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Prenatal stressors in rodents: Effects on behavior

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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

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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

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Table 2
Influence of stress regimen in dam, time of application and duration on maternal and pup weight.

Stressor no. (Table 1)	Authors	Rodent	Strain	Stress regimen			Body weight age (days)	
				Days	Sessions/day	Duration (hr)	Dams	Pups
1	Van den Hove et al., 2005	Rat	Fischer	14–21	3	0.75	↔	0:↓; 21:↔ #
1	Van den Hove et al., 2014	Rat	SD	14–21	3	0.75	↓	0, 21:↓ M, F
1	Zuena et al., 2008	Rat	SD	11–21	3	0.75		
1	Yeh et al., 2012	Rat	SD	15–21	3	0.75		0, 7–56: ↔ M, F
1	Sun et al., 2013	Rat	SD	14–21	3	0.75		1: ↔ #
1		Rat	SD	8–21	2	0.5		
1	Zhao et al., 2013	Mouse	C57BL	15–21	3	0.75		
1	Dong et al., 2015	Mouse	SA	7–20	3	0.75		0: ↓ M
1	Akatsu et al., 2015	Mouse	C57BL	12–18	3	0.75		
2	Butkevich et al., 2011	Rat	Wistar	15–20	1	1		90: ↔ M, F
2	Lui et al., 2011	Rat	SD	14–21	1	6		0: ↓ M
2	de Souza et al., 2013	Rat	Wistar	15–21	4	0.5		
2	Palacios-Garcia et al., 2015	Rat	SD	11–20	1	2	↓	
2	Miyagawa et al., 2011	Mouse	ICR	5.5–17.5	2	6		
2	Matrisciano et al., 2013	Mouse	SA	7–21	2	0.5		0: ↓ M, F
3	Fujita et al., 2010	Rat	Wistar	10–19	1	1	↓	
3	Guan et al., 2013	Rat	SD	14–20	3	0.75		
3	Schroeder et al., 2013	Rat	Wistar	14-20; 4-20	1*	1	↔	↔ M, F
3	Schroeder et al., 2013	Rat	WKY	14-20; 4-20	1*	1		9: ↓ M, F
4	Zhang et al., 2013	Rat	SD	7-13, or 14-20	3	0.75		
5	Yaka et al., 2007	Rat	Wistar	17–22	1	R 0.5		
5	Zohar et al., 2016	Rat	Wistar	13–21	1	R 0.75	↔	0: ↔ M, F
6	Markham et al., 2010	Rat	SD	14–21	2–3	R 1		
6	Schulz et al., 2011	Rat	SD	14–21	2–3	R 0.5		Adult: ↑ M ↔F
6	Paris and Frye, 2011	Rat	LE	17–21	1	R 1		
6	Wilson and Terry, 2013	Rat	SD	14–21	1–3	R 1		21: ↓ M, F
6	Bourke et al., 2013	Rat	SD	10–20	3	R 0.75		21, 95: ↔ M
6	Sickmann et al., 2015	Rat	SD	13–21	3	R 0.5	↓	0-21: ↔M, F
6	Ratajczak et al., 2015	Rat	Wistar	14–22	1	R 1		
7	Modir et al., 2014	Rat	Wistar	0-9; 11-20	1	3		0: ↓ M
7	Wang et al., 2015a,b	Rat	SD	7–20	1			
8	Benoit et al., 2015	Mouse	C57BL	1–21	2–4	0.25–12		
9	Abe et al., 2007	Rat	SD	13–20	3	1	↔	60, 105: ↔ M, F
9	Mychasiuk et al., 2011	Rat	LE	12–16	2	0.17	↑	0:↓ M, F
9	Mychasiuk et al., 2011	Rat	LE	12–16	2	0.5	↓	0: ↓ M, ↑F
10	Brunton and Russell, 2010	Rat	SD	16–20	1	0.17		0: ↓ F, ↔M
11	Barzegar et al., 2015	Rat	Wistar	14–21	1	1, 2 or 4		

SD= Sprague-Dawley; LE = Long-Evans; SA = Swiss Albino; R = Restraint; M = male; F = Female; ↓ = decrease; ↑ increase; ↔ no change.
# Sex not specified. *Rats were either stressed once daily on days 14–20, or 7 times during days 4–20.

Zohar et al., 2016) (Table 2). Varied stressors had no effect on birth weight in pups of either sex (Zohar and Weinstock, 2011), or in males (females were not tested) (Abe et al., 2007; Sun et al., 2013). Birth weight was also unaffected in pups of LE rats, restrained from day 10–19 of gestation for periods of 15–75 min, but a reduction was seen in growth rate in both sexes (Baker et al., 2009). A selective effect in the birth weight in female pups was induced by two forms of "bystander" stress from day 12–14 of gestation. In one, the pregnant rat was placed in proximity of a lactating female (Brunton and Russell, 2010), and in the other, of a rat that was stressed by being put on an elevated platform under bright light for 30 min twice daily (Mychasiuk et al., 2011).

