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Invited review

Modeling treatment-resistant depression

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ABSTRACT

Depression is a polygenic and highly complex psychiatric disorder that is currently a major burden on society. Depression is highly heterogeneous in presentation and frequently exhibits high comorbidity with other psychiatric and somatic disorders. Commonly used treatments, such as selective serotonin reuptake inhibitors (SSRIs), are not ideal since only a subset of patients achieve remission. In addition, the reason why some individuals respond to SSRIs while others don't are unknown. Here we begin to ask what the basis of treatment resistance is, and propose new strategies to model this phenomenon in animals. We focus specifically on animal models that offer the appropriate framework to study treatment resistance with face, construct and predictive validity.

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1. Introduction

Understanding the neurobiological basis of a highly complex disease like depression remains one of the foremost challenges for modern psychiatry. In patients, the essential feature of a major depressive episode is defined as a persistent period of at least 2 weeks in which there is either depressed mood or the loss of interest or pleasure in nearly all activities (DSM-IV). Approximately 32–35 million adults in the US population (16%) experience an episode of major depression in their lifetime (Kessler et al., 2003). Fortunately some approved classes of drugs with antidepressant activity have been developed, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), selective norepinephrine reuptake inhibitors (NRIs) and monoamine oxidase inhibitors (MAOIs) (Wong et al., 2010a). Unfortunately there are two major problems with these lines of treatment. First, there is a significant delay between the start of treatment and response. Second, many patients do not respond to antidepressant treatment with these drugs. As an example, only 47% of patients respond and only 33% of patients achieve remission in the first line of treatment with a widely used SSRI (Trivedi et al., 2006). Therefore, while currently available treatments are amongst the most widely prescribed drugs, they fail to have an effect on many patients and have incomplete effects for many others. The development of the next generation of novel antidepressants is therefore subjected to considerable challenges (Wong et al., 2010b), and understanding the basis of treatment-resistant depression should offer insights into new approaches.

When prescribing medication, there is increasing pressure on clinicians to follow decision-tree medical algorithms, such as the Texas Medication Algorithm project (TMAP), in attempts to combat depression in patients that are non-responsive to initial lines of treatment. These involve multiple levels of treatments, each with varying success. Recently, STAR*D, a large study designed to mirror clinical practice, was conducted at 25 different sites. The study enrolled over 4000 patients with a broad range of symptoms and involved 4 possible steps for treatment (Fava and Covino, 2007). If patients failed to achieve remission at any level, they would be randomized for the next step of treatment. As patients moved from levels 2–4 of treatment, remission rates dropped dramatically (from approximately 35% at level 2 to16% at level 4). Therefore,

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failure to achieve remission with 2 consecutive treatments is associated with very low remission rates in subsequent treatments. This suggests that the usefulness of current lines of treatment is limited and underscores the need for discovery of new treatments.

2. Animal models of depressive phenotypes and treatment resistance

Given the problems with current lines of antidepressant treatment in the clinic, it is incumbent upon basic research to yield novel methods of treatment. In order for basic research to provide potential advances, a critical first step is to create useful animal models with relevant phenotypic features to reveal treatment responsiveness. However, some of the original animal models designed to address this problem suffered from a flawed tautological approach in that they were based solely on responsiveness to known antidepressants. Since no genetic variants with high penetrance that cause depression are known, in recent years there has been a move toward animal models that mainly rely on chronic exposures to stressful experiences, or sensory tract lesions such as in olfactory bulbectomy. Importantly these manipulations induce states that present depression- and anxiety-like characteristics not only in a wide variety of behavioral tests, but also at the cellular and molecular level. Subsequently, the animals can then be treated with antidepressants to test for responsiveness. Overall, current depression models achieve face and construct validity to a considerable extent. While anxiety and depression have a high comorbidity with co-occurrence rates up to 60% in patients (Gorman, 1996; Leonardo and Hen, 2006), they have generally been conceived of as distinct psychiatric disorders, believed to be caused by alterations of different brain circuits (Nestler and Hyman, 2010; Krishnan and Nestler, 2011). However, given that depression is a highly heterogenous disease (there are at least 140 different ways to meet criteria), it is unlikely that any one animal model will accurately replicate the ensemble of complex phenotypes seen in depression. Instead, a multidisciplinary approach combining the data and utilizing the beneficial aspects from several different animal models is likely to be the most rewarding.

