Methylation of the NR3C1 Gene and Behavior

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Abstract

Background: Methylation of the NR3C1 gene affects the glucocorticoid receptors, which are directly related to the stress response via the HPA axis. Exposure to various stressors can lead to methylation, causing significant changes in how a person interacts with their environment.

Methods: A brief review was conducted of three research studies examining the interactions between the environment and the NR3C1 gene.

Results: Research indicates an interplay between the type of stressor experienced, the degree of methylation, and an individual's level of resilience. NR3C1 methylation, which occurs in infants as a response to perinatal stressors, may be, at least temporarily, adaptive. In adolescents, NR3C1 methylation is affected by exposure to stressors and trauma.

Conclusion: Methylation of the NR3C1 gene can occur in response to the environment, and these changes impact a person’s behavior to varying degrees.

Keywords: NR3C1, methylation, stressors

Introduction

The NR3C1 gene encodes the glucocorticoid receptors, which play an essential role in the stress response of the hypothalamic-pituitary-adrenal (HPA) axis. Methylation of the NR3C1 gene can affect cortisol circulation and glucocorticoid sensitivity (Folger et al., 2019). Methylation of the NR3C1 gene and resulting changes in cortisol concentrations can also affect reward processing in the brain, potentially affecting personal resilience and "susceptibility to environmental exposures and may result in different neurodevelopmental and behavioral outcomes" (Xu et al., 2025, p.2). Research has indicated that NR3C1 methylation has occurred in response to perinatal stress, childhood abuse, and neglect, or other traumas (van der Knaap et al., 2014). However, there is still much to learn about how and why these epigenetic changes occur and the effects they may have.

NR3C1 Methylation, Childhood Maltreatment, and Reward Responsiveness

A study completed by Xu et al. (2025) examined the relationship between childhood maltreatment, methylation of the NR3C1 gene, and reward responsiveness. The researchers hypothesized that "the Epi X E (Epigenome X Environment) interaction might work on RewP (reward positivity), gain-related delta and self-reported RR (reward responsiveness) but not loss-related theta" (p. 3). Their hypothesis asserted that these interactions would relate to experiences of depression and anxiety and have a significant effect on the experience of anhedonia, a common symptom of depression defined as the inability to experience pleasure (Xu et al., 2025).

Participants in the study included 192 young adults of both genders, of Han descent, and with no diagnosed developmental, neurological, or significant physical disorders. The study included a baseline assessment and a follow-up assessment one year following. At baseline, participants completed the Childhood Trauma Questionnaire, which assessed five types of

maltreatment (sexual, emotional, or physical abuse and emotional or physical neglect). Cheek swabs were used to analyze genomic DNA, focused on methylation in the NR3C1 region. EEG data was collected while participants completed a computerized reward task, which included 40 gain and 40 loss trials. Participants completed a self-reported RR scale to assess motivation and approach behaviors, and The Beck Depression Inventory (BDI) and Self-Rating Anxiety Scale (SAS) were used to assess depression and anxiety. At the one-year follow-up, the BDI and SAS were repeated (Xu et al., 2025).

The results demonstrated a negative association between severity and number of exposures to childhood maltreatment and RewP in individuals with increased NR3C1 methylation but a positive association in individuals with "blunted" methylation (Xu et al., p. 10). The Epi X E effect was driven by emotional abuse and neglect but not by other types of maltreatment. Interaction effects were linked to anhedonia but not to gain-related delta, loss-related theta, or self-reported RR. The research did not demonstrate a linkage to total depression or anxiety ratings (Xu et al., 2025).

The authors concluded that the results of the study demonstrated some evidence for the Epi X E model, noting that the effects of maltreatment seemed to be affected by type, severity, amount of maltreatment, and the amount of NR3C1 methylation. The results also demonstrated support for the "goodness-of-fit" model, which proposes that "some individuals might develop resilience when their characteristics can successfully deal with the stress; otherwise, the stress might defeat them and lead to dysfunction" (Xu et al., 2025, p. 10).

