

Behavioral neuroendocrine studies of the influences of early adverse experiences on the development of emotional and social behaviors

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Increasing number of evidence supports the view that the early life period is a sensitive age in which adverse experiences enhance the risk of developing psychopathologies throughout life in humans. Maternal separation (MS) is a well-established animal model that mimics the stress of early adverse experiences. Numerous studies using this model in mice and rats have shown MS effects on emotionality, depression-like, and anxiety-related behaviors in both sexes. Furthermore, recent studies have demonstrated that the adverse effects of MS may greatly modify various social behaviors and neuroendocrine functions in adulthood. In this article, we overviewed 1) sex, species, and strain-dependent behavioral effects of MS in both non-social and social contexts, and 2) possible neuroendocrine mechanisms of behavioral changes caused by MS. Our focus was to demonstrate how these studies in the field of behavioral neuroendocrinology might help for better understanding the effects of early life experience on the development of social and emotional behavior.

Key words: early life stress, maternal separation, anxiety, aggression, animal model, HPA axis

1. Introduction

The prevalence of a variety of psychopathologies including emotional and adjustment disorders, as well as anti-social behavior has become a serious problem in the human society. Under these circumstances, the importance of understanding biopsychological and neurobiological bases of social and emotional behavior development has greatly increased. There is a growing collection of evidence demonstrating that exposure to an adverse early environment can increase the vulnerability to develop psychopathologies in adulthood. Individuals with childhood trauma, abuse, and/or neglect are more at risk to exhibit a psychopathological disorder, as well as having a high rate of comorbid disorders later in life (Agid, Shapira, Zislin, Ritsner, Hanin, Murad, Troudart, Bloch, Heresco-Levy & Lerer, 1999; Heim & Nemeroff, 2001). Children exposed to high lev-

els of stress exhibit elevated levels of cortisol, the primary stress hormone, which lead to emotional and behavioral difficulties that persist throughout adulthood (Essex, Klein, Cho & Kalin, 2002). This suggests that the early life period is a sensitive age in which stressful events can adversely affect brain development and subsequent behavioral phenotypes (Tomoda, Sheu, Rabi, Suzuki, Navalta, Polcari & Teicher, 2010). Therefore, it is of great interest and importance to investigate the detrimental effects of early adverse experiences. The utilization of animal models mimicking early life stress is an essential alternative for gaining insight into the impact of adverse experiences on the later behavioral, cognitive, and neuroendocrine functions.

2. Maternal Separation Model

Rodents are a highly attractive model system

to study the effects of postnatal experience on brain and behavior development. In particular, rats and mice can be bred in large numbers under controlled environmental conditions and be tested in a wide variety of behavioral assays. The pioneering research conducted by the Levine and Denenberg group and the Plotsky and Meaney group demonstrated that alterations during the neonatal period have long-lasting behavioral and neuroendocrine consequences as adults (Denenberg, 1964; Levine, Haltmeyer, Karas & Denenberg, 1967; Plotsky & Meaney, 1993). Their work then promoted numerous studies using the maternal separation (MS) model as early life stress. There are a variety of MS paradigms utilized in studies performed in rats and mice. Variations across different studies consists of two main factors, one is the length and frequency of separation periods and the other is whether separation of pups from the dam is done as a litter or individually. Among all, the most commonly used method is the daily separation of pups from their mother as a litter for 3 hours during their first two weeks of life (Plotsky et al., 1993). During this postnatal period, pups of rats and mice depend on their mother for food, warmth, and waste secretion (Gubernick & Alberts, 1983) and the forced absence of the dam produces long-lasting effects in the offspring that persist into adulthood (Plotsky et al., 1993; Wigger & Neumann, 1999). Here, studies that examined the adverse effects of MS on subsequent non-social and social behaviors and neuroendocrine functions are discussed.

3. Behavioral Effects of Maternal Separation

There are a large number of literatures documenting the effects of MS on emotionality and anxiety-related behaviors in both sexes across various species, but MS effects on social behaviors still remain largely unknown. By reviewing a number of studies, it has also become apparent that certain species or sex may be more vulnerable to early adverse experiences than others. Here, we not only address what behaviors are more susceptible to neonatal MS stress, but also, discuss the sex, species and strain differences in the behavioral changes caused by MS.