The oldest and most commonly used paradigm to induce a depression-like state is chronic mild stress (CMS), which was initially developed in rats. Initial observations suggested that animals subjected to multiple stressors over a prolonged period of time reduced their intake of saccharine or sucrose, a potential behavioral model of anhedonia (Katz, 1982). Furthermore, this effect was selectively reversed by chronic treatment with the TCA imipramine (Katz, 1982). Further work was able to repeat this result using more mild stressors, such as periods of food and water deprivation, small temperature reductions and changes of cage mates (Willner, 2005; Willner et al., 1987). Following these studies the CMS procedure, and modified versions such as chronic unpredictable stress (CUS or UCMS), became commonly used and much work demonstrated that other depression-like changes were induced in animals, such as decreased sexual and aggressive behavior, decreased self-care, and altered sleep patterns (Willner, 2005). Furthermore these behaviors are all reversible by chronic, but not acute, treatment using multiple classes of antidepressants (Surget et al., 2008). Historically potential pitfalls of the CMS procedure are that it is notoriously labor intensive, and that there has been some difficulty in replicating results across laboratories (Nestler et al., 2002). However, the modified versions of the CMS have proven more useful.

Recently, there have been some reports using CMS or variants to model treatment resistance in rodents. In one study, CMS significantly decreased sucrose consumption and the proliferation of adult hippocampal neural progenitors (Jayatissa et al., 2006). Following chronic treatment with a SSRI (escitalopram), the subjects were retested for sucrose consumption. A bimodal distribution was found where one group recovered (increased sucrose consumption) while another was refractory to treatment (no increase in sucrose consumption). Interestingly, there was a correlation between the animals in the group that recovered with a reversal of the decreased proliferation that was absent in the group resistant to treatment (Jayatissa et al., 2006). More recently, follow-up work has taken a proteomic approach in an attempt to find molecular differences in the rat ventral hippocampus between responders and non-responders (Bisgaard et al., 2007). Another study demonstrated that if animals are on a high fat diet during multiple UCMS procedures they become resistant to treatment with a SSRI (fluoxetine) (Isingrini et al., 2010).

A distinct procedure that has gained traction is the usage of a social defeat model. In this paradigm a mouse is forced into the territory of a mouse from a larger, more aggressive strain leading to an interaction resulting in intruder subordination. Repeated defeats over 10 days can result in a long lasting reduced social interaction, sexual dysfunction, sleep dysregulation, anxiety, metabolic deficits and anhedonia (Berton et al., 2006; Krishnan et al., 2007; Krishnan and Nestler, 2008; Tsankova et al., 2006). Interestingly, following the social defeat procedure there remains a large variance in behavior outcomes in spite of using an inbred mouse strain (C57BL/6). Some animals display a resistance to social defeat (resilience) while others are susceptible (determined by interaction with a social target relative to an empty enclosure). If animals are separated based on this measure, susceptible mice demonstrate decreased sucrose intake, a blunted circadian rhythm, and conditioned place preference to cocaine (Krishnan et al., 2007). Furthermore, phenotypes induced by social defeat in susceptible mice can be reversed by antidepressant treatment (Tsankova et al., 2006). Given that molecular mechanisms for resilience to the stressful procedure are now being worked out (Krishnan et al., 2007; Vialou et al., 2010), it would be intriguing to see if similar pathways are necessary for mediating response to antidepressants.

