Neonatal hypoxia increases hippocampal excitability in adulthood: Gender differences and prevention by neurosteroid treatment

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Perinatal events can profoundly influence health and wellbeing throughout life. Perinatal hypoxia is a major adverse effect of pregnancy and birth. Epidemiological evidence suggests that obstetric complications are correlated with impaired neural function postnatally that includes cognitive disability, schizophrenia, cerebral palsy and epilepsy.

Rat pups were placed in a chamber containing 3% oxygen in N_2 (hypoxia) or normal air (control) for 15-20 min on postnatal day 10. Some treated pups were injected subcutaneously with the stable allopregnanolone analogue, alfaxalone 4 mg/kg, 30 min before hypoxia. Brain activity was tested when the rats were 10-12 weeks of age. Rats were decapitated under isoflurane anaesthesia and the hippocampus cut into 300 µm slices. A stimulating electrode was placed on the Schaffer collateral nerve tract and activity was recorded from CA1 and CA3 neurons. Slices were studied electrophysiologically: (1) network activity was tested by exposing slices to Mg^{2+}-free solution until electrical activity appeared; (2) pre-synaptic events were tested using paired pulse facilitation (PPF), with pulses delivered 70 ms apart; (3) post-synaptic events were tested in terms of potentiation of synaptic responses for 2 h following tetanic stimulation (4 episodes of 100 Hz stimulation for 1 s).

Following hypoxia, the time for network bursts to commence in Mg^{2+}-free solution was halved (Table), suggesting increased excitability. PPF was increased by 50% indicating facilitation of transmitter release. Tetanus-induced increases in excitability were immediately increased by 116% in hippocampal CA1 neurons and this potentiation was sustained for at least 2h in females, indicating immediate and medium-term changes in post-synaptic responsiveness. In males, immediate potentiation of post-synaptic responses did not occur, but medium-term synaptic responses did not fade as they did in control animals, indicating delayed excitability. The changes in excitability, PPF and post-synaptic potentiation observed as a result of brief neonatal hypoxia were all prevented when the pups were treated with alfaxalone before hypoxia.

	Time to burst onset (min)	PPF (%)	Tetanus treatment (% at 2 h)
Control (n=10)	28±4	175±6	117±16
Hypoxia (n=10)	11±2	225±11	233±22
Hypox+alfaxalone (n=6)	21±2	186±6	92±14

In conclusion, a single brief episode of hypoxia on day 10 of life leads to increased excitability in hippocampal neurons at 10-12 weeks of age. This is prevented by pre-treatment with a stable analogue of the endogenous neurosteroid allopregnanolone, an agonist at inhibitory $GABA_A$ receptors. This suggests that brief hypoxia disrupts normal development of pathways in the neonatal brain, and that synthetic neurosteroids may be suitable for treating neonates at risk of hypoxic events.