DEFICIENT TETRAHYDROBIOPTERIN EXPLAINS THE DOUBLE–HIT OF FETAL BRAIN DAMAGE IN HYPOXIA-ISCHEMIA: A ROLE FOR NOS UNCOUPLING?

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Perinatal hypoxia-ischemia (HI) brain damage is an important risk factor for disabilities in children. Brain damage from HI often causes a wide range of motor impairments such as those found in cerebral palsy and dystonia. It is also known that deficiency in brain tetrahydrobiopterin (BH\textsubscript{4}) causes dystonia at birth. In a normal fetal rabbit model we have found that BH\textsubscript{4} concentrations in the brain at embryonic age 22 (E22) days corresponding to ~70\% full gestational term are in a low range compared to late gestation and postnatal life especially in the thalamus and basal ganglia. We showed that HI depletes BH\textsubscript{4} in the thalamus, basal ganglia and frontal but not parietal and occipital region. These changes correlate with development of severe dystonia hypertonia after HI. Thus, development of motor deficits in HI may be explained by a two hit model where the HI in combination with developmentally low BH\textsubscript{4} results in critical BH\textsubscript{4} deficiency with motor disabilities. One of the best known actions of BH\textsubscript{4} is its cofactor activity for neuronal nitric oxide synthase (nNOS). Low BH\textsubscript{4} increases nNOS uncoupled activity causing unbalanced formation of superoxide and hydrogen peroxide depending on the degree of deficiency and L-arginine supply. Examining the expression pattern of nNOS in the E22 fetal brain, we found that the thalamus expresses the highest level of enzyme compared to frontal, parietal, occipital and hippocampus. The second most abundant region is the basal ganglia. To test the idea that the critical BH\textsubscript{4} deficiency after HI is linked to motor impairments, pregnant rabbits were supplemented prior to HI with sepiapterin (a BH\textsubscript{4} precursor) via mini osmotic pump for a period of 5.5 days (E17-E22). This treatment increased BH\textsubscript{4} in all fetal brain regions, especially in the thalamus, and drastically decreased the number of newborns with severe dystonia. EPR evidence suggests that HI increases EPR active iron-proteins in the brain which may reflect both increased oxidants and iron disturbances. The significance of this finding in the mechanism causing motor disabilities is discussed.

References