A third procedure for inducing a depression-like state in animals is administration of chronic glucocorticoids in order to mimic the effects of chronic stress. A significant proportion of depressed patients display altered activity of the HPA axis, and stress generally leads to hypersecretion of corticosteroids, which imposes an increased risk for depression (Antonijevic, 2006; Brown et al., 2004; Carroll et al., 1981; de Kloet et al., 2005; Leonardo and Hen, 2006; Nemeroff et al., 1984; Sachar et al., 1970; Strohle and Holsboer, 2003). Chronic treatment of rodents with corticosterone effectively induces multiple anxiety- and depression-like changes in behavior, neurochemistry and brain morphology (Ardayfio and Kim, 2006; David et al., 2009; Gourley et al., 2008a; Murray et al., 2008). Behaviorally, depression-related changes include suppression of sucrose intake and decreased self-care (David et al., 2009; Gourley et al., 2008b), while anxiety-related changes include increased latency to emerge into the light compartment in the light/dark test, decreased time, entries and percent distance in the center of an open field and increased latency to take a bite of food in the novelty suppressed feeding (NSF) test (Ardayfio and Kim, 2006; David et al., 2009). Behaviorally, approximately 85% of C57BL/6 mice demonstrate anxiety and depression-related signs in response to chronic corticosterone, suggesting that, similar to social defeat, there is a small population that is resilient to the manipulation (David et al., 2009; David unpublished data). Interestingly, mouse subjects that participate in the NSF test do tend to show a bimodal distribution in response to antidepressant treatment, suggesting a responder and non-responder divide (Fig. 1). The NSF test is conducted by depriving animal subjects of food for 24 h and then placing them into

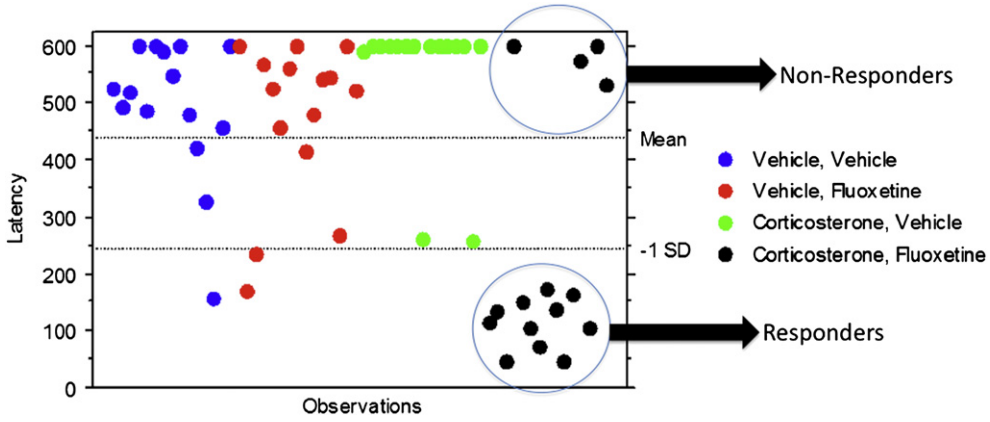

Fig. 1. Responders and Non-Responders to Antidepressant Treatment in the Novelty Suppressed Feeding Test. 60 C57BL/6 mice were divided into four groups depending on drug treatment (Vehicle Only blue dots; Vehicle + Chronic Fluoxetine red dots; Chronic Corticosterone + Vehicle green dots; and Chronic Corticosterone + Chronic Fluoxetine black dots). C57BL/6 mice that have not been exposed to stress show a wide distribution of responses. Most C57BL/6 that have been exposed to chronic corticosterone show an increased latency to take a bite of a food pellet in an anxiogenic environment (compare green dots to blue dots). There are a few subjects that show resilience to the chronic corticosterone procedure (green dots around 250 s). This increased anxiety phenotype induced by chronic corticosterone is reversible in some, but not all, subjects with chronic antidepressant treatment (black dots), resulting in a bimodal distribution. Therefore, this distribution may provide of model of responders and non-responders to chronic antidepressant treatment.

a brightly lit, open arena containing a pellet of food in the center. The latency it takes for animals to take a bite of the food pellet is recorded. While the effects are somewhat strain-dependent, in general chronic antidepressant treatment will decrease the latency of the animal to take a bite of food. However, there is usually a group of animals given chronic antidepressants that do not enter the center of the arena and eat and, therefore, have a much higher latency. These animals are possible non-responders to antidepressant treatment. In the experiment shown here, some animals were first given chronic corticosterone to induce an anxiety/depression-like state, and then were put on a chronic fluoxetine regimen. Within this treatment group of animals, there is a distinct bimodal distribution to the antidepressant treatment (Fig. 1) that could potentially be used to study differences between responders and non-responders with clear face validity. If animals are run through multiple tests, and their behavior across tests are compared, generally there is a very high correlation between antidepressant responsiveness across tests. For example, the mice that are non-responders in the NSF also tend to have the highest immobility scores in the Forced Swim Test. However since the immobility scores in the FST follow a more normal distribution it would be somewhat arbitrary to define responders and non-responders based on this behavior alone. The bimodal distribution seen in the NSF allows for this delineation.

