Impact of High-Caffeine Intake on Adolescent Brain Development: Epigenetic and Behavioral Perspectives

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Caffeine is the world's most widely consumed psychoactive substance, with intake levels rising steadily among adolescents. However, the neurobiological consequences of excessive caffeine exposure during critical years of neurodevelopment remain poorly understood. This study employs an integrated, multi-model approach, combining public omics datasets with experimental assays to investigate caffeine-induced alterations across molecular, cellular, and behavioral levels. A transcriptomic analysis of mouse hippocampal tissues revealed widespread gene expression perturbations following caffeine exposure, with enrichment of neurobehavior related pathways. Consistent with these molecular signatures, primary neuronal cultures treated with caffeine displayed a dose-dependent compromise in neurite outgrowth and branching complexity. At the organismal level, zebrafish larvae exposed to caffeine exhibited significant downregulation of key neurodevelopmental and neurotrophic genes (Sox2, nestin, Bdnf, and Gdnf), accompanied by anxiety-like hyperactivity and impaired cognitive task performance. Collectively, these findings suggest that elevated caffeine exposure during development may perturb neurodevelopmental gene programs and neuronal morphology, accompanied by measurable behavioral changes. Further studies with developmentally matched mammalian models and physiologically relevant exposure paradigms are warranted to define causal mechanisms and translational relevance.

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