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Research report

Prenatal stress induces spatial memory deficits and epigenetic changes in the hippocampus indicative of heterochromatin formation and reduced gene expression

Jamie D. Benoit[a], Pasko Rakic[b], Karyn M. Frick[c,*]

[a] Department of Psychology, Yale University, New Haven, CT 06520, United States
[b] Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520, United States
[c] Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI 53211, United States

HIGHLIGHTS

- Effects of chronic unpredictable prenatal stress were tested in adult offspring.
- Prenatal stress impaired spatial memory in adult male and female offspring.
- Prenatally stressed females had less H3 acetylation and higher DNMT1 levels.
- Prenatally stressed females had higher plasma corticosterone levels than males.
- The female brain may be more susceptible to the effects of prenatal stress.

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ABSTRACT

Stress during pregnancy has a wide variety of negative effects in both human [1] and animal offspring [2]. These effects are especially apparent in various forms of learning and memory such as object recognition [3] and spatial memory [4]. The cognitive effects of prenatal stress (PNS) may be mediated through epigenetic changes such as histone acetylation and DNA methylation [5]. As such, the present study investigated the effects of chronic unpredictable PNS on memory and epigenetic measures in adult offspring. Mice that underwent PNS exhibited impaired spatial memory in the Morris water maze, as well as sex-specific changes in levels of DNA methyltransferase (DNMT) 1 protein, and acetylated histone H3 (AcH3) in the hippocampus, and serum corticosterone. Male mice exposed to PNS exhibited decreased hippocampal AcH3, whereas female PNS mice displayed a further reduction in AcH3, as well as heightened hippocampal DNMT1 protein levels and corticosterone levels. These data suggest that PNS may epigenetically reduce transcription in the hippocampus, particularly in females in whom this effect may be related to increased baseline stress hormone levels, and which may underlie the sexual dimorphism in rates of mental illness in humans.

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Stress has a variety of detrimental effects on both health and cognition in adult animals and humans [1,2]. Perhaps less well known is that chronic stress in pregnant mothers can substantially impact the well being of their children [1]. In rodents, experimentally-induced prenatal stress (PNS) can lead to reduced birth weight [3], masculinization of female behavior and vice versa [6], reduced immune function [7], retarded motor development and motor deficits [3,8], changes in the length of telomeric DNA [9], reduced exploratory behavior [10], and increased anxiety [3]. Furthermore, rodents exposed to PNS are impaired in a variety of cognitive tasks, including those mediated by the hippocampus. For example, prenatally stressed rodents exhibit impaired object recognition [3], active avoidance learning [11], and spatial learning in the Morris water maze [4,12].

Interestingly, the effects of PNS on behavior appear dependent on sex, although relatively few studies have examined sex differences in response to PNS. One study by Bowman et al. [6] indicated that PNS significantly increased anxiety in an open field in females relative to same sex controls, but not in males. This increased anxiety in PNS females may result from the masculinization of the

* Corresponding author at: Department of Psychology, University of Wisconsin-Milwaukee, 2441 E. Hartford Ave. Milwaukee, WI 53211, United States.
Tel.: +1 414 229 6615; fax: +1 414 229 5219.
E-mail address: frickk@uwm.edu (K.M. Frick).

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female stress response, as corticosteroid levels in PNS females were similar to those of control and PNS males after a restraint stress challenge. This conclusion is consistent with the fact that corticosteroid release in all three of these groups became attenuated over the 2-h monitoring period, in stark contrast to the sustained high corticosteroid levels measured in control females [6]. Other work shows that sex-differences in neuronal gene expression are reduced in rats exposed to PNS, further supporting an overall feminization of male animals and/or masculinization of females [13]. Interestingly, the study by Bowman et al. found that PNS had no effect on object recognition memory, but instead eliminated the observed male advantage in spatial working memory tested in the radial arm maze [6]. However, other work has shown that PNS impairs object recognition and extinction of cued fear conditioning in male, but not female, rats [12]. Other studies using the Morris water maze have shown that PNS impairs spatial memory in males relative to females only when the task is conducted using cold (10 °C) water [14]. PNS has been reported to impair passive avoidance learning in females [15], but improves spatial memory in females [16], highlighting how substantially sex-differences in the effects of PNS depend on task and testing conditions.

