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REVIEW

PATHOGENESIS OF DEPRESSION: INSIGHTS FROM HUMAN AND RODENT STUDIES

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Abstract—Major depressive disorder (MDD) will affect one out of every five people in their lifetime and is the leading cause of disability worldwide. Nevertheless, mechanisms associated with the pathogenesis of MDD have yet to be completely understood and current treatments remain ineffective in a large subset of patients. In this review, we summarize the most recent discoveries and insights for which parallel findings have been obtained in human depressed subjects and rodent models of mood disorders in order to examine the potential etiology of depression. These mechanisms range from synaptic plasticity mechanisms to epigenetics and the immune system where there is strong evidence to support a functional role in the development of specific depression symptomology. Ultimately we conclude by discussing how novel therapeutic strategies targeting central and peripheral processes might ultimately aid in the development of effective new treatments for MDD and related stress disorders.

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Key words: major depressive disorder, synaptic plasticity, epigenetics, immune system, cytokines, astrocytes.

Contents

INTRODUCTION

Mood disorders affect ~20% of the American population over their lifetime and yearly prevalence rates are close to 10%, including 6.7% for major depressive disorder (MDD) (Kessler et al., 1993, 2005). This represents approximately 35 million adults in the US that will experience an episode of major depression in their lifetime (Kessler et al., 2003), with women having a higher risk of first onset and twice the occurrence of men (Kessler et al., 1993). Moreover, depression is the leading cause of disability worldwide (Lopez and Murray, 1998) — the economic burden of depression was estimated to be

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Abbreviations: BBB, blood–brain-barrier; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CNS, central nervous system; CMS, chronic mild stress; CRF, corticotropin-releasing factor; CSDS, chronic social defeat stress; Dnmt, DNA methyltransferase; ECS, electroconvulsive seizure therapy; FST, forced swim test; GFAP, glial-fibrillary-acidic protein; GSK-3β, glycogen synthase kinase 3β; HDAC2, histone deacetylase 2; HPA, hypothalamic-pituitary-adrenal; IKK, IκB kinase; IL, interleukin; LH, learned helplessness; MDD, major depressive disorder; MSN, medium spiny neurons; mTOR, mammalian target of rapamycin; NAc, nucleus accumbens; NF-κB, nuclear factor-kappa B; NMDA, N-methyl-D-aspartate; OBX, olfactory bulbectomy; PFC, prefrontal cortex; PTSD, post-traumatic stress disorders; PVN, paraventricular nucleus; Rac1, RAS-related C3 botulinum toxin substrate 1; RSD, repeat social defeat; TNFα, tumor necrosis factor alpha; VEGF, vesicular endothelial growth factor; VTA, ventral tegmental area.

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83.1 billion USD in the year 2000 (Greenberg et al., 2003). MDD is characterized by symptoms of emotional, motivational, cognitive and physiological domains making it a complex disease to treat. Furthermore, depression is often associated with chronic illnesses (Evans et al., 2005) or other mood disorders such as co-morbid anxiety, all of which can be predictors of poor response to antidepressant treatments (Brent et al., 1998). In fact, it is estimated that only 50% of depressed patients are responsive to currently available antidepressant treatments (Rush et al., 2006). This may reflect the fact that depression diagnosis is based solely on behavioral symptoms and the drugs used to treat these symptoms are not specific to the underlying disease pathology (Berton and Nestler, 2006). Here we provide an overview of insights from human and rodent studies identifying new disease mechanisms that are relevant to developing novel, efficient treatments of depression.