In addition to pharmacological and social stress models, there are other rodent models that have been used to study depression-like behavior and antidepressant treatment. One such model is the Flinders Sensitive line (FSL) of rats. Flinders lines were originally developed through a selective breeding strategy, which ultimately led to a line that was genetically sensitive to the neurotoxin diisopropyl fluorophosphate (DFP) (Overstreet et al., 2005). Further work eventually showed that FSL rats exhibit several behavioral characteristics associated with depression-like signs, including lower body weight and reduced appetite, abnormal REM sleep patterns, psychomotor retardation, and reduced bar pressing for rewards (Overstreet et al., 2005). Multiple classes of antidepressants are effective at reversing some of these depression-related phenotypes (Overstreet, 2002; Overstreet et al., 2005), suggesting that FSL rats have pharmacological validity as a model for testing antidepressants. Other examples of generating rodent models through selective breeding strategies include rats that swim or move more or less in the forced swim or tail suspension test, are hyperactive, and are resistant to stress-induced reduction in ambulatory activity (El Yacoubi et al., 2003; Scott et al., 1996; Weiss et al., 2008).

3. The serotonin-1A receptor

The most commonly used drugs to treat major depression today increase serotonergic signaling either directly or indirectly. The effects of altering brain serotonin levels by SSRI treatment are potentially mediated through more that 14 identified serotonin receptors (Barnes and Sharp, 1999; Wong et al., 2008). One receptor of particular interest is the serotonin-1A receptor (5-HT1A), an inhibitory G protein coupled receptor that is expressed on serotonergic neurons in the raphe where it functions as an autoreceptor to control overall serotonergic tone through feedback inhibition (Blier and de Montigny, 1987; Blier et al., 1998). It is also expressed on non-serotonergic neurons throughout the brain where it functions as a heteroreceptor, mediating inhibitory responses to released serotonin (Barnes and Sharp, 1999).

The 5-HT1A autoreceptor has long been thought to be at least partially responsible for the delay that exists in treatment response to selective serotonin reuptake inhibitors (SSRI's) (Artigas et al., 1996; Blier and De Montigny, 1983; Gardier et al., 1996). This is due to the feedback inhibition provided by the receptor that prevents increases in serotonin levels in the brain after acute blockade of the serotonin transporter. Over time, the autoreceptors desensitize, removing feedback inhibition and allowing increased extracellular serotonin levels at nerve terminals. This "autoreceptor hypothesis" has led to significant effort to develop drugs that target and block these receptors in attempts to accelerate the drug response with mixed results (Artigas et al., 1994; Berman et al., 1997; Moreno et al., 1997; Perez et al., 1997).

Other lines of evidence have implicated the 5-HT1A receptor more directly in the pathophysiology of anxiety as well as depression. Of particular relevance for this review, is an association between a C(-1019)G polymorphism in the promoter region of the Htr1a gene, and a variety of mood related variables, including risk of depression, risk of suicide, amygdala reactivity, and response to treatment with antidepressants (Fakra et al., 2009; Fisher et al., 2006; Le Francois et al., 2008; Lesch and Gutknecht, 2004; Strobel et al., 2003). The polymorphism is thought to result in altered levels of 5-HT1A autoreceptors, as the G allele of the polymorphism results in the loss of a raphe specific repressor (Lemonde

et al., 2003). These data led to the hypothesis that levels of 5-HT1A autoreceptors can control the susceptibility to depression and the response to antidepressant treatment (Lemonde et al., 2004). Indeed, PET imaging of humans carrying the G allele to suggest high densities of 5-HT1A receptors (Lothe et al., 2010).

