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Review

Stress-based animal models of depression: Do we actually know what we are doing?

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ABSTRACT

Depression is one of the leading causes of disability and a significant health-concern worldwide. Much of our current understanding on the pathogenesis of depression and the pharmacology of antidepressant drugs is based on pre-clinical models. Three of the most popular stress-based rodent models are the forced swimming test, the chronic mild stress paradigm and the learned helplessness model. Despite their recognizable advantages and limitations, they are associated with an immense variability due to the high number of design parameters that define them. Only few studies have reported how minor modifications of these parameters affect the model phenotype. Thus, the existing variability in how these models are used has been a strong barrier for drug development as well as benchmark and evaluation of these pre-clinical models of depression. It also has been the source of confusing variability in the experimental outcomes between research groups using the same models. In this review, we summarize the known variability in the experimental protocols, identify the main and relevant parameters for each model and describe the variable values using characteristic examples. Our view of depression and our efforts to discover novel and effective antidepressants is largely based on our detailed knowledge of these testing paradigms, and requires a sound understanding around the importance of individual parameters to optimize and improve these pre-clinical models.

1. Depression: a silent epidemic

Major depressive disorder (MDD), also known as clinical depression, is a serious mood disorder with a high prevalence in all developed countries. In 2007, a study from the World Health Organization (WHO) estimated that depression affected health more profoundly compared to many other chronic diseases (Moussavi et al., 2007). As depression is often comorbid with other health conditions, there is an urgency to both improve its treatment and reduce its burden. Although clinical symptoms of depression vary, patients generally struggle to cope with their daily personal and social lives. They experience loss of self-worth, disturbed sleep, reduced pleasure and concentration, increased fatigue and irritability (Paris, 2014). At its worst, depression is an important risk factor of suicide (Angst et al., 1999). In 2012 alone, depression caused a million deaths worldwide and contributed to 12.5% of all suicide cases caused by mental disorders (Marcus et al., 2012; WHO, 2012), representing a serious public health concern till today. The complexity of depression is reflected from the variety of known causal factors of this disorder, such as genetic/epigenetic, environmental, medications and secondary to other neuropsychological conditions. Although the genetic factors are thought to contribute up to 50% of depression cases (Fava and Kendler, 2000), recent advances in the epigenetics of depression suggest that regulation of certain genes but not their actual sequence may contribute to the high heritable component of depression (Krishnan and Nestler, 2008; Krishnan and Nestler, 2010).

It is widely known that chronic stress is associated with the onset of depression. There is significant evidence proving that most of the depression episodes are likely consequence of prolonged stressful life (Dumont and Provost, 1999; Frazer and Morilak, 2005; Hammen, 2005; Salavecz et al., 2014). Chronic or lifetime stress is a strong predictor for the development of depressive symptoms (Gutman and Nemeroff, 2011), associated with pathophysiological changes in brain function and structure. For instance, it has been shown that stressful

Abbreviations: MDD, major depressive disorder; WHO, The World Health Organization; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; FST, forced swimming test; TST, tail suspension test; LH, learned helplessness; HPA, hypothalamic-pituitary-adrenal; CMS, chronic mild stress; NS, non-shock; IS, inescapable shock; ES, escapable shock; SIA, stress-induced analgesia

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Table 1
Classification of current animal models of depression and description of their main pros and cons as described in the literature.

Main Classes	Models	Stressor	Main Advantages	Main Disadvantages	Example references
Acute and sub-chronic stress-induced	FST	Inescapable forced swimming	Fast induction and drug-screening, cheap & easy setting	Unspecific response to non-antidepressants, weak validities, present single symptom	(Chourbaji et al., 2005; Cryan et al., 2005a; Slattery and Cryan, 2012)
	TST	Tail suspension			
	LH	Inescapable electric shocks	Strong validation, variety of behaviors and symptoms	Comprehensive protocol & equipment, strong stressors	(Chourbaji et al., 2005)
Chronic stress-induced	CSI	Prolonged-chronic isolation	Strong validity, variety of depressive symptoms	Long experimental duration, complex setting, anxiety symptoms	(Hill et al., 2012)
	CSD	Repeated bouts of social subordination			
	CMS	Chronic expose to alternate and variable stressors	Strong validity, long lasting symptoms	Long experimental duration, anxiety symptoms	
Models of secondary depression	HPA axis dysregulation	Administration of corticosterone	Correlation with pathophysiological and molecular mechanisms of depression, present various depressive symptoms	Questionable correlation with depression	(O'Reilly et al., 2008; Pariante and Lightman, 2008; Udina et al., 2014; Van Winkel et al., 2008)
	Retinoic acid model	Prolong use of retinoic acid			
	Immune system dysregulation	Administration of pro-inflammatory cytokines			
Immutable models	Olfactory bulbectomy	Surgical removal of olfactory bulb	Variety of symptoms, specificity in studies of particular pathways	Indistinguishable adaptation mechanisms	(Kelly et al., 1997; Overstreet and Wegener, 2013)
	Genetically modified models	Genetically selected for hypersensitivity to drugs, receptor knockouts etc.			