An additional confound in these experiments is whether, or not, the rat dam adapted to the stressor, but relatively few experiments examined this in pregnant rats. Adaptation to a stressor is indicated by a decline in the increase in plasma corticosterone (COR) after each exposure compared to that after the first time. Plasma COR ceased to rise in male rodents on the fourth day after they were subjected to restraint once daily, at the same time of day (Melia et al., 1994), or to other stressors (Dhabhar et al., 1997; Fride et al., 1986). Plasma COR increased in pregnant rats after each exposure to noise and flashing lights when these were delivered on a random basis at different times of day, but not at the same time on each successive day (Weinstock et al., 1988). Furthermore, only the pups of dams subjected to random stress showed significant retardation in their development (Fride and Weinstock, 1984). Others also showed that adaptation did not occur when different stressors were applied each day in a random order (Modir et al., 2014; Salomon et al., 2011; Sickmann et al., 2015; Wilson et al., 2013) or when the dam was subjected to bystander stress (Brunton and Russell, 2010).

Circulating maternal COR can reach the developing fetus (Zarrow et al., 1970), impair the regulation of its HPA axis (Fujioka et al., 1999; Henry et al., 1994; Weinstock et al., 1992) and induce

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behavioral alterations in the offspring (Weinstock, 2005). This was demonstrated by means of maternal adrenalectomy, which prevented the impairment of HPA axis regulation by gestational stress (Barbazanges et al., 1996) and the induction of anxiety-like behavior in the offspring (Salomon et al., 2011; Zagron and Weinstock, 2006). Administration of COR to the pregnant, adrenalectomized dams in amounts that mimicked the levels achieved by stress, reinstated anxiety and impaired HPA axis regulation. Although maternal adrenalectomy also prevented learning and memory deficits in PS offspring, they were not re-instated by COR administration (Salomon et al., 2011), indicating that they resulted from the action of another adrenal hormone (see Section 7).

3. Anxiety and depressive-like behavior

3.1. Anxiety

Generalized anxiety and affective disorders are considered stress-related and their incidence is increased in human subjects subjected to stress during pregnancy (Davis and Sandman, 2012). From the 1950−70s, the open field (OF) test has been used to detect potential anxiety-like behavior resulting from prenatal stress in rodents. The test is based on the assumption that fearful or anxious animals take more time than controls to enter a well-lit novel environment from their home cage and make fewer incursions into its center. In 1986, following the description of the elevated plus maze (EPM) by Handley and Mithani (Handley and Mithani, 1984) as depicting a conflict between the animal's desire to explore and fear of open spaces, File and her colleagues used it as a screening test for anxiolytic drugs (Pellow and File, 1986). Experiments were performed in bright light to deter entry by untreated rats into the open arms, thereby enabling the authors to detect an increase in those treated with the drugs. Since our aim was to use the test to detect anxiety-like behavior in PS rats (Fride and Weinstock, 1988), we performed the experiments in dim light to encourage the controls to enter into the open arms. In subsequent experiments, we showed that a larger difference in the behavior of control and PS rats was obtained when the rats had been housed on a reversed light cycle for at least a week and experiments were carried out under dim light during the rats' active period (Weinstock, 2015; Zohar et al., 2015).

Since 2008, most of the studies have replicated our original findings and those of Thompson (Thompson, 1957) and showed an increase in anxiety-like behavior in the EPM or OF tests in juvenile (Jia et al., 2015; Xu et al., 2013) and adult rat and mouse offspring of both sexes (Akatsu et al., 2015; Glombik et al., 2015; Palacios-Garcia et al., 2015; Salomon et al., 2011; Wang et al., 2015a; Walf and Frye, 2007; Zohar et al., 2015; Zohar and Weinstock, 2011), or when only males were tested (Barzegar et al., 2015; de Souza et al., 2013; Miyagawa et al., 2011; Sun et al., 2013). The stage of the estrus cycle influenced the percent of time the rats spent in the open arms of the maze, but this was reduced by prenatal stress at each stage (Salomon et al., 2011; Walf and Frye, 2007).