Although much of the literature assumes that the mnemonic effects of PNS are due to activation of corticosteroid receptors [1,8,17], the means by which this might occur is unclear. Indeed, the relationship between cognitive function and corticosterone levels in PNS rats can be counterintuitive. For example, high levels of corticosterone are typically associated with impaired memory [18]. Yet at least one study of PNS rats tested in the Morris water maze found that the stress response was highest in mnemonically unimpaired PNS females, and minimal in mnemonically impaired PNS females [14]. As such, other neurobiological alterations may contribute to the effects of PNS on memory in males and females. For example, PNS also appears to influence neurotransmitter function, synaptic plasticity and gene expression in a sex-dependent manner. In rats and mice, PNS reduces dopamine levels in the hippocampus and prefrontal cortex of males [6] and NMDA receptors (NMDARs) in the hippocampus of both sexes [19]. The latter effect leads to reduced NMDA excitatory post-synaptic potentials (EPSPs) and decreased hippocampal long-term potentiation (LTP) [19]. This diminished NMDA activity was more substantial for female rats, which may be related to their heightened corticosteroid response to PNS [20]. However, the effects of PNS on the hippocampus are not limited to NMDARs and LTP, as neurogenesis over the lifespan decreases and age-related granule cell loss is accelerated in PNS rats of both sexes [21]. These data suggest that PNS may induce a cascade of neural events that lead to a maladaptive and dysregulated stress response, as well as impaired learning and memory, particularly in females.

Recently, epigenetic alterations have been shown to substantially regulate hippocampal memory [22–26], yet the role of epigenetic processes in mediating the effects of PNS on memory is not well understood. The most well characterized epigenetic alterations that affect hippocampal learning and memory are histone acetylation and DNA methylation [27]. The most basic unit of chromatin above the level of DNA, the nucleosome, is a segment of DNA coiled around an octamer of proteins called histones. This octamer consists of two each of the histones H2A, H2B, H3, and H4. The N-tails of these proteins protrude from the nucleosome complex and are, thus, accessible to various enzymes in the nucleus. The addition and subtraction of chemical groups on the N-tails of DNA histones plays a major role in gene regulation, particularly as it relates to vertebrate learning and memory [24,28]. This regulation at the level of the histone is referred to as the histone code [23]. The amino acid residues on histone tails can be altered by numerous post-translational modifications including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation [24,29]. In particular, histone acetylation is necessary for many forms of hippocampal-dependent memory in both sexes, including spatial memory, object recognition, and contextual fear conditioning [22,30–34]. Acetyl groups are added by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs). Lysine-14 acetylation on histone H3 leads to overall transcriptional activation [35], and increases expression of genes necessary for hippocampal synaptic plasticity [26]. As such, one of the goals of the present study was to determine the effects of PNS on H3 (Lysine-14) acetylation in the hippocampus.

Emerging evidence links histone acetylation with DNA methylation. DNA methylation involves the addition of a methyl group to a cytosine adjacent to a guanine in so-called CpG islands. The molecule MeCP2, which binds to methylated CpG regions on DNA and silences them, can bind HDAC1 and HDAC2 to induce histone deacetylation [36]. Although DNA methylation typically leads to transcriptional repression, this process is critical for development [37], imprinting [38], and genome stability [39], as well as many other important processes in vertebrates. DNA methylation is catalyzed by three DNA methyltransferase (DNMT) enzymes: DNMT 1, a maintenance methyltransferase, and DNMT 3a and 3b, which are *de novo* methyltransferases [25,42]. In particular, DNMT1 is a large enzyme (193.5 kDa) composed of a C-terminal catalytic domain with a large N-terminal regulatory domain possessing several functions [41]. Because DNMT1 has the highest expression of the three DNMTs in the brain, and directly binds to HDAC1 to suppress gene expression [43], levels of this DNMT are likely to reflect the overall amount of methylation in the genome. Relevant to the present study, DNA methylation is required for hippocampal function, as illustrated by data showing that intrahippocampal infusion of DNMT inhibitors blocks induction of hippocampal LTP, memory consolidation, and acquisition of a conditioned fear response [25,40,41]. Therefore, another goal of the present study was to examine the effects of PNS on hippocampal DNMT1 levels in males and females.

The overall goal of the present study was to determine the effects of chronic unpredictable prenatal stress on spatial memory, histone H3 acetylation, DNMT1 levels, and serum corticosterone levels. In contrast to chronic immobilization stress (CIS), where the animal is closely confined in a tube on a daily basis, chronic unpredictable stress (CUS) generally uses milder daily stressors such as light cycle disruption and overnight food deprivation given in a random order and at random times throughout the day and night [3]. There are two advantages to CUS. First, by employing a series of variable random stressors, CUS more closely resembles stressors encountered in the everyday lives of humans than restraint or footshock stressors. Second, CUS more effectively maintains an elevated stress response than CIS because it prevents habituation to the stressor [3]. As such, CUS will be used here to examine the effects of prenatal stress on memory and epigenetic mechanisms. Pregnant mouse dams were treated with CUS for 4 weeks prior to parturition. Spatial memory and levels of acetylated histone H3, DNMT1, and serum corticosterone levels were then measured in the resultant adult offspring to investigate the effects of PNS on memory, epigenetic processes, and hypothalamic-pituitary-adrenal (HPA) axis activation.

1. Methods

1.1. Subjects

Subjects were 22 female and 22 male C57BL/6 mice bred in the laboratory from dams obtained from Taconic Farms (Germantown, NY). Of these mice, 21 were born of non-stressed mothers and 23 from mothers who underwent CUS. This resulted in four groups: female control ($n = 8$), male control ($n = 13$), female prenatal stress

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