3.1. MS Effects on Emotionality and Anxiety-Related Behaviors

Over the years, there has been a vast amount of studies reporting the effects of MS on subsequent emotional and anxiety-related behaviors in adulthood. Most MS studies use the open-field test (OFT) and elevated plus maze test (EPM) to measure emotionality and anxiety-related behaviors. These studies revealed that MS indeed affect OFT and EPM behaviors in adult mice and rats. For instance, MS stress modified the levels of locomotor activity and the time spent in the center area in OFT (Ogawa, Mikuni, Kuroda, Muneoka, Mori & Takahashi, 1994; Romeo, Mueller, Sisti, Ogawa, McEwen & Brake, 2003; Veenema, Bredewold & Neumann, 2007) and the number of entries into the open arms and cumulative duration spent on the open arms in EPM (Kalinichev, Easterling, Plotsky & Holtzman, 2002; McIntosh, Anisman & Merali, 1999; Romeo et al., 2003; Veenema et al., 2007; Wigger et al., 1999). However, the direction of MS effects has often been variable, i.e., some studies have reported an increase of emotionality and anxiety levels whereas others have shown a decrease. Methodological differences of behavior tests may be partly responsible for this variability, but sex and strain differences may be more crucial.

3.1.1. Sex Differences in the Behavioral Effects of MS

In humans, women are more vulnerable to the negative effects of early adverse experiences during childhood (Breslau & Anthony, 2007) and the prevalence of anxiety-related disorders is twice as many in women than in men (Earls, 1987; Weinstock, 1999). Animal studies using the MS model report alterations in subsequent behaviors in adulthood in both sexes, although most of them have examined either male or female separately. Results from these studies collectively suggest that there may be sex differences in the effects of MS. In a few studies examining emotionality and anxiety-related behaviors in both sexes derived from the same litter, MS increased the levels of anxiety as measured in EPM and OFT in both female and male rats, however, males were found to be more strongly affected than females (Kalinichev et al., 2002; Wigger et al., 1999). On the other hand, there are also studies showing that MS had no effect in male rats and

rather decreased levels of fear- and anxiety-related behaviors in female rats in acoustic startle and EPM tests (de Jongh, Geyer, Olivier & Groenink, 2005; McIntosh, Anisman & Merali, 1999). It should also be mentioned that there are a number of other studies reporting no sex differences in the effects of MS on emotionality and anxiety levels in both rats and mice (Millstein & Holmes, 2007; Rhees, Lephart & Eliason, 2001; Veenema et al., 2007). These inconsistencies, at least in females, may be attributed to the confounding effects of estrogen at the time of testing.

Nearly all studies test females as gonadally intact and do not account for the influence of estrous cycle on the day of testing. In a recent study, Romeo et al. (2003) reported that MS female mice showed decreased levels of emotionality and anxiety compared to non-MS females in OFT and EPM when they were tested in diestrus (when estrogen levels were low), but not when they were tested in estrus (when estrogen levels were high). On the other hand, Rees, Steiner & Fleming (2006) reported in rats, although they have not tested females during diestrus, that MS females tested during estrus displayed decreased center area exploration in OFT compared to non-MS females, indicative of increased anxiety. It is well known that estrogen modulates emotionality and anxiety levels in non-social and social contexts in female mice in a dose-dependent manner (Tomihara, Soga, Nomura, Korach, Gustafsson, Pfaff & Ogawa, 2009). Therefore, it is assumed that fluctuating levels of endogenous estrogen may be a confounding factor in the effects of MS on emotionality and anxiety-related behaviors in females and it may be essential to test females as ovariectomized or under controlled hormonal conditions throughout testing to further elucidate sex differences in the effects of MS.

3.1.2. Strain Differences in the Behavioral Effects of MS

It is well known that there is a clear strain difference in basal levels of emotionality and anxiety in both mice and rats (Clement, Calatayud & Belzung, 2002; Glowa & Hansen, 1994). Overview of MS studies in rats and mice revealed that there might also be strain differences in the effects of MS on emotionality and anxiety behaviors. In rats, many groups use either Long-Evans, Sprague-Dawley, or

Wistar rats to examine MS effects on anxiety, but these strains are differently affected by MS. For instance, MS reduced the time spent in open arms in EPM, suggesting increased levels of anxiety, in Wistar and Long-Evans male rats, however, Sprague-Dawley males were unaffected by MS stress (Kalinichev et al., 2002; McIntosh et al., 1999; Wigger et al., 1999). In mice, Millstein & Holmes (2007) investigated the effects of MS using eight different inbred strains in multiple behavioral tests for measurements of anxiety-related behaviors. They demonstrated that neonatal MS stress increased the levels of anxiety-related behaviors in BALB/cByJ males but decreased in DBA/2J and FVB/NJ males whereas other five strains (C57BL/6J, 129S1/SvImJ, 129P3/J, A/J, and BALB/cJ) of mice were largely unaffected by MS.