Others found an increase in anxiety-like behavior only in males (Zuena et al., 2008) or females (Schulz et al., 2011; Van den Hove et al., 2014), in spite of the fact that the identical stressor was used in SD rats. This may have been due to the conditions under which offspring behavior was assessed, but such information was not supplied. For example, whether the rats were subjected to an additional stress by their transport to the experimental room only a short time before the experiment (Hogg, 1996), or whether or not, the area of the maze was brightly lit (Morato and Castrechini, 1989). The behavior of rats in the EPM was shown to be age dependent, with male rats aged 90 days or more, and females 120 days or more spending less time in the open arms than younger rats (Imhof et al., 1993). Thus, it is likely that an increase in anxiety-like behavior was not seen in two of the studies because the males were aged 100 days (Van den Hove et al., 2014) or 170 days (Schulz et al., 2011). This was probably also true in younger controls that, for an unknown reason, spent very little time in the open arms of the EPM, thereby showing a “floor” effect (Wilson et al., 2013). Anxiety was also not seen because the same mice (Kiryanova et al., 2016) and rats (Bourke et al., 2013; Schroeder et al., 2013) were subjected to a number of different, stressful, behavioral tests, which is known to influence behavior (Voikar et al., 2004).

3.2. Depressive-like behavior

Anxiety and depression frequently occur concurrently or sequentially in childhood and adolescence (Garber and Weersing, 2010) in association with prenatal stress (Van Lieshout and Boylan, 2010). Depression is a very complex psychological disorder comprising some, or all of these symptoms, low mood, anhedonia, feeling sad, hopeless, helpless and worthless or ashamed. Clearly, it is not possible to detect and quantify such feelings in rodents. In the absence of direct methods for assessing depression, researchers have used the forced swim test (FST) (Porsolt et al., 1978), or a decrease in sweet preference when presented with a choice of water or a solution of sucrose as a measure of anhedonia. Behavior in both tests responds to drugs that have antidepressant activity in human subjects (Moreau, 2002). In the FST, a rat or mouse is exposed to inescapable forced swim for 15 min on one day and tested for “learned helplessness” 24 h later, characterized by floating or virtual immobility and fewer attempt to swim or climb on the walls of the cylinder. Clinically effective antidepressants decrease the duration of floating and increase swimming and/or climbing. Behavior in the FST is influenced by the stage of the estrus cycle. Females in diestrus exhibit more, and in proestrus, less, learned helplessness than males (Jenkins et al., 2001).

By means of the FST, it was found that different stressors, applied during the last week of gestation, increased depressive-like behavior in juvenile (Guan et al., 2013; Jia et al., 2015) and adult offspring of Wistar or SD dams (Abe et al., 2007; Butkevich et al., 2011; Fujita et al., 2010; Glombik et al., 2015; Sickmann et al., 2015; Zohar et al., 2015), but not in the offspring of dams stressed during the second week (Jia et al., 2015). Those who failed to detect an effect of prenatal stress in this test either left the rats in the cylinder of water for 10 min instead of 5, resulting in a relatively long duration of immobility in PS and controls (Van den Hove et al., 2014). Others researchers applied the FST after additional tests in the same rats (Schroeder et al., 2013; Bourke et al., 2013; Wilson et al., 2013), unlike the majority of studies, The foregoing data from recent studies confirm earlier reports that prenatal stress can cause anxiety and depressive-like behavior in rats and mice. To date, there is no consistent evidence of a sex difference in the incidence of these behaviors in rats.

4. Learning deficits

4.1. Spatial learning and memory

The effect of prenatal stress on spatial learning and memory retention has most often been examined by means of the Morris water maze (MWM) test in which rats are placed into a large circular pool of water from which they can escape onto a hidden platform. Normal rats learn quickly to swim directly to the escape platform (Morris, 1984). To assess the rate of acquisition of spatial learning, rats are given two or more trials a day and the position of entry of the rat into the maze is changed each day, while the platform remains in the same position. Memory is assessed by

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removing the platform and measuring the time spent by the rat in the quadrant in which the escape platform was situated.

Like other behavioral tests, the majority of the early experiments were performed only in males and these showed impaired spatial learning in adulthood (Weinstock, 2008). Since then, only a few have assessed the effect of prenatal stress in both sexes. In adult female rats, no effect was found on the rate of learning (Weinstock, 2011; Zuena et al., 2008), but this was slower than in controls in pre-pubertal females (Weinstock, 2011). Others showed a deficit in memory consolidation in the passive avoidance test in rats of both sexes (Palacios-Garcia et al., 2015). In adult males of the SD and Wistar strains, prenatal stress slowed the rate of acquisition of spatial learning and memory retention, irrespective of the nature of the maternal stressor (Barzegar et al., 2015; Lui et al., 2011; Markham et al., 2010; Modir et al., 2014; Ratajczak et al., 2015; Schulz et al., 2011). In contrast to the findings in the majority of studies, thrice-daily restraint improved learning in the MWM test in adult SD male offspring (Zuena et al., 2008).

