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DNA Methylation and Histone Post-Translational Modifications in Human and Non-Human Primate Brain Following Prenatal Alcohol Exposure

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Background:

Neurodevelopmental abnormalities associated with prenatal alcohol exposure (PNAE) have been attributed (in part) to epigenetic modifications. Epigenetics refers to external modifications made to nucleosomes that regulate gene expression without causing changes to the DNA sequence. Many *in vivo* studies in animals have established the effects of PNAE on epigenetic processes such as DNA methylation and histone post-translational modifications in the developing brain. However, none have looked in human PNAE brains.

Objective:

Investigate possible epigenetic changes that are occurring as a result of PNAE in human autopsy brains.

Methods:

PNAE and age-, sex-, and post-mortem delay matched control fetuses and infants (n=18 pairs; 21 to 70.5 weeks post-conception) who had undergone autopsy, along with comparable brain tissue from a macaque monkey model of PNAE (n=6 pairs), were subjected to immunohistochemical detection with antibodies targeting 4 DNA cytosine, 4 histone methylation, and 6 histone acetylation modifications. Images were taken, analyzed semiquantitatively and subjected to statistical analysis (p-values reported; $p<0.05$).

Results:

Human temporal lobe (7 regions) demonstrated statistically significant increases in epigenetic marks 5mC, 5fC, H3K27me3, H3K36me3, H3K9ac, H3K14ac and H3K27ac, decreases in 5mC, 5caC, H3K4me3, H3K27me3, H3K36me3, H3K9ac, H3K14ac, H3K27ac, H4K5ac, H4K12ac, and H4K16ac, and no change in 5hmC. H3K4me3 (active transcriptional mark) demonstrated a consistent decrease in 5 of the 7 brain regions studied. In macaques, PNAE was associated with statistically significant decreases in 5fC, 5caC, H3K9ac, H3K9me2/K9me3, and H3K36me3, particularly in the temporal ependyma. Comparison of the human and macaque brain findings showed overlap in epigenetic marks H3K9ac (ependyma) and H3K36me3 (white matter), both having decreased in PNAE.

Conclusion:

These effects are region specific, appear to coincide with the development of neuronal and glial cells, and support the general hypothesis that PNAE is associated with an overall decrease in DNA methylation, a decrease in histone methylation, and an increase in histone acetylation.