Taken together, these studies suggest that not only basal levels but also susceptibility to MS in terms of emotionality and anxiety is greatly variable among different strains of mice and rats. Therefore, it is necessary to consider this fact and specify the strain in use for future MS studies. It should also be noted that a set of inbred strains variable in their vulnerability to MS stress could be a powerful tool to study neural bases of behavioral changes caused by MS.

3.2. MS Effects on Social Behaviors

Most MS studies to date have mainly focused on the effects of MS on non-social behaviors and effects on social behaviors are not extensively studied. Only a few studies examined the possible link between MS and adult social behaviors in rats and mice. Among different types of social behaviors, aggressive and sexual behavior in adulthood has been most studied (Boccia & Pedersen, 2001; Rhees et al., 2001; Veenema, Blume, Niederle, Buwalda & Neumann, 2006; Veenema et al., 2007; Veenema & Neumann, 2009). Studies on the effects of MS on these behaviors during juvenile to adolescent periods as well as other social behaviors, such as social preference and social recognition, are emerging only recently.

3.2.1. Male Aggressive Behaviors

In recent years, the adverse effects of MS on aggressive behaviors have become more evident and by reviewing the few studies examining male aggres-

sion, it has also become apparent that there are species-dependent consequences of MS. In Wistar rats, MS stress has been reported to increase the levels of aggressive behaviors in juvenile as well as adult males (Veenema et al., 2006; Veenema et al., 2009). During the juvenile age (5 weeks old), MS greatly altered social play behaviors essential for the normal development of social and aggressive behaviors in male rats. Juvenile MS male rats exhibited elevated levels of aggressive play-fighting behaviors, such as offensive nape attacks, pulling and biting, and diminished frequency of submissive play behaviors, compared to non-MS juvenile control rats (Veenema et al., 2009). As adults, MS rats display enhanced aggressive behaviors, indicated by increased frequency of lateral threat, offensive upright, and keep down aggressive behaviors during the resident-intruder paradigm compared to non-MS control males (Veenema et al., 2006). In contrast to male rats, MS has been demonstrated to decrease male aggressive behaviors in C57BL/6 mice, both in adulthood as well as the adolescent period (Tsuda, Tanahara, Nagata & Oga-wa, 2009; Veenema et al., 2007). In adolescent mice, MS reduced number and duration of aggressive bouts, as well as increased the latency to engage in an aggressive bout in males tested from 5 weeks to 9 weeks of age (Tsuda et al., 2009). In adulthood, male mice subjected to neonatal MS stress displayed longer latencies to attack an intruder male mouse placed into their home-cage (Veenema et al., 2007), indicative of reduced aggression levels.

Results from both rats and mice collectively suggest that the direction in which MS manifests long-lasting changes in male aggressive behaviors is dependent on the species being examined, but within species, MS has similar effects on aggressive behavior in both adolescent and adult periods. Although these recent studies have given great insight into the species-specific effects of MS on male aggression, there is still surprisingly very little literature documenting MS effects on aggression particularly in mice. The tools of modern genetics, such as transgenic and knockout models, are currently available predominantly in mice. In future studies, it is desired to examine the effects of MS stress in various genetically modified mice to understand the interaction between genetic factor and rearing environment on the development of aggressive behavior.

