Neurobiology of Stress xxx (2016) 1–11

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Prenatal stressors in rodents: Effects on behavior

Marta Weinstock

Institute of Drug Research, Hebrew University Medical Center, Ein Kerem, Jerusalem 91120, Israel

ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form
7 August 2016
Accepted 8 August 2016
Available online xxx

Keywords:
Anxiety and depressive-like behavior
BDNF
Epigenetic mechanisms
Glutamate receptors
Memory
Social interaction

ABSTRACT

The current review focuses on studies in rodents published since 2008 and explores possible reasons for any differences they report in the effects of gestational stress on various types of behavior in the offspring. An abundance of experimental data shows that different maternal stressors in rodents can replicate some of the abnormalities in offspring behavior observed in humans. These include, anxiety, in juvenile and adult rats and mice, assessed in the elevated plus maze and open field tests and depression, detected in the forced swim and sucrose-preference tests. Deficits were reported in social interaction that is suggestive of pathology associated with schizophrenia, and in spatial learning and memory in adult rats in the Morris water maze test, but in most studies only males were tested. There were too few studies on the novel object recognition test at different inter-trial intervals to enable a conclusion about the effect of prenatal stress and whether any deficits are more prevalent in males. Among hippocampal glutamate receptors, NR2B was the only subtype consistently reduced in association with learning deficits. However, like in humans with schizophrenia and depression, prenatal stress lowered hippocampal levels of BDNF, which were closely correlated with decreases in hippocampal long-term potentiation. In mice, down-regulation of BDNF appeared to occur through the action of gene-methylating enzymes that are already increased above controls in prenatally-stressed neonates. In conclusion, the data obtained so far from experiments in rodents lend support to a physiological basis for the neurodevelopmental hypothesis of schizophrenia and depression.

Contents

E-mail address: martar@ekmd.huji.ac.il.

http://dx.doi.org/10.1016/j.ynstr.2016.08.004

1. Introduction

It is now recognized that the offspring of women exposed during gestation to inescapable stressors like natural disasters, adverse life events or social pressures have a higher risk of psychopathology than those not exposed to such stressors (Charil et al., 2010; Weinstock, 2008). These include, generalized anxiety states and depression (Van den Bergh et al., 2008; Van Lieshout and Boylan, 2010), attention (Grizenko et al., 2012; Li et al., 2010; Park et al., 2014; Zhu et al., 2015) and learning deficits (Laplante et al., 2008), autism (Kinney et al., 2008) and schizophrenia (Fineberg et al., 2016; Khashan et al., 2008; Levine et al., 2016). Studies that are more recent have reported sex differences in the behavioral alterations induced by prenatal stress. They suggest that affective disorders are more prevalent in girls (Davis and Pfaff, 2014), while schizophrenia and attention deficits are more likely to occur in boys (Fineberg et al., 2016) if the mother was exposed to the stressor in the second trimester (Zhu et al., 2015). Autism has been associated with objective stress during the first trimester but its preponderance in boys has been disputed (Walder et al., 2014). In an attempt to provide a sounder scientific basis for these observations a large number of preclinical studies were performed, largely in rodents. These will be discussed in the current article.

The term “stress” has have been given different definitions in the literature (see Huizink et al., 2004; McEwen, 2000; Selye, 1950), but for the purpose of this review the term “stressor” will be used as referring to the event, while “stress” refers to the impact on the organism and its response to it. The stressor is designed to cause “distress” and involves adaptive physiological responses and the release of hormones that cause emotional changes in the pregnant female and in her offspring (Graignic-Philippe et al., 2014). The first study by Thompson (Thompson, 1957) was aimed at achieving “psychological stress” in the pregnant rats that would not cause tissue damage to her fetuses. Rat dams were trained before pregnancy in a conditioned avoidance test and were subjected to the stimulus daily throughout pregnancy. Assessments were made on behavior of the offspring in adulthood. Most of the subsequent studies did not use stressors that were only psychological, but may also cause pain or discomfort. These include intermittent electric shocks (Takahashi et al., 1998; Yang et al., 2006) or restraint in cylinders in strong light for periods of 45 min-6 h, up to three times a day (Lesage et al., 2004; Vallee et al., 1997; Van den Hove et al., 2005; Ward, 1972; Williams et al., 1999). Restraint can have a direct effect on the fetuses by restricting their movements (Choe et al., 2011). Also, Kinsley and Svare (1986) reported that restraint decreased the mother's food intake and body weight and that of her offspring. Nevertheless, the majority of studies has continued to use this stressor once or thrice daily.

