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Aberrant Epigenomic Modulation of Glucocorticoid Receptor Gene (NR3C1) in Substance Use Disorder (SUD) Implicated in Early Life Stress and Major Depressive Disorder (MDD) Correlation

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Background: Early life stress (ELS) induced by psychological trauma, child maltreatment, and substance use disorders (SUD), maternal separation, and domestic violence predisposes to psycho-behavioral pathologies during adulthood. , namely major depressive disorder (MDD). While environmental data are available, data remain to be established on the epigenomic underpinning of the nexus between ELS and MDD.

Rationale/Significance: Despite the observed aberrant epigenomic modulation (AEM) of the NR3C1, a glucocorticoid receptor gene (GRG), in early social adversity and social threats in animal and human models, reliable scientific data for intervention mapping in reducing social adversity and improving human health are relevant.

Hypothesis /Methods: AEM, mainly DNA methylation resulting in MDD following ELS associated with SUD. A quantitative evidence synthesis (QES) were utilized with the random effect method. Of the 1534 studies identified, 592 studies were screened, 11 met the eligibility criteria for inclusion in the QES.

Results: The dense DNA methylation of the 1F exon of the NR3C1, implying the hypermethylated region of the GRG, was observed in the nexus between ELS (SUD) and MDD, common effect size (CES) = 14.96, 95%CI, 10.06-19.85. With respect to epigenomic modulation associated with child ELS, hypermethylation was observed, CES = 23.2%, 95%CI, 8.00-38.48. In addition, AEM was indicated in MDD, where hypermethylation was associated with increased risk of MDD, CES = 2.12%, 95%CI, -0.63-4.86.

Conclusion: AEM identified in ELS and MDD episodes involves dysfunctional glucocorticoid-mediated negative feedback as a result of allostatic overload. These data will facilitate early intervention mapping in reducing MDD in the USA.

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