University of Missouri – St. Louis

The Graduate School
Announcement

An oral examination in defense of the dissertation for the degree
Doctor of Philosophy in Psychology with an emphasis in Behavioral Neuroscience

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M.A. in Psychological Sciences, May, 2012, University of Missouri – St. Louis
M.S. in Experimental Psychology, May, 2010, University of Louisiana – Lafayette

Caffeine Combined with Sedative/Anesthetic Drugs Used in Neonatal Medicine and
Apoptotic Neurotoxicity in Developing Mouse Brain

Date: April 19, 2016
Time: 4:00 pm to 5:00 pm
Place:  Stadler 432

Abstract
Each year, millions of premature babies are administered sedative/anesthetic drugs (SADs) in the neonatal intensive care unit (NICU) for procedural sedation and surgeries. Furthermore, pulmonary dysfunction is ubiquitous in premature infants, and caffeine (CAF) is the drug of choice to improve respiratory drive. Thus, premature babies are often co-exposed to CAF + SADs for days, weeks, or months in the NICU.

Acute exposure of the developing brain to SADs triggers programmed cell death (apoptosis) in rodents and non-human primates and causes permanent neurodevelopmental impairment (NDI). Importantly, studies of preterm infants corroborate these data, reporting that exposure to SADs significantly correlates with increased risk of NDI. In addition, recent animal data suggest that SAD-induced developmental neurotoxicity is potentiated by co-administration of CAF. A working hypothesis is that CAF + SAD is a neurotoxic cocktail, killing millions of cells that would contribute to preterm infant brain function. However, the interaction of CAF + SADs is not fully understood, nor is the effect of multiple exposures of these agents since they are often given chronically in the NICU.

Using a mouse model of prematurity, I administered CAF with the NICU SADs midazolam, ketamine, or fentanyl. In the postnatal day (PND) 3 mouse brain, CAF + SAD significantly increased apoptotic cell death compared to CAF or SAD alone. Thus, a single, early exposure to CAF + SAD was sufficient to cause massive apoptosis during brain development. I also tested whether multiple exposures to CAF + SAD are more neurotoxic than a single exposure. Pups were treated with CAF plus midazolam, ketamine, or fentanyl on PND3 and PND6. A separate cohort received treatment on PND6. Interestingly, there was no difference in cell death between PND3 + PND6 and PND6 animals. Since brain regions mature at different time points, these data suggest that premature infants exposed to chronic regimens of CAF + SADs likely experience a widespread, devastating loss of cells in neural substrates responsible for normal brain function. Based on my results, neonatologists should exercise caution by limiting CAF + SADs co-exposure to durations necessary to ensure the survival of babies born prematurely.

Defense of Dissertation Committee
George T. Taylor, Ph.D. (Chairperson)
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