Psychopharmacology (2011) 214:131–140
DOI 10.1007/s00213-010-2096-0

REVIEW

Early life stress paradigms in rodents: potential animal models of depression?

Mathias V. Schmidt · Xiao-Dong Wang · Onno C. Meijer

Received: 21 September 2010 / Accepted: 3 November 2010 / Published online: 18 November 2010
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Abstract
Rationale While human depressive illness is indeed uniquely human, many of its symptoms may be modeled in rodents. Based on human etiology, the assumption has been made that depression-like behavior in rats and mice can be modulated by some of the powerful early life programming effects that are known to occur after manipulations in the first weeks of life.
Objective Here we review the evidence that is available in literature for early life manipulation as risk factors for the development of depression-like symptoms such as anhedonia, passive coping strategies, and neuroendocrine changes. Early life paradigms that were evaluated include early handling, separation, and deprivation protocols, as well as enriched and impoverished environments. We have also included a small number of stress-related pharmacological models.
Results We find that for most early life paradigms per se, the actual validity for depression is limited. A number of models have not been tested with respect to classical depression-like behaviors, while in many cases, the outcome of such experiments is variable and depends on strain and additional factors.
Conclusion Because programming effects confer vulnerability rather than disease, a number of paradigms hold promise for usefulness in depression research, in combination with the proper genetic background and adult life challenges.

M. V. Schmidt (✉) · X.-D. Wang
RG Neurobiology of Stress, Max Planck Institute of Psychiatry,
Kraepelinstr. 2-10,
80804, Munich, Germany
e-mail: mschmidt@mpipsykl.mpg.de

O. C. Meijer
Division of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research and Leiden University Medical Center,
Leiden 2300 RA, The Netherlands

Keywords Early life stress · Depression · Animal model · Stress

Affective disorders

Affective disorders affect the life of millions of people worldwide and are estimated to be one of the leading causes of disability. Life time prevalence of depression was reported to range between 15% and 20%, with a twice-as-high risk for women than for men (Kendler et al. 2002; Wittchen and Jacobi 2005). Core symptoms of depression include a depressed, irritable, or apathetic mood, a loss of interest and enjoyment, and reduced energy. These symptoms, which are often accompanied by reduced attention, feelings of guilt, disturbed sleep, and loss of appetite, are present over a prolonged period of time with a minimum of 2 weeks and seem to be beyond personal control. Next to its devastating impact on the patient, the disease is also associated with impairment at work and in personal or family relationships. In addition, depression negatively affects the outcome and prognosis of a number of other diseases, including coronary heart disease or diabetes (Paile-Hyvärinen et al. 2007). As a consequence, the direct and indirect costs associated with depression are enormous and are in Europe estimated at about 1% of the total gross economic product of the European Union.

Diagnosis of affective disorders is based on diagnostic rating scales as, e.g., the Hamilton depression scale. Unfortunately, many of the patients may remain undiagnosed or are inadequately treated by their general practitioner, and only a small percentage of patients are transferred to a psychiatrist. The standard pharmacological treatment options for affective disorders are selective serotonin reuptake inhibitors (SSRIs) or selective noradren-

alin reuptake inhibitors (SNRIs). These drugs are based on the serendipitous discovery of tricyclic antidepressants in the 1950s, which function as non-selective serotonin and noradrenalin reuptake inhibitors. While the refined successor drugs are in general safe and effective, there has been little improvement regarding efficacy. It was recently estimated that only about half of the patients treated with two sequential treatment interventions achieve remission, with relapse rates of more than 40% (Huynh and McIntyre 2008). Some authors even claim based on meta-analyses that currently available antidepressants are not more effective than placebo treatment in mild or moderate depression (Kirsch et al. 2008). While these conclusions may be premature and need to be treated with caution, it is nonetheless clear that current treatment options for affective disorders are unsatisfactory. Therefore, the identification of alternative strategies (e.g., new pharmacological targets) to treat the disease or to prevent its development would be of great benefit to many.

Early life stress as a risk factor for depression

Depression is a multifactorial disease and has been shown to include a substantial heritable, thus genetic, portion. Kendler and colleagues estimated the heritability of depression to be in the range of 30–50%, depending on sex and symptom severity (Kendler et al. 2002). On the other hand, environmental challenges seem to have a decisive impact on the disease, either increasing or decreasing the individual disease risk. Among the best studied and validated environmental risk factors for depression are stressors or traumatic situations early in life (Heim et al. 2008), giving rise to a two-hit model for the susceptibility for depressive disease.