This hypothesis was recently tested through the generation of transgenic mice whose 5-HT1A autoreceptors could be conditionally altered, generating animals with either relatively higher or lower levels of autoreceptors (Richardson-Jones et al., 2010). Importantly, in this study, autoreceptors were only altered by about 30% between the two groups, consistent with the variation that has been observed within human populations (Lothe et al., 2010; Moller et al., 2007). This study demonstrated that animals with lower levels of 5-HT1A autoreceptors are more resilient to repeated exposures of forced swim stress compared to animals with higher levels of autoreceptors. In addition, animals with lower levels of autoreceptors were found to respond to treatment with fluoxetine in the NSF paradigm, a test commonly used to assess chronic response to treatment with antidepressants, while animals with higher levels of autoreceptors did not. Interestingly, both the animals with high and the animals with low autoreceptor levels fully desensitized their receptors after four weeks of treatment with fluoxetine, suggesting that differences in negative feedback between the two strains could not account for the differential response. The high and low 5-HT1A autoreceptor expressing animals demonstrate that alterations in 5-HT1A autoreceptor levels alone are sufficient to alter both resilience to stress and response to treatment with SSRIs. In addition, the 5-HT1A high autoreceptor expressing mice provide a molecularly defined model for SSRI non-responders, which could in turn be used for the development of alternative treatments for depression. Recent work has compared 5-HT1A autoreceptor and heteroreceptor levels after chronic SSRI treatment in humans using PET imaging (Hahn et al., 2010). Currently, clinical trials are underway to evaluate 5-HT1A autoreceptor levels in responders and non-responders using PET imaging and buspar challenges.

4. Future directions for treatment

In addition to new potential targets for treatment-resistant depression that will be uncovered via basic research, recent clinical trials have sparked interest in potentially faster acting antidepressants and treatment-resistant patients. The NMDA receptor antagonist ketamine, and the anti-cholinergic scopolamine, as well as deep brain stimulation, have been shown through multiple trials in the last decade to produce a rapid antidepressant response (Berman et al., 2000; Krystal, 2007; Mayberg et al., 2005; Zarate et al., 2006). In the case of ketamine after just one dose, 35% of treatment-resistant patients were able to maintain response for at least one week (Zarate et al., 2006). However, all but two patients relapsed within two weeks of ketamine infusion. One recent study attempted to address the safety and efficacy of repeated-dose intravenous ketamine, and found that most patients continued to meet response criterion after six infusions (aan het Rot et al., 2010). However, given that ketamine must be administered intravenously and has high abuse potential, as well as the fact that several patients experienced significant (although transient) dissociative symptoms, it will be critical for basic research to reverse engineer the antidepressant effects of the drug. For example, one can explore whether engaging more selective blockade of NR2B subunits of NMDA receptors can reduce the psychotomimetic effects. Interestingly, recent work has demonstrated that in rats ketamine rapidly activates the mTOR pathway, leading to increased synaptic signaling proteins and an increased number of functional new synapses in the prefrontal cortex (Li et al., 2010). Blockade of mTOR signaling completely blocks ketamine-induced synapse formation and antidepressant effects of ketamine in the forced swim and novelty suppressed feeding tests, suggesting that the synaptogenic properties of ketamine are essential for rapid antidepressant effects (Li et al., 2010). Although the forced swim and NSF test do not necessarily model depression, repeated administration of ketamine has been used successfully in the chronic mild stress procedure to reverse anhedonia-like behavior in rats (Garcia et al., 2009).

5. Conclusions

In summary, current antidepressant treatments are not sufficient, as many patients do not respond. Future basic and clinical research will need to take new approaches to advance the understanding and discover new methods for treatment-resistant depression. Since many animal models of depression have previously focused mainly on pharmacological validity, there has been an overemphasis on mechanisms underlying currently used drugs rather than the discovery of new targets that could benefit patients suffering from treatment-resistant depression. Therefore, selective manipulation of the 5-HT1A system, where the autoreceptors play a crucial role in governing SSRI sensitivity, may be important to address treatment-resistant depression. Furthermore, using animal models will be valuable in providing a translational framework to study SSRI insensitivity, and validation of any findings in humans as potential biomarkers for treatment responsiveness will pave the way to break a tradition of using SSRI sensitive behavioral assays to interrogate novel approaches for relieving depressive phenotypes.

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