FST: Forced swimming test, TST: tail-suspension test, LH: learned helplessness, CSI: chronic social isolation, CSD: chronic social defeat, CMS: chronic (unpredicted) mild stress.

situations over an extended period of time can lead to reduced hippocampal size, a brain area that regulates mood in both animals and humans (Czéh et al., 2001). This strong link between stress and depressive symptoms have been used as a cornerstone of creating animal models of depression, which are vital for the study of this disorder as well as for research in novel antidepressant medications.

1.1. Antidepressants

The molecular pathology of depression is still not very well understood and current pharmacological treatments rely heavily on the monoamine theory of depression, which postulates that reduced levels of serotonin, dopamine and noradrenaline in the brain are linked to the manifestation of depressive symptoms (Koch et al., 2002). Current antidepressants used in the clinic are largely based on this theory and aim to increase levels of monoaminergic neurotransmitters in the synaptic cleft through inhibiting reuptake or the reduction of metabolism, ultimately increasing the activity of hypothalamic-pituitary-adrenal (HPA) axis (Frazer and Morilak, 2005; Pariante, 2003). These drugs include selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). While the development of SSRIs in the 1980s significantly improved the tolerability of antidepressant therapy compared to TCAs, the pharmacological antidepressants still remains largely suboptimal and challenging. It is important to note that conventional antidepressants exhibit varying effects in different animal models of depression. Furthermore, differences have even been observed in the same model across tests and laboratories. In the FST, imipramine (15 mg/kg/day, i.p.) reduced depressive-like symptoms by 82.4%, (Vitale et al., 2009a), which was nearly twice the effect seen in the LH model (54.4%) using the same dose and treatment duration (Joca et al., 2003). In contrast, desipramine decreased the depression-like symptoms by 45.5% in the LH paradigm (Reed et al., 2009), whereas twice of the dose had to be applied in the FST to achieve the same effect (Carr et al., 2010). It is worth noting that even the same class of drugs showed inconsistent effects in the same model. For example, the MAO-inhibitor, tranylcypromine, significantly decreased the symptoms in the FST whereas another MAO-inhibitor, phenelzine, showed no effect at the same dose (Bourin et al., 2002). However, phenelzine used by another group did reduce behavioral despair in the rat FST (Khursheed et al., 2014). Since the pharmacological effects of antidepressants also heavily depend on the experimental design, the differences of model parameters could be one of the major reasons that directly affect the inconsistency of test results. Therefore, in addition to the development of new, improved therapies, it is essential to develop and improve animal models of depression in parallel that are associated with consistent results across studies and labs, as well as increased accuracy. Although current animal models were crucial to develop and evaluate current antidepressant therapies over the last two decades, a number of limitations have to be addressed, to maximize our efficiency to discover effective, new antidepressant drugs.

1.2. Current animal models of depression

A number of pre-clinical models are currently used to evaluate the pharmacological effects of potential antidepressants (Krishnan and Nestler, 2008). These models have been evaluated on the basis of three major criteria, or 'validities': construct validity (the experimental conditions of the animal model replicate the cause of disease in patients), face validity (the symptoms observed in the animal model replicate clinical features of the disease), and predictive validity (the animal response to the drugs can predict the potential drug activities in patients) (Willner and Mitchell, 2002). The more valid a particular animal model is, the more accurate and reliable are the data it produces. Current animal models of depression can be generally