3.2.2. *Maternal Aggression*

Few studies have examined the effect of MS on female social behaviors by focusing on maternal aggressive behaviors. Boccia et al. (2001) first reported that MS decreased levels of aggressive behavior in lactating MS female Long-Evans rat. Specifically, MS dams attacked the intruder male placed into her home-cage less frequently and less quickly compared to non-separated control dams on postpartum day 6, indicative of reduced maternal aggression. On the contrary, MS elevated levels of maternal aggression in C57BL/6 female mice from postpartum days 3 through 5 against an intruder male mouse (Veenema et al., 2007). Similar to male aggression, direction of MS effects on maternal aggression is different between mice and rats. Interestingly, MS increased the levels of maternal aggression but decreased those of intermale aggression in mice, whereas in rats, MS decreased maternal aggression and increased intermale aggression. The differential effect of MS on intermale and maternal aggression may in part be related to the fact that these two forms of aggression differ behaviorally as well as functionally. Intermale aggression has been considered to be offensive and territorial, whereas maternal aggression is a defensive form of aggression (Blanchard, Wall & Blanchard, 2003). Whether MS modifies defensive type of aggression as well as any other forms of offensive aggression, i.e. sexual or competitive, in males, and offensive type of aggression in females (i.e., testosterone-inducible aggression) is presently unknown. It will be imperative for future studies to examine the effects of MS on offensive and defensive aggression in both sexes of rats and mice to gain further knowledge of whether the direction in which MS alters aggressive behaviors within each species correspond to certain forms of aggression.

3.2.3. *Sexual Behaviors*

While it is becoming apparent that MS greatly alters aggressive behaviors in both rats and mice, MS effects on sexual behaviors are still poorly understood. So far, it is known that MS does not necessarily affect pubertal maturation of reproductive functions in male rats (Biagini & Pich, 2002), but indeed modifies aspects of sexual behaviors of male rats in adulthood. Rhees et al. (2001) first revealed that male Sprague-Dawley rats subjected to neonatal MS stress displayed significantly longer

mount and intromission latencies. MS also reduced the percentage of males that exhibited ejaculation in a 60 min sexual behavior test, suggesting decreased levels of male sexual behaviors. On the other hand, Greisen, Bolwig, Husum, Nedergaard & Wörtwein (2005) demonstrated that MS heightened sexual performance in male Sprague-Dawley rats. They found that MS decreased the latency to exhibit mount, intromission, and ejaculation behaviors in a 20 min test. Additionally, they investigated whether MS altered the preference for a receptive female over a non-receptive female in a partner preference test in male rats and found that the preference for the receptive female was not influenced by neonatal MS stress. Inconsistencies between the two studies may be attributed to factors such as differences in MS procedures and the use of different types of control groups, i.e. handled or non-handled, for comparisons with MS group. Further investigation of MS effects on male sexual behaviors is necessary to elucidate the behavioral changes induced by MS in rats.

In order to investigate whether MS stress also modified male sexual behaviors in mice, we recently conducted a study in which adult C57BL/6 male mice exposed to neonatal MS stress were tested for sexual behaviors in a 30 min test over the course of 3 weeks. Unlike male rats, we were not able to observe any MS effect on male sexual behaviors, such as mount, intromission, and ejaculation, in adult mice (Tsuda, 2010b). Further research will need to clarify MS effects in mice and to determine whether MS effects on male sexual behaviors are also dependent on species. Moreover, it should be mentioned that nothing is known about the effect of MS on female sexual behavior in both mice and rats.

3.2.4. Social Investigative Behaviors

The effects of MS on other social behaviors, such as social interaction and social preference, have not been studied until recently. A series of studies in our laboratory using both sexes of C57BL/6 mice collectively demonstrated a substantial effect of MS on female social interactive behaviors, whereas males were largely unaffected (Tsuda, Ozawa, Fukushi & Ogawa, 2006; Tsuda & Ogawa, 2010a). Specifically, adult MS female mice (tested as ovariectomized) exhibited reduced levels of social investigation and increased number of stretched approaches towards an unfamiliar stimulus mouse of both sexes, suggest-

ing heightened levels of social anxiety. Long-term observation of social interaction revealed that these behavioral characteristics in MS females were more evident when they were exposed to social stimuli for the first time. After prolonged exposure to stimulus mice, MS females showed decreased levels of social anxiety and increased levels of social investigation towards a female opponent while they did not show such tendency towards the male opponent. These results suggest that MS stress greatly modifies social interactive behaviors towards unfamiliar conspecifics, particularly towards a male opponent, in female mice.

On the other hand, we found no alterations in social interactive behaviors towards a same sex opponent in adult male mice (Tsuda, 2010b). In contrast, MS in male rats have been reported to decrease duration and frequency of social interaction with another male rat in adulthood (Toth, Avital, Leshem, Richter-Levin & Braun, 2008). These results suggest that MS induced changes in social interactive behaviors may possibly be species- as well as sex-dependent.