Child abuse and neglect is a major problem, with recently verified 1.2 million incidents in the USA per year (Sedlack et al. 2010). A number of meta-analyses and large-scale studies indicated a significantly increased risk for depression in relation to early life stress, e.g., childhood abuse (Jumper 1995; Molnar et al. 2001; Paolucci et al. 2001). Representative of many other studies, MacMillan found childhood abuse to be significantly associated with lifetime rate of depression in a community sample of 7,016 individuals, with a bigger effect size in women (MacMillan et al. 2001). These findings are also supported by a number of more recent studies, also demonstrating a clear link between traumatic or stressful live events during childhood and adult psychopathology (Kim and Cicchetti 2006; Larkin and Read 2008; Weber et al. 2008).

However, it is also unquestionable that the majority of individuals exposed to early life stress are resilient and do not develop a psychiatric pathology later in life. It was therefore hypothesized that early adverse experiences may impact on a preexisting genetic or epigenetic individual vulnerability, resulting in an individual with an increased risk for disease under certain environmental conditions. The first clear evidence for gene×environment interaction for depression came from Caspi and colleagues, demonstrating that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene influenced the individual risk to develop depression as a consequence of stressful life events in young adults (Caspi et al. 2003). This finding has now been replicated several times (Kim et al. 2007; Wilhelm et al. 2006) and was also widely supported by findings in animal models (Suomi 2006). However, while the failure of a recent meta-analysis to show an overall effect (Risch et al. 2009) needs to be interpreted with caution, it illustrates that one genetic risk factor can only account for a small overall effect.

A few other genetic risk factors have by now been identified (Binder et al. 2004, 2008; Bradley et al. 2008), including polymorphisms in the fkbp5 and crhr1 gene, which significantly interact with early life events and thereby modulate adulthood risk of depression. It is therefore clear that animal models for depression need to encompass both genetic and environmental risk factors in order to match the situation in humans.

Modeling depression in rodents

A first important decision with regard to modeling depression is the choice of the model system, i.e., the species. It seems obvious that complex psychiatric diseases are best modeled in animals that are closely related to humans, as e.g. primates. While there are a number of outstanding researchers working with non-rodent models for depression (Barr et al. 2003; Fuchs 2005; Pryce et al. 2005), there are many ethical, political, and practical issues that prevent research with these models on a larger scale. Most of the scientific community therefore relies on rodent models for psychiatric disorders, which is also the focus of this review. A second important question is then whether or not a complex psychiatric disease as depression can actually be modeled in rats or mice. This is a critical issue given some core symptoms of depression, as e.g. low self-esteem, feelings of guilt, or suicidality. While some of these aspects may have their correlates in non-human primates (if hard to address), they cannot be modeled in rodents. However, a number of core symptoms of depression in humans do have an equivalent in animals (see Table 1). It is therefore possible to reach a certain level of face validity with animal models of depression, even though it has to be acknowledged that the available tests are often only a very crude approximation of the desired readout. For a detailed description and evaluation

Table 1 Comparison of core symptoms of depression in humans with the possible analogous parameters assessable in rodents

Core symptoms in humans	Analogous parameter in rodents
Loss of enjoyment	Anhedonia
Loss of motivation	Passive coping strategies; low locomotor activity
Sleep disturbances	Altered sleep/activity patterns
Anxiety	Anxiety-related behavior
Cognitive deficits	Cognitive deficits
Hypercortisolism	Hyperactivity of the stress system

of the different available tests, please refer to other review articles (Pryce and Seifritz 2010). In addition, many models have to settle for a subset of validity aspects, which moreover are not highly specific for depression (Veenema 2009). However, the lack of specificity of symptoms also reflects the actual complexity of the depression syndrome, which is also becoming apparent from human polymorphisms that are associated with multiple diseases (Knight et al. 2009).

Face validity, thus the level of similarity in the disease symptoms, is one of the core validity criteria proposed by Willner and colleagues (McKinney and Bunney 1969; Willner 1984). Two other often considered validity criteria for a possible animal model of depression are construct validity and predictive validity. Construct validity implies that the theoretical rationale of the model is matching the actual human situation. Thus, the more known risk factors of depression, both genetic and environmental, are incorporated in an animal model, the higher the validity of this model would be rated. Construct validity also demands that the actual psychopathological mechanisms are similar between disease and model. The demand for similar etiology of a condition in humans and in the animal model has also been defined as etiological validity (Geyer and Markou 1995). Obviously, such validity is not perfect just because of "early life" events, but would need to incorporate factors like emotional neglect. Predictive validity addresses the ability of successful treatment options in humans to improve the symptomatology in the animal model. These validity criteria, although sometimes limited in their applicability, are still very helpful in assessing the validity of a model and comparing the various model approaches with each other.

