antidepressant treatment response. Curr Psychiatry Rep. 2012; 14:129–137. [PubMed: 22198824]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]

Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, Kim DK. Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. JAMA. 2006; 296:1609–1618. [PubMed: 17018806]

Kitagawa K, Kitamura Y, Miyazaki T, Miyaoka J, Kawasaki H, Asanuma M, Sendo T, Gomita Y. Effects of pramipexole on the duration of immobility during the forced swim test in normal and ACTH-treated rats. Naunyn Schmiedebergs Arch Pharmacol. 2009; 380:59–66. [PubMed: 19274453]

Kitamura Y, Araki H, Gomita Y. Influence of ACTH on the effects of imipramine, desipramine and lithium on duration of immobility of rats in the forced swim test. Pharmacol Biochem Behav. 2002; 71:63–69. [PubMed: 11812508]

Kitamura Y, Doi M, Kuwatsuka K, Onoue Y, Miyazaki I, Shinomiya K, Koyama T, Sendo T, Kawasaki H, Asanuma M, Gomita Y. Chronic treatment with imipramine and lithium increases cell proliferation in the hippocampus in adrenocorticotropic hormone-treated rats. Biol Pharm Bull. 2011; 34:77–81. [PubMed: 21212521]

Kitamura Y, Yagi T, Kitagawa K, Shinomiya K, Kawasaki H, Asanuma M, Gomita Y. Effects of bupropion on the forced swim test and release of dopamine in the nucleus accumbens in ACTH-treated rats. Naunyn Schmiedebergs Arch Pharmacol. 2010; 382:151–158. [PubMed: 20526847]

Kobayashi T, Hayashi E, Shimamura M, Kinoshita M, Murphy NP. Neurochemical responses to antidepressants in the prefrontal cortex of mice and their efficacy in preclinical models of anxiety-like and depression-like behavior: a comparative and correlational study. Psychopharmacology (Berl). 2008; 197:567–580. [PubMed: 18274731]

Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ. Molecular

adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell. 2007; 131:391–404. [PubMed: 17956738]

Kubera M, Curzytek K, Duda W, Leskiewicz M, Basta-Kaim A, Budziszewska B, Roman A, Zajicova A, Holan V, Szczesny E, Lason W, Maes M. A new animal model of (chronic) depression induced by repeated and intermittent lipopolysaccharide administration for 4 months. Brain Behav Immun. 2013; 31:96–104. [PubMed: 23313516]

Kuwatsuka K, Hayashi H, Onoue Y, Miyazaki I, Koyama T, Asanuma M, Kitamura Y, Sendo T. The mechanisms of electroconvulsive stimuli in BrdU-positive cells of the dentate gyrus in ACTH-treated rats. J Pharmacol Sci. 2013; 122:34–41. [PubMed: 23615225]

Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Huang CH, Tsai GE. RGS4 polymorphisms predict clinical manifestations and responses to risperidone treatment in patients with schizophrenia. J Clin Psychopharmacol. 2008; 28:64–68. [PubMed: 18204343]

Levinstein MR, Samuels BA. Mechanisms underlying the antidepressant response and treatment resistance. Front Behav Neurosci. 2014; 8:208. [PubMed: 25018708]

Li B, Suemaru K, Cui R, Araki H. Repeated electroconvulsive stimuli have long-lasting effects on hippocampal BDNF and decrease immobility time in the rat forced swim test. Life Sci. 2007; 80:1539–1543. [PubMed: 17306836]

Li B, Suemaru K, Cui R, Kitamura Y, Gomita Y, Araki H. Repeated electroconvulsive stimuli increase brain-derived neurotrophic factor in ACTH-treated rats. Eur J Pharmacol. 2006; 529:114–121. [PubMed: 16330021]

Lin YL, Wang S. Prenatal lipopolysaccharide exposure increases depressionlike behaviors and reduces hippocampal neurogenesis in adult rats. Behav Brain Res. 2014; 259:24–34. [PubMed: 24177209]

Lindholm JS, Autio H, Vesa L, Antila H, Lindemann L, Hoener MC, Skolnick P, Rantamaki T, Castren E. The antidepressant-like effects of glutamatergic drugs ketamine and AMPA receptor potentiator LY 451646 are preserved in bdnf(+)/(−) heterozygous null mice. Neuropharmacology. 2012; 62:391–397. [PubMed: 21867718]