Impaired learning in male Wister rats aged 4–5 weeks (Yaka et al., 2007; Yang et al., 2006) and 6–7 weeks (Barzegar et al., 2015) was associated with a decrease in hippocampal long term potentiation (LTP) and an increase in long term depression (LTD). Females were not tested. Others found a reduction in hippocampal LTP in PS, SD males and females aged 3 and 5, but not 8 weeks, while LTD was only increased in rats aged 5 weeks (Yeh et al., 2012). No assessments of learning and memory were made in these rats. Prenatal stress also reduced spatial learning but not memory retention in pre-pubertal and adult male C57/BL mice, (Zhao et al., 2013), or in adults of both sexes (Benoit et al., 2015). Those that did not detect an effect of prenatal stress either subjected the mice to multiple tests (Kiryanova et al., 2016), or housed them singly (Akatsu et al., 2015), which is very stressful and may have adversely affected the performance of both control and PS offspring. The data show clearly that prenatal stress can slow the rate of spatial learning and decrease hippocampal LTP in juvenile and adult males but in the latter, it does not always impair memory retention. The paucity of studies in females precludes a conclusion that such deficits are more prevalent in males. The protective effect of estrogens on brain regions associated with learning and memory (Liu et al., 2008; Ping et al., 2008) is consistent with the likelihood of greater resilience of female offspring to the effects of gestational stress.

4.2. Recognition memory

In rodents, the tendency to explore novel objects more than familiar ones has been exploited as a sensitive test of stimulus recognition memory (Ennaceur and Delacour, 1988). The test involves the substitution of a familiar object with a novel one in a memory retention trial. Since rats also have an innate tendency to explore objects in a novel place, the test can be adapted for assessment of spatial memory by changing the position of one of the objects, which remain identical (Ennaceur et al., 2005). In the hooded Lister strain, novel object and place recognition in young adult males and females depended on the inter-trial interval (ITI) that differed according to the test and sex of the rat. Males showed preference for new objects at ITIs of up to 30 min and for a new place, for up to one hour. Females showed novel object recognition (NOR) at ITIs of up to three hours and novel place recognition, up to an ITI of one hour (Sutcliffe et al., 2007). In Wistar rats, females, but not males, showed NOR at ITIs of 40 and 60 min (Biala et al., 2011). Varied forms of mild prenatal stress had no effect on the behavior of females at either time interval but increased NOR in males to resemble the female phenotype (Biala et al., 2011; Salomon et al., 2011). It may be significant that the PS males had a shorter ano-genital distance, which is associated with lower levels of testosterone (Gerardin et al., 2005). Results of the assessment of prenatal stress in SD rats differed from those in Wistar rats and in different studies. Adult rats of both sexes showed significant NOR at 15 min, one and three hours. PS females lost their discrimination at an ITI of one hour, and males, at three hours. (Wilson and Terry, 2013). However, others found that prenatal stress abolished object discrimination in SD males at ITI of 60 min. Other times and females were not tested. (Markham et al., 2010). In addition to the strain of rat, it is possible that the differences in the findings cited above result from the nature of the maternal stressor and ITI, but also if the nature if objects used in the test are too similar for the rats to distinguish.

5. Schizophrenia

It has been reported that the offspring of mothers who were exposed to stress or a viral infection during gestation have an increased likelihood to develop schizophrenia (Brown et al., 1996; Fineberg et al., 2016; Levine et al., 2016; Mednick et al., 1994). The period most sensitive to stressors appears to be the second trimester, when the frontal cortex (FC) and hippocampus develop (Bayer et al., 1993). Subjects with schizophrenia show abnormalities in structure and neurotransmission in several brain regions. The hippocampus is reduced in size (Harrison, 2004) and its cell layers are disorganized (Heckers and Konradi, 2010; Stefanis et al., 1999). In the FC, excitatory neurotransmission is decreased, resulting in less inhibitory neurotransmission in the ventral tegmental area (Volk and Lewis, 2010). This is believed to contribute to the negative symptoms in schizophrenia including, disordered thought processes, social withdrawal, anhedonia, and blunted affect (Kirkpatrick et al., 2006; Lynch, 1992; Sesack and Carr, 2002). Direct experimental investigation of these symptoms in animals is especially problematic. The only ones that can be identified and quantified are anhedonia and social withdrawal, indicated by a decrease in social interaction that is seen also in depression (described in Section 3.2.).

In mice and rats, social interaction with their novel peers is assessed by placing the two animals in a neutral cage and measuring the percentage of time during which are in direct physical contact and perform ano-genital exploration, sniffing with direct contact, crawling, grooming, and play behaviors. Pre-pubertal or adult male offspring of SD dams subjected to random stressors from days 14–21 (Lee et al., 2007; Wilson et al., 2013), or unpredictable foot shocks on days 17–20 of gestation (Ehrlich and Rainnie, 2015) showed significantly less social interaction than controls. In adolescent SD rats, a decrease in social interaction was only found if both rats of the pair were stressed prenatally, but not if one was a control. Prenatal stress caused a reduction in social interaction in adult male Swiss albino mice (Dong et al., 2015; Matrisciano et al., 2013). It is noteworthy that none of the foregoing studies examined social interactions in female offspring, which might have lent support to the suggestion that the condition is more prevalent in males.

