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Cocaine-mediated microglial activation involves miR-148b-lncRNA XIST-DNMT1 axis-mediated epigenetic promoter DNA methylation of an anti-inflammatory gene, PPARG

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Background: Cocaine, one of most commonly abused drugs, has been shown to activate microglia both *in vitro* and *in vivo*. Detailed epigenetic and molecular mechanism(s) underlying cocaine-mediated microglial activation remain poorly understood. **Rationale/significance:** Cocaine can modulate the levels of targeted genes through the epigenetic mechanism(s). In recent times along with DNA methylation, non-coding RNAs have also been discovered as a novel family of regulators of gene expression. Emerging evidence demonstrates that interplay between lncRNAs and DNA methylation machinery is an essential layer of epigenetic regulation. **Hypothesis:** In this study, we tested the hypothesis that exposure of mouse primary microglial cells (MPMs) to cocaine resulting in cellular activation involves hypermethylation of the peroxisome proliferator-activated receptor gamma (PPARG) promoter via the miR-148b-DNMT1-lncRNA XIST axis. **Results:** RT2 lncRNA PCR Array Mouse lncFinder was performed on cocaine-exposed MPMs that demonstrated increased expression of lncRNA XIST compared with control. qPCR analysis further validated the increased expression of lncRNA XIST in cocaine-exposed MPMs. Bioinformatics analysis, miR target validation and RNA immunoprecipitation assays suggested the possible binding of lncRNA XIST with miR-148b and DNMT1 thereby resulting in increased expression of DNMT1 in cocaine-exposed MPMs. Bisulfite sequencing of cocaine-exposed MPMs showed significant hypermethylation of PPARG gene promoter. Overexpression and gene-silencing approaches were employed to rule out the involvement of miR-148b-lncRNA XIST-DNMT1 signaling axis in PPARG-mediated proinflammatory cytokines production in the cocaine-exposed MPMs. **Discussion:** These findings demonstrated the role of miR-148b-lncRNA XIST-DNMT1-mediated PPARG promoter DNA methylation in cocaine-mediated microglial activation.