Liou YJ, Chen CH, Cheng CY, Chen SY, Chen TJ, Yu YW, Nian FS, Tsai SJ, Hong CJ. Convergent evidence from mouse and human studies suggests the involvement of zinc finger protein 326 gene in antidepressant treatment response. PLoS One. 2012; 7:e32984. [PubMed: 22666313]

Liu X, Gershenfeld HK. Genetic differences in the tail-suspension test and its relationship to imipramine response among 11 inbred strains of mice. Biol Psychiatry. 2001; 49:575–581. [PubMed: 11297714]

Liu X, Stancliffe D, Lee S, Mathur S, Gershenfeld HK. Genetic dissection of the tail suspension test: a mouse model of stress vulnerability and antidepressant response. Biol Psychiatry. 2007; 62:81–91. [PubMed: 17125744]

Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, Debonnel G, Sadikot AF, Lam RW, Howard AK, Ilcewicz-Klimek M, Honey CR, Mayberg HS. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J Neurosurg. 2012; 116:315–322. [PubMed: 22098195]

Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol. 1997; 8:523–532. [PubMed: 9832966]

Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. Psychopharmacology (Berl). 2001; 155:315–322. [PubMed: 11432695]

Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine. 1997; 9:853–858. [PubMed: 9367546]

Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci. 2000; 20:9104–9110. [PubMed: 11124987]

Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, Greenberg BD. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry. 2009; 65:267–275. [PubMed: 18842257]

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. Neuron. 2005; 45:651–660. [PubMed: 15748841]

Mayorga AJ, Dalvi A, Page ME, Zimov-Levinson S, Hen R, Lucki I. Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. J Pharmacol Exp Ther. 2001; 298:1101–1107. [PubMed: 11504807]

McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, Thase ME, Davis L, Biggs MM, Shores-Wilson K, Luther JF, Niederehe G, Warden D, Rush AJ. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry. 2006; 163:1531–1541. (quiz 1666). [PubMed: 16946177]

McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, Wagner KD, Asarnow JR, Ryan ND, Birmaher B, Shamseddeen W, Mayes T, Kennard B, Spirito A, Keller M, Lynch FL, Dickerson JF, Brent DA. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry. 2012; 51:404–411. [PubMed: 22449646]

Mikoteit T, Beck J, Eckert A, Hemmeter U, Brand S, Bischof R, Holsboer-Trachsler E, Delini-Stula A. High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. Psychopharmacology (Berl). 2014

Millstein RA, Holmes A. Effects of repeated maternal separation on anxiety- and depression-related phenotypes in different mouse strains. Neurosci Biobehav Rev. 2007; 31:3–17. [PubMed: 16950513]

Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. Trends Pharmacol Sci. 2010; 31:580–586. [PubMed: 20965579]

Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA. 2004; 101:10827–10832. [PubMed: 15249684]

Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, Parada LF, Nestler EJ. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biol Psychiatry. 2007; 61:187–197. [PubMed: 16697351]

Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. Psychiatr Serv. 2014

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013; 170:1134–1142. [PubMed: 23982301]

Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG. A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord. 2014; 156:24–35. [PubMed: 24388038]

Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006; 59:1151–1159. [PubMed: 16566899]

Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA Jr, Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. Annu Rev Pharmacol Toxicol. 2014; 54:119–139. [PubMed: 24392693]

O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. J Psychiatr Res. 2007; 41:326–331. [PubMed: 16870211]

O'Donnell JM, Marek GJ, Seiden LS. Antidepressant effects assessed using behavior maintained under a differential-reinforcement-of-low-rate (DRL) operant schedule. Neurosci Biobehav Rev. 2005; 29:785–798. [PubMed: 15893376]

O'Leary OF, Cryan JF. Towards translational rodent models of depression. Cell Tissue Res. 2013; 354:141–153. [PubMed: 23525777]

O'Leary OF, Zandy S, Dinan TG, Cryan JF. Lithium augmentation of the effects of desipramine in a mouse model of treatment-resistant depression: a role for hippocampal cell proliferation. Neuroscience. 2013; 228:36–46. [PubMed: 23069753]

Oh YS, Gao P, Lee KW, Ceglia I, Seo JS, Zhang X, Ahn JH, Chait BT, Patel DJ, Kim Y, Greengard P. SMARCA3, a chromatin-remodeling factor, is required for p11-dependent antidepressant action. Cell. 2013; 152:831–843. [PubMed: 23415230]