NR3C1 Methylation and Early Development

Folger et al. (2019) reported on a pilot study completed with mother-child dyads participating in an early intervention home visit program. Their hypothesis asserted that “the

mean NR3C1 DNAm (DNA methylation) across 10 CpG (cytosine-guanine dinucleotides) sites in the promotor region would be significantly associated with subsequent infant social-emotional functioning" (Folger et al., 2019, p. 2).

The participants of this study included 53 adult mothers who were pregnant during the first visit of the study and then completed a second visit one month post-partum. Follow-up assessment of some participating infants occurred at 6 and 18 months. There was a high drop-out rate due to a variety of factors. At the first visit, The Edinburgh Postnatal Depression Scale (EPDS) screened for major or minor depression in the mother, and the Interpersonal Support Evaluation List (ISEL-40) measured the mother's perceived interpersonal support. Multiple cheek swabs were taken from the infants at the second visit to look for methylation in the NR3C1 region. The Ages and Stages Questionnaire: Social-Emotional (ASQ:SE) was used during the two follow-up visits to assess social-emotional function. (Folger et al., 2019).

The percentage of NR3C1 methylation and the ASQ:SE scores at the 6-month mark. Lower ASQ:SE scores indicated higher functioning. At the 18-month mark, there continued to be a negative correlation, although it was no longer statistically significant. Further analysis showed that specific CpG sites seemed to have the strongest associations with the ASQ:SE scores (Folger et al., 2019). Folger et al. (2019) wrote this about their results: "Increased DNAm may reflect a compensatory response to prenatal adversity among some infants who have parents enrolled in an HV (home visit) program" (p. 7). They pointed out that while the increase in methylation may have served some protective functions, a larger study would be warranted to clarify this phenomenon. They also referred to another study that showed that, while methylation may be protective in one area of development, other areas may be adversely affected. (Folger et al., 2019).

NR3C1 Methylation and Stressful Events over Childhood and Adolescence

A study reported by van der Knaap et al. (2014) used data collected through the Tracking Adolescents' Individual Lives Survey (TRAILS) to examine the connection between NR3C1 methylation in adolescence and previous life stressors. The researchers hypothesized that "perinatal stress, many SLEs (stressful life events), and traumatic youth experiences would relate to higher NR3C1 methylation in adolescence" (van der Knaap et al., 2014, p.2).

The TRAILS study followed over 2,000 male and female Dutch youth from pre-adolescence into adulthood, collecting data every two or three years starting around age 11. Van der Knaap et al. (2014) focused their study on 468 participants who had, around age 16, undergone blood work to analyze DNA. This group of participants, admittedly, included a disproportionate (66%) percentage of "high-risk adolescents" who were deemed more likely to experience mental health issues due to increased risk factors (van der Knaap et al., 2014).

Interviews with parents and records review were used to determine exposure to perinatal stress. Researchers gathered information about stressful life events and traumatic experiences via parental interviews or self-reports. Stressful life events included things like parental divorce, death or illness of family or friends, lack of friends, hospitalization, etc. In contrast, traumatic events included sexual assault/abuse, physical abuse, life-threatening experiences, etc. (van der Knaap et al., 2014).

Data analysis showed an association between stressful life events during adolescence, traumas, and higher methylation. However, results of this research did not show an association between methylation of NR3C1 and perinatal or childhood stress (van der Knaap et al., 2014). The authors proposed that because these results conflict with past research demonstrating

NR3C1 methylation associated with perinatal stress, further research was warranted to see if some epigenetic changes are short-term and reversible (van der Knaap et al., 2014). Van der Knaap et al. (2014) acknowledged that it would have been helpful if DNA was analyzed more than once to see if methylation changed over time and to help determine causation.

Conclusion

There is much to learn about epigenetics and the relationship between genes and the environment. Research into NR3C1 has shown that methylation can occur in response to the environment, and these changes can significantly impact how an individual continues to react to the environment. The research also demonstrates a need for further work to elucidate the specific mechanisms and effects.

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