

MINIREVIEW

Animal models of maternal depression for monitoring neurodevelopmental changes occurring in dams and offspring

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ITX100117A05 • Received: 16 January 2017 • Accepted: 17 March 2017

ABSTRACT

Depression is one of the most prevalent and life-threatening forms of mental illness affecting about 20% of the population. Depressive disorder as a biochemical phenomenon, was first recognized in the mid-20th century of research, however the etiology of this disease is still not well understood. Although the need to investigate depressive disorders has emerged from the needs of clinical practice, there are many preclinical studies, which brought new insights into this field of research. During experimental work it was crucial to develop appropriate animal models, where the neurohumoral mechanism was similar to humans. In the past decades, several animal models of maternal depression have been developed. We describe the three most popular rodent models of maternal depression which are based on 1. stress prior to gestation, 2. prenatal stress and 3. early life stress. The above-mentioned animal models appear to fulfill many criteria for a relevant animal model of depression; they alter the regulation of the HPA, induce signs of depression-like behavior and several antidepressant treatments can reverse the state induced by maternal stress. Although, they are not able to model all aspects of maternal depression, they are useful models for monitoring neurodevelopmental changes occurring in dams and offspring.

KEY WORDS: rat; animal model; depression; pregnancy

Introduction

Depression is a mood disorder that causes a persistent feeling of sadness, loss of interest or pleasure in normal activities, sleep disturbances, tiredness, reduced appetite, feelings of worthlessness or suicidal thoughts (DSM-V). Depressive disorder as a biochemical phenomenon, was first recognized in the mid-20th century (Ashcroft *et al.*, 1966; Schildkraut, 1965). Nowadays, depression is one of the most prevalent and life-threatening forms of mental illness affecting about 20% of the population (Pearlstein, 2015; Gentile, 2017). Despite half a century of research, the etiology of this disease is still not well understood and the treatment for depression also raises many questions. Currently, the symptoms of depressive disorders are related to monoamine depletion, excess of

corticotrophin-releasing hormone (CRH) and cortisol levels, glucocorticoid receptor (GR) resistance and modified cytokines levels. These alterations might be intimately involved in major mood changes.

Although the need to investigate depressive disorders has emerged from the needs of clinical practice, there are many preclinical studies, which brought new insights into this field of research. During experimental work it was crucial to develop suitable animal models, where the neurohumoral mechanism was similar to humans. However, designing a proper animal model of depression has some difficulties, since in animals we cannot detect signs of depressive disorder such as depressed mood, low self-confidence, feeling of worthlessness or suicidal thoughts. On the other hand, there are some depression-associated endophenotypes that can be modelled in rodents. For example, anhedonia, which relates to loss of interest in pleasurable and/or rewarding actions. In rodents, anhedonia, can be assessed by the preference for a reward, such as sucrose solution (sucrose test) (Belzung & Lemoine, 2011). Another manifestation can be behavioral despair of rats, which can be assessed with the forced swim test

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or with the tail suspension test (Belzung & Lemoine, 2011; Wainwright & Galea, 2013). Moreover, signs of depression both in humans and in rodents can be manifested by several other changes: 1. physiological (weight gain), 2. endocrinological (adrenocortical hormones) and 3. neuroanatomical (loss of neurons and dendritic atrophy in hippocampus), which can be reliably reproduced and evaluated in rodents (Deussing, 2006; Wainwright & Galea, 2013).

In the past several animal models of depression have been developed. Most of the models were based on exposure to different types of excessive stress (Willner, 2005; Deussing, 2006; Mairesse *et al.*, 2015). Stressful events have been shown to play an important role in the development and manifestation of psychiatric illnesses. When an organism is exposed to stress, catecholamines are released from the sympathetic nervous system. This release triggers secretion of CRH by neurosecretory cells in the hypothalamus. Subsequently CRH enhances the activation of adrenocorticotrophic hormone (ACTH). Glucocorticoids are released from the adrenal gland in response to increased level of ACTH. This physiological stress response is a fundamental adaptation for an organism to cope with emergencies. However, when stress is excessive the mentioned alterations might lead to psychopathological disorders, such as depressive disorder (Korte, 2001). Chronic excessive stress results in glucocorticoid hypersecretion and can lead to long lasting hypothalamic-pituitary-adrenal (HPA) responses. Furthermore, elevated levels of glucocorticoids inhibit HPA activity, which is associated with impaired glucocorticoid negative feedback in depressed patients. Indeed, depressed individuals have an abnormal HPA function which is manifested by hypersecretion of cortisol (Burke *et al.*, 2005; Schüle, 2007; Brummelte & Galea, 2010) and with abnormal cortisol rhythms, with lower cortisol levels in the morning and higher levels in the evening (Burke *et al.*, 2005). While increased evening cortisol levels predict a greater risk for persistent depressive episodes (Goodyer *et al.*, 2001). Moreover, elevation of cortisol level during chronic stress exerts neurotoxic effect on hippocampal neurons, which results in decreased neurogenesis, disrupted synaptogenesis, reduced dendritic spines. The morphological loss of neurons further leads to functional deficits, loss of long-term potentiation or long-term depression of hippocampus (Egeland *et al.*, 2015). These neurochemical changes together determine the background of depressive disorders.