Ohgi Y, Futamura T, Kikuchi T, Hashimoto K. Effects of antidepressants on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol Biochem Behav. 2013; 103:853–859. [PubMed: 23262300]

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; 29:739–759. [PubMed: 15925699]

Paterson NE, Fedolak A, Olivier B, Hanania T, Ghavami A, Caldarone B. Psychostimulant-like discriminative stimulus and locomotor sensitization properties of the wake-promoting agent modafinil in rodents. Pharmacol Biochem Behav. 2010; 95:449–456. [PubMed: 20346966]

Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric disorders in Cushing's syndrome. Neuroendocrinology. 2010; 92(Suppl 1):65–70. [PubMed: 20829621]

Picciotto MR, Caldarone BJ, King SL, Zachariou V. Nicotinic receptors in the brain. Links between molecular biology and behavior. Neuropsychopharmacology. 2000; 22:451–465. [PubMed: 10731620]

Piubelli C, Gruber S, El Khoury A, Mathe AA, Domenici E, Carboni L. Nortriptyline influences protein pathways involved in carbohydrate metabolism and actin-related processes in a rat gene-environment model of depression. Eur Neuropsychopharmacol. 2011a; 21:545–562. [PubMed: 21168998]

Piubelli C, Vighini M, Mathe AA, Domenici E, Carboni L. Escitalopram modulates neuron-remodelling proteins in a rat gene-environment interaction model of depression as revealed by proteomics. Part I: Genetic background. Int J Neuropsychopharmacol. 2011b; 14:796–833. [PubMed: 21054914]

Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther. 1977; 229:327–336. [PubMed: 596982]

Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol. 2008; 28:631–637. [PubMed: 19011431]

Prins J, Denys DA, Westphal KG, Korte-Bouws GA, Quinton MS, Schreiber R, Groenink L, Olivier B, Korte SM. The putative antidepressant DOV 216,303, a triple reuptake inhibitor, increases monoamine release in the prefrontal cortex of olfactory bulbectomized rats. Eur J Pharmacol. 2010; 633:55–61. [PubMed: 20153745]

Prins J, Kenny PJ, Doomernik I, Schreiber R, Olivier B, Mechiel Korte S. The triple reuptake inhibitor DOV 216,303 induces long-lasting enhancement of brain reward activity as measured by intracranial self-stimulation in rats. Eur J Pharmacol. 2012; 693:51–56. [PubMed: 23010469]

Prins J, Westphal KG, Korte-Bouws GA, Quinton MS, Schreiber R, Olivier B, Korte SM. The potential and limitations of DOV 216,303 as a triple reuptake inhibitor for the treatment of major depression: a microdialysis study in olfactory bulbectomized rats. Pharmacol Biochem Behav. 2011; 97:444–452. [PubMed: 20934452]

Pryce CR, Azzinnari D, Sigrist H, Gschwind T, Lesch KP, Seifritz E. Establishing a learned-helplessness effect paradigm in C57BL/6 mice: behavioural evidence for emotional, motivational and cognitive effects of aversive uncontrollability per se. Neuropharmacology. 2012; 62:358–372. [PubMed: 21864549]

Pryce CR, Azzinnari D, Spinelli S, Seifritz E, Tegethoff M, Meinlschmidt G. Helplessness: a systematic translational review of theory and evidence for its relevance to understanding and treating depression. Pharmacol Ther. 2011; 132:242–267. [PubMed: 21835197]

Quesseveur, G.; Guiard, B. New strategies for the treatment of mood disorders: the triple reuptake inhibitors. In: Dremencov, BPGaE, editor. Neurobioloby of Mood Disorders. Bentham Science Publishers; 2013. p. 234-253.

