European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Rodent models of treatment-resistant depression

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ARTICLE INFO

Article history:
Accepted 9 October 2014

Keywords:
Antidepressant
Treatment resistant depression
Animal model
Genetic
Behavior
Pharmacology

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.

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 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 of $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

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http://dx.doi.org/10.1016/j.ejphar.2014.10.063
0014-2999/

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.

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