The main focus of the current review is animal models incorporating early life stress as a risk factor for depression. This is obviously not the only described risk factor for depression and there are many other valid approaches, which have previously been summarized in a number of excellent reviews (Willner and Mitchell 2002; Frazer and Morilak 2005; Fuchs and Flügge 2006; Müller and Holsboer 2006; El Yacoubi and Vaugeois 2007;Kalueff et al. 2007). There are also already a number of outstanding reviews on the topic of early life stress paradigms as potential models for depression, which should be used as complementary source of information (Kaufman et al. 2000; Ladd et al. 2000; Pryce et al. 2005). The term early life stress has a broad range and can be roughly subdivided in the prenatal phase, the early postnatal phase (until P21), and the early adolescent phase (P21–P30), with the current review focusing primarily on models in the early postnatal phase. In the following paragraphs, the most frequently used animal models of early life stress will be described and discussed in terms of their potential validity as

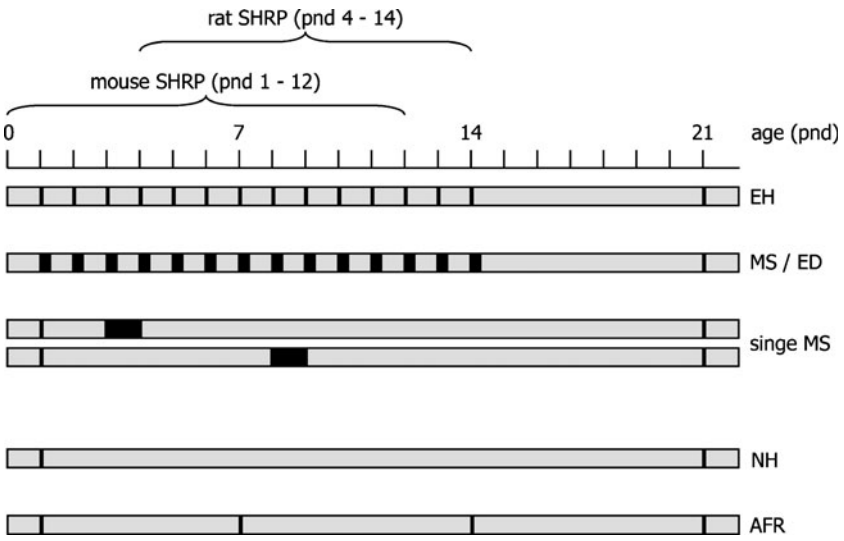

Fig. 1 Illustration of the different types of maternal separation paradigms. *Black bars* indicate times of interference with mother–pup interaction

models for depression (see Fig. 1). Other approaches may be mentioned, but will not be discussed in detail, mainly due to the lack of available data that would make an evaluation of these models possible.

Rodent models of early life stress

Interventions in mother–pup interaction time periods

Early handling 3–15 min

One of the first experimental paradigms described in rodents that manipulate mother–pup interaction periods is the early handling (EH) paradigm developed by Levine (Levine 1957). The central characteristic of this model is a daily physical manipulation of the litter, where the pups are separated from the mother for a short period of time (maximally 15 min). It has been shown that this procedure, which is carried out during the first 2–3 weeks of life, stimulates maternal care behavior towards the offspring (Liu et al. 1997) and elicits acute neuroendocrine responses from the pups (Meaney et al. 1991). A critical issue with regard to the EH paradigm is the choice of the appropriate control or comparison group. Historically, EH was compared to non-handled (NH) pups, thus litters that are not exposed to any physical human disturbance. However, this procedure can be regarded as an experimental group as well, as the lack of any external stimulation also affects maternal care behavior. It was therefore suggested that both EH and NH groups should be compared to litters exposed to normal animal facility rearing, thus regular exposure to, e.g., cage changes (Pryce and Feldon 2003). This so-called animal facility rearing (AFR) group is therefore an intermediate group between EH and NH.

