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Review

Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health

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ABSTRACT

Research efforts during the past decades have provided intriguing evidence suggesting that stressful experiences during pregnancy exert long-term consequences on the future mental wellbeing of both the mother and her baby. Recent human epidemiological and animal studies indicate that stressful experiences *in utero* or during early life may increase the risk of neurological and psychiatric disorders, arguably *via* altered epigenetic regulation. Epigenetic mechanisms, such as miRNA expression, DNA methylation, and histone modifications are prone to changes in response to stressful experiences and hostile environmental factors. Altered epigenetic regulation may potentially influence fetal endocrine programming and brain development across several generations. Only recently, however, more attention has been paid to possible transgenerational effects of stress. In this review we discuss the evidence of transgenerational epigenetic inheritance of stress exposure in human studies and animal models. We highlight the complex interplay between prenatal stress exposure, associated changes in miRNA expression and DNA methylation in placenta and brain and possible links to greater risks of schizophrenia, attention deficit hyperactivity disorder, autism, anxiety- or depression-related disorders later in life. Based on existing evidence, we propose that prenatal stress, through the generation of epigenetic alterations, becomes one of the most powerful influences on mental health in later life. The consideration of ancestral and prenatal stress effects on lifetime health trajectories is critical for improving strategies that support healthy development and successful aging.

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1. Introduction

The stressful childhoods of our forebears may influence our personality and mental health by altering epigenetic regulation of gene expression in the brain. Notably, such programming by stress may significantly affect the risk of anxiety and depression in the human population. About half the world's population is afflicted by depression, anxiety disorders, or other mental illnesses at some point in their lives, which affects people's ability to function in everyday life and generates a serious economic burden to society. The causes of mental illnesses are poorly understood, however, striking evidence suggests that they may be influenced by stress in previous generations (Franklin et al., 2010). In fact, stress may be the single most potent factor in the vulnerability to mental illness (Kinney et al., 2008b). This is opposed to resilience, which represents the ability to withstand stress and its health risks by adapting and overcoming adversity (Franklin et al., 2012). Transgenerational epigenetic inheritance, which in part manifests itself in altered stress response in the progeny of stressed parents, may critically determine both, stress vulnerability and resilience, thus acting as a maladaptive or an adaptive mechanism.

In this review, we will address the epigenetic mechanisms including changes in the level of non-coding RNAs, DNA methylation and histone modifications that may potentially mediate stress resilience and stress vulnerability. We hypothesize that prenatal stress has epigenetically regulated effects on health and disease of the nervous system from early development to old age. This review will discuss transgenerational epigenetic inheritance and the role of stress and epigenetic mechanisms in fetal programming and brain development. Furthermore, we will highlight the role of prenatal stress and associated epigenetic marks in influencing the risk of mental disorders such as schizophrenia, anxiety- and depression-related disorders, attention deficit hyperactivity disorder and autism later in life.

2. Transgenerational epigenetic inheritance: significance and definitions

Epigenetics is the study of heritable changes in the gene expression profile of a cell that are not caused by changes in the nucleotide sequence of the DNA. There are four main epigenetic components: DNA methylation, histone modification and chromatin remodeling as well as non-coding RNA-mediated modifications. Out of these, DNA methylation is the most widely investigated and best understood component, followed by a recent increase in interest to determine the role of small non-coding RNAs, such as microRNAs (miRNAs), in health and disease.

Transgenerational epigenetic inheritance can be broadly defined as the transfer of epigenetic information across generations. It has been textbook knowledge for decades that the DNA sequence is the only heritable component that defines a phenotype; however, strong evidence now suggests a pivotal involvement of epigenetic components in determining phenotypic inheritance (Bruxner and Whitelaw, 2008). Despite a recent surge of interest in transgenerational epigenetic responses, the nature of these heritable effects remains controversial (Kovalchuk, 2012). A considerable variety of existing definitions of epigenetics itself as well as the definition of transgenerational epigenetic changes makes it difficult to provide a comprehensive summary of current advances in the field. The current review will use the terminology proposed by Crews (2008) and Kovalchuk (2012) that are described below.

Crews (2008) suggested the classification of epigenetic changes into heritable and context-dependent modifications. Heritable (meiotic, across generation) epigenetic modifications are those that occur in the germline, whereas context-dependent (mitotic, within generation) changes occur in somatic cells and persist only for the duration of the lifetime of an organism (Crews, 2008). It was aptly noted by Crews (2008) and Skinner (2008) that there are two critical criteria required to demonstrate the germline-dependent epigenetic inheritance of the observed alteration in the phenotype.

The first criterion is the exposure of one generation to an (usually adverse) event that was never again repeated in subsequent generations and the number of generations that passed since that exposure (Crews, 2008; Skinner, 2008). Accordingly, the second criterion is a minimum of two generations in case of male exposure or three generations in case of female exposure to claim truly transgenerational inheritance (Skinner, 2008). Thus, it is worth noting that intergenerational changes seen in the F1 and F2 generations are not necessarily heritable, since some of the modifications found in the subsequent generations may be attributed to the direct effects of germline exposure.

At the same time, as noted by Kovalchuk (2012), transgenerational variations are not always epigenetic in nature. For example, the accumulation of proteins and metabolites in the cytoplasm of maternal gametes in response to stress may have a profound effect on the development and cellular functions of the organism and the ultimate phenotype of the offspring. These transgenerational effects, however, are hardly epigenetic in nature (Kovalchuk, 2012). In the current review we will use the definition proposed by Kovalchuk (2012), noting that transgenerational epigenetic inheritance is a transfer of the phenotypic appearance as a result of the transfer of epigenetic marks that are solely responsible for the observed phenotypic changes.

Some examples of transgenerational epigenetic inheritance have been described in different organisms, including plants, worms, fruit flies, and rodents. For example, in plants transgenerational epigenetic inheritance was demonstrated for flower symmetry in *Linaria vulgaris* (Cubas et al., 1999), for flower color in maize (Brink, 1956; Woodhouse et al., 2006), and in stress tolerance and changes in genome stability in *Arabidopsis* and tobacco exposed to various abiotic and biotic stressors (Boyko et al., 2010, 2007; Kathiria et al., 2010; Kovalchuk and Kovalchuk, 2003; Luna et al., 2012; Rasmann et al., 2012; Slaughter et al., 2012). Furthermore, in the nematode *Caenorhabditis elegans*, transgenerational epigenetic effects were described with regard to sterility (Katz et al., 2009) as well as longevity (Greer et al., 2011), and in *Drosophila melanogaster* with regard to eye color (Cavalli and Paro, 1998, 1999) as well as heat stress response (Seong et al., 2011).

In mammals, evidence of transgenerational epigenetic changes was reported for the coat color in mice (Blewitt et al., 2006; Morgan et al., 1999), and in rats with regard to the effects of endocrine disruptors during pregnancy on spermatogenesis and subfertility in males (Anway et al., 2005; Skinner et al., 2013). Effects of chemical endocrine disruptors on F1-F3 generations were also demonstrated in female rats, where vinclozolin exposure during gonadal sex determination led to the transgenerational increase in pregnancy abnormalities and female adult onset of diseases (Nilsson et al., 2008). However, these examples of transgenerational epigenetic effects are just the tip of the iceberg and we do not have a comprehensive understanding of the mechanisms of this heritable phenomenon yet. Data on humans are very limited at this time. Only a few epidemiological studies highlighted the possibility of transgenerational epigenetic changes, including the Överkalix study (Kaati et al., 2002) and the Dutch Famine Cohort studies (Heijmans et al., 2008; Kaati et al., 2002). The above mentioned examples of transgenerational epigenetic changes and inheritance will be discussed in more detail below.

3. Epigenetic reprogramming during mammalian embryonic development

Most of the current knowledge about epigenetic reprogramming during embryonic development in mammals stems from work using mice (Dean et al., 2001). In this context, epigenetic reprogramming refers to the erasure of DNA methylation marks and histone modifications (Guibert et al., 2012; Hajkova et al., 2002, 2008; Popp et al., 2010; Yamazaki et al., 2003). Mouse studies revealed at least two global genome-wide epigenetic reprogramming events during mammalian development [reviewed in Migicovsky and Kovalchuk, 2011; Seisenberger et al., 2013]. The first event occurs between embryonic day E7.25 and E13.5 in mouse primordial germ cells (PGCs) after they reach the embryonic gonads (Ginsburg et al., 1990; Hemberger et al., 2009; Seisenberger et al., 2012; Seki et al., 2005, 2007; Surani, 1998). The recent study by Seisenberger et al. (2012) identified two specific phases of demethylation in the mouse PGCs: at first global demethylation occurs early during migration of PGCs, when methylation of specific regions is actively maintained, whereas the second demethylation event occurs upon entry of PGCs into the genital ridges (Seisenberger et al., 2012). The following wave of remethylation is sex-specific. It begins on E14.5 in prospermatogonia in male germ cells, and after birth in growing oocytes in females (Davis et al., 2000; Hajkova et al., 2008; Li et al., 2004; Ueda et al., 2000). The second reprogramming event starts in the zygote immediately after fertilization and extends to the morula stage of preimplantation development in the early embryo (Mayer et al., 2000; Oswald et al., 2000; Smith et al., 2012). Both, germ cells and zygote, require epigenetic reprogramming that ensures erasure of DNA methylation and histone modifications to restore their totipotency (Surani et al., 2007). Around the implantation period both maternal and paternal genomes undergo a wave of *de novo* methylation (Borgel et al., 2010; Howlett and Reik, 1991; Monk et al., 1987; Sanford et al., 1987). Interestingly, mouse mutants with inactivated *de novo* methyltransferases Dnmt3a and Dnmt3b die at postimplantation stages or early after birth (Okano et al., 1999). This observation highlights that appropriate functioning of DNA methylation mechanisms is vitally important for proper mammalian development, particularly during early postimplantation embryonic stages.

Some epigenetic marks, however, may escape the reprogramming process, including imprinted genes [reviewed in Bartolomei, 2009] and some regulatory elements (Borgel et al., 2010; Hackett et al., 2013; Smallwood et al., 2011), resulting in transgenerational epigenetic inheritance and novel phenotypic traits. For example, work by Hackett et al. (2013) suggested that transgenerational epigenetic inheritance may result from the ability of rare regulatory elements (identified in the study) to escape the DNA demethylation in primordial germ cells. In this study the authors identified 11 cpG islands that escaped 5mC reprogramming in E13.5 PGCs (Hackett et al., 2013). The whole-genome bisulfite sequencing of the mouse PGCs revealed that 4730 loci escaped demethylation. Most of the loci that escaped demethylation were associated with repeats and corresponded predominantly to intracisternal-A-particles or telomeric regions (Hackett et al., 2013). Based on these findings, the authors suggest that by evading both reprogramming events during embryonic development these 5mC epialleles may be inherited over multiple generations (Hackett et al., 2013), but their potential functional role still needs to be investigated.

4. Transgenerational epigenetic changes in mammals

Despite the occurrence of genome-wide epigenetic reprogramming during both gametogenesis and embryogenesis in mammals, several incidents of epigenetic inheritance were shown for a small number of genes in mice (Herman et al., 2003; Morgan et al., 1999; Rakyan et al., 2003; Rassoulzadegan et al., 2006). One of the strongest pieces of evidence of transgenerational epigenetic inheritance was demonstrated in a classic study using agouti mice (Morgan et al., 1999). Other well established experimental work using animal models dealt with the transgenerational effects of endocrine disruptors (Anway et al., 2005, 2006a, 2006b; Anway and

Skinner, 2008; Crews et al., 2007) and stress (Franklin et al., 2010). These studies and related evidence derived from human cohorts will be discussed in the following sections.