4. Neuroendocrine Bases of Maternal Separation-Induced Behavioral Changes

Studies examining the effects of early life stress with the MS model have provided great insight into the adverse effects on social and nonsocial behaviors in adulthood in both sexes of rats and mice. These findings have promoted studies aimed at understanding the underlying neuroendocrine bases that contribute to the MS-induced behavioral changes. Most studies to date have mainly focused on the effects of MS on neuroendocrine systems related to the regulation of stress, such as the hypothalamic-pituitary-adrenal axis, vasopressinergic, oxytocinergic, and serotonergic systems. Here, we not only address how MS affects these stress-related neuroendocrine systems, but also discuss their behavioral consequences.

4.1. Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis is one of the major regulatory systems that control reactions to stress. HPA activation consists of the release of corticotropin releasing hormone (CRH)

from the paraventricular nucleus of the hypothalamus (PVN) into the anterior pituitary gland, where CRH stimulates the secretion of adrenocorticotrophic hormone (ACTH) into the blood, which then stimulates the adrenal glands to produce and release glucocorticoids, such as corticosterone (CORT) in rodents and cortisol in human. The dysregulation of HPA-axis hormones has been reported to contribute to alterations in anxiety-related and social behaviors in adult rats and mice (Dunn & Berridge, 1990; Haller, Halasz, Mikics & Kruk, 2004).

Neonatal MS stress causes long-lasting alterations in HPA activity in adult rats and mice of both sexes, as shown by increased CRH mRNA expression in the PVN and elevated plasma levels of ACTH and CORT under basal conditions and in response to stressors (Kalinichev et al., 2002; Parfitt, Levin, Saltstein, Klayman, Greer & Helmreich, 2004; Wigger et al., 1999). The hyperreactivity of the HPA axis in MS animals has been considered to be mainly due to an impaired glucocorticoid-negative feedback (Ladd, Huot, Thirivikraman, Nemeroff & Plotsky, 2004). Some of these studies examined the relationship, although correlational, between MS induced changes in HPA axis hormones and levels of anxiety-related behaviors. For example, augmentation of CORT release in response to stress was parallel to enhanced levels of anxiety in EPM in adult male MS rats (Kalinichev et al., 2002; Renard, Rivarola & Suarez, 2007; Wigger et al., 1999). Recent studies also investigated the possible link between stress hormones and social behaviors. It is reported that increased levels of aggression in MS rats are correlated with increased basal levels of CORT (Veenema et al., 2009), while heightened levels of sexual behavior in MS male rats are associated with a decreased number of CRH immunopositive cells in the PVN (Greisen et al., 2005). These results are consistent with studies reporting that HPA axis hormones play a facilitatory and inhibitory effect on male aggressive and sexual behaviors, respectively (Haller, Millar, van de Schraaf, de Kloet & Kruk, 2000; Sirinathsinghji, 1987). Altogether, these findings suggest that MS induced alterations in the HPA system may be responsible for modification in non-social as well as social behaviors.

Gonadal steroid hormones, such as testosterone and estradiol, may affect the development of the

HPA axis through their organizational action during neonatal period, which then later influences the sensitivity of the HPA axis in response to stress in a sex-dependent manner (McCormick, Furey, Child, Sawyer & Donohue, 1998; Seale, Wood, Atkinson, Lightman & Harbuz, 2005). There is a clear sex difference in the effects of MS on HPA functions, in which MS female rats show higher CRH and CORT responses to stress compared to MS male rats (Desbonnet, Garrett, Daly, McDermott & Dinan, 2008; Renard et al., 2007). However, there are also other studies reporting augmented ACTH response to stress in male rats, but not in females (Wigger et al., 1999). These differences between studies may in part depend on the type of stressor examined. Furthermore, in mice, the influence of neonatal steroid hormones on MS-inducible alterations in brain functions and behaviors remain largely unknown. Future studies will need to further examine sexually dimorphic effects of MS on HPA axis hormones and determine their role in sex-dependent non-social and social behavioral changes caused by MS.

4.2. *Oxytocin and Vasopressin*

Arginine vasopressin (AVP) and oxytocin (OT) are two closely related neuropeptides mainly produced in the PVN and supraoptic nuclei of the hypothalamus and released peripherally via posterior pituitary as well as centrally to various brain regions. Central release of both neuropeptides are known to play a role not only in stress responses (Engelmann, Landgraf & Wotjak, 2004) but also in the regulation of anxiety-related behaviors (Appenrodt, Schnabel & Schwarzberg, 1998; Mantella, Vollmer, Li & Amico, 2003), social behaviors, including aggressive and sexual, and social cognition (Caldwell, Lee, Macbeth & Young, 2008; Ferris, 2005; Insel, Winslow, Wang & Young, 1998; Veenema & Neumann, 2008).