6. Neurochemical basis of behavioral alterations

6.1. 5HT transmission

A link has been made between anxiety disorders (Martin et al., 2009) and depression (Drevets et al., 2007) and a decrease in the serotonergic innervation of limbic structures, prefrontal cortex (PFC), amygdala and hippocampus. 5HT innervation to these areas arises in the medial and dorsal raphe nucleus (DRN) (Azmitia and Segal, 1978). This has led to the examination of the effect of

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prenatal stress on 5HT transmission is association with alterations in behavior. In PS male mice, there was an increase in the number of 5HT positive cells in the DRN, measured by staining with an antibody to tryptophan hydroxylase (TPH) (Miyagawa et al., 2011). This, and other measurements associated with 5HT innervation, were not made in any other brain area. In PS, SD rats of both sexes, which showed increased anxiety, but no depressive-like behavior, there was an increase in TPH in the dentate gyrus and CA3 region of the hippocampus and in 5HT immunoreactivity in the PFC and hippocampus in males but not in females. In the DRN, there was a decrease in overall 5-HT immunoreactivity and 5-HT immunoreactive cell density in males but not in females. However, the alterations in 5HT and in TPH were unrelated to the observed changes in behavior induced by prenatal stress (Van den Hove et al., 2014). Moreover, the authors offered no explanation as to why the effect of prenatal stress on TPH in the DRN of male rats was the opposite of that in mice, in spite of the similar effect on behavior.

5HT release in target areas is also dependent on the balance of activity on 5HT1A inhibitory autoreceptors on 5HT cell bodies and GABAergic inhibitory interneurons in the DRN. Although neither anxiety nor depressive-like behavior were assessed in the study, the number of 5HT1A receptors (5HT1AR) in the whole DRN region, measured by reversed transcription PCR, was significantly reduced in PS rats (sex not defined) (Said et al., 2015). By means of fluorescence immunohistochemistry with specific antibodies directed to different cell groups, we found that anxiety and depressive-like behavior of PS, Wistar rats was accompanied by a decrease in the expression of 5HT1AR on 5HT cell bodies and GABAergic interneurons in the DRN and PFC in males. In PS females, the density of 5HT1AR receptors in the PFC was unchanged, but reduced in 5HT and GABAergic interneurons, together with corticotrophin releasing factor (CRF) type 2 receptors (CRFR2) in the DRN. The expression of 5HT in the DRN was much lower in females than in males and both were unaffected by prenatal stress (Zohar et al., 2015). We also found that prenatal stress reduced the expression of TPH in the DRN in both sexes (Zohar et al., 2016). Chronic treatment of juvenile PS rats with the antidepressant drug, citalopram reversed the anxiety and depressive-like behavior in adulthood and also the alterations in the expression of 5HT1AR and CRFR2 (Zohar et al., 2015), testifying to their relation to the behavioral measures.

6.2. Glutamate receptors and learning

Glutamate-gated cation channel receptors N-methyl-D-aspartic (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors are located primarily on neuronal cell membranes. Their activation results in modulation of synaptic plasticity that plays an essential role in learning and memory (Debanne et al., 2003). In the hippocampus, NMDAR are heteromeric assemblies of a core NR1 subunit and modulatory NR2 subunits, NR2A and NR2B (Monyer et al., 1994). An increase or decrease in the number of ionotropic NMDA or AMPA glutamate receptors on a postsynaptic cell may lead to changes in LTP or LTD of that cell, respectively (Asztely and Gustafsson, 1996; Maren et al., 1993; Perez-Otano and Ehlers, 2005). Metabotropic glutamate receptors (mGluR) can also modulate synaptic plasticity by regulating postsynaptic protein synthesis through second messenger systems (Weiler and Greenough, 1993). They include mGlu1R and mGlu5R, which are coupled to polyphospho-inositide hydrolysis and mGlu2-3R that are coupled to Gi proteins (Riedel et al., 2003; Simonyi et al., 2005).