Rabenstein RL, Caldarone BJ, Picciotto MR. The nicotinic antagonist mecamylamine has antidepressant-like effects in wild-type but not beta2- or alpha7-nicotinic acetylcholine receptor subunit knockout mice. Psychopharmacology (Berl). 2006; 189:395–401. [PubMed: 17016705]

Radhakrishnan R, Santamaria A, Escobar L, Arias HR. The beta4 nicotinic receptor subunit modulates the chronic antidepressant effect mediated by bupropion. Neurosci Lett. 2013; 555:68–72. [PubMed: 23981664]

Reus GZ, Abelaira HM, Agostinho FR, Ribeiro KF, Vitto MF, Luciano TF, Souza CT, Quevedo J. The administration of olanzapine and fluoxetine has synergistic effects on intracellular survival pathways in the rat brain. J Psychiatr Res. 2012; 46:1029–1035. [PubMed: 22575330]

Richardson-Jones JW, Craige CP, Guiard BP, Stephen A, Metzger KL, Kung HF, Gardier AM, Dranovsky A, David DJ, Beck SG, Hen R, Leonardo ED. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron. 2010; 65:40–52. [PubMed: 20152112]

Ripoll N, David DJ, Dailly E, Hascoet M, Bourin M. Antidepressant-like effects in various mice strains in the tail suspension test. Behav Brain Res. 2003; 143:193–200. [PubMed: 12900045]

Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castren E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci. 2003; 23:349–357. [PubMed: 12514234]

Sah A, Schmuckermair C, Sartori SB, Gaburro S, Kandasamy M, Irschick R, Klimaschewski L, Landgraf R, Aigner L, Singewald N. Anxiety-rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. Transl Psychiatry. 2012; 2:e171. [PubMed: 23047242]

Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology (Berl). 1993; 112:285–292. [PubMed: 7871032]

Samuels BA, Leonardo ED, Dranovsky A, Williams A, Wong E, Nesbitt AM, McCurdy RD, Hen R, Alter M. Global state measures of the dentate gyrus gene expression system predict antidepressant-sensitive behaviors. PLoS One. 2014; 9:e85136. [PubMed: 24465494]

Samuels BA, Leonardo ED, Gadient R, Williams A, Zhou J, David DJ, Gardier AM, Wong EH, Hen R. Modeling treatment-resistant depression. Neuropharmacology. 2011; 61:408–413. [PubMed: 21356220]

Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat Rev Drug Discovery. 2008; 7:426–437.

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003; 301:805–809. [PubMed: 12907793]

Savitz J, Lucki I, Drevets WC. 5-HT(1A) receptor function in major depressive disorder. Prog Neurobiol. 2009; 88:17–31. [PubMed: 19428959]

Schmidt EF, Warner-Schmidt JL, Otopalik BG, Pickett SB, Greengard P, Heintz N. Identification of the cortical neurons that mediate antidepressant responses. Cell. 2012; 149:1152–1163. [PubMed: 22632977]

Schmuckermair C, Gaburro S, Sah A, Landgraf R, Sartori SB, Singewald N. Behavioral and neurobiological effects of deep brain stimulation in a mouse model of high anxiety- and depression-like behavior. Neuropsychopharmacology. 2013; 38:1234–1244. [PubMed: 23325324]

Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, De Loore K, Leysen JE. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl). 1996; 124:57–73. [PubMed: 8935801]

Schramm NL, McDonald MP, Limbird LE. The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. J Neurosci. 2001; 21:4875–4882. [PubMed: 11425914]

Shanks N, Anisman H. Strain-specific effects of antidepressants on escape deficits induced by inescapable shock. Psychopharmacology (Berl). 1989; 99:122–128. [PubMed: 2506597]

Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology. 2003; 28:1400–1411. [PubMed: 12784105]

Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. CNS Drugs. 2010; 24:131–161. [PubMed: 20088620]

Shytle RD, Silver AA, Lukas RJ, Newman MB, Sheehan DV, Sanberg PR. Nicotinic acetylcholine receptors as targets for antidepressants. Mol Psychiatry. 2002; 7:525–535. [PubMed: 12140772]

Skolnick P, Krieter P, Tizzano J, Basile A, Popik P, Czobor P, Lippa A. Preclinical and clinical pharmacology of DOV 216,303, a “triple” reuptake inhibitor. CNS Drug Rev. 2006; 12:123–134. [PubMed: 16958986]

Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. Antidepressant-like actions of DOV 21,947: a “triple” reuptake inhibitor. Eur J Pharmacol. 2003; 461:99–104. [PubMed: 12586204]

Skolnick P, Popik P, Trullas R. Glutamate-based antidepressants: 20 years on. Trends Pharmacol Sci. 2009; 30:563–569. [PubMed: 19837463]

Sonino N, Boscaro M, Ambroso G, Merola G, Mantero F. Prolonged treatment of Cushing’s disease with metyrapone and aminoglutethimide. IRCS Med Sci. 1986; 14:485–486.

Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. J Clin Psychiatry. 2006; 67(Suppl 6):16–22. [PubMed: 16848672]

Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl). 1985; 85:367–370. [PubMed: 3923523]

Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Friedman L, Rajkowska G. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. J Neurosci. 1998; 18:7394–7401. [PubMed: 9736659]

Stratinaki M, Varidaki A, Mitsi V, Ghose S, Magida J, Dias C, Russo SJ, Vialou V, Caldarone BJ, Tamminga CA, Nestler EJ, Zachariou V. Regulator of G protein signaling 4 [corrected] is a crucial modulator of antidepressant drug action in depression and neuropathic pain models. Proc Natl Acad Sci USA. 2013; 110:8254–8259. [PubMed: 23630294]

Su S, Ohno Y, Lossin C, Hibino H, Inanobe A, Kurachi Y. Inhibition of astroglial inwardly rectifying Kir4.1 channels by a tricyclic antidepressant, nortriptyline. J Pharmacol Exp Ther. 2007; 320:573–580. [PubMed: 17071817]

Sugimoto Y, Kajiwara Y, Hirano K, Yamada S, Tagawa N, Kobayashi Y, Hotta Y, Yamada J. Mouse strain differences in immobility and sensitivity to fluvoxamine and desipramine in the forced swimming test: analysis of serotonin and noradrenaline transporter binding. Eur J Pharmacol. 2008; 592:116–122. [PubMed: 18655786]

Sugimoto Y, Yamamoto M, Tagawa N, Kobayashi Y, Mitsui-Saitoh K, Hotta Y, Yamada J. Differences between mice strains in response to paroxetine in the forced swimming test: involvement of serotonergic or noradrenergic systems. Eur J Pharmacol. 2011; 672:121–125. [PubMed: 22004611]

Sukoff Rizzo SJ, Neal SJ, Hughes ZA, Beyna M, Rosenzweig-Lipson S, Moss SJ, Brandon NJ. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl Psychiatry. 2012; 2:e199. [PubMed: 23212583]

Svenningsson P, Berg L, Matthews D, Ionescu DF, Richards EM, Niciu MJ, Malinger A, Toups M, Manji H, Trivedi MH, Zarate CA Jr, Greengard P. Preliminary evidence that early reduction in p11 levels in natural killer cells and monocytes predicts the likelihood of antidepressant response to chronic citalopram. Mol Psychiatry. 2014

Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, El Yacoubi M, Vaugeois JM, Nomikos GG, Greengard P. Alterations in 5-HT1B receptor function by p11 in depression-like states. Science. 2006; 311:77–80. [PubMed: 16400147]

Svenningsson P, Kim Y, Warner-Schmidt J, Oh YS, Greengard P. p11 and its role in depression and therapeutic responses to antidepressants. Nat Rev Neurosci. 2013; 14:673–680. [PubMed: 24002251]

Talkowski ME, Chowdari K, Lewis DA, Nimgaonkar VL. Can RGS4 polymorphisms be viewed as credible risk factors for schizophrenia? A critical review of the evidence Schizophr Bull. 2006; 32:203–208.

Terzi D, Stergiou E, King SL, Zachariou V. Regulators of G protein signaling in neuropsychiatric disorders. Prog Mol Biol Transl Sci. 2009; 86:299–333. [PubMed: 20374720]

Tran P, Skolnick P, Czobor P, Huang NY, Bradshaw M, McKinney A, Fava M. Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Psychiatr Res. 2012; 46:64–71. [PubMed: 21925682]

Trillat AC, Malagie I, Bourin M, Jacquot C, Hen R, Gardier AM. [Homozygote mice deficient in serotonin 5-HT1B receptor and antidepressant effect of selective serotonin reuptake inhibitors]. C R Seances Soc Biol Fil. 1998; 192:1139–1147. [PubMed: 10101609]

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. 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. [PubMed: 16390886]

Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. Br J Psychiatry. 2004; 184:386–392. [PubMed: 15123501]

van der Heyden JA, Molewijk E, Olivier B. Strain differences in response to drugs in the tail suspension test for antidepressant activity. Psychopharmacology (Berl). 1987; 92:127–130. [PubMed: 3110823]

van Enkhuizen J, Janowsky DS, Olivier B, Minassian A, Perry W, Young JW, Geyer MA. The catecholaminergic-cholinergic balance hypothesis of bipolar disorder revisited. Eur J Pharmacol. 2014

van Heesch F, Prins J, Konsman JP, Korte-Bouws GA, Westphal KG, Rybka J, Olivier B, Kraneveld AD, Korte SM. Lipopolysaccharide increases degradation of central monoamines: an in vivo microdialysis study in the nucleus accumbens and medial prefrontal cortex of mice. Eur J Pharmacol. 2014; 725:55–63. [PubMed: 24444442]

van Heesch F, Prins J, Konsman JP, Westphal KG, Olivier B, Kraneveld AD, Korte SM. Lipopolysaccharide-induced anhedonia is abolished in male serotonin transporter knockout rats: an intracranial self-stimulation study. Brain Behav Immun. 2013; 29:98–103. [PubMed: 23274951]

van Loo HM, Cai T, Gruber MJ, Li J, de Jonge P, Petukhova M, Rose S, Sampson NA, Schoevers RA, Wardenaar KJ, Wilcox MA, Al-Hamzawi AO, Andrade LH, Bromet EJ, Bunting B, Fayyad J, Florescu SE, Gureje O, Hu C, Huang Y, Levinson D, Medina-Mora ME, Nakane Y, Posada-Villa J, Scott KM, Xavier M, Zarkov Z, Kessler RC. Major depressive disorder subtypes to predict long-term course. Depress Anxiety. 2014

Vieta E, Thase ME, Naber D, D'Souza B, Rancans E, Lepola U, Olausson B, Szamosi J, Wilson E, Hosford D, Dunbar G, Tummala R, Eriksson H. Efficacy and tolerability of flexibly-dosed adjunct TC-5214 (dexmecamylamine) in patients with major depressive disorder and inadequate response to prior antidepressant. Eur Neuropsychopharmacol. 2014; 24:564–574. [PubMed: 24507016]

Walker AJ, Burnett SA, Hasebe K, McGillivray JA, Gray LJ, McGee SL, Walder K, Berk M, Tye SJ. Chronic adrenocorticotrophic hormone treatment alters tricyclic antidepressant efficacy and prefrontal monoamine tissue levels. Behav Brain Res. 2013a; 242:76–83. [PubMed: 23276607]

Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, Dantzer R. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6 J mice. Neuropsychopharmacology. 2013b; 38:1609–1616. [PubMed: 23511700]

Wang Y, Chang T, Chen YC, Zhang RG, Wang HN, Wu WJ, Peng ZW, Tan QR. Quetiapine add-on therapy improves the depressive behaviors and hippocampal neurogenesis in fluoxetine treatment resistant depressive rats. Behav Brain Res. 2013; 253:206–211. [PubMed: 23876404]

Wang Y, Cui XL, Liu YF, Gao F, Wei D, Li XW, Wang HN, Tan QR, Jiang W. LPS inhibits the effects of fluoxetine on depression-like behavior and hippocampal neurogenesis in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:1831–1835. [PubMed: 21791234]

Warner-Schmidt JL, Chen EY, Zhang X, Marshall JJ, Morozov A, Svenningsson P, Greengard P. A role for p11 in the antidepressant action of brain-derived neurotrophic factor. Biol Psychiatry. 2010; 68:528–535. [PubMed: 20591415]

Warner-Schmidt JL, Flajolet M, Maller A, Chen EY, Qi H, Svenningsson P, Greengard P. Role of p11 in cellular and behavioral effects of 5-HT4 receptor stimulation. J Neurosci. 2009; 29:1937–1946. [PubMed: 19211900]

Warner-Schmidt JL, Schmidt EF, Marshall JJ, Rubin AJ, Arango-Lievano M, Kaplitt MG, Ibanez-Tallon I, Heintz N, Greengard P. Cholinergic interneurons in the nucleus accumbens regulate depression-like behavior. Proc Natl Acad Sci USA. 2012; 109:11360–11365. [PubMed: 22733786]

Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology (Berl). 1997; 134:319–329. [PubMed: 9452163]

Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology. 2005; 52:90–110. [PubMed: 16037678]

Wisor J. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. Front Neurol. 2013; 4:139. [PubMed: 24109471]

Witkin JM, Overshiner CD, Li X, Catlow JT, Wishart GN, Schober DA, Heinz B, Nikolayev A, Tolstikov VV, Anderson WH, Higgs RE, Kuo MS, Felder CC. M1 and M2 muscarinic receptor subtypes regulate the antidepressant-like effects of the rapidly-acting antidepressant scopolamine. J Pharmacol Exp Ther. 2014 [Epub ahead of print].

