## Maternal obesity results in impaired brain function in the offspring by mechanisms involving electrical hyperactivity

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Children gestated in an obesogenic environment are at increased risk of neurodevelopmental problems. A study of 1.4 million children reported a doubling in the rate of childhood epilepsy in those of obese mothers. Due to the greater number of excitatory cells with feedback circuitry, focal excitation and seizures are more likely to occur in the hippocampus, a major centre for memory, learning and decision making, and emotional regulation. Inhibitory neurons are relatively easily damaged. We hypothesized that the inflammatory environment of maternal obesity reduces inhibitory regulation of excitatory activity, leading to hippocampal hyperactivity, in a rat model.

All experimental procedures were approved by the Animal Ethics Committee of Monash University and were conducted in accordance with the regulations set out by NHMRC. Rat dams were placed on control chow (CC) or high fat/cafeteria (HF) diet for 6 weeks before mating. Offspring were retained on the diet of the dam or switched to the other diet at weaning. At 11-13 weeks of age reference and working memory function were tested using a radial arm maze (8-arm). At 14-16 weeks of age a female and male of each litter were deeply anaesthetized using isoflurane (5%), the brains were removed and activity studied *in vitro* using multi-electrode arrays to record electrical activity in hippocampal and cortical brain slices in 0-$Mg^{2+}$ artificial aCSF. In other individuals from the same litters, anaesthesia was induced by 5% isoflurane and maintained at 2.5%, and electrodes were implanted onto the dura and secured in place using dental wax, using aseptic surgical procedures. Following one week of recovery, EEG activity was recorded *in vivo* in conscious, free-funning animals for 1-2 hours per day for 1 week. Other animals were deeply anaesthetized using 5% isoflurane and the brains perfused with phosphate-buffered saline (PBS) delivered *via* the heart and then with PBS containing 4% paraformaldehyde. The brains were removed, cryoprotected, cut into 10μm slices and stored at −80 degrees C. Inhibitory neurons and activated astrocytes were visualized using immunohistochemistry.

Offspring exposed to HF had impaired reference and working memory, assessed on an 8-arm maze. *In vivo*, EEG recordings displayed spike-wave discharges (SWDs), a pattern of activity associated with epilepsy. Bursts of SWDs occurred with greater frequency and much greater duration in HF males. In brain slices, 0-Mg-aCSF resulted in bursts of epileptiform activity that occurred with a shorter latency for HF *versus* CC animals. Block of inhibition *via* GABA receptors reduced the latency to onset of these bursts for CC animals such that bursts of activity were similar for CC and HF. This is consistent with loss of inhibition contributing to the hippocampal hyperactivity in HF animals. Inhibitory nerve terminal density was markedly reduced and astrocyte pro-inflammatory markers were increased in HF hippocampus.

We found reduced cognitive capacity and hyperactivity, and this was associated with reduced inhibitory nerve terminals and astrocyte activation in hippocampal slices in offspring of obese dams. These observations shed explanatory insights on observations in children of obese mothers, in which the occurrence of childhood seizures is enhanced.