Similarly, it has been shown, that rats exposed chronically to a variety of unpredictable stressors showed sign of anhedonia and depressive-like behavior (Willner *et al.*, 1987; Gross & Pinhasov, 2016a). Animal studies have suggested that excessive stress is associated with higher corticosterone and aldosterone level (Jezova *et al.*, 1996; Varga *et al.*, 2013), impaired hippocampal neurogenesis and development of dendrites and synapses (Muhammad & Kolb, 2011; Rayen *et al.*, 2015), changes in social memory (Grundwald & Brunton, 2015), alterations in circadian systems of the rats (Kiryanova *et al.*, 2017) and

with altered reactivity to pain or stress (Knaepen *et al.*, 2014). Therefore, well-controlled animal studies could play an important role in the preclinical study of stress-related disorders.

Models of early life stress

Women are more likely to have depression, especially with their first depressive episodes often occurring during pregnancy or lactation. Perinatal mood disorders occur in 10–15% of pregnant women (Pearlstein, 2015; Kiryanova *et al.*, 2017; van den Bergh *et al.*, 2017). The stress experienced during pregnancy and lactation or even prior to gestation can negatively affect the mother and the offspring (Clements *et al.*, 2015; Braun *et al.*, 2017). Early adverse experiences have profound and long-lasting effects on the development of neurobiological systems. Stress during pregnancy leads to activation of the maternal, fetal and placental hypothalamic–pituitary–adrenal (HPA) axis, which stimulates a response contributing to maintain physiological conditions and at the same time avoiding the adverse effects of stress on the mother and the offspring. However, when this exceeds certain limits of intensity, a number of obstetric complications may occur (Voltolini & Petraglia, 2014). The consequences of antenatal or postnatal depression during critical early brain development may lead to adverse effects on emotional, social and neurocognitive development in infants and increase vulnerability to psychiatric disorders in adulthood (Talge *et al.*, 2007; Tarantino *et al.*, 2011). Nevertheless, treatment during gestation and lactation raises also a number of questions, which are mainly related to the safety use of psychiatric drugs during this period. The main concern is, that antidepressants cross the placental and blood-brain barrier and are excreted into the breastmilk, which increases the level of monoamines in the developing fetus. Since these neurotransmitters play an important role in the fetal maturation of the brain – during proliferation, myelination and synaptogenesis, antidepressant therapy could interfere with these sensitive developmental processes in the brain and might have neurobehavioral consequences in later life. In clinical studies it is often difficult to separate consequences of the treatment alone and the effect of maternal depression. Preclinical work using appropriate animal models can give us answers about long-term consequences of prenatal stress and/or antidepressant therapy.

Although, rodent gestation is different from human pregnancy – neuroendocrinological changes during pregnancy and right after the birth are similar. However, from the developmental point of view it is important to note, that rodents are among the altricial (non-precocial) species, where an intensive maturation of the brain occurs in the postpartum period with a peak of around days 10–12 (Dobbing & Sands, 1979). In humans, the intensive brain maturation culminates in the period around childbirth. Therefore, neurodevelopment in rats during pregnancy and in the first 10 postnatal days appears to correspond

roughly to the third trimester of pregnancy and first month in humans neurodevelopment (Dobbing & Sands, 1979; Rice *et al.*, 2000). Consequently, rodent models could be useful tools for monitoring neurodevelopmental changes occurring in the prenatal period of humans.

In the past decades, several animal models of maternal depression have been developed. Models of maternal depression are based on prenatal and/or early life stress (Pereira-Figueiredo *et al.*, 2017). Maternal depression models can be classified based on period (stress prior to gestation, prenatal stress and early life stress), stressor properties (*e.g.*, physical or social) and duration (acute or chronic) of the exposure (Stepanichev *et al.*, 2014). We describe the three most popular rodent models of maternal depression which are based on 1. stress prior to gestation, 2. prenatal stress and 3. early life stress. The diversity of approaches, which are used to investigate maternal depression in animal models contribute to the variety of the observed changes in the prenatally stressed offspring.

