Effect of Lamotrigine Therapy on Consequences of Acute Hypoxia in the Developing Brain

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Objective: Determine the effects of chronic lamotrigine therapy on the consequences of acute hypoxia in the developing brain.

Background: P10 hypoxia in rats is a powerful model for human neonatal hypoxia. Whether chronic lamotrigine therapy is protective against acute hypoxia in the neonatal brain is not known.

Design/Methods: Rat pups were given intraperitoneal lamotrigine from P0 through P21, then subjected to acute hypoxia at P10. Handling and Morris Water Maze tests were performed at P81. At P98, rats were sacrificed for hippocampal histological examination.

Results: Handling test revealed increased aggressivity ($p<0.001$) in the hypoxia without lamotrigine group (21.9 + 1.1) as compared to Control (11.8+ 0.7), Control + Vehicle (14.2 ± 0.6), and the Hypoxia + LTG group (14.3 + 0.6). Control group and hypoxia + lamotrigine group showed no difference ($p>0.05$). Morris Water Maze Test showed that the Hypoxia group (times to reach platform on days 1, 2, 3 and 4 were 1359±26, 242±27, 197±31 and 130±14 seconds, respectively) had long term memory impairment as compared to the Control (263±27, 156 ±15, 121±15, and 90±9), Control + Vehicle (266± 20, 162± 26, 143 ±26, and 80 ±8) and Hypoxia + LTG groups (330±10, 167±27, 113±21, and 79±11). The Control, Control + Vehicle and Hypoxia + LTG groups were not different from each other ($p>0.05$ in all paired comparisons). CA1 cell counts showed that Hypoxia group had reduced cell density in the CA1 (53.5±4.7) region as compared to Control (90.8±2.4) and to Control + Vehicle (65.3±3.9) groups ($p<0.01$ in both comparisons); while the Hypoxia + LTG group (58.7±2.9) was lower than Control group ($p<0.05$) but not different from Control + Vehicle or from Hypoxia groups ($p>0.05$).

Conclusions: Our findings support the notion that chronic use of Lamotrigine in the developing brain may be protective against the consequences of a single superimposed acute hypoxic episode.