4.1. Metastable epialleles in mice

Using an agouti mouse model, Morgan and colleagues provided a classic example of transgenerational epigenetic inheritance in mammals (Morgan et al., 1999; Rakyan et al., 2003). In their studies the authors examined the metastable epialleles among genetically identical mice. Metastable epialleles are alleles that may be differentially expressed in genetically identical individuals due to the different epigenetic state of the loci (Rakyan et al., 2002). Examples of such alleles include the *agouti viable yellow* (A^{vy}) and *axin fused* ($Axin^{Fu}$). Both epialleles contain an intracisternal A particle (IAP) transposable element that regulates the expression of linked genes *via* changes in the methylation status of a cryptic promoter in the IAP long terminal repeat (Youngson and Whitelaw, 2008). A^{vy} alleles are caused by the insertion of an IAP element 100 kb upstream of agouti coding sequences (Duhl et al., 1994). Mutations at the agouti gene are also associated with adult-onset obesity, diabetes, and tumorigenesis (Miltenberger et al., 1997; Morgan et al., 1999). The level of CpG methylation in the A^{vy} IAP promoter region correlates inversely with the ectopic expression of agouti protein, resulting in considerable individual variation in the coat color of isogenic A^{vy}/a mice (Morgan et al., 1999). The variation in the fur color ranges from dark-brown pseudoagouti (methylated) to yellow (unmethylated) in A^{vy} isogenic mice. Interestingly, IAPs are largely resistant to DNA methylation reprogramming during early embryogenesis, thus enabling heritable epimutations of neighboring genes (Lane et al., 2003). Similarly, in $Axin^{Fu}$ isogenic mice the phenotypic variability correlates with the differential methylation state of an IAP sequence at the *Axin* locus, where hypomethylation is associated with an aberrant "kinky tail" phenotype (Rakyan et al., 2003).

4.2. "Paramutation-like" effects in mice and the role of sperm RNA in transgenerational epigenetic inheritance

Paramutation is a pattern of inheritance that contradicts the classical Mendelian laws and results in heritable changes in gene expression that occur upon allelic interactions. This phenomenon is well documented in plant research (Bateson and Pellew, 1915; Brink, 1958; Meyer et al., 1993; Sidorenko and Peterson, 2001). Intriguingly, cases of paramutation-like effects have also been reported in mouse studies (Cuzin and Rassoulzadegan, 2010; Grandjean et al., 2009; Herman et al., 2003; Kiani et al., 2013; Rassoulzadegan et al., 2006; Wagner et al., 2008). The first insights into this phenomenon in mice were provided in a study by Rassoulzadegan et al. (2006), in which the authors observed an interallelic cross-talk at the *Kit* gene. *Kit* mouse mutants created by lacZ cassette insertion display obliterated production of the KIT protein. Null mutants of the *Kit* gene are lethal in the homozygous state and die shortly after birth, whereas heterozygous mice are characterized by white feet and a white tail tip (Rassoulzadegan et al., 2006). Interestingly, the progeny of intercrosses between heterozygotes or crosses with wild-type animals showed a reduced number of offspring with wild-type phenotype than was expected according to Mendelian inheritance. Closer molecular analysis revealed that some mice that displayed the mutant phenotype were in fact genetically wild-type at the *Kit* locus, thus displaying a paramutation-like effect (Rassoulzadegan et al., 2006). Their phenotype was termed *Kit**.

Interestingly, *Kit** mice transmitted their mutant-type phenotype to the progeny (Rassoulzadegan et al., 2006). The number of *Kit* transcripts in these animals was reduced on a posttranscriptional level, however, the rate of transcription was elevated in both somatic and germ cells. Microinjections of RNA from somatic and germ cells of heterozygotic mice to the wild-type one-cell embryo increased the frequency of the heritable white tail phenotype, whereas wild-type RNA injections of the control embryos showed the mutant phenotype at a low efficacy with inefficient transmission to the progeny (Rassoulzadegan et al., 2006). Moreover, the injection of two miRNAs (miR-221 and -222) that are partially complementary to the *Kit* RNA was also able to induce the paramutated state in contrast to injection of the variety of other miRNAs tested (Cuzin et al., 2008; Rassoulzadegan et al., 2006).

In a subsequent study by the Rassoulzadegan laboratory, the authors were able to demonstrate another paramutation-like effect by injecting fertilized mouse eggs with RNAs targeting Cdk9 (a key regulator of cardiac growth), inducing cardiac hypertrophy (Wagner et al., 2008). Microinjections of miR-1 or fragments of the Cdk9 coding regions induced elevated expression of homologous RNA. Interestingly, cardiac hypertrophy in miR-1 injected mice was not caused by the down-regulation of the miRNA, since no significant changes in the miR-1 expression were observed in embryonic hearts. The observed paramutation-like effect was heritable and correlated with miR-1 presence in the sperm nucleus (Wagner et al., 2008). Cardiac hypertrophy was inherited in crosses of either male or female miR-1-injected parents with normal partners. The crosses generated progenies with enlarged hearts in about 90% of the cases across at least three generations (Wagner et al., 2008). Thus, the above mentioned experiments highlight the possibility that sperm RNA is a candidate signal responsible for paternal inheritance.

Further research provided evidence supporting the role of sperm RNA, including miRNAs as a transgenerational signal (Grandjean et al., 2009). This time researchers from the Rassoulzadegan group injected miR-124 into fertilized eggs that increased the size of the mouse pups born by 30%. It is important to note that miR-124 is a brain-specific miRNA that is important for central nervous system development (Cao et al., 2007; Makeyev et al., 2007; Visvanathan et al., 2007). The observed "giant" phenotype was maintained into adulthood and was transmitted to the second generation, whereas the F3 progeny of crosses between miR-124-injected animals with wild-type partners displayed the normal average weight. Similarly to the previous studies, the paramutant phenotype was not associated with the altered miR-124 expression, since its copy numbers returned to the levels of the control animals shortly after the microinjections (Grandjean et al., 2009). Thus, the authors suggested that it is more likely that the induced phenotype is a result of initial exposure of the fertilized eggs to the RNA with sequence homology to the targeted transcript rather than the result of the permanent alteration in miRNA expression (Grandjean et al., 2009). Indeed, the authors found that transcripts from the loci with sequence similarities to miR-124, such as *Sox9*, *LamC1*, and *Acaa2*, were significantly up-regulated in embryos developing from miR-124-injected eggs.

Grandjean et al. (2009) also demonstrated that miR-124 injections into eggs induced permanent heritable changes to the chromatin structure at the *Sox9* promoter region. On day E6.5 of development, miR-124 injection into fertilized eggs caused an increase in the methylated forms of histone H3 (H3K9me2 and me3) (Grandjean et al., 2009). Finally, a recent study by Kiani et al. (2013) demonstrated that the expression of the Dnmt2 RNA methyltransferase is required for the establishment and hereditary maintenance of paramutation-like effects at both *Sox9* and *Kit* loci (Kiani et al., 2013). The authors reported that *Sox9* paramutation was not established in $Dnmt2^{-/-}$ embryos. Similarly, the injection of the RNA from the brains and testes of Dnmt2-deficient *Kit* heterozygotes was not able to induce the paramutant *Kit* phenotype.

4.2.1. Implication of sperm RNA in transgenerational inheritance of stressful experiences

The role of sperm RNA in transgenerational inheritance was recently demonstrated in mice subjected to traumatic stress (Gapp et al., 2014). Using a mouse model of unpredictable maternal separation combined with unpredictable maternal stress, Gapp et al. (2014) showed that traumatic stress in early life altered mouse miRNA expression in sperm, serum and brain, as well as behavioral and metabolic responses in the progeny. MiRNA and piRNA profiles of sperm from F1 males subjected to early life stress were altered. MiRNAs were also affected in serum, hippocampus and hypothalamus of stressed F1 and F2 animals, but not in F2 sperm (Gapp et al., 2014). Interestingly, miRNA profiles were normal in the F3 generation. Microinjection of sperm RNAs from stressed males into fertilized wild-type oocytes produced similar behavioral and metabolic alterations in the progeny (Gapp et al., 2014).

The important role of sperm miRNAs in HPA stress axis regulation was previously demonstrated by Rodgers et al. (2013). Six weeks of chronic stress exposure of male mice before breeding caused reduced HPA stress axis response in the offspring accompanied by the alteration of miRNA profiling in paternal sperm (Rodgers et al., 2013). Another recent study examined transgenerational effects of stressful experiences (Dias and Ressler, 2014). In this study the parental generation (F0) of male mice was subjected to odor fear conditioning before conception and subsequent F1 and F2 generations were investigated. The results showed that subsequently conceived generations displayed F0-like behavioral sensitivity toward the F0-conditioned odor. Moreover, bisulfite sequencing of olfactory receptor genes in the sperm DNA from conditioned F0 and naive F1 males showed CpG hypomethylation in the *Olfr151* gene. Thus, these studies highlight the importance of stress and ancestral experience before conception for the well-being of the future offspring, as well as the intriguing role of sperm RNA in transgenerational inheritance.

4.3. Transgenerational non-genetic effects

The transmission of a specific phenotype to subsequent generations has been studied since the early 1980s. A line of research by Kahn (1970, 1982) began with a study in a mouse model, which demonstrated that restricted air circulation during adulthood prior to mating causes altered blood hemoglobin concentrations in the female but not in the male offspring (Kahn, 1970). A follow-up study reported transgenerational transmission of changes in hemoglobin concentration in response to an adverse prenatal environment (Kahn, 1982). Gestational females were kept either in poorly ventilated cages or provided with a diluted yeast RNA in their drinking water (Kahn, 1982). Experimental and control lines were then studied for three successive generations. Their results showed that hemoglobin concentration were significantly higher in F1 generation experimental animals than in control animals, whereas F2 and F3 progenies of experimental animals exhibited decreased levels of hemoglobin in comparison to controls (Kahn, 1982).

Further evidence of non-genetic transgenerational effects derived from a study by Huck et al. in 1987. Using a hamster model the authors investigated the long-lasting consequences of food restriction during the first 50 days of life on sex ratios and offspring growth trajectories in subsequent generations (Huck et al., 1987). Intriguingly, they showed that food-restriction in F1 females resulted in significantly restricted growth and smaller litters in the F3 generation by the age of 5–25 days compared to control litters fed an *ad libitum* diet. Moreover, the sex ratio in the F3 generation offspring that descended from food-restricted females was altered, with a significantly lower percentage of males per litter. In summary, these reports of inherited phenotypic traits suggest the existence of transgenerational non-genetic effects that may be transmitted *via* the gametes.

4.4. Transgenerational effects of endocrine disruptors

Exceptional examples of transgenerational epigenetic inheritance have been reported in studies involving endocrine disruptors in rats. It is widely accepted that endocrine-disrupting chemicals can alter molecular epigenetic regulation, including DNA methylation and histone modifications. As defined in a Statement of Principles by *The Endocrine Society*, an endocrine-disrupting chemical (EDC) is "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" (Zoeller et al., 2012). There is a substantial body of evidence of transgenerational epigenetic effects induced by EDCs, such as vinclozolin, diethylstilbesterol, bisphenol A, and polychlorinated biphenyls, in mammals (Walker and Gore, 2011). Compelling examples of disturbing actions of EDCs on future generations *via* epigenetic perturbations are reviewed in Walker and Gore (2011), and the potential evolutional impact is discussed by Crews and Gore (2012) (Crews and Gore, 2012; Walker and Gore, 2011).

The laboratory of Michael Skinner has extensively studied the transgenerational epigenetic effects in response to prenatal exposure to different endocrine disruptors, such as fungicides, pesticides, and other environmental toxins (Anway et al., 2005, 2006a, 2006b; Anway and Skinner, 2008; Crews et al., 2007). The authors found that prenatal exposure to vinclozolin, a common dicarboximide fungicide, produced wide-ranging adverse health effects in both male and female offspring. In males, for example, it led to a number of adult disorders, including reproductive abnormalities, cancer, prostate and kidney diseases (Anway et al., 2006a). Among effects on female offspring, the authors found an association between prenatal exposure to endocrine disruptors and the onset of ovarian diseases later in life across multiple generations (Nilsson et al., 2012). In these studies, the F0 generation of gestating female rats was exposed to different EDCs during embryonic gonadal sex determination. Ovarian diseases were then assessed in the F1 and F3 progeny (Nilsson et al., 2012). Interestingly, both the F1 and F3 generations of offspring displayed ovarian disease phenotypes, including an increase in cysts resembling human polycystic ovarian disease (PCO) and a decrease in the ovarian primordial follicle pool size resembling primary ovarian insufficiency (POI) (Nilsson et al., 2012). Moreover, this group of researchers reported differences in mRNA expression and DNA methylation in the granulosa cells in F3 generation progeny of EDC-exposed animals as compared to controls (Nilsson et al., 2012). Since F3 generation animals were not exposed to EDC, changes in their epigenome likely represent a truly transgenerational effect.