The effect of prenatal stress on the expression of the components of NMDAR, AMPAR and mGluR in rats and mice in summarized in Table 3. In PS, ICR mice aged 7 weeks, which showed spatial learning deficits and a reduction in hippocampal LTP, there was a reduction in the protein levels of NR1 and NR2B measured in whole hippocampal homogenates (Son et al., 2006). Gene expression of NR2B was also reduced in 3-week-old male C57Bl/6J mice in conjunction with that of KIF17, a kinesin protein that helps synaptic transmission by moving NR2B along dendrites (Zhao et al., 2013). In 4-5 week-old male Wistar rats, prenatal stress also decreased the protein levels of NR2B, together with those of AMPA GluR1, but not those of NR1 and NR2A (Yaka et al., 2007). However, NR1, NR2A or NR2B, measured only in the hippocampal CA1 region, did not differ from controls in 3 and 5-week-old PS, SD rats of both sexes, although they showed a reduction in hippocampal LTP and increase in LTD. (Yeh et al., 2012). In addition, in adult PS, SD rats in which learning and memory was not assessed, no difference was found from controls in the in the expression of hippocampal NR2B, mGlur2/3 and mGlur 5 (Wang et al., 2015b). In the only study in adult SD males which showed a faster acquisition of the spatial learning task, there was a decrease in GluR2-3 and mGluR5 but no change in the expression of hippocampal mGluR1 (Zuena et al.,

Table 3
Glutamate receptors.

Reference	Stress no. (Table 1)	Rodent	Strain	Behavioral test	Age (weeks)	NMDAR			AMPAR	mGluR		
						NR1	NR2a	NR2b	GluR1	GluR1	GluR2-3	GluR5
Yaka et al., 2007	5	Rat	Wistar	MWM ↓ M	4–5	H: ↔	H: ↔	H: ↓	H: ↓	H: ↓		
Lui et al., 2011	2	Rat	SD	MWM ↓ M	16	H: ↔	H: ↔	H: ↓				
Zuena et al., 2008	1	Rat	SD	MWM ↑ M, ↔ F	12					H: ↔ M, F	H: M, F	H: ↓M, ↔F
Zhao et al., 2013	1	Mouse	C57BL	MWM ↓ M	3, 9			H: ↓mRNA				
Laloux et al., 2012	1	Rat	SD	EPM, OF ↓ M	2, 3						H: ↔ day 14, ↓ day 22	H: ↓
Zhang et al., 2013	4	Rat	SD	TST ↓ #	4					FC: ↔ M ↑F		
Jia et al., 2015	4	Rat		FST ↓ M, F	3.5					H, PFC: ↑M, F; S: ↔		H, PFC, S: ↑M, F
Sun et al., 2013	1	Rat	SD	EPM ↔ F, ↓ M	12	H: ↓ #	PFC, H, S: #					
Wang et al., 2015a	7	Rat	SD	EPM ↓ M, F	12–13	H: ↔M.F PFC: ↑M ↔F		H: ↔M, F PFC: ↔M, F		H: ↔M, F PFC: ↔M, F	H: ↔M, F PFC: ↑M, ↔F	H: ↔M, F PFC: ↑M, ↔F

H = hippocampus; FC=Frontal Cortex; PFC=Prefrontal Cortex; S=Striatum # males and females together. TST = tail suspesion test (measure of depressive-like activity). ↓ decrease, ↑ increase, ↔ no change.

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2008). No measurements were made of the expression of the components of the NMDAR receptor.

The forgoing data suggest that the levels of NR2B and possibly NR1, subgroups of the NMDAR and GluR1 of the AMPA receptor are altered in young rats and mice with impaired spatial learning and reduced LTP. Failure to replicate this finding in some experiments could be a function of the methodology used to quantify them, animal species, strain, timing or nature of the maternal stressor. More experiments are needed in adults of both sexes in which LTD, learning and memory are measured, together with the expression of different forms of glutamate receptors.

6.3. Glutamate receptors, anxiety and depressive like behavior

Alteration in glutamate activity at metabotropic receptors has also been implicated in schizophrenia, depressive and anxiety-related disorders (Bauer et al., 2002; Konradi and Heckers, 2003). Accordingly, the effect of prenatal stress was examined on mGluR in the prefrontal PFC or FC, hippocampus and amygdala, in association with anxiety or depressive-like behavior. However, the findings in these studies are inconsistent and do not show a clear relation to these behaviors. Here are some examples of the inconsistencies. Prenatal stress that increased anxiety in 3-week old males but not in females, reduced the expression of hippocampal mGluR2-3 and GluR5 (Laloux et al., 2012), but increased expression of GluR5 in the hippocampus and PFC in both sexes. However, in male and female rats aged 4 weeks, with anxiety and depressive-like behavior, prenatal stress increased mGluR1 and mGluR5 in the FC and hippocampus (Jia et al., 2015). In addition, in spite of the fact that adult PS males and females both showed increased anxiety-like behavior, mGluR2-3 and mGluR5 increased in the PFC of males but not in females and there was no change in the hippocampus in either sex (Wang et al., 2015a). In the same study, there was no difference from controls in the expression of NR1, NR2B or mGluR1 in these brain regions in PS males or females. By contrast, others found that prenatal stress increased mGluR1 expression in the FC only in females, although both sexes showed depressive-like activity (Zhang et al., 2013). These discordant findings suggest that either alterations in mGLUR are not a directly associated with the behaviors measured in rodents, or that their inconsistencies stem from differences in the methodology used to assess them.