ANIMAL MODELS OF DEPRESSION

Modeling human depression in animals is challenging considering the subjective nature of the multiple psychological and physiological symptoms and lack of objective biomarkers (for review, see Nestler and Hyman, 2010). Validity of an animal model is generally evaluated with the following criteria: (1) manifestation of symptoms are reasonably analogous to the human disorder, (2) behavioral changes can be monitored objectively and (3) behavior changes can be reversed with therapeutically effective antidepressant treatments (McKinney and Bunney, 1969). None of the animal models developed so far perfectly reproduce the depression-like phenotype observed in humans (for review, see Berton and Nestler, 2006). Moreover, unlike other psychiatric disorders, genome-wide association studies have not identified a single risk allele associated with MDD, thus, the field lacks true genetic models of the disease. Nevertheless, overlapping studies in human post mortem samples and translational rodent models have led to significant discoveries over the last few decades and drug discovery efforts are now geared toward testing the efficacy of drugs targeting known disease mechanisms. The next sections will briefly describe the relevance of established rodent depression models within the context of recent disease mechanisms identified in human MDD subjects.

Olfactory bulbectomy (OBX)

Surgical bilateral OBX has been used to screen antidepressant drugs for the past 40 years in both rats (van Riezen et al., 1976; Kelly et al., 1997; Mar et al., 2002) and mice (Han et al., 2009). OBX induces major dysfunction of the cortical-hippocampal-amygdala circuits (for review, see Russo and Nestler, 2013) affecting behaviors such as locomotion, food seeking and avoidance (for review, see Song and Leonard, 2005). Cognitive deficits, loss of libido, reduced social interaction and exploration of a novel environment was associated with cortical neuronal degeneration in OBX rats (Wang et al., 2007). Impaired structural plasticity of the hippocampus was also recently linked to emotional and spatial memory deficits in this model (Morales-Medina et al., 2013). Chronic antidepressant treatments can reverse both behavioral and structural changes (Song and Leonard, 2005). While the direct link between OBX and human MDD is controversial, clinical studies have reported decreased olfactory sensitivity in acute major depression (Atanasova et al., 2008) and there is a significant negative correlation between olfactory bulb volume and depression severity (Negoias et al., 2010). Still, less invasive and more ethologically valid models have been characterized.

Maternal separation and models of early-life stress

Early-life traumatic events contribute to the development of individual differences in the ability to react and cope with subsequent stressful events. Victims of childhood abuse or parental neglect have significantly higher probabilities of developing mood disorders (for review, see Anacker et al., 2014) and studies of institutionalized children indicate that global deprivation induces persistent behavioral and cognitive deficits (Chugani et al., 2001). Rodent models of maternal separation suggest that offspring of separated pups are more submissive and generally adopt a more passive coping strategy in response to stress throughout life (Gardner et al., 2005). These early-life events permanently alter endocrine responses to stress (Plotsky et al., 2005) and confer vulnerability to drug abuse in adulthood (for review, see Moffett et al., 2007). Additionally, individual differences in maternal behaviors, such as licking and grooming, can correspond with offspring vulnerability and promote resilience (Fleming et al., 1999; Meaney, 2001; Weaver et al., 2004; Weinstock, 2008). As adults, the offspring of high licking and grooming mothers are less fearful and characterized by lower hypothalamic–pituitary–adrenal (HPA) responses to stress (Liu et al., 1997; Caldji et al., 1998; Francis et al., 1999a; Tang et al., 2014). In an elegant study, Weaver et al. (2004) showed that mother–pup contacts alter the offspring epigenome thus affecting regulation of the glucocorticoid receptor promoter in the hippocampus. Moreover, mother–pup licking and grooming behaviors are stably transmitted across generations (Francis et al., 1999a), and cross-fostering studies suggest that these might be inherited through the nursing mother and not the biological one (Champagne and Meaney, 2001). Interestingly, social deprivation and maternal care models seem to have distinct behavioral and neurochemical consequences depending upon the developmental stage of the offspring (Hall, 1998). This highlights the importance of future studies to identify causative factors in the development of depressive behaviors during these critical windows in order to translate findings to human disease.

Learned helplessness (LH)

In humans and rodents, LH is defined as a deficit to escape an aversive stimulus induced by prior exposure to uncontrollable stress (Pryce et al., 2011). It is interpreted as a depression-like coping deficit in avoidable situations (Vollmayr and Gass, 2013). The original protocol