4.5. Transgenerational effects of stress

Stress may be able to induce phenotypic epigenetic changes across multiple generations similar to those seen in environmental toxicant studies (Skinner, 2014). The laboratory of Mansuy and colleagues studied the effects of chronic and unpredictable maternal separation in early life on the F2 and F3 offspring (Franklin et al., 2010). F1 offspring were exposed to chronic and unpredictable maternal separation from postnatal day 1 to 14. Subsequently, adult F1 male offspring (both stressed and control) were bred with wild-type females to produce the F2 generation. Adult F2 offspring (both stressed and control lineage) were bred with wild-type females to produce the F3 generation. Therefore the actual stress exposure occurred in the F1 generation only. This experimental design allowed the authors to assess the impact of the stress exposure during early life on the subsequent F2 and F3 generation offspring. The authors observed a depressive-like phenotype

in the F1 male offspring that were subjected to stress in early life in comparison to controls, but not in F1 females. Interestingly, similar behavioral traits were observed in F2 female but not F2 male offspring. Strikingly, F3 male offspring expressed similar symptoms of depression as F1 males. These results suggest that depressive-like symptoms can be transmitted across generations in a complex and sex-specific mode (Franklin et al., 2010). Moreover, this study reported that chronic and unpredictable maternal separation alters the DNA methylation profile in the promoter of several candidate genes in the germline of stressed males, thus propagating to the F3 generation. Some of these changes were also present in the brains of F1 offspring (Franklin et al., 2010).

In addition, our recent study demonstrated that prenatal stress increases the risk of shortened gestational length that is present across multiple generations of rats (Yao et al., 2014). Pregnant dams of the parental generation (F0) were exposed to stress from gestational days 12 to 18. Their pregnant daughters (F1) and grand-daughters (F2) were either stressed or remained non-stressed. Both of the stress-treated lineages (stress only in the F0 generation or across all generations) showed gradually reduced gestational length, maternal weight gain and maternal behavioral activity across subsequent generations. Moreover, a family history of stress impaired offspring sensorimotor development with the most severe impairments occurring in the F3 generation. The behavioral and physiological changes in these animals were accompanied by altered miRNA expression in the brain and uterus of F2 mothers (Yao et al., 2014). Altered miRNA expression included the miR-200 family, such as upregulation of miR-200b and downregulation of miR-429 (Yao et al., 2014), both of which were suggested to modulate gestational length through interaction with their gene targets (Renthal et al., 2010). The findings by Yao et al. (2014) suggest that recognizable epigenetic signatures of preterm birth, behavior and physiology are programmed through the maternal lineage.

4.6. Transgenerational effects of diet in mice

Another potentially adverse experience with associated epigenetic changes involves the experimental variation of dietary regimens. A series of classic studies have demonstrated that dietary components can modulate DNA methylation patterns related to obesity. The agouti viable yellow mouse model (discussed in Section 4.1) allows researchers to investigate the impact of environmental and dietary influences on the fetal epigenome (Dolinoy, 2008). It has been shown that diet-induced hypermethylation during development can rescue an obese phenotype in agouti mice (Cooney et al., 2002; Waterland et al., 2008; Wolff et al., 1998). To verify transgenerational inheritance of induced epigenetic variation, Waterland et al. (2007) examined three generations offspring that were weaned on either a methyl-supplemented or a control diet (Waterland et al., 2007). Their results showed that in the methyl-donors-supplemented groups coat colors were darker than in controls, however, no cumulative effects of supplementation across successive generations were observed. Thus, the authors concluded that diet-induced hypermethylation at agouti viable yellow is not inherited transgenerationally through the female germ-line (Waterland et al., 2007).

Interesting evidence of transgenerational inheritance in mice was demonstrated by the Bale laboratory (Dunn and Bale, 2009, 2011). In these studies the authors reported that maternal high-fat diet exposure led to increased body size and reduced insulin sensitivity that persisted to the F2 generation *via* both maternal and paternal lineages (Dunn and Bale, 2009). To verify a robust heritable transgenerational epigenetic effect, Dunn and Bale analyzed the F3 generation (Dunn and Bale, 2011). Interestingly, their results revealed no alterations in insulin sensitivity in the F3 offspring, and transgenerational inheritance of the increased body size phenotype was observed in females only. Intriguingly, these effects were transmitted *via* the paternal lineage, suggesting involvement of genomic imprinting (Dunn and Bale, 2011). Analysis of the expression of imprinted genes, involved in growth, in the livers of F3 females derived from the paternal lineage revealed a trend toward greater volatility (greater than 50% deviation from baseline in either direction) of expression than those of the maternal lineage (Dunn and Bale, 2011). These findings provide evidence of sex-specific transgenerational programming of phenotypic traits, such as growth and body size, being likely due to epigenetic modifications (*e.g.* a stable epigenetic mark in the paternal gametes) rather than genetic changes. The potential role of imprinted genes in this sex-specific epigenetic programming requires further investigation.

4.7. Transgenerational epigenetic inheritance in humans

Despite the intriguing examples of transgenerational epigenetic inheritance in rodents, the idea that epigenetic marks can be inherited in humans remains controversial. To date several studies reported heritable germline epimutations in humans (Buiting et al., 2003; Chan et al., 2006; Hitchins et al., 2007; Suter et al., 2004). However, it still needs to be verified whether the described cases of epimutations are causally related to transgenerational inheritance, since heritable germline epimutations differ from transgenerational epigenetic inheritance (Chong et al., 2007; Horsthemke, 2007). Heritable epimutations (aberrant methylation marks observed in more than one generation) may not necessarily be the result of transgenerational epigenetic inheritance, since atypical methylated states can be erased during gametogenesis and then re-established in the zygote as a result of a change in the DNA sequence (Chong et al., 2007; Horsthemke, 2007). Work from two epidemiological cohorts, described below, suggests, however, the intriguing possibility of transgenerational epigenetic inheritance.

4.7.1. The Dutch Famine Cohort Study

The Dutch Famine or “Hunger Winter” took place in 1944–1945 in a part of the Netherlands that was occupied by Germany. As a result of the German blockade access to food supplies in the occupied part of the country was extremely limited and millions of people were unable to maintain adequate nutrition during unusually harsh winter conditions. Daily adult rations ranged from 580 to 1000 kilocalories per day. The Dutch Famine Birth Cohort was created to include affected mothers and fathers and their children to form a systematic study of the effects of perinatal undernutrition. This cohort has been extensively studied and multiple consequences of famine exposure were reported in perinatal epidemiology. For example, it was shown that children of pregnant women exposed to the famine during pregnancy were more susceptible to coronary heart disease, diabetes, obesity, microalbuminuria and accelerated cognitive aging (Painter et al., 2006, 2005a, 2005b; Ravelli et al., 1999; Roseboom et al., 2001). The effects of prenatal undernutrition on adult health, however, significantly depended on the timing of exposure during gestation (Roseboom et al., 2001).

The mechanisms of the observed phenotypic changes are yet to be clarified, however, it is likely that epigenetic regulation is involved. Heijmans et al. (2008) investigated the changes in the DNA methylation in the offspring of the mothers who were exposed to the Dutch Famine. Their results showed that individuals that were conceived during the Dutch Hunger Winter had less DNA methylation of the imprinted IGF2 gene compared with their unexposed, same-sex siblings 60 years later (Heijmans et al., 2008). No such changes in DNA methylation were found in individuals who were exposed while being *in utero* later during gestational periods. This study suggests that potentially heritable DNA imprinting

caused by periconceptional exposure to undernutrition has potential consequences for health in late adulthood. Another human study that is discussed below highlights the possibility that even grandparents' exposure to an adverse environment and nutritional resources may influence their grandchildren through epigenetic modifications.

4.7.2. The Överkalix Cohort Study

Another unique historical cohort is investigated by the Överkalix studies. Överkalix is a small isolated municipality in Sweden that has an extensive set of historical records about its population, which includes the information on food availability during different years, land ownership, causes of death, *etc.* Taking advantage of the Överkalix historical records on harvests and food prices, Bygren and colleagues investigated whether food availability during a child's slow growth period (SGP) can influence the descendants' longevity as well as risk of death from cardiovascular disease and diabetes (Bygren et al., 2001; Kaati et al., 2002). Their results suggest that paternal grandfathers' overeating during the SPG increases the likelihood of grandchildren's death from diabetes by four-fold (Kaati et al., 2002). Interestingly, if a father experienced poor food availability or a famine during his SGP then his son was protected against cardiovascular death (Kaati et al., 2002).

This group of researchers also investigated an association between longevity and food availability during the grandparents' SGP (Bygren et al., 2001). In their study data from children of different ages from the Överkalix cohort were analyzed, including the ages of 0–2 years for girls and boys, 3–7 years for girls, 3–8 years for boys, 11–15 years for girls, and 13–16 years for boys. Notably, food availability during the prepubertal period only appeared to have a profound effect on the grandchildren longevity, skipping the generation of children (Bygren et al., 2001). The survival of the grandchildren was shortened by 16.5 ± 6 years if there was a surfeit of food in the environment during their grandfathers' SGP (when he was 9–12 years old). Good and poor food availability had the opposite effects on grandchild survival in contrast to moderate food supply that had no effect. There were no significant effects of food availability during parental or grandmothers' SGPs or other age periods (Bygren et al., 2001). Despite this convincing evidence from human cohorts, the mechanisms and stability of epigenetic inheritance of complex phenotypes in experimental studies is still being discussed (Berger, 2012).

5. Fetal programming

The concept of fetal origins of adult disease or fetal programming was developed by David Barker and colleagues based on the observation that a low birth weight increases the risks of cardiovascular disease and type 2 diabetes in later life (Barker et al., 1993). This concept proposes that fetal adaptations to the intrauterine and maternal environments shape the structure and function of organs, leading to permanent physiological alterations in adulthood (Swanson et al., 2009). Therefore, this approach suggests that the predisposition to diseases in adulthood is "programmed" *in utero*. Barker's early observation about the role of the fetal environment in the future development of cardiovascular disease has since been extended to other diseases, including conditions affecting the brain, such as psychiatric disorders. For example, evidence from epidemiological studies related maternal psychological stress caused by bereavement, unwanted pregnancies, military invasions and natural disasters to an elevated risk for the offspring to develop schizophrenia later in life (Huttunen and Niskanen, 1978; Khashan et al., 2008, 2011; Kinney et al., 1999; Myhrman et al., 1996; Selten et al., 1999; van Os and Selten, 1998). Yet the molecular mechanisms of fetal programming remain poorly understood. Over the past two decades, epigenetic studies have become a promising field in revealing the mystery of fetal programming. Many of epigenetic differences arise during development and remain stable throughout life. For example, it has been shown that environmental influences during early postnatal life can cause DNA methylation changes in the promoter regions of glucocorticoid receptors, one of the two receptor types for glucocorticoids, the main stress hormones, in the brain (McGowan et al., 2009; Weaver et al., 2004). Accordingly, maternal stress during pregnancy may critically influence the density of glucocorticoid receptors in areas of the fetal brain, particularly the hippocampus, and permanently alter the sensitivity to stress throughout life (McGowan et al., 2009; Weaver et al., 2004) arguably through epigenetic mechanisms involving DNA methylation and miRNA expression (Babenko et al., 2012a; Weaver et al., 2004).

It is important to note that these studies present the challenge of dissociating the environmental effects *per se* from a potential genetic predisposition of an individual to certain diseases. For example, gene–environment interactions that occur when adverse environmental factors synergistically interact with a certain genetic predisposition, may in fact account for a significant fraction of psychiatric disease cases (Caspi and Moffitt, 2006). According to the hypothesis of genetic moderation, differences between individuals that derive from differences in the DNA sequence promote individual variation in the response to environmental conditions (Caspi and Moffitt, 2006). This should be taken into consideration when studying fetal or early-life programming aspects, since there is substantial evidence for the role of gene–environment interactions in determining stress sensitivity in both human (Caspi et al., 2002, 2003; Kim-Cohen et al., 2006) and animal studies (Ayhan et al., 2009; Barr et al., 2004; Oliver and Davies, 2009).