6.4. Glutamate receptors and schizophrenia

A possible association between behaviors associated with schizophrenia (but also with depression) resulting from prenatal stress has only been investigated in mice. Male PS mice showing a significant reduction in social interaction had an early and long-lasting reduction in the expression of mGluR2-3mRNA and protein in the FC. This was associated with increased binding of type-1 DNA methyl transferase (DNMT1) (see section below) to CpG-rich regions of the mGlu2 and mGlu3 receptor promoters (Matrisciano et al., 2013). Metabotropic Glu2-3 receptors are also expressed in GABAergic neurons. Their altered expression or methylation resulting from prenatal stress lends support to the hypothesis of glutamatergic/GABAergic dysfunction in schizophrenia.

6.5. Brain derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) is a member of the family of neurotrophins that plays a key role in the development and survival of neurons in the central nervous system. BDNF is required for proper development and survival of dopaminergic, GABAergic, cholinergic, and serotonergic neurons and is crucial for learning and memory processes (Autry and Monteggia, 2012). BDNF binds to a specific tyrosine kinase receptor (tropomyosin-related kinase B receptor (trkB)) and regulates many functions related to neuron development (Bibel and Barde, 2000). The expression of BDNF mRNA is reduced in the PFC in affective disorders (Ikegame et al., 2013; Martinowich et al., 2007; Weickert et al., 2003), supporting the suggestion that they have a strong developmental component (Grayson and Guidotti, 2013). This prompted recent studies in rodents on the effect of prenatal stress on the levels of BDNF mRNA and its possible modifications by epigenetic mechanisms.

PS mice or rats with a reduction in social interaction (Dong et al., 2015), memory (Ratajczak et al., 2015) and LTP (Yeh et al., 2012), or an increase in measures of anxiety and depression (Jia et al., 2015), all showed a decrease in BDNF mRNA in the FC and hippocampus. Prenatal stress reduced the activity of the proteolytic enzyme, tissue plasminogen activator (tPA), thereby increasing pro-BDNF that is converted by the enzyme to BDNF. The expression of BDNF was positively correlated with LTP and negatively correlated with LTD (Yeh et al., 2012), showing its relation to synaptic transmission. In other experiments in which no behavioral measurements were performed, no change was found in the gene expression of BDNF in the PFC of adult PS, SD male or female rats, but there was a decrease in the pool of BDNF transcripts with long 30 UTR (Luoni et al., 2014). By contrast, PS, SD male rats, that showed improvement in spatial learning, but an increase in anxiety, also had higher levels of BDNF and pro-BDNF in the hippocampus. Moreover, PS females that did not differ from controls in their behavior in the MWM showed no difference in hippocampal levels of BDNF (Zuena et al., 2008). These data provide strong support for a role of BDNF in the mediation of hippocampal LTP/LTD and learning and other changes induced by prenatal stress.

6.6. Epigenetic mechanisms

Alteration in chromatin structure and gene expression termed “epigenetic events” in telencephalic GABAergic and glutamatergic systems are believed to play a role in the etiology of schizophrenia (Matrisciano et al., 2016). The best characterized epigenetic events that affect hippocampal learning and memory are histone acetylation and DNA methylation (Levenson and Sweatt, 2005). Acetyl groups are added by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs). Lysine-14 acetylation on histone H3 leads to overall transcriptional activation (Crosio et al., 2003) and increases expression of genes necessary for hippocampal synaptic plasticity (Wood et al., 2006). DNA methyl transferases (DNMT1 and 3a) and ten-eleven translocation hydroxylase (TET1) are important components of the DNA-methylation/demethylation system that regulates the expression of key molecules involved in brain function (Grayson and Guidotti, 2013). These enzymes are overexpressed in GABAergic neurons in postmortem brains of patients with schizophrenia and are probably responsible for the downregulation of BDNF, reelin and glutamic acid decarboxylase 67 (Gad67) (Grayson and Guidotti, 2013).

Support for a role of gene methylation in the behavioral changes induced by prenatal stress was obtained in mice and in rats of the LE strain. Gene and protein expression of DNMT1, 3a and TET1, detected a day after birth, was increased in the FC and hippocampus of PS male mice showing a reduction in social interaction. The DNMT1 that was co-localized with GAD 67 in GABAergic neurons in the FC and hippocampus was associated with a decrease in the levels of reelin and GAD 67. However, prenatal stress did not change the expression of histone tail acetylating or methylating enzymes, or other chromatin remodeling factors (Dong et al., 2015; Matrisciano et al., 2016).