Ye R, Carneiro AM, Han Q, Airey D, Sanders-Bush E, Zhang B, Lu L, Williams R, Blakely RD. Quantitative trait loci mapping and gene network analysis implicate protocadherin-15 as a determinant of brain serotonin transporter expression. Genes Brain Behav. 2014; 13:261–275. [PubMed: 24405699]

Yoshida K, Takahashi H, Higuchi H, Kamata M, Ito K, Sato K, Naito S, Shimizu T, Itoh K, Inoue K, Suzuki T, Nemeroff CB. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. Am J Psychiatry. 2004; 161:1575–1580. [PubMed: 15337646]

Zhang W, Bymaster FP. The in vivo effects of olanzapine and other antipsychotic agents on receptor occupancy and antagonism of dopamine D1, D2, D3, 5HT2A and muscarinic receptors. Psychopharmacology (Berl). 1999; 141:267–278. [PubMed: 10027508]

Zhang W, Perry KW, Wong DT, Potts BD, Bao J, Tollefson GD, Bymaster FP. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Neuropsychopharmacology. 2000; 23:250–262. [PubMed: 10942849]

Zisook S, Rush AJ, Haight BR, Clines DC, Rockett CB. Use of bupropion in combination with serotonin reuptake inhibitors. Biol Psychiatry. 2006; 59:203–210. [PubMed: 16165100]

Table 1

Antidepressants by drug class.

Drug	Primary mechanism of action
Monoamine oxidase inhibitors (MAOIs)	
Tranylcypramine	MAOI (nonselective)
Phenelzine	MAOI (nonselective)
Moclobemide	MAOI (MAOA selective)
Tricyclic antidepressant (TCA)	
Desipramine	NRI
Nortriptyline	NRI
Amitriptyline	SRI+NRI
Imipramine	SRI+NRI
Selective serotonin reuptake inhibitor (SSRI)	
Fluoxetine	SRI
Paroxetine	SRI
Sertraline	SRI
Fluvoxamine	SRI
Citalopram	SRI
Escitalopram	SRI
Norepinephrine reuptake inhibitor (NRI)	
Reboxetine	NRI
Serotonin norepinephrine reuptake inhibitor (SNRIs)	
Venlafaxine	NRI+SRI
Milnacipran	NRI+SRI
Duloxetine	NRI+SRI
Norepinephrine dopamine reuptake inhibitor (NDRIs)	
Bupropion	NRI+DRI

Serotonin reuptake inhibitor (SRI)—prevents serotonin reuptake by inhibition of the serotonin transporter.

Norepinephrine reuptake inhibitor (NRI)—prevents norepinephrine reuptake by inhibition of the norepinephrine transporter.

Dopamine reuptake inhibitor (DRI)—prevents dopamine reuptake by inhibition of the dopamine transporter.

Table 2

Rodent behavioral models of treatment-resistant depression.

