Behavioural correlates of periconceptional ethanol exposure in aged offspring

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Background: Maternal alcohol consumption prior to recognition of pregnancy is a common social practice. This time frame is referred to as the periconceptional period (PC) and has been recognised as a critical developmental window as the developing embryo is highly responsive to its environment. Excess alcohol consumption during pregnancy can have severe teratogenic effects on the developing foetus, particularly the developing brain, the most severe of which is foetal alcohol syndrome (FAS). However, very little is known about the impact of PC alcohol exposure on long term cognitive function. It has been suggested that long lasting changes to the epigenome are a mechanism of alcohol induced teratogenesis. The modifications of the activity and expression of epigenetic regulators in various brain regions of rodents exposed to alcohol in the PC period suggests alcohol may be impacting the epigenome and its regulators (Perkins *et al.*, 2013). These modifications could be an underlying mechanism of alcohol teratogenesis leading to impaired long term cognitive function.

Methods: Female Sprague-Dawley rats were exposed to a liquid diet containing ethanol (EtOH) (12.5% vol;vol) or a control diet during the PC period (from embryonic day (E)-4 to E4). Male (n=8, Control; n=8 EtOH) and female (n=9 Control; n=7 EtOH). Offspring were put through a battery of behavioural tests at 15-18 months of age to assess aspects of anxiety like behaviour and spatial memory. Brain tissue (hippocampus) was collected and examined for gene expression levels of epigenetic modifiers (DNA methytransferases and histone deacetylases).

Results: PC EtOH exposure resulted in a significant (P=0.0001) increase in directed exploring/head dipping behaviour during holeboard testing in both male and female offspring. However, PC EtOH exposure did not result in an anxiety-like phenotype (elevated plus maze). Interestingly, female offspring exposed to PC EtOH displayed a significant decrease (P<0.04) in the percentage (%) of time spent in the novel arm of the Y maze suggesting short term spatial memory impairments. Expression of DNA methyltransferase-1 (DNMT-1) was increased in male offspring exposed to PC EtOH.

Conclusion: Exposure to PC EtOH did not lead to anxiety-like behaviour in the aged offspring. However an increase in directed exploration indicates that PC EtOH may be associated with less inhibitive behaviour. The decrease in the % of time spent in the novel arm indicates exposure to PC EtOH may induce sex specific impairments in spatial memory with females more affected than males. This highlights that consumption of alcohol prior to brain development may have long term neurological consequences. Preliminary gene expression studies suggest there may be changes in expression of epigenetic modifiers in the hippocampus. Further research is essential to investigate if the epigenome of the brain is modified at differential time points following PC EtOH exposure.

Perkins A, Lehmann R, Lawrence C, Kelly SJ. (2013) *International Journal of Developmental Neuroscience* **31**: 391-397.