5.1. MicroRNAs (miRNA) are important epigenetic regulators of brain development

MiRNAs are small non-coding RNAs approximately 22 nucleotides long that function as regulators of gene expression at the transcriptional and post-transcriptional levels. Despite the fact that miRNAs were first discovered in the early nineties, their role in the nervous system only recently started to be appreciated. During the past decade, growing evidence demonstrated the essential role of miRNAs in neuronal development and neuronal function (Krichevsky et al., 2003; Schratt et al., 2006) (reviewed in Sun et al., 2013). For example, microRNA expression patterns were studied during brain development in specific cell populations, including neurons (Kim et al., 2004; Kye et al., 2007), oligodendrocytes (Lau et al., 2008; Letzen et al., 2010), astrocytes (Smirnova et al., 2005), and microglia (Ponomarev et al., 2011). In addition to these studies performed in rodents and cell cultures, a recent report by Moreau et al. (2013) measured miRNA expression in the developing human brain. Their expression profiling revealed distinct temporal expression patterns of miRNAs in post-mortem brain tissues representing gestational ages 12–24 weeks, as well as early postnatal and adult time points (Moreau et al., 2013).

Despite the recent interest in neuronal miRNA expression the understanding of exact miRNA functions in the healthy and injured nervous system is far from being complete. The fact that single microRNA can modulate the expression of multiple genes adds an additional level of complexity to the unambiguous identification of the role of a specific miRNA in the brain. The current agreement in the literature suggests the function of miRNA in fine-tuning gene expression. Compared to transcriptional repressors, miRNAs can influence target protein levels more rapidly at the post-transcriptional level (Tsang et al., 2007). Interestingly, it was demonstrated that miRNAs control *de novo* DNA methylation

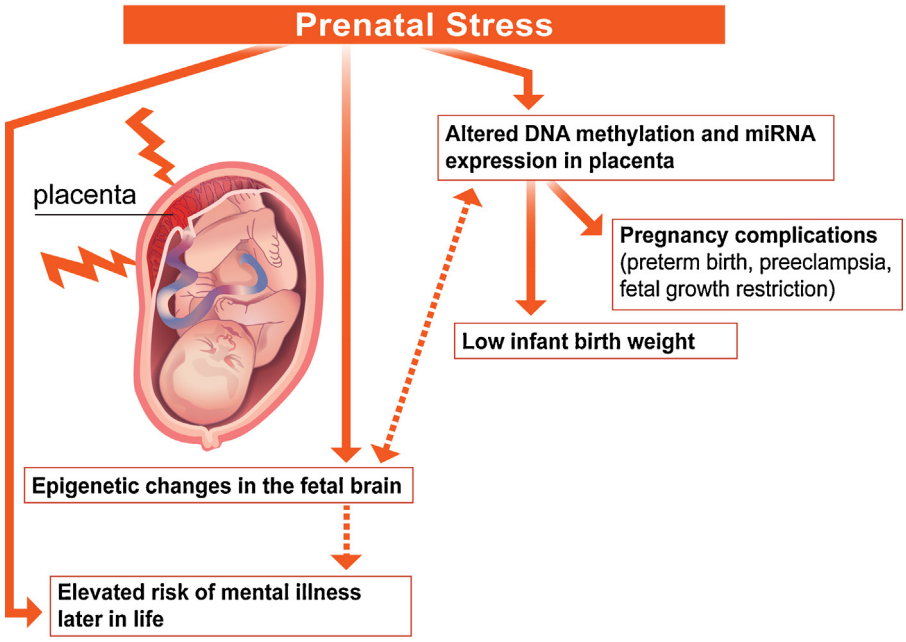

Fig. 1. Association between prenatal stress and mental health. Proper functioning of miRNA and DNA methylation mechanisms are required for normal placental and brain development. Human studies showed that alteration in these epigenetic mechanisms are associated with pregnancy complications and low infant birth weight. Animal studies demonstrated that stress can induce epigenetic changes in placenta and brain. Whether stress-induced epigenetic changes in the placenta and fetal brain are causally linked to the risk of mental illness later in life is yet to be verified.

in mouse embryonic stem cells through regulation of transcriptional repressors (Sinkkonen et al., 2008). On the other hand, it was also shown that post-mitotic neural development and dendritic morphogenesis is regulated by miRNAs *via* switching of chromatin-remodeling complexes (Yoo et al., 2009). Thus, miRNAs may be involved in different levels of epigenetic regulation.

5.2. *miRNAs in placenta*

The placenta is a vital transient organ that connects the developing fetus to the maternal uterine wall. It participates in the exchange of gases, nutrients, hormones and waste between embryonic and maternal environments, and it serves important endocrine and protective functions. Pathological processes in the placenta are frequently associated with complications during pregnancy, including preterm birth, preeclampsia, and fetal growth restriction (Faye-Petersen, 2008; Huppertz, 2011) (Fig. 1). The role of miRNAs in regulating placental-specific gene expression in normal and pathological conditions is not clear. Increasing evidence suggests that miRNAs are important regulators of placental development, however, their role in the placental stress response have not been sufficiently studied. Abnormal miRNA expression in placenta has been reported in compromised pregnancies (Fu et al., 2013; Mouillet et al., 2011). Previous studies particularly focused on preeclampsia, which is associated with specific miRNA signatures, such as overexpression of miR-34a in preeclamptic placentas (Doridot et al., 2014). Studies like these highlight the potential of placental miRNAs as biomarkers of pregnancy outcomes and offspring development.

5.3. *DNA methylation in the embryonic brain*

DNA methylation is one of the best characterized epigenetic modifications (recently reviewed by Smith and Meissner, 2013; Wu and Zhang, 2010). In mammals, DNA methylation occurs predominantly at CpG dinucleotides and involves a covalent addition of a methyl group to the 5-position of cytosines by enzymes called DNA methyltransferases (DNMTs). Some members of the DNMT family serve as *de novo* methyltransferases, for example DNMT3A and DNMT3B (Okano et al., 1999), while DNMT1 ensures that an established DNA methylation pattern is maintained during cell divisions (Bestor, 2000). The process of establishing and maintaining a DNA methylation pattern is complex and involves the interaction between DNMTs and methyl-CpG binding proteins (MBDs). MBDs are the proteins that read and interpret the information about methylation patterns (Newell-Price et al., 2000; Wade, 2001).

DNA methylation plays a critical role during mammalian development (Li et al., 1992). It has a variety of functions and is required for several processes, such as silencing of transposable elements and pericentromeric repeats to ensure genome integrity (Chen et al., 2004; Kaneko-Ishino and Ishino, 2010; Walsh et al., 1998; Xu et al., 1999), inactivation of X-chromosomes (Lock et al., 1987; Mohandas et al., 1981; Sado et al., 2004) and genomic imprinting (Feil and Khosla, 1999; Reik et al., 1987).

It was recently discovered that in addition to the classical DNA methylation variant (5-mC), the family of TET proteins (cytosine oxygenase enzymes) is responsible for oxidizing 5-methylcytosine into 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC), thus giving rise to other DNA methylation variants (Cadet and Wagner, 2014; Williams et al., 2012). The 5-hmC variant is now considered as a sixth DNA base and has unique properties in the brain (Nestor et al., 2012). It was shown by Nestor et al. (2012) that the levels of 5-hmC in the brain are drastically higher than those of other tissues. The biological function of 5-hmC remains unknown, however, some evidence suggests its role as an intermediate agent in the DNA demethylation processes, as well as a possible role in transcriptional regulation through modifying levels of chromatin accessibility to the transcription machinery or to the MBDs (Nestor et al., 2012; Song et al., 2011; Tahiliani et al., 2009; Valinluck et al., 2004). Cytosine hydroxymethylation is present in the germline and at fertilization, suggesting a compelling role in transgenerational epigenetic inheritance (Smith and Meissner, 2013).

A critical role of DNA methylation in embryonic development was demonstrated in experiments using mutant mice lacking DNA methyltransferases. DNMT1 mutant mice fail to develop beyond the stage characteristic of normal E9.5 embryos and die prior to E11 (Li et al., 1992). To overcome early embryonic lethality Fan et al. (2001) generated DNMT1 conditional mutants to study the particular role of this methyltransferase in the developing brain. Their approach allowed to investigate the function of DNMT1 either on E12 in the fetal neuroblasts, or after birth, in postmitotic neurons of postnatal mice (Fan et al., 2001). Their results showed that mitotic neuroblasts are sensitive to Dnmt1 deletion that caused DNA hypomethylation in daughter cells. Mouse mutants possessing 95% hypomethylated cells in the brain died immediately after birth. Interestingly, postmitotic Dnmt1 deletion did not compromise cell survival during postnatal life and did not affect the levels of global DNA methylation in postmitotic neurons (Fan et al., 2001).

Further genetic manipulation studies demonstrated that double knockout mice lacking both Dnmt1 and Dnmt3A in adult forebrain neurons have impaired synaptic plasticity, learning and memory deficits (Feng et al., 2010; Hutnick et al., 2009). Hutnick et al. (2009) produced conditional DNMT1 mouse mutants that carried about 90% of hypomethylated cortical and hippocampal cells in the dorsal forebrain starting on E13.5 onward. Those animals displayed severe cortical and hippocampal degeneration between E14.5 and three weeks postnatally (Hutnick et al., 2009). A recent study by Zhang et al. (2013) showed that Tet1 is also required for adult neurogenesis and normal cognitive functions of the mouse hippocampus (Zhang et al., 2013). Moreover, DNMT1 was recently implicated in retinal network formation during brain development (Rhee et al., 2012). Mouse mutants lacking DNMT1 in the retina displayed signs of abnormal neuronal differentiation of photoreceptors as well as rapid cell death of several types of neurons in the postnatal retina (Rhee et al., 2012).

Interestingly, in humans DNTMT1 mutations cause neurodegeneration in the form of hereditary sensory neuropathy with dementia and hearing loss (Klein et al., 2011). Mutations in another player of the DNA methylation machinery, the methyl binding protein MeCP2, were also implicated in various neurodevelopmental disorders, including severe neonatal encephalopathy, X-linked mental retardation, autism, and Rett syndrome [Goffin et al., 2012; for more details see Gonzales and LaSalle, 2010]. Despite recent insights that indicated a causal connection between epigenetic regulation and cognitive function, little is known about the underlying molecular mechanisms (Bender and Weber, 2013).

To reach further conclusions about the role of DNA methylation, Lister et al. (2013) took a genome-wide mapping approach at a single-base resolution in both human and mouse frontal cortex throughout their lifespan (Lister et al., 2013). The authors found that levels of DNA methylation in a non-CG context (mCH, where H = A, C or T) were negligible in the fetal cortex but occurred abundantly in the adult frontal cortex. In mice, rapid accumulation of DNA methylation in a non-SG context during early postnatal development was accompanied by the up-regulation of DNMT3a, suggesting that this DNA methyltransferase may be responsible for non-CG methylation (Lister et al., 2013). However, methylation at 5-hmC that is acquired in the cortex during postnatal development, occurred exclusively in the CG context. Their results also showed that of the total methylated fraction in adult human neuronal cortex, mCG accounted for ~47%, whereas non-CG context constitutes ~53%, with mCH regions being highly conserved between unrelated individuals (Lister et al., 2013). These authors also found a small number of "mCH deserts", which represent megabase-sized regions in the adult cortex that do not accumulate mCH and 5-hmC (however, mCG is not depleted in these regions) (Lister et al., 2013). Furthermore, in this study mCH deserts had lower chromatin accessibility and were enriched for large clusters of genes involved in immunity and receptors for sensory neuron function. Cell type-specific variation in methylation patterns was also observed, where mCH was accumulated in mature neurons, while adult glial cells had low mCH levels, similarly to the fetal and early postnatal brain (Lister et al., 2013). This rapid developmental increase in mCH coincided with synaptogenesis. Moreover, their analysis showed that there is a subset of genes, in both humans and mice, with greater intragenic mCH levels (but not mCG levels) in female neurons compared with males. This mCH signature corresponded to genes that escape the X-inactivation in females (Lister et al., 2013).

DNA methylation also plays an important role in cell fate determination during embryonic brain development. For example, DNA methylation was shown to be critical for astrocyte differentiation during mouse brain development (Takizawa et al., 2001). Astrocyte differentiation is activated by a transcription factor, STAT3 (Bonni et al., 1997). It was demonstrated by Takizawa et al. (2001) that the STAT3 binding region in the glial fibrillary acidic protein (GFAP) promoter is highly methylated on embryonic day 11.5, which abolishes the accessibility of STAT3 and therefore inhibits transcription activity in neuroepithelial cells (Takizawa et al., 2001). Later during mouse brain development, on embryonic day 14.5, when neuroepithelial cells differentiate into astrocytes, the same binding element in GFAP was demethylated in STAT3-responsive cells (Takizawa et al., 2001).