Animal model	Findings	Validation with treatment active in antidepressant resistant patients	References
Separation into antidepressant responders and non responders			
Chronic mild stress	Chronic mild stress lowered sucrose preference. Escitalopram or sertraline restored sucrose preference to baseline in 50% of rats	Not tested	Bergstrom et al. (2007), Bisgaard et al. (2007), Christensen et al. (2011), Jayatissa et al. (2006)
	Chronic mild stress produced deterioration of coat state in mice. Fluoxetine restored coat state in approximately 50% of mice	Yes, deep brain stimulation	Dournes et al. (2013)
Chronic social defeat	Chronic social defeat elevated brain reward thresholds. Fluoxetine or desipramine returned brain reward threshold levels to baseline in 50% stress-susceptible rats	Not tested	Der-Avakian et al. (2014)
Chronic corticosterone	Chronic corticosterone increased latency to feed in novelty-suppressed feeding assay in majority of C57BL/6 mice. Chronic fluoxetine produce antidepressant-like effect in subset of mice	Not tested	Samuels et al. (2011)
Treatments that render rodents resistant to antidepressants			
Chronic adrenocorticotropic hormone (ACTH)	Rats and mice administered chronic ACTH are insensitive to tricyclic antidepressants in the FST	Yes (ECS, lithium augmentation in rat model)	Caldarone and Brunner (2009), Iwai et al. (2013), Kitamura et al. (2002), Li et al. (2006), Walker et al. (2013a,b)
Induction of inflammation with interleukin 6	Central administration of interleukin 6 in mice and mice with endogenous overexpression of brain interleukin 6 (LPR mice) reduced response to acute fluoxetine in TST and FST	Yes lithium augmentation	Sukoff Rizzo et al. (2012)
Chronic mild stress+induction of inflammation with lipopolysaccharide (LPS)	Rats that received LPS each day prior chronic mild stress showed an attenuated response to fluoxetine in the FST and novelty-suppressed feeding tests	Not tested	Wang et al. (2011)
Chronic mild stress+high fat diet	Fluoxetine reversed effects of chronic mild stress on coat state in mice fed normal, but not high fat diet	Not tested	Isingrini et al. (2010)
Chronic mild stress+environmental stress during drug treatment	Fluoxetine reversed effects of chronic stress on anhedonia (sucrose preference) when administered in an enriched but not a stressful environment	Not tested	Branchi et al. (2013)
Genetic models			
Inbred strains			
BALB/cOLaHsd mouse strain	Reduced sensitivity to the behavioral effects of chronic desipramine in the novelty-induced hypophagia test	Yes, lithium augmentation	O'Leary et al. (2013)
Selectively bred lines			
HAB selectively bred line	HAB male mice are also insensitive to chronic administration of three SSRIs (fluoxetine, paroxetine, and citalopram) in the FST	Yes, DBS	Schmuckermair et al. (2013)

Animal model	Findings	Validation with treatment active in antidepressant resistant patients	References
Flinders sensitive line rats+maternal separation stress	Maternal separation stress blocked effects of escitalopram and nortriptyline in FST	Not tested	Piubelli et al. (2011a, 2011b),
Single gene effects			
Serotonin transporter knockout mice	Resistant to fluoxetine in the TST	Not tested	Holmes et al. (2002)
Serotonin 5-HT_{1A} receptor knockout mice	$5HT_{1A}$ knockout mice (129SvEvTac background), resistant to chronic fluoxetine (novelty-suppressed feeding and adult hippocampal neurogenesis)	Not tested	Santarelli et al. (2003)
Serotonin $5HT_{1A}$ autoreceptor mutant mice	Mice with higher levels of presynaptic autoreceptors resistant to fluoxetine in the NSF test	Not tested	Richardson-Jones et al. (2010)
p11 knockout mice	Reduced behavioral responses to imipramine in the TST; reduced neurogenic and behavioral response to fluoxetine in novelty-suppressed feeding	Not tested	Egeland et al. (2010), Svenningsson et al. (2006), Warner-Schmidt et al. (2010)
p11 cortex specific knockout mice	Reduced behavioral response to fluoxetine in NSF and TST	Not tested	Schmidt et al. (2012)
Norepinephrine transporter knockout mice	Reduced sensitivity to desipramine and reboxetine in TST	Not tested	Dziedzicka-Wasylewska et al. (2006)
Dopamine beta hydroxylase knockout mice	Resistant to a wide range of antidepressants	Not tested	Cryan et al. (2004)
α2a Adrenergic receptor knockout mice	Resistant to imipramine in the FST	Not tested	Schramm et al. (2001)
β2 Subunit nicotinic acetylcholine receptor knockout mice	Insensitive to amitriptyline in TST, FST, and learned helplessness and no increased cell proliferation	Not tested	Caldarone et al. (2004)
Brain derived neurotrophic factor (BDNF) heterozygous null mice	Resistant to chronic imipramine in the resident intruder and TST tests following chronic mild stress and to acute imipramine in the forced swim test	Yes, ketamine active in the FST	Ibarguen-Vargas et al. (2009), Lindholm et al. (2012), Saarelainen et al. (2003)
BDNF conditional (cortex and hippocampus) knockout mice	Attenuated antidepressant response to desipramine in the FST	No, ketamine inactive in FST	Autry et al. (2011), Monteggia et al. (2004), Monteggia et al. (2007)
Regulator of G protein Signaling 4 (RGS4) constitutive and nucleus accumbens knockout	Reduced sensitivity to desipramine, fluoxetine and reboxetine in the FST	Yes, increased sensitivity to ketamine in FST	Stratinaki et al. (2013)