Prior to 2006, almost all of the experiments on the effects of prenatal stress in rodents were performed only on male offspring (Weinstock, 2007). Recently, more reports have included females, and a few have determined the stage of the estrus cycle in association with the measurement of their behavior (Brunton and Russell, 2010; Salomon et al., 2011). In order to reduce potential variability, others have performed the behavioral tests when all the females were in diestrus (Wang et al., 2015a). The current review will focus on the findings in recent studies published after previous reviews (Weinstock, 2007, 2008) and explores possible reasons for any differences they report in the effects of gestational stress on various types of behavior in the offspring. These will include the influence of the strain of rat or mouse, time of stressor application during gestation, its nature, and the age of offspring at which behavior is examined.

2. Gestational stressors

Restraint, with or without bright light, is still the most popular stressor used in experimental animals in general (Buynitsky and Mostofsky, 2009) and in pregnant rats in particular, because the duration of the stressor can easily be controlled and it is convenient for taking blood samples from the tail for hormonal measurements. The degree of rat movement can also be regulated according to the size and construction of the restraining device. Almost all the studies described in this review incorporated a period of restraint in the regimen of maternal stress in rats or mice that ranged from 30 min to 6 h, either as the sole stressor, or with others. As shown in Table 1, the same or different stressors was applied up to three times daily.

More recent studies have replicated the reduction of maternal body weight by restraint described earlier in Sprague-Dawley (SD) rats when it was applied thrice daily for 45 min each time (Van den Hove et al., 2014), once daily for 60 min in Wistar rats (Fujita et al., 2010), or for 75 min in Long-Evans (LE) rats (Baker et al., 2008). Interestingly, thrice daily restraint reduced body weight in SD rats (Van den Hove et al., 2014), but not in the inbred Fischer strain (Van den Hove et al., 2005). Restraint also increased maternal adrenal weight (Fujita et al., 2010; Palacios-Garcia et al., 2015), testifying to the activation of her hypothalamic pituitary adrenal (HPA) axis. In only a few studies was the effect of other stressors measured on the body weight of the dam (Table 2). The findings indicate that the duration of the stress rather than its nature appears to determine the weight loss. Thus, when different stressors, or only restraint were applied thrice daily for 45 min, or once daily for one-six hours, maternal body weight was decreased (Fujita et al., 2010; Palacios-Garcia et al., 2015; Sickmann et al., 2015). No reduction in maternal weight occurred when the stressor was given once daily for no more than 45 min (Abe et al., 2007; Goelman et al., 2014;

Table 1
List of stressors.

No	Stressor
1	Restraint, same time of day + bright light
2	Restraint, same time of day, no light
3	Restraint, random schedule different duration + bright light
4	Restraint, random schedule different duration, no light
5	One of three stressors daily in a random order, elevated platform, forced swim, restraint
6	Any of the following stressors were used in a random order: restraint (1 h), exposure to cold (6 h), overnight food deprivation, prevention of sleep during the light cycle (1.5 h), forced swim (0.25 h), overcrowding (during the active phase of the light cycle)
7	Two or more stressors from the list in 6
8	Cat meowing, social isolation, food deprivation, cage tilting, etc
9	Bystander stress: cage mate was stressed by putting on an elevated platform + bright light or exposed to foot shocks
10	Housed with lactating rat
11	Noise 95 db

Please cite this article in press as: Weinstock, M., Prenatal stressors in rodents: Effects on behavior, Neurobiology of Stress (2016), http://dx.doi.org/10.1016/j.ynstr.2016.08.004