5.4. DNA methylation in placenta

In contrast to other tissues, the human placenta displays some unique patterns of DNA methylation (Christensen et al., 2009; Novakovic and Saffery, 2012). The placenta is known to reveal a lower global DNA methylation profile, which may be due to hypomethylation at repetitive elements (Gama-Sosa et al., 1983; Grigoriu et al., 2011; Perrin et al., 2007). Proper functioning of the DNA methylation machinery is required for normal development of placenta. The most important influence of DNA methylation in the placenta is genomic imprinting (Monk et al., 2006).

Changes in DNA methylation in the placenta are associated with low infant birth weight and several pregnancy complications, such as preterm birth, fetal growth restriction, and preeclampsia (Banister et al., 2011; Filiberto et al., 2011; Kulkarni et al., 2011). For example, a recent study showed alterations in the DNA methylation of promoter regions of cortisol-signaling and steroidogenic genes in preeclamptic placentas (Hogg et al., 2013). In placentas with early onset preeclampsia, DNA methylation was increased at CpG sites within genes encoding the glucocorticoid receptor and corticotropin releasing hormone (CRH) binding protein, and decreased within CRH in comparison to normal placental tissues (Hogg et al., 2013). It is possible that such changes may significantly affect fetal brain development.

5.5. Partially methylated domains and their role in brain and placenta

Early studies have revealed that the major portion of the human genome in most tissues is highly methylated (Ehrlich et al., 1982). However, it was demonstrated in human fetal and neuronal cell lines that there are large regions within the human genome with partially methylated domains (PMDs) that are associated with inactive chromatin and repressed transcription (Lister et al., 2009; Schroeder et al., 2011). PMDs cover up to 40% of the genome and are over 100 kb in length in the cell lines. Nevertheless, they are absent in many mature tissues, including cerebral cortex (Maunakea et al., 2010; Xin et al., 2010). Therefore, it remains an open question whether PMDs are only a mark of transient cell development stages when cells are not fully differentiated yet, or whether they also exist in mature neuronal tissues (Schroeder et al., 2011).

Intriguingly, a recent study by Schroeder et al. (2013) showed that PMDs are present not only in cultured cells and cancers, but also in normal tissues, such as full-term human placenta (Schroeder et al., 2013). Their results showed that PMDs are stable throughout gestation and between individuals and are enriched in genes with tissue-specific functions. Further functions of PMDs in the human genome are still to be verified (Schroeder et al., 2013).

5.6. Histone modifications and chromatin remodeling in the brain

Chromatin remodeling and histone modifications play a key role in the accessibility of the nucleosome to the transcription machinery, and thus in gene silencing. The level of gene expression depends on different factors, including modifications in the histone N-terminal tails by methylation, acetylation, phosphorylation, SUMOylation, ubiquitination, and ADP-ribosylation. A pivotal role of chromatin remodeling was established in the inactivation of sex chromosomes as well as in telomere clustering and DNA damage responses (Celeste et al., 2003a, 2003b; Fernandez-Capetillo et al., 2003a, 2003b).

Chromatin remodeling and histone modifications are also important factors in brain development and functioning of the nervous system. For example, they were shown to play a role in the conversion of oligodendrocyte precursors to neural stem cells, which can then generate neurons and glial cells (Kondo and Raff, 2004). In a mouse model of neurodegenerative conditions in the adult brain, increased histone acetylation by inhibition of histone deacetylases was shown to induce sprouting of dendrites, an increased synapse number, and reinstate cognitive function together with improved retrieval of long-term memories (Fischer et al., 2007). Another line of evidence supporting a pivotal role of chromatin remodeling in brain development stems from studies showing that mutations in genes that encode chromatin remodeling factors underlie different forms of X-linked mental retardation (Berube et al., 2005; Chelly and Mandel, 2001). For example, the chromatin-remodeling protein ATRX was shown to play a critical role in neuronal survival during brain development in a mouse model (Berube et al., 2005). Conditional inactivation of the *Atrx* gene in the embryonic forebrain caused significant neuronal loss during early stages (E11–E13.5) of corticogenesis (Berube et al., 2005). For further details on chromatin remodeling in neuronal development and plasticity see Ho and Crabtree (2010), Hsieh and Gage (2005), and Yoo and Crabtree (2009).

6. Stress and epigenetic regulation

6.1. Stress: general terms and definitions

Stress initiates a cascade of biochemical reactions in the body and, depending on its duration and severity, may represent a risk factor for a variety of health complications, including neurological and mental illnesses. The first definition of stress was provided by Walter Bradford Cannon in 1914. According to Cannon, stress "is the body's ability to prepare itself instantaneously to respond to physical threat" (Cannon, 1914). Yet the classical definitions of stress originate from the seminal work of Hans Selye, who introduced the concept of the General Adaptation Syndrome in 1936 (Selye, 1936). Selye defined stress as "the nonspecific response of the body to any demand made on it" (Selye, 1936). According to more contemporary stress researchers like Robert Sapolsky, the negative consequences of stress on health are related to the non-specificity of the stress response (Sapolsky, 2000). As noted by Sapolsky, in mammals the stress response evolved to cope mostly with short-term physical stressors (Sapolsky, 2000). Therefore, a chronically activated stress response to continuous psychological stressors in day-by-day life may eventually lead to stress-related disease. Effective coping with stress or stress resilience involves not only a rapid activation of physiological and behavioral responses to reinstate the homeostasis, but also an effective termination of the stress response (de Kloet et al., 2005).

The stress response can be generally defined as physiological and behavioral adaptation to the emotional or physical threats, or disrupted homeostasis, either actual or anticipated. Stress may have beneficial, harmless or harmful consequences, depending on many factors, such as duration and intensity of stress, type of stressor, and individual differences in coping with stress. In response to acute stress the paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) that activate the pituitary gland. In turn, the pituitary gland releases adrenocorticotrophic hormone (ACTH), which triggers the secretion of the glucocorticoids from the adrenal gland into the bloodstream. Excessive amounts of circulating glucocorticoids (here referred to as CORT i.e., cortisol in primates or corticosterone in most rodents) are beneficial or harmless for a short period of time. However, chronic elevation of CORT due to persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis may lead to the development of various pathological conditions including those that can damage nervous system (Brown et al., 2004). The negative effects of chronic stress are not limited to the action of the glucocorticoids. The role of CORT and other hormones and their receptors in the brain in response to stress is discussed below.

6.2. Role of stress in brain development

In contrast to the biological effects of man-made chemicals discussed previously, chronic exposure to stress hormones could be considered as a natural source of endocrine disruption. The developing brain is very sensitive to the effects of stress, especially due to the programming properties of glucocorticoids (Seckl, 1998). Intriguingly, it was shown *in vitro* using microarray analysis, that chronic CORT exposure of the fetal brain for three weeks alters the expression of 1648 mRNA transcripts (Salaria et al., 2006). This *in vitro* model supports the well accepted concept of the potential contribution of prenatal stress to the reprogramming of the HPA axis and stress response systems in the brain (Harris and Seckl, 2011).

Experiments by Henry and colleagues in the mid-nineties used rats to investigate the long-lasting effects of prenatal stress on the functioning of the HPA axis in the offspring at different ages (Henry et al., 1995). Pregnant dams were exposed to restraint stress during the third week of gestation and long-lasting outcome on the male offspring at the age of 3, 21 and 90 days was assessed. The results revealed a significant increase in plasma CORT levels in prenatally stressed offspring at the age of 3 and 21 days after exposure to a novel environment, whereas at the age of 90 days prenatally stressed rats exhibited a longer duration of CORT secretion after novelty exposure when compared to their non-stressed counterparts (Henry et al., 1995). Prenatal restraint stress exposure also resulted in the decrease of GR and MR densities in the hippocampus of 21- and 90-day old offspring (Henry et al., 1994). In another study the authors also showed that prenatal stress causes long-lasting changes in the dopamine sensitivity of the nucleus accumbens in the adult offspring (Henry et al., 1995). Thus, maternal exposure to stress during pregnancy permanently programs the offspring's stress response with potential significant effects on lifelong health trajectories.

The effects of glucocorticoids and other steroid hormones (such as mineralocorticoids, androgens, estrogens, progestrogens, *etc.*) on the brain cannot be underestimated. The brain is an important target for steroid hormones and any agent that perturbs

the delicate hormonal balance can disrupt normal brain development (McEwen, 1992; McEwen et al., 1979). The importance of steroid hormones in brain development emerges as early as their receptors appear in neurons (McEwen, 1987). Most of the brain receptors for steroid hormones belong to the nuclear receptor family and are transcription factors. As transcription factors they recruit many other proteins that are sensitive to epigenetic modifications (McCarthy et al., 2009). Thus, as highlighted by McCarthy et al. (2009), steroid hormones and their receptors in the brain represent a unique component within the complex endocrine pathways that is vulnerable to epigenetic regulation during brain development and define adult sex differences in brain and behavior (McCarthy et al., 2009). Besides their action as transcription factors steroid hormone receptors also play an important role in intracellular signaling (Blaustein, 2012).

Interestingly, the role of steroid hormone receptors is not limited to their interaction with cognate hormones (Blaustein, 2004). Many studies demonstrated that steroid hormone receptors could be activated by neurotransmitters and intracellular signaling systems in the absence of the respective hormone (Auger, 2001; Ciana et al., 2003; O'Malley et al., 1995; Olesen et al., 2005). It has been recognized since the early 1980s that neurotransmitters can regulate the density of steroid hormone receptors in the brain in response to environmental stimuli (McGinnis et al., 1985; Nock et al., 1981; Thornton et al., 1986). Thus, stressful experiences during vulnerable time periods of development, such as the prenatal period, early life or puberty can permanently modulate the brain's response to hormones. For example, experiencing shipment stress during puberty was reported to alter sexual behavior response to ovarian hormones later in adulthood in mice (Ismail et al., 2011; Laroche et al., 2009). Extensive studies in human cohorts are outlined in Section 6.5.

Notably, long-term consequences of stressful experiences in early postnatal life on hormone receptor expression were shown to be regulated by epigenetic mechanisms (Champagne et al., 2006; Weaver et al., 2004). Variations in maternal behavior were shown to be associated with differences in expression of estrogen receptors and glucocorticoid receptors in the brain of the offspring (Champagne et al., 2003; Liu et al., 1997). Changes in maternal behavior were shown to be transmitted through generations and were associated with cytosine methylation of promoter regions of hormone receptors (Champagne et al., 2006; Francis et al., 1999). Epigenetic mechanisms mediating intergenerational and transgenerational programming of maternal behavior *via* alteration in the expression of stress hormones are discussed in more detail below.

6.3. Experience-dependent programming of stress response and epigenetic marks

A classic example of an environment–epigenome interaction regulating stress responses originated from a series of studies by the laboratories of Michael Meaney and Moshe Szyf using a rat model. Together these studies highlight the importance of early-life experiences in HPA axis development with potentially lasting consequences throughout the lifetime. The authors related the phenotype of maternal care, as exemplified by licking/grooming and arched-back nursing (LG-ABN), during the first 10 days of their offspring's life to their stress response in adulthood. Maternal licking/grooming of pups represents a central aspect of mother–infant interaction. The studies showed that if mothers displayed low LG-ABN behavior, *i.e.* a reduced quality of maternal care, their offspring will show impaired behavioral and physiological coping responses to stress in adulthood as compared to offspring born to mothers with high LG-ABN traits (Caldji et al., 1998, 2000). Moreover, the progeny of the low LG-ABN mothers showed decreased open-field exploration as well as longer latencies to begin eating food in a novel environment, paired with increased levels of corticotropin-releasing hormone (CRH) receptors in the amygdala (Caldji et al., 1998). On the other hand, the offspring of high LG-ABN showed reduced responses to restraint stress, such as reduced plasma adrenocorticotropic hormone and corticosterone, in adulthood along with increased hippocampal glucocorticoid receptor (GR) density and decreased hypothalamic CRH mRNA level (Liu et al., 1997).