It can now be discussed whether any of the two extreme groups—NH or EH—display a depression-like phenotype as adults. Unfortunately, in spite of the long history of this model, the available data with regard to face validity for depression are sparse, which may also be due to the fact that this model was never intended to be a stand-alone model for depression. The available data are also often conflicting, with some authors reporting differential phenotypes, while others find no differences. In Sprague–Dawley rats, EH has no effect on sucrose preference, a frequent measure of hedonic behavior, in comparison to NH (Maniam and Morris 2010). In male Wistar or Fischer rats, no differences in the performance of EH or NH animals were observed in the forced-swim test in recent studies (Papaioannou et al. 2002; Rüedi-Bettschen et al. 2006), while an older study in Wistar rats did report a shorter immobility time on the forced-swim test in EH animals (Hilakivi-Clarke et al. 1991). In Fischer rats, EH resulted in escape and avoidance deficits in a two-way shuttle box compared to NH animals (Rüedi-Bettschen et al. 2004), suggesting that under certain conditions and genetic backgrounds, EH can even be detrimental for the adult phenotype. In mice, Millstein and Holmes found no clear evidence of altered anxiety- or depression-like behavior when comparing EH and AFR in different strains (Millstein and Holmes 2007). The situation is somewhat different for anxiety-related behavior, where many authors observed a decreased anxiety in EH animals compared to NH (Durand et al. 1998). However, as there are no consistent indications of the EH/NH paradigm in terms of depression-like behavior in either rats or mice, this paradigm seems not suited to be used as a potential model for depression *per se*. The observed molecular, neuroendocrine, and behavioral alterations observed with this model rather suggest that growing up in an AFR, EH, or NH environment alters the degree of vulnerability to environmental challenges later in life.

Repeated maternal separation for 1–8 h

While EH stimulates maternal care, prolonged separations of the dam from the litter are meant to reduce the amount of maternal care for the pups, thereby modeling emotional as well as physical neglect. The applied methodologies are highly variable not only in the separation time and duration but also with respect to temperature (warm or cold), type of separation (mother or litter removed from the home cage), or isolation (pups separated in isolation or as whole litter). As a consequence, the nomenclature of this paradigm is also highly variable. In the current review, we will apply the nomenclature suggested by Pryce and Feldon (2003). Thus, maternal separation (MS) is used to describe the repeated separation of the intact litter from the dam for one or more hours per day across several days, while early deprivation (ED) is used to describe a separation of a pup from the dam as well as the litter for one or more hours across several days. Nonetheless, the technical variability of these paradigms makes the interpretation and comparison of the data obtained in different laboratories extremely difficult. One specific problem is the choice of the comparison group, which in some cases is NH, in others AFR.

One important aspect with regard to maternal separation paradigms is that they usually take place during the so-called stress hypo-responsive period (SHRP) in rodents, which lasts from postnatal day 4–14 in the rat and from postnatal day 1–12 in the mouse (Levine et al. 1967; Levine 1970; Schmidt et al. 2003; Enthoven et al. 2010). First described by Schapiro and colleagues (Schapiro et al. 1962), this period is characterized by a low basal corticosterone secretion and the relative inability of mild stressors to elicit a corticosterone response (Levine 2001).

As with the NH–EH paradigm, there are only few data available for the MS or ED models with regard to depression-like behavior. In rats, some authors report an increased immobility in the forced-swim test (FST) in MS (Rüedi-Bettschen et al. 2005; Lee et al. 2007; Lambas-Senas et al. 2009), while others find no effect (Marais et al. 2008). For mice, there are also no consistent effects of MS in the FST (MacQueen et al. 2003; Bhansali et al. 2007; Millstein and Holmes 2007). Interestingly, marked strain differences in the response to MS indicate that lasting effects of this paradigm can only be expected in animals with a specific of genetic vulnerability (El Khoury et al. 2006), probably in combination with a specific adult environment. The same is true for learned helplessness, where ED Wistar rats show actually an improved escape behavior compared to NH, while Fisher rats subjected to ED display deficits in escape behavior compared to NH counterparts (Rüedi-Bettschen et al. 2005). The literature on anhedonia-like behavior, thus sucrose consumption and sucrose preference, is also not consistent. While most authors report no effects of MS on sucrose preference (Shalev and Kafkafi 2002; Matthews and Robbins 2003), there are also reports of decreased sucrose preference compared to NH (Michaels and Holtzman 2007). Interestingly, when sucrose is not freely available but requires effort in terms of bar presses on a progressive ratio schedule, ED male Wistar rats have been shown to consume significantly less sucrose (Rüedi-Bettschen et al. 2005; Leventopoulos et al. 2009). However, from the inconsistency in the literature with regard to the depression-like phenotype elicited by MS or ED, it can only be concluded that other—mostly not controlled—factors influence the outcome of the study. Thus, (epi)genetic predispositions carried by the individual animals of the different rat and mouse strains are likely determinants of the beneficial or detrimental effects of a disrupted maternal care. As with the EH/NH paradigm, repeated separations has been shown to clearly affect neuroendocrine and physiological parameters, which are likely to impact on the vulnerability or resilience of the individuals to subsequent challenges.

