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Physiologic and Cellular Mechanisms of Neonatal GABA Mediated Neurotoxicity

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There is a critical gap in knowledge of the cellular, molecular and physiologic mechanisms underlying the behavioral deficit from neonatal anesthetic/sedative neurotoxicity. Understanding this mechanism is a step toward the long-term goal of providing safe anesthesia and sedation for children by eliminating risks for developing associated cognitive deficits. Our preliminary data suggests that this deficit may be caused by GABA mediated excitation. Thus, the overall objective of this proposal is to determine how GABA mediated excitation deleteriously alters early postnatal brain development. The central hypothesis is that a critical period defined by Chloride transporter protein levels, enables anesthetic/sedative drugs to induce GABA mediated excitation which alters cortical development and leads to fewer GABAergic interneurons and a reduction in dendritic spine density. This proposal aims to define the critical period by which GABA excitation imparts susceptibility to neurotoxicity AND to determine the downstream effects of GABA excitation on neurons. At the conclusion of the proposed research, our expected outcome is to define the relationship between excitatory GABA modulation and susceptibility to anesthetic/sedative neurotoxicity. These studies will have a positive impact on our most vulnerable patients by improving our understanding of the parameters for GABA mediated excitation to cause deficits. This contribution is expected to be significant because understanding the mechanism of perinatal anesthetic/sedative neurotoxicity will identify the window of maximum vulnerability, expose processes which lead to cognitive deficits, and highlight developmental milestones where interventions are likely to succeed.