Interestingly, these studies demonstrated evidence of epigenetic transmission of the maternal phenotype of LG-ABN behaviors in a set of cross-fostering experiments (Francis et al., 1999). The alteration in the stress response system observed in the progeny of low LG-ABN can be reversed if those animals were raised by high LG-ABN and *vice versa* (Francis et al., 1999). The reversal of impaired stress response programming by rat pups born to a low LG-ABN mothers and fostered by a high LG-ABN mother indicates that maternal care alters the stress response independently of information passed on in the womb, but rather through postnatal environmental conditions. An important finding in this context was that increased levels of GR mRNA in the hippocampus of the offspring of the high LG-ABN were due to low levels of DNA methylation at the exon 1_7 of the GR promoter region (Weaver et al., 2004). This was in contrast to the observed DNA methylation pattern in the hippocampus of the offspring of low LG-ABN, where exon 1_7 of the GR promoter region was always methylated (Weaver et al., 2004). Intriguingly, the authors provided evidence of non-germ line transmission of the maternal behavior to the adopted offspring *via* epigenetic mechanisms. Cross-fostering experiments showed that the DNA methylation status of the exon 1_7 promoter of the GR gene depends on the rearing condition rather than the genetic background (Weaver et al., 2004). In the offspring of low LG-ABN mothers raised by high LG-ABN mothers the DNA methylation status within 5′ CpG dinucleotide of the 1_7 GR promoter region was indistinguishable from that of the biological offspring of high LG-ABN (Weaver et al., 2004). Similar evidence of non-genomic transmission was observed when biological offspring of high LG-ABN was fostered to the low LG-ABN mothers (Weaver et al., 2004). Notably, the distinctive maternal care traits can be transmitted to the subsequent generations of female offspring (Francis et al., 1999) potentially through epigenetic mechanisms (Ward et al., 2013; Zucchi et al., 2013).

This series of studies of maternal care also demonstrated altered histone acetylation and binding of the transcription factor (NGFI-A) to the GR promoter. The adult offspring of high LG-ABN mothers displayed an increase in histone H3-K9 acetylation as well as a three-fold increase in the binding of NGFI-A protein to exon 1_7 of the GR promoter in the hippocampus (Weaver et al., 2004). Interestingly, central infusion of histone deacetylase inhibitor, trichostatin A (TSA), reversed the observed epigenetic changes and eliminated the maternal effect on HPA responses to stress in the offspring of the low LG-ABN mothers (Weaver et al., 2004). Intracerebroventricular infusion of TSA into the adult offspring of LG-ABN mothers abolished the hypermethylated state of the GR promoter and removed the differences in GR expression, histone acetylation and NGFI-A binding in the hippocampus between the progenies of low- and high LG-ABN mothers (Weaver et al., 2004). Thus, these studies highlight a crucial role of early-life experience in life-time stress responses by means of epigenetic changes. However, more experiments are required to verify the exact molecular mechanisms of how maternal behavior is able to produce stable alterations in the DNA methylation and chromatin structure in the offspring (Weaver et al., 2004, 2007). One of the proposed mechanisms of regulation of GR transcription in the hippocampus involves a thyroid hormone-serotonin-NGFI-A signaling cascade (Hellstrom et al., 2012). Hellstrom et al. (2012) demonstrated that thyroid hormones and serotonin (5-HT) are key mediators of the

effects of both, pup licking and grooming and tactile stimulation, on NGFI-A binding to the exon 1_7 of the hippocampal GR promoter.

More translational research is required to evaluate the causal mechanisms that lead to benefits of tactile stimulation. Interestingly, a recent human study by Sharp et al. (2012) investigated whether self-reported maternal stroking over the first weeks of life has beneficial effects on the offspring, similar to those observed as a result of high licking/grooming in rodents (Sharp et al., 2012). This study found an association between increased maternal depression and decreased physiological adaptability, accompanied with increased negative emotionality in the offspring, only in the presence of low frequency of maternal stroking (Sharp et al., 2012). In another translational study, the authors investigated whether maternal depression/anxiety during third trimester in humans has an effect on methylation of NR3C1 at a predicted NGFI-A binding site in the infant (Oberlander et al., 2008). Similarly to findings in animal models, Oberlander et al. (2008) found that prenatal exposure to increased maternal depression/anxiety was associated with an increased methylation at a predicted NGFI-A binding site, paired with an increase in salivary cortisol stress responses at the age of three months in the infant.

Another example of how early life experience can induce long-lasting changes in physiology and behavior comes from a mouse model (Murgatroyd et al., 2009). Murgatroyd et al. (2009) demonstrated that exposure to stress during first 10 days of life caused corticosterone hypersecretion under basal conditions and in response to acute stressors, at the age of six weeks, three months and one year in mice. In addition, they observed increased arginine vasopressin (AVP) expression in the hypothalamic paraventricular nucleus that was associated with DNA hypomethylation of the enhancer of *Avp* gene (Murgatroyd et al., 2009). Their results indicated that the Avp enhancer contains high-affinity DNA-binding sites for CpG binding protein 2 (MeCP2) that regulates activity-dependent transcription of the *Avp* gene, and phosphorylation of MeCP2 prevents Avp enhancer occupancy (Murgatroyd et al., 2009). Furthermore, molecular changes in the brain of mice exposed to early-life stress were accompanied by an altered behavioral phenotype. The stressed mice demonstrated increased immobility in the forced swim test and memory deficits in an inhibitory avoidance task (Murgatroyd et al., 2009). Taken together, the above mentioned studies highlight a pivotal role of early-life experiences in the alteration of stress response systems later in life that are in part regulated by epigenetic mechanisms.

6.4. Stress-induced epigenetic changes in placenta may be associated with epigenetic changes in brain

According to the examples outlined in the previous chapters, stress or other types of adverse experience will modify epigenetic profiles in the placenta and brain. In a recent report by Howerton et al. (2013), O-linked-N-acetylglucosamine transferase (OGT) has been identified as a placental biomarker of maternal stress (Howerton et al., 2013). OGT is an enzyme that catalyzes the addition of a single N-acetylglucosamine in O-glycosidic linkage to serine or threonine residues of intracellular proteins. OGT is an X-linked gene that plays an important role in regulating proteins involved in chromatin remodeling. In mice, levels of both OGT and its biochemical mark O-GlcNAcylation in placental tissue showed a sex-specific pattern with low expression in males and a further reduction by prenatal stress (Howerton et al., 2013). Importantly, OGT levels in human placenta showed a similar sexually dimorphic pattern (Howerton et al., 2013).

A central question in the search for new biomarkers of disease is if epigenetic changes in the placenta reflect functional and/or epigenetic changes in the developing organs such as the brain. A recent study by Jensen Pena et al. (2012) assessed the role of epigenetic mechanisms in the placenta and fetal brain in response to prenatal stress in rats (Jensen Pena et al., 2012). The study focused on the expression of 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), which catalyzes the interconversion of active glucocorticoids (such as corticosterone in rats) and inert 11-keto forms (cortisone, 11-dehydrocorticosterone) in placenta and fetal brain in response to chronic stress. Chronic restraint stress during gestational days 14–20 caused a significant decrease in *Hsd11b2* mRNA, paired with an increase in DNA methylation at CpG sites within the *Hsd11b2* gene promoter in placenta (Jensen Pena et al., 2012). The authors also found an increased level of *Dnmt3a* mRNA in the fetal hypothalamus, as well as decreased methylation at *Hsd11b2*. However, the level of *Hsd11b2* mRNA in the embryonic hypothalamus was not altered (Jensen Pena et al., 2012).

It is worth noting that fetuses and placenta in the latter study were obtained *via* cesarean section. It was demonstrated recently that cesarean section can alter the epigenetic state of neonatal hematopoietic stem cells (Almgren et al., 2014). Infants delivered by cesarean section presented with increased global DNA methylation in CD34+ cells in comparison to those that were delivered vaginally. In addition, locus-specific analysis showed that 76% of the differentially methylated loci in neonatal CD34+ cells were hypermethylated after vaginal delivery (Almgren et al., 2014). Thus, this recent study highlights the possibility that cesarean section by itself may represent an additional contributing factor that determines the epigenetic states of the offspring in addition to prenatal stress and other factors.

The involvement of epigenetic mechanisms in the placental and brain stress response has been previously demonstrated in mice (Mueller and Bale, 2008). In this study, prenatal stress caused significant sex-specific elevation of DNMT1 expression in female placentas. Interestingly, males but not females displayed maladaptive behavioral stress responsiveness paired with altered methylation and gene expression of glucocorticoid receptor and corticotropin-releasing factor in the fetal brain (Mueller and Bale, 2008). Furthermore, prenatal stress resulted in a sex-specific increase in the placental expression of PPARα (peroxisome proliferator-activated receptor α), IGFBP-1 (insulin-like growth factor binding protein 1), HIF3α (hypoxia-inducible factor 3α) and GLUT4 (glucose transporter 4) in males (Mueller and Bale, 2008). These studies suggest that placental epigenetic patterns may serve as predictive signatures of stress response in later life, however, the mechanisms of this programming and their consequences on life health trajectories still remain to be investigated.

6.5. Stress-induced epigenetic signatures of disease

6.5.1. miRNAs as markers of stress and disease

The role of miRNAs in stress responses in general has been extensively studied (reviewed in Leung and Sharp, 2010), including their role in the brain under stressful conditions in particular (Schouten et al., 2013). Research from our laboratory showed that even very mild psychological stress can induce long-lasting changes in miRNA expression in the rat brain (Babenko et al., 2012a). We demonstrated that expression of miR-186 and miR-709 in the brain was altered in response to restraint stress. In our experiment adult male rats were stressed for 20 min daily for two weeks (Babenko et al., 2012a). MiRNA expression analysis showed that miR-186 and miR-709 remained altered in the prefrontal cortex even when animals had two weeks of recovery from chronic stress (Babenko et al., 2012a). Interestingly, in a separate study we found that expression of miR-186 was also altered in the frontal cortex of rat mothers that experienced stress during late gestation (Zucchi et al., 2013). Furthermore, the latter study found that prenatal stress in the offspring induces miRNA signatures linked to neurological and psychiatric disorders in humans, which indicates

that early adverse experiences are associated with potentially long-term epigenetic biomarkers in the brain (Zucchi et al., 2012, 2013). It seems reasonable to expect that some of these miRNA signatures of stress may transmit to subsequent generations of progeny with potentially adaptive or maladaptive consequences on behavior and endocrinology. The critical role of miRNAs in programming lifetime health in response to an adverse prenatal environment and their impact across generations has not yet been systematically explored and still remains underappreciated.

MiRNAs were implicated in many diseases of the nervous system, including stroke, Alzheimer's disease, Parkinson's diseases, Huntington's disease, multiple sclerosis, schizophrenia, autism, anxiety, depression and bipolar disorder (reviewed by Babenko et al., 2012b; Miller and Wahlestedt, 2010). The most intriguing conclusion of previous studies is the emerging role of circulating miRNAs as potential biomarkers for diagnostics and prognosis of CNS diseases (Jin et al., 2013). Despite the fact that epigenetic inheritance is receiving increasing attention during the recent decades, the transgenerational inheritance of miRNAs was not yet demonstrated in mammals.

6.5.2. Changes in brain DNA methylation in response to stress and disease

Many studies in both humans and animal models pointed out that stress has multiple effects on DNA methylation. For example, a study by Unternaehrer et al. (2012) examined whether acute psychological stress in humans causes changes in DNA methylation of genes related to brain plasticity and endocrine regulation, such as brain-derived neurotrophic factor (*Bdnf*) and oxytocin receptor (*Oxtr*) (Unternaehrer et al., 2012). The study includes the results for 76 participants at the age of 61–67 years that underwent the Trier social stress test. Comparisons of quantitative DNA methylation patterns in whole blood before stress, 10- and 90 min after the experience of stress revealed increased methylation of the *Oxtr* gene pre-stress compared to 10 min post-stress and decreased methylation from 10 min post-stress compared to 90 min post-stress. These observations reflect the dynamic nature of DNA methylation regulation in response to psychological stress. By contrast, no changes in DNA methylation were observed at the examined *Bdnf* region (Unternaehrer et al., 2012). Interestingly, Roth et al. (2009) used a rodent model of childhood maltreatment to investigate how adverse early-life experience influences DNA methylation of the *Bdnf* gene. For the first week of postnatal life new-born rat pups were exposed to stressed caretakers that predominantely displayed abusive behaviors. Their results showed long-lasting increase in the *Bdnf* DNA methylation pattern in the adult prefrontal cortex (Roth et al., 2009). Similar changes were observed in the offspring of female rats exposed to adversity in infancy (Roth et al., 2009). In addition, animals exposed to abusive behavior in early childhood had significantly less *Bdnf* mRNA expression in prefrontal cortex throughout the life span, which was accompanied by an increase in DNA methylation at various regions of the *Bdnf* gene (Roth et al., 2009). It is worth noting that maltreatment-induced *Bdnf* expression deficiency was reversed by chronic infusion of zebularine, a DNA methylation inhibitor (Roth et al., 2009).