Single maternal separation for 24 h

First developed by Levine and colleagues, this paradigm consists of a single separation period of mother and pups for 24 h, which can be applied at different time points during postnatal development (Stanton et al. 1988). While it has been extensively used to study the neuroendocrine function of the developing rat or mouse pup (Dent et al. 2000, 2001; Liebl et al. 2009) and a number of neuroendocrine effects in adult animals were reported (Ladd et al. 1996; Rots et al. 1996; Sutanto et al. 1996; Workel et al. 1997, 2001; Suchecki et al. 2000), there are only a few reports addressing the influence of single MS on depression-like behavior. CD1 mice subjected to 24-h maternal separation at postnatal day 12 showed no differences in floating or struggling time in the FST at adulthood (Macri and Laviola 2004). Similarly, 24-h maternal separation at postnatal day 9 resulted in no clear FST phenotype during adolescence (Marco et al. 2009). Thus, while single MS has been proposed as a valid model for other psychiatric diseases, as e.g. schizophrenia (Ellenbroek and Cools 2000), there is no apparent validity for the study of depression-like phenotypes. Again, a combination of early experience with other risk or triggering factors is needed to have a useful model for depression. As with the other paradigms discussed so far, it becomes apparent that the crucial experiments with regard to depression have not yet been performed. Thus, animals with a history of early life stress should be combined with additional genetic or environmental risk factors, e.g. a specific genetic knockout or a second stress exposure during adulthood. This critical issue will also be discussed at the end of this review.

Models based on the quantity and/or quality of maternal care

Naturally occurring differences in maternal care

First reported by the group of Meaney and colleagues, this model is based on the hypothesis that early handling mirrors naturally occurring differences in maternal care (Liu et al. 1997). During an observation period of postnatal day 0 to 8, high or low licking and grooming/arched-back nursing mothers are identified as those where both measures are one standard deviation above or below the mean of the cohort, respectively. This model, which is routinely used with Long–Evans rats, lacks a control group problem in relation to the experimentalist's influence, as present in the EH/NH paradigm (De Kloet et al. 2005). While this paradigm has been extensively studied with respect to neuroendocrine regulation (Liu et al. 1997), hippocampal function (Liu et al. 2000; Champagne et al. 2008), and anxiety-related behavior (Caldji et al. 1998), little or no data are available suggesting a depression-like phenotype.

Enriched postnatal social environment

Another way to manipulate maternal care behavior in a naturalistic way is the communal nesting paradigm (Branchi 2009). In a communal nest (CN), three females breed and keep pups together, and share care-giving behavior in a single nest from birth to weaning (P1 to P25), representing natural ecologic condition of (altricial) rodents. This early social enrichment provides pups with high level of maternal care and peer interaction. Compared

to mice reared in standard laboratory conditions (SN), CN mice display more passive behavior in the forced-swim test, which could be modulated by acute, but not chronic, fluoxetine treatment (Branchi et al. 2006, 2010). However, the finding that chronic fluoxetine treatment does not affect the duration of immobility in CN mice while increasing immobility in SN mice may seem counterintuitive and warrants further investigation. Further, adult CN mice display increased anxiety-related behavior (Branchi et al. 2006), which can be ameliorated when the test is performed in a social context. Adult CN mice also show greater sucrose preference under both basal and stressful conditions, and display a lower corticosterone response following an acute stressor. In addition, CN mice have elevated brain NGF and BDNF levels and increased survival of adult-born new neurons in the hippocampus (Branchi et al. 2006). Taken together, these studies point to the possibility that standard nesting conditions may represent an impoverished environment and communal nesting could represent a model for resilience to depression later in life under specific environmental circumstances.

Impoverished postnatal environment

An opposite effect to the CN paradigm is achieved by the limited nesting material model recently established by the group of Baram in rats and mice (Brunson et al. 2005; Ivy et al. 2008, 2010; Rice et al. 2008), where mothers are provided with reduced nesting and bedding material from postnatal days 2 to 9 of their litter. This manipulation results in frequent changes of maternal behavior and inconsistent or fragmented maternal care, resulting in a higher stress exposure of the offspring. So far, this promising model has only been investigated in terms of anxiety-related behavior and cognitive performance, so future studies will reveal whether this paradigm also results in alterations of depression-like phenotypes.