Model of chronic unpredictable stress CUS

This model study was designed to clarify whether pre-gestational stress affects offspring in later life. Non-gravid females are exposed to 3-weeks of stress in the form of different stressors, which are changed every day at different points in time (Willner *et al.*, 1987; Willner & Mitchell, 2002; Willner, 2005; Xing *et al.*, 2013). Pre-gestational stress caused neuroendocrinological changes in rat dams and their offspring by a significant increase in CRH and corticosterone via maternal, fetal, and placental HPA axis (Huang *et al.*, 2012). These early neurochemical changes might alter the entire programming of the hypothalamic–pituitary–adrenal (HPA) axis function. Furthermore, alterations in HPA axis activity could be related to functional changes in serotonin activity and serotonin transporter expression in the hippocampus and hypothalamus of fetuses in a sexually dimorphic way (Huang *et al.*, 2012, 2016). Pre-gestational stress also appears to cause long-lasting changes in hippocampal mechanisms in the offspring rats (Huang *et al.*, 2013; Gemmel *et al.*, 2017). Moreover, changes in HPA axis are linked to alterations in depressive-like and social behavior. Offspring of affected mothers showed decreased coping ability in the forced swimming and deficits in sibling play behavior of juvenile offspring (Grundwald *et al.*, 2016; Gemmel *et al.*, 2017). All these neurochemical, neurobehavioral changes could result in the decreased ability of an organism to respond and adapt to stressful stimuli later in adolescent or in adulthood (Huang *et al.*, 2016). At the same time, perinatal antidepressant exposure had an enduring effect on the HPA system and the central serotonergic system by increasing serotonin and CBG levels in the hippocampus (Gemmel *et al.*, 2017).

Restraint stress

Restraint stress involves exposure of pregnant dams to restraint stress by placing them in restraint tubes for a period of time over several days. Dams undergoing this

model, have shown increased depression-like behavior (Mairesse *et al.*, 2015). The offspring of affected mothers exhibit increased ultrasonic vocalization in juvenile age, reduced social play during adolescence and increased immobility time in the forced swim test during adulthood and other behavioral changes including disturbed circadian rhythms, altered HPA axis feedback mechanisms and neuroplasticity (Maccari & Morley-Fletcher, 2007; Mairesse *et al.*, 2015). Moreover, adult offspring of affected mothers showed a reduced density of benzodiazepine recognition sites at GABA receptors in the hippocampus and in amygdala (Barros *et al.*, 2006), as well as reduced hippocampal neuroplasticity (Zuena *et al.*, 2008). Early postnatal exposure to maternal fluoxetine reversed the decrease in immobility in the FST, hippocampal cell proliferation and hippocampal neurogenesis in maternally stressed adolescent offspring (Rayen *et al.*, 2011), however, this preventative effect of SSRIs against the effects of maternal stress is not evident during adulthood (Rayen *et al.*, 2015).

Maternal separation

This early life stress model is based on the paradigm that stress during critical periods in development can have severe long-term consequences in later life. During separation sessions, pups are removed from their mother. Multiple variations of the maternal deprivation procedure have been developed, with different length of the separation episodes (1–24h in 1–14 days). While the time frame and length of mother segregation correlates with the severity of adolescence and adulthood disorders (Ladd *et al.*, 1996), maternal separation leads to an increased anxiety- and depression-like behavior during adolescent and adulthood (Finamore & Port., 2000; Gonzalez *et al.*, 2001) and to changes in the HPA axis in terms of elevated corticosterone level (Ladd *et al.*, 1996; Ladd *et al.*, 2000). Furthermore, excessive glucocorticoid activity in this model has been shown to decrease hippocampal neurogenesis (Bredy *et al.*, 2003). Brain monoamine systems also appear to be altered by maternal separation. Especially, rats showed increased CRF expression in locus coeruleus and raphe nuclei (Plotsky & Meaney, 1993). Maternal separation can cause various endocrinological and behavioral changes manifested in later life, which could be caused by alterations in HPA system and through epigenetic mechanisms.

Conclusion

The above-mentioned animal models appear to fulfill many criteria for a relevant animal model of depression; they alter the regulation of the HPA, induce signs of depression-like behavior and several antidepressant treatments can reverse the state induced by maternal stress. Although, they are not able to model all aspects of maternal depression, they are useful models for monitoring neurodevelopmental changes occurring in dams and offspring.

Acknowledgement

This study was supported by the Slovak Research Agency by realization of the project: „Transfer of Knowledge and Technologies from Research and Development in Toxicology on Evaluation of Environmental and Health Risks“(ITMS 26240220005).

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