Recently, it has been found that AVP and OT systems are altered by MS experience in rats and mice. Some studies have reported that the number of AVP-immunopositive cells in the PVN are decreased by MS in adult male rats (Desbonnet et al., 2008). On the other hand, there are also studies showing that MS increased AVP immunopositive cell density in the PVN of adult male rats and mice (Veenema et al., 2006; Veenema et al., 2007). These studies also examined the relationship between MS

induced changes in AVP expression and the levels of intermale aggression and reported that increased levels of AVP positive cells are correlated with an increase of aggression in MS rats whereas they are correlated with a decrease of aggression in MS mice. These findings demonstrate that even if MS has a similar effect on AVP expression in adult rats and mice, behavioral consequences may vary between the two species.

Remarkably, no MS effects on the levels of AVP were found in female rats or mice, despite alterations in maternal aggression (Boccia et al., 2001; Veenema et al., 2007). On the other hand, MS has been reported to decrease OT immunopositive cell density in the PVN of female, but not male mice (Veenema et al., 2007). This study also examined the relationship between MS induced changes in levels of OT positive cells and levels of maternal aggression and found that decreased levels of OT immunopositive cells were associated with increased levels of maternal aggression in MS female mice. These findings suggest that MS differentially alters AVP and OT in males and females. However, AVP and OT neuropeptides are known to play a role in regulating both female and male social behaviors (Gutzler, Karom, Erwin & Albers, 2010; Veenema et al., 2008; Winslow, Hearn, Ferguson, Young, Matzuk & Insel, 2000). Thus, the possibility of AVP playing a role in female and OT in male social behaviors cannot be completely excluded. Additional studies are necessary to elucidate MS effects on these neuropeptides to gain a further understanding in behavioral alterations caused by MS, particularly aggression.

4.3. Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) is known to play an important role in the regulation of emotional and social behaviors and the dysregulation of 5-HT system is associated with psychopathologies involving depression and excessive aggression (Lucki, 1998). Recently it has been reported that neonatal MS stress altered 5-HTergic neurotransmission by decreasing mRNA expression of 5-HT transporter in the dorsal raphe nuclei as well as reducing levels of 5-HT and its metabolites in the hippocampus in male rats (Lee, Kim, Kim, Ryu, Kim, Kang & Jahng, 2007). The same study also examined the link between alteration in 5-HTergic neurotransmission

caused by MS and depression-like and anxiety-related behaviors in adult male rats. It is reported that decreased expression of 5-HT transporter in the dorsal raphe nuclei in MS males is correlated with increased levels of depressive-like behavior in the forced swim test and anxiety-like behaviors in the EPM. Furthermore, Veenema et al. (2006) showed that MS increased levels of aggression in male rats and these behavioral changes were negatively correlated with the number of 5-HT immunopositive cells in the anterior hypothalamus. These findings suggest that behavioral alterations caused by MS stress may in part be associated with MS-induced alterations in central 5-HT activity in males. However, to date, the effect of MS on serotonergic system other than male rats is unknown. Therefore, it is necessary to further investigate whether MS induced alterations in anxiety-related and social behaviors are associated with modifications in the central 5-HT system.

5. Future directions

The early postnatal environment influences the development of emotional and social behaviors. Adverse experiences during this sensitive period can produce detrimental effects on subsequent behaviors. In this article, we reviewed the adverse effects of neonatal MS stress by focusing on sex, species, and strain-dependent behavioral effects of MS in both social and non-social contexts. As possible neural mechanisms of behavioral changes caused by MS, we described neuroendocrine systems related to the regulation of stress, such as the HPA axis, vasopressinergic, oxytocinergic, and serotonergic systems. There are still a number of other factors we need to consider that may modulate the detrimental effects of MS. These include factors such as genetic vs. epigenetic factors, and mother-infant interactions during the postnatal period that may greatly influence the behavioral and neuroendocrine alterations caused by MS stress. Further studies are necessary to fully understand behavioral alterations imposed by early life stress and their neuroendocrine bases.

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