Pharmacological models

Effects of early life environment may be mediated by any of a number of hormones, neurotransmitters/peptides, or inflammatory mediators. Signaling by these mediators can be modulated directly during early life by classical pharmacology. While a review of all the pharmacological approaches to mimic an early life stress exposure would be beyond the scope of the current review, we will mention and discuss the most common ones in the next paragraphs.

Postnatal glucocorticoids

Much work with glucocorticoids (GCs) has focused on the use of high doses of the synthetic GC dexamethasone. This surely models the treatment of premature children and the many associated programming effects, i.e., long-term effects that emerge at a later age, such as impaired neuromotor skills, cognitive deficits, and disrupted HPA axis activity at school age (Karemaker et al. 2008; Yeh et al. 2004). However, dexamethasone may display quite different pharmacodynamic characteristics from corticosterone, and its superagonistic properties probably affect development in a manner that is quite different from the endogenous corticosteroids that are associated with actual early life circumstances. Postnatal dexamethasone treatment has been shown to increase anxiety-related behavior and the time immobile in the FST in adult Wistar rats (Felszeghy et al. 1993; Neal et al. 2004). Adolescent and adult rats with early life dexamethasone exposure also show impaired hormonal response to stress (Flagel et al. 2002; Neal et al. 2004). On the other hand, mice exposed to excessive corticosterone levels during the SHRP due to a conditional knockout of pituitary GR receptors display no depression- or anxiety-related phenotype as adults (Schmidt et al. 2009). On the contrary, it was recently demonstrated that those mice are resilient to the behavioral effects of chronic social defeat stress in adulthood (Wagner et al. 2010). Thus, while early postnatal GCs treatment can strongly program development, it is far from proven that these effects mimic those of endogenous hormones. These approaches are of little use when developing animal models of depression based on early life stress.

Postnatal lipopolysaccharide

The immune system has been implicated in the development of psychopathologies, including depression (Dantzer et al. 2008). It has been argued that in adult animals, chronic exposure to lipopolysaccharide (LPS) can be useful to model aspects of depression (De La Garza 2005). Early life exposure to such endotoxins is common and represents a prominent environmental challenge due to the fragile immune system of the newborn (Shanks and Meaney 1994). Thus, postnatal LPS treatment in rodents would mimic a mild (gram-negative) bacterial infection of the human infants.

It is clear that LPS administration in early life has immediate effects on the HPA axis, disrupts the development of stress system, and results in changed neuroendocrine and neuroimmune responses in adulthood (Shanks et al. 1995, 2000; Kohman et al. 2008; Walker et al. 2008). Behavioral changes occur in several domains including social behavior, cognitive capacity, and anxiety (Granger et al. 2001; Harre et al. 2008). Effects on cognition and anxiety both are relevant for depression but are not regarded as core features of the disease. Kentner and colleagues observed no effect of postnatal LPS treatment on

sucrose preference (Kentner et al. 2010). Further, postnatal LPS treatment did not affect adult behavior in the FST in either male or female mice (Lucchina et al. 2010). Thus, a combination with additional risk factors would be a prerequisite when using postnatal LPS treatment as a model for depression.

Conclusions

Many parameters in early life determine the stress and behavioral responsiveness in adulthood, and many of these potentially qualify for a "second hit" in a vulnerability model consisting of genomic background, predisposing events, and precipitating events. Obviously, these parameters are not independent, for example because maternal responsiveness to stressed neonates can ameliorate the social–developmental effects of early illness (Hood et al. 2003). A major question obviously is *how* changes in early life can increase the risk to develop depression. As will be clear from this volume, a vast number of changes in neurochemistry can be the consequence of early life stress, and the strongest explanation for such enduring changes is that they are mediated through epigenetic modification of the DNA and/or chromatin (Tania Roth, this volume) that are triggered by any of the neuronal and hormonal mediators associated with the early life event. The review of the available literature on the different early life stress models underscores the importance of the genetic predisposition as well as the later (adult) environment. When studied out of the genetic and environmental context, none of the established models of early life stress can be regarded as robust model of depression. Therefore, more studies are needed that actually address this complex interplay of genetic vulnerability or resilience to postnatal stressors. In addition, the adult environment will be decisive for the outcome, where an early life stress event may have adaptive consequences in aversive adult environments, but may be maladaptive in non-aversive environments (Schmidt 2010).

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