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7. Early maternal influence on behavioral outcome

In addition to changes in the maternal milieu induced by stress during gestation, offspring behavior can be modified by the mother-pup relationship (Caldji et al., 1998). Attempts made to assess the relative contribution of pre- and postnatal factors by measuring maternal behavior in stressed rats have yielded conflicting results. Some studies showed a decrease in the time spent by stressed rat (Carini and Nephew, 2013; Moore and Power, 1986; Power and Moore, 1986) or mouse mothers (Akatsu et al., 2015; Golub et al., 2016) in one or more measures of maternal care, but others found no difference in maternal behavior of stressed rats (Melniczek and Ward, 1994; Poltyrev and Weinstock, 1999) or mice (Kiryanova et al., 2016; Meek et al., 2001) from that of controls.

An alternative strategy used to assess the influence of postnatal rearing was to foster PS pups onto control mothers at birth and compare the behavior of the pups with those reared by their own mothers. Fostering by control mothers abolished the increase in activity of the HPA axis and associated changes in COR receptors in PS rats (Maccari et al., 1995). It also prevented the increase in anxiety and decrease in social interaction in males (Barros et al., 2006; de Souza et al., 2013). However, being reared by a control mother did not prevent the learning deficits in the MWM, reduction in LTP and LTD (Yang et al., 2006; Yeh et al., 2012) or lack of novel object recognition (Paris and Frye, 2011).

Why does fostering prevent anxiety and alterations in the HPA axis but not memory deficits? As mentioned in Section 2, the former, but not learning deficits in the MWM or object recognition, are mediated by excess maternal levels of COR (Barbazanges et al., 1996; Salomon et al., 2011). While the genes for the two COR receptors are found in the rat brain on embryonic days 13 and 16 respectively, their protein expression is relatively low and continues to increase for some time after birth (Weinstock, 2008). Maternal stress also increases COR in the mothers' milk and this remains elevated until the pups are weaned (Pfister and Muir, 1989). Thus, COR could continue to contribute to the alterations in behavior in the early postnatal period. Fostering PS pups onto a control dam avoids this exposure to excess postnatal COR thereby preventing only the alterations in behavior that COR mediates.

Maternal stress also releases catecholamines from the adrenal gland and sympathetic nervous system that reach the fetal brain (Rohde et al., 1983). Noradrenaline (NA) appears to play a role in neurodevelopment and has a strong effect on learning and memory by modifying hippocampal and neocortical functions (Berridge and Waterhouse, 2003) through activation of β-adrenergic receptors (Bramham et al., 1997). Alterations in noradrenergic activity and its receptors during development cause morphological changes in the brain (Felten et al., 1982). Maternal malnutrition, like gestational stress, can induce learning deficits in the offspring and impair hippocampal LTP (Austin et al., 1986), in association with down regulation of β-adrenergic receptors (Flores et al., 2011). There appear to be no data showing that prenatal stress also reduces brain noradrenergic receptors. However, in hippocampal slices of PS males, LTP induced by a β receptor agonist was lower than in controls in the dorsal hippocampus (associated with spatial learning and memory), and higher in the ventral hippocampus, (associated with emotional behavior) (Grigoryan and Segal, 2013), that accords with the behavioral changes usually observed. This suggests that prenatal stress may selectively change the number and/or sensitivity of β-receptors in a brain region-selective manner. In contrast to the effect of maternal malnutrition and possibly prenatal stress, administration of a β-receptor antagonist, propranolol to pregnant rats caused up-regulation of β-receptors and an increase in NA activity in the brain of the offspring in later life (Erdtsieck-Ernste et al., 1993). Treatment of stressed rats during gestation by propranolol prevented the development of spatial memory deficits in their male offspring (females were not tested) (McGivern et al., 1986), presumably by blocking the effect of excess noradrenergic activation in the developing brain.

8. Conclusions

The preclinical data described in this review support the hypothesis that alterations in early brain development induced by maternal stress are risk factors for psychopathology. This is shown in a large number of experiments in pregnant rats and mice that were subjected to different stressors at the time when the fetal limbic system develops. In their offspring, increases were found in those behaviors that are associated with anxiety, depression and schizophrenia in human subjects. Prenatal stress, like schizophrenia and depression, decreased the expression of proteins like BDNF and reelin that mediate neural plasticity, and the expression of NR2B subtype of NMDAR in the hippocampus. It is necessary to perform further experiments to ascertain the direction of change of mGLUR and their various subtypes in the hippocampus and cortex of PS offspring of both sexes showing changes consistent with those found in depression or schizophrenia. Evidence from recent studies in mice supports a role of gene methylation in the down-regulation of BDNF and other components of the glutamatergic and GABAergic systems. It is less clear whether the changes in various behaviors, expression of genes and proteins differ in males and females because of the paucity of experiments in rodents, which included both sexes.

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