In line with these studies, Sterrenburg et al. (2011) used an animal model of chronic stress to investigate DNA methylation changes in another stress-related gene, encoding corticotropin-releasing factor (CRF). Their results showed that chronic variable mild stress causes site-specific DNA methylation changes in various parts of the brain (Sterrenburg et al., 2011).

In humans, a recent study by Fuchikami et al. (2011) investigated methylation profiles of the *Bdnf* gene in patients with major depression. Analysis of methylation profiles of CpG units within the *Bdnf* promoter using genomic DNA from peripheral blood allowed distinguishing between patients with major depression and healthy controls in concordance with clinical diagnoses (Fuchikami et al., 2011). Hence these findings indicate that DNA methylation profiles of the BDNF gene may serve as a diagnostic biomarker of major depression. Changes in the DNA methylation profiles of peripheral blood were also demonstrated for a number of other genes in patients suffering from major depression (Rotter et al., 2011; Uddin et al., 2011).

Aberrant DNA methylation is also linked to other mental illnesses, such as schizophrenia, bipolar disorder, major psychosis, and autism spectrum disorders (Dempster et al., 2011; Kuratomi et al., 2008; Mill et al., 2008; Nguyen et al., 2010). For example, analysis of saliva of patients with schizophrenia and bipolar disorder showed hypomethylation of the serotonin receptor type-2A gene (Ghadirivasfi et al., 2011). Hypomethylation of another gene, reelin, was found in the post-mortem cortices of schizophrenia patients (Grayson et al., 2005). Using whole blood samples from schizophrenia patients, Liu et al. (2014) reported that DNA methylation changes in the blood may play a protective role and reduce delusion and hallucination symptoms in patients (Liu et al., 2014). The authors found 11 CpG sites with altered methylation patterns in the patients that significantly correlated with reality distortion symptoms (Liu et al., 2014). Taking into consideration that this study may be confounded by various proportions of leukocyte subtypes in the whole blood samples, further investigations are needed. It is worth noting that DNA methylation of brain tissues may be more directly related to schizophrenic symptoms than DNA methylation from peripheral blood of the patients (Liu et al., 2014). These findings emphasize the potential predictive or diagnostic value of epigenetic markers in human mental and neurological disease.

7. Stress during pregnancy and risks of neurological disorders later in life

As discussed above, stress can play an important regulatory role in both brain development and disease etiology. On the other hand, several lines of evidence point toward the role of stressful experiences in transgenerational programming and their critical ability to alter epigenetic regulation. Thus, we hypothesize that stress during pregnancy may affect mental health in the offspring across a lifetime and across multiple generations through heritable changes at the epigenetic level. Below we review the role of stress in relation to the risk of neurological disorders later in life and discuss evidence that suggests a causal role for epigenetic mechanisms in the predisposition to mental illness.

Many previous clinical and animal studies suggested a causal association between an adverse prenatal environment and an elevated risk of cardiovascular disorders and psychiatric diseases later in life (Cottrell and Seckl, 2009). Interestingly, a recent study by Booij et al. (2012) investigated whether perinatal adversity in humans has long-term consequences on central serotonin neurotransmission in adulthood (Booij et al., 2012). Their results showed that a history of obstetric complications, such as a delivery with signs of fetal physiological distress, predicted lower brain serotonin synthesis in the medial orbitofrontal cortex and hippocampus in 27-year-old adults (Booij et al., 2012). Since serotonin neurotransmission in these brain regions is involved in emotional regulation, affective state and stress coping, these findings support the notion that a reduction in serotonin activity caused by perinatal stressors may contribute to the susceptibility for psychiatric disorders in later life (Booij et al., 2010).

One approach to investigate the role of prenatal stress on the offspring's future health is to study the effect of prenatal exposure to exogenous steroids in obstetrics [reviewed in Schwab, 2009; Sloboda et al., 2005]. Synthetic steroids, such as dexamethasone or

betamethasone, are administered to about 6% of pregnant women who are at risk of premature labor to facilitate fetal lung maturation (Mahony et al., 2010). Notably, about half of the treated pregnant women do not deliver within 7 days (Boesveld et al., 2014). While in children at 5 years of age conclusive evidence of effects of antenatal corticosteroids on neurodevelopmental outcomes could not be confirmed (Asztalos et al., 2013), long-lasting effects of antenatal corticosteroid treatment in term-born children revealed increased cortisol reactivity in response to acute stress at the age of 6 to 11 years (Alexander et al., 2012). In sheep such developmental consequences of antenatal dexamethasone treatment were linked to reduced fetal cerebral blood flow and altered fetal electrocortical activity (Schwab et al., 2000, 2001).

Another approach investigated the short- *versus* long-term consequences of stress experienced by the mother during pregnancy on the future health of the offspring. Epidemiological studies revealed some links between stress experienced by the mother during pregnancy and higher risk of developing depression, anxiety, schizophrenia, ADHD and autism in the offspring (Kinney et al., 2008b; Markham and Koenig, 2011). Some human data and animal studies also suggest a critical role of prenatal stress in developing anxiety- and depression-related behaviors later in life (Markham and Koenig, 2011). Further details linking perinatal stress to future mental health and wellbeing in the offspring are discussed in the following chapter.

7.1. Prenatal stress and risk of developing schizophrenia later in life

Schizophrenia is likely multifactorial in origin, however, an adverse maternal environment during fetal development arguably represents a predisposing or precipitating factor for this mental disorder. Several epidemiological studies reported a relationship between maternal psychological stress and an elevated risk of schizophrenia in the adult offspring (Huttunen and Niskanen, 1978; Khashan et al., 2008, 2011; Kinney et al., 1999; Myhrman et al., 1996; Selten et al., 1999; van Os and Selten, 1998) (Fig. 2). Growing evidence supports the hypothesis that at least one form of schizophrenia has a neurodevelopmental cause and has its origins in prenatal disturbances (Watson et al., 1999).

Evidence of this relationship derives from traumatic war experiences that occurred during pregnancy. A study by van Os and Selten (1998) investigated the lifetime risk for developing schizophrenia in individuals whose mothers were pregnant during the German invasion in the Netherlands in the 1940s. The incidence of developing schizophrenia was higher in the offspring of mothers who experienced the invasion during pregnancy in comparison to those unexposed (van Os and Selten, 1998). Furthermore, Malaspina reported a raised incidence of schizophrenia in offspring whose mothers were pregnant during the Arab-Israeli war of 1967 (Malaspina et al., 2008). By contrast, more recent study by Selten et al. failed to find an association between prenatal exposure to stress during major wars in Israel and subsequent risk of schizophrenia (Selten et al., 2003).

The risk to develop schizophrenia may be influenced by the timing of adverse experiences in relation to critical periods of brain development. A retrospective epidemiological study by Huttunen and Niskanen (1978) suggested for the first time that children, whose fathers had died before their birth had higher risks of developing schizophrenia than those children whose fathers died during the first year of their lives. Subjects who were still *in utero* during the time when they lost their fathers were six times more likely to be hospitalized due to their schizophrenia than respective controls (Huttunen and Niskanen, 1978). These findings indicate that prenatal stress may have more potent effects on brain development than postnatal experiences. A more recent population-based study by Khashan et al. (2008, 2011) showed that the risk of schizophrenia was elevated in offspring whose mothers were exposed to the death of a relative during the first trimester (Khashan et al., 2008, 2011). These studies indicate that prenatal stress may elevate the risk of psychiatric disorders in the offspring as a function of pregnancy stage (Buss et al., 2012a,b).

In addition to this intriguing human evidence, animal studies also highlighted the role of prenatal stress in a schizophrenia-like phenotype (Fig. 2). For example, Markham et al. (2013) demonstrated that prenatal stress exposure during late gestation causes sex-specific alterations in the maturation of the prefrontal cortex during adolescence in rats. Male but not female rats had signs of disrupted maturation of the apical dendrites in the prefrontal cortex (Markham et al., 2013). These findings are in line with reports that suggested a causal role for prenatal stress in a schizophrenia-like phenotype and cognitive deficits, including hypersensitivity to amphetamine, blunted sensory gating, disrupted social behavior, impaired HPA axis regulation, and aberrant expression of genes involved in synaptic plasticity in the prefrontal cortex (Kinnunen et al., 2003; Koenig et al., 2005; Lee et al., 2007; Markham et al., 2010). Recently, prenatal stress has also been shown to cause schizophrenia-like behavioral changes and molecular alterations in expression of serotonin 2A and metabotropic glutamate 2 receptors in the mouse adult frontal cortex (Holloway et al., 2013).

Interestingly, prenatal stress in mice was shown to induce alterations in DNA methylation in association with a schizophrenia-like phenotype (Matrisciano et al., 2013). Offspring born to non-stressed mothers had high levels of DNMT1 and DNMT3a mRNA expression in the frontal cortex at birth, but these levels progressively decreased at postnatal days 7, 14, and 60 (Matrisciano et al., 2013). This is in contrast to prenatally stressed offspring that displayed high levels of DNMTs compared to controls at all time-points (Matrisciano et al., 2013). These prenatally stressed mice showed hyperactivity and deficits in social interaction, prepulse inhibition, and fear conditioning in adulthood. Interestingly, the deficits were corrected by administration of a histone deacetylase inhibitor, valproic acid, and by clozapine, which acts as an antipsychotic agent with DNA-demethylation activity (Matrisciano et al., 2013). These findings propose a causal function of DNA methylation underlying the cognitive deficits of a schizophrenia-like phenotype.

7.2. Prenatal stress and risk of anxiety- and depression-related disorders later in life

Exposure to prenatal stress represents a major determinant of lifelong affective and emotional wellbeing. In humans, several epidemiological studies pointed out a link between prenatal stress and risk of anxiety- and depression-related disorders later in life (Brown et al., 2000; O'Connor et al., 2002, 2003; Torrey et al., 1996; van den Bergh et al., 2008; Watson et al., 1999). For example, Watson et al. (1999) reported that 18-year-old males but not females, exposed *in utero* during the second trimester of gestation to the Tangshan earthquake in China in 1976, present with a significantly increased risk of severe depression (Watson et al., 1999). Exposed subjects had significantly more depressive symptoms when compared to a control group of non-exposed students (Watson et al., 1999).

Aside from prenatal stress *per se*, maternal mental illness also bears the risk to affect mental health in her children, possibly through routes of behavioral and/or endocrine programming. For example, O'Connor et al. (2003) investigated the influence of maternal anxiety and depression on behavioral abnormalities in 6–7 year-old children. Their results showed that offspring born to mothers who experienced high levels of anxiety during pregnancy had higher rates of behavioral/emotional problems, as reported by the parents (O'Connor et al., 2003). Further, van den Bergh et al. (2008) found a striking link between maternal anxiety during pregnancy

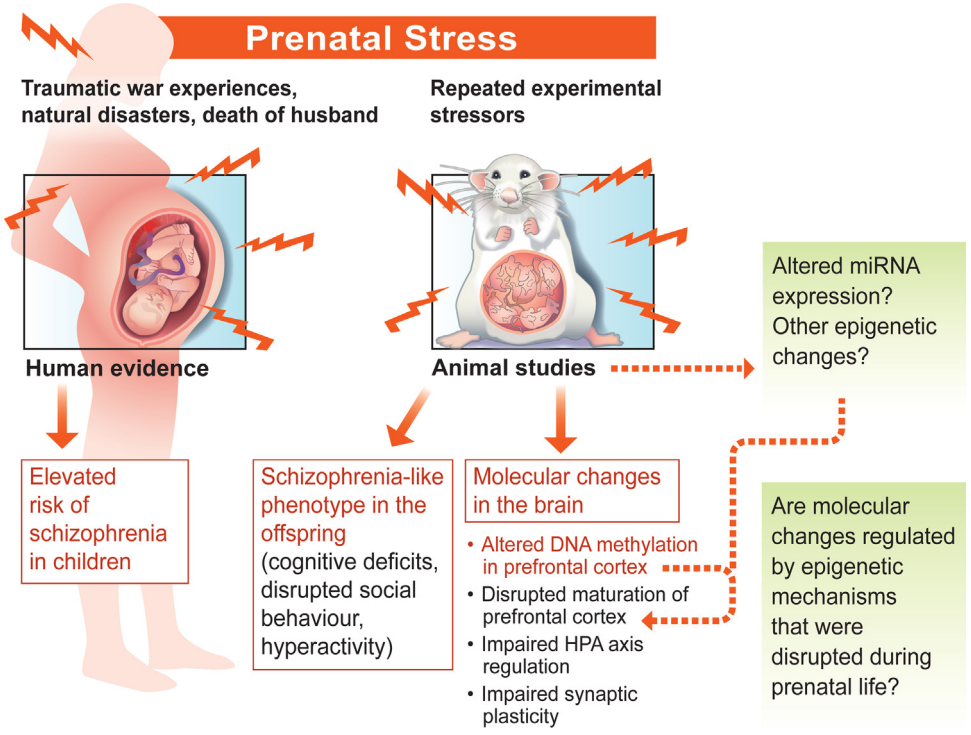

Fig. 2. Prenatal stress and risk of developing schizophrenia later in life. Evidence from human observations indicated that stressful experiences during pregnancy are associated with a higher risk of schizophrenia in children. On the other hand, studies in rodents demonstrated that a schizophrenia-like phenotype in prenatally stressed offspring is accompanied by molecular changes in the brain, including altered DNA methylation in the prefrontal cortex. The involvement of other epigenetic mechanisms, such as altered miRNA expression, in a schizophrenia-like phenotype remains to be characterized.

and self-reported depressive symptoms in 14- and 15-year-old adolescents (van den Bergh et al., 2008). The authors used the State Trait Anxiety Inventory to establish the levels of maternal anxiety during pregnancy. Their results indicated that maternal anxiety during the 12–22nd weeks of pregnancy was associated with altered cortisol profiles in the offspring. Furthermore, in girls, but not boys, the flattened cortisol profile was also associated with depressive symptoms, as measured using the Children's Depression Inventory (van den Bergh et al., 2008). An interesting set of studies by Yehuda and colleagues investigated the consequences of prenatal stress exposure during the World Trade Center attacks on the future health of both mothers and their babies (Yehuda, 2002; Yehuda et al., 2005, 2009). Their data suggested that stress during pregnancy is associated with subsequent formation of posttraumatic stress disorder (PTSD) in mothers. In turn, the mother's PTSD was linked to lower cortisol levels in their babies very early in life, thus highlighting the importance of *in utero* contributors to putative biological risk for PTSD (Yehuda et al., 2005).

In addition to human data, growing evidence from animal studies supports the notion that depression-like and anxiety-like behaviors in adulthood may have neurodevelopmental origins. For example, the role of prenatal stress in causing depression-like behavior in rats has been recognized since the early nineties (Alonso et al., 1991). The study by Alonso et al. (1991) demonstrated that adult female rats, when exposed to stress while *in utero*, display more depressive-like behavior in a forced swimming task (Alonso et al., 1991). Secoli and Teixeira also reported that chronic prenatal stress caused behavioral symptoms of depression in a rat model (Secoli and Teixeira, 1998). These studies indicate a mechanistic link between prenatal stress exposure and an elevated risk of altered affective state.

Anxiety and other behavioral changes linked to prenatal stress were shown by Vallee et al. (1997), who compared the effects of prenatal stress *versus* postnatal handling on rat behavior in adulthood (Vallee et al., 1997). In this study, *in utero* stressed rats demonstrated high anxiety-like behavior, which correlated with elevated secretion of corticosterone in response to stress. On the other hand, postnatally handled rats showed low anxiety-like behavior, which correlated with low levels of circulating plasma corticosterone levels in response to stress in adulthood. Interestingly, neither prenatal nor postnatal stresses altered spatial learning or memory performance in these animals (Vallee et al., 1997). In a more recent study by Kapoor and Matthews (2005), the authors examined the long-term consequences of prenatal stress on adult male offspring in a guinea pig model (Kapoor and Matthews, 2005). Pregnant guinea pigs were exposed to a strobe light for 2 h on different days during late gestation. The results showed that prenatal stress caused a long-lasting decrease in the body weight, as well as elevated plasma cortisol levels in an adrenocorticotropic hormone challenge, and signs of anxiety in prenatally stressed offspring when compared to non-stressed controls (Kapoor and Matthews, 2005).

Using a selective breeding line, Bosch et al. (2006) investigated whether prenatal stress can modulate genetic predisposition to anxiety-like behavior in rats (Bosch et al., 2006). Their results showed that rats bred for high (HAB) or low (LAB) anxiety-related behavior were differentially affected by prenatal stress during gestational days 4–18. Interestingly, prenatally stressed HAB rats became less anxious in adulthood, whereas LAB rats became more anxious, when compared to their respective non-stressed controls. Prenatally stressed HAB rats had decreased levels of CRH mRNA in the paraventricular nucleus of the hypothalamus, whereas prenatally stressed LAB rats showed an increase in hypothalamic vasopressin mRNA expression, when compared to their respective controls (Bosch et al., 2006).

Various studies have investigated the mechanisms of such behavioral alterations. For example, depressive-like behavior, as indicated by increased immobility time in the forced swimming task, exhibited by prenatally stressed adult rats, might be mediated in part through the down-regulation of GR (Karandrea et al.,

2002) and MR (Tamura et al., 2011) in the hippocampus. In the latter study, pregnant dams were exposed to daily restraint stress during late gestation (Tamura et al., 2011). The results revealed that the offspring of stressed mothers had reduced dendritic complexity and spine density in neonatal granule cells, which persisted into adulthood (Tamura et al., 2011). Interestingly, it was shown previously that a single 20-min restraint stress exposure of a pregnant rat on day 18 after mating leads to a sex-specific reduction of hippocampal granule cells in adult female offspring (Schmitz et al., 2002). Thus, even short-term prenatal stress may already lead to sexually dimorphic effects on neuronal morphology in areas relevant to stress response regulation and cognitive performance.

Further animal studies highlighted the pivotal role of the placenta in prenatal reprogramming of the stress response (Welberg et al., 2000, 2005). To demonstrate placental contribution to the adult alterations of the HPA axis and anxiety-like behavior, Welberg et al. (2000) inhibited feto-placental 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) in rats, using carbenoxolone (CBX) (Welberg et al., 2000). The enzyme HSD11B2 assumes a critical role in the placenta that breaks down maternal cortisol or corticosterone and thus prevents them from crossing the placenta. Thus, HSD11B2 serves a major protective role for the developing fetal brain by rapidly inactivating the main stress hormones (Yang, 1997). In the studies by Welberg et al. (2000, 2005), CBX treatment of pregnant dams reduced fetal birth weight as well as offspring weight in adulthood. Moreover, adult offspring of CBX-treated rats displayed increased basal corticosterone levels and CRH, as well as reduced GR mRNA in the paraventricular nucleus of the hypothalamus and increased GR mRNA expression in the amygdala (Welberg et al., 2000). Interestingly, no changes in either GR or MR were observed in the hippocampus of adult offspring of CBX-treated dams when compared to the offspring of untreated controls. The results of the open field and forced swim tests suggest that disturbance of the feto-placental barrier to maternal corticosterone produced anxiety-like behaviors in adult offspring in stressful situations (Welberg et al., 2000).

In a follow-up study, Welberg et al. (2005) compared the effects of acute *versus* chronic restraint stress during the third week of gestation on placental HSD11B2 activity in rats (Welberg et al., 2005). Their results showed that acute stress up-regulates HSD11B2 activity by 160% in placenta, thus protecting the fetus from excessive levels of maternal corticosterone. Interestingly, chronic stress exposure did not have a significant effect on placental HSD11B2 activity when compared with unstressed pregnant rats, however, it reduced the ability to increase the placental HSD11B2 activity in the face of an acute stressor (Welberg et al., 2005). These studies support the general notion that the effects of prenatal stress depend on its duration and severity.

Interestingly, a study by Uddin et al. suggests that mechanisms of epigenetic regulation are altered in the patients with lifetime depression (Uddin et al., 2011). Their results showed that genome-wide methylation profiles are different in depressed *versus* non-depressed individuals in a community-based setting (Uddin et al., 2011). Another epidemiological study by Fuchikami et al. (2011) suggests that DNA methylation profiles of CpG (island I) of the *Bdnf* gene may serve as a diagnostic biomarker for major depression (Fuchikami et al., 2011). Thus, these studies indicate a close interplay between epigenetic regulation and depression. For a more detailed review see El-Sayed et al. (2012).

7.3. Prenatal stress and predisposition to attention deficit hyperactivity disorder and autism

Attention deficit hyperactivity disorder (ADHD) and autism are two conditions that are significantly influenced by adverse environmental conditions, such as stress. For instance, Rodriguez and Bohlin investigated the association between maternal smoking during pregnancy and perceived stress with the risks of ADHD in 7-year-old offspring (Rodriguez and Bohlin, 2005). Results of multiple regression analysis showed that prenatal stress and exposure to maternal smoking were independently associated with the symptoms of ADHD in the offspring later in life. The results of logistic regression analysis revealed that stress during pregnancy contributed to ADHD diagnostic criteria, especially in the boys. In particular, the levels of perceived stress during pregnancy predicted nearly 87% of the ADHD cases in the male population studied (Rodriguez and Bohlin, 2005). Ronald et al. reported that maternal stressful events, such as a divorce or a residential move, during pregnancy significantly predicted ADHD behaviors and autistic traits in the 2-year-old offspring, both males and females (Ronald et al., 2010). Similarly, Grizenko et al. (2012) showed that mothers with an ADHD-affected child have been more likely to perceive high stress during pregnancy when compared to an unaffected sibling. Moreover, the authors found that the DRD4 7/7 genotype was associated with more severe symptoms of ADHD in the offspring of the mothers who were highly stressed during pregnancy (Grizenko et al., 2012).

Another study investigated the link between maternal state anxiety during pregnancy and later ADHD deficits in the 15-year-old offspring (Van Den Bergh et al., 2006). State anxiety is a measure of the intensity of transitory anxiety in response to real-life stress and is characterized by perceived tension as well as an increased activity of the autonomous nervous system (Van Den Bergh et al., 2006). The results showed that adolescent boys, but not girls, whose mothers experienced high levels of anxiety during pregnancy, had more difficulties with sustained attention/self-regulation than boys whose mothers reported low or moderate anxiety levels in the State-Trait Anxiety Inventory (Van Den Bergh et al., 2006).

Many insights into the developmental origins of health and disease are derived from the study of natural disasters occurring during pregnancy (King et al., 2012). For example, using the Louisiana state cohort Kinney et al. found a significantly higher prevalence of autism disorder (AD) in children whose mothers experienced hurricanes or severe tropical storms during pregnancy (Kinney et al., 2008a). Interestingly, the negative influence of natural disasters on offspring health was dose-dependent. The severity of the disaster was assessed using two storm factors: the intensity of a storm's impact on a parish, and the vulnerability of the residents of a parish to a storm's effects (Kinney et al., 2008a). AD prevalence (of 6.06 per 10,000 births) was higher in children exposed *in utero* to one or the other storm factor in comparison to the control cohort that had no storm exposure where the prevalence was 4.49 AD cases per 10,000 births. Notably, the prevalence of AD in children exposed *in utero* to both storm factors was 13.32 (Kinney et al., 2008a). It is worth noting that children who were exposed to the storm during 5–6 months or the last month of gestation had 3.83 times higher risk of developing AD than those with a different timing of exposure (Kinney et al., 2008a).

Possible involvement of the epigenetic alterations in the etiology of AD and ADHD has been suggested (Mill and Petronis, 2008; Schanen, 2006), however the exact mechanisms are yet to be identified.

8. Conclusion

The studies discussed in this review highlight the susceptibility of the fetal brain to an adverse maternal environment during a particularly vulnerable period in life through mechanisms that are associated and potentially even mediated by epigenetic regulation. The extent to which maternal stress and anxiety during pregnancy contribute to the development of mental and psychiatric conditions

in the child is still far from being understood. However, effective stress management strategies that allow reducing, preventing and effectively coping with stress and anxiety may be of great importance for the health of both pregnant women and their offspring. The consideration of prenatal stress effects in disease outcomes is critically important to realistically improve current prevention and intervention strategies and assist a healthy life trajectory. Such evidence-based decision making is critical for developing recommendations for a life style that supports healthy development and successful aging in the presence of a stressful environment. Because altered epigenetic regulation may potentially be reversible, the identification of epigenetic signatures of disease presents a promising diagnostic and therapeutic avenue for generations to come.

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