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Introduction to the special issue “Developmental neurotoxicity associated with pediatric general anesthesia: Preclinical findings”

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General anesthesia has been in clinical use for over two centuries. Nevertheless, while the field has achieved significant mastery over its clinical applications and protocols which allow for efficient delivery and sophisticated monitoring of our patients, significant uncertainty remains about the intricate mechanisms by which these agents act and the potential for long-term harm associated with their application.

Whereas adults typically recover from anesthesia without prolonged adverse consequences, observations over the last two decades suggest that exposure to general anesthetics during critical stages of brain development may not be as innocuous as was previously believed. In particular, exposure during periods of rapid synaptogenesis, often referred to as the brain growth spurt, appears to exert negative long-term sequelae. That is, recent studies using animal models and evidence from the clinic suggest that early exposure to general anesthesia disturbs brain development and can, in some cases, lead to permanent cognitive and behavioral impairment.

Safe and reliable pediatric anesthesia is required in modern clinical practice: more than four million children require anesthesia for therapeutic procedures annually in the United States alone. Thus, the clinical importance of the observations of possible adverse effects of early postnatal anesthesia demands our attention and calls for a much better understanding of the mechanisms responsible for the observed outcomes. In light of this dilemma, the FDA recently issued a warning about the potentially detrimental effects of general anesthetics on the brain in children exposed to general anesthesia before the age of 3 years for longer than 3 h¹.

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¹FDA Drug Safety Communications [12-14-2016] FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women.

The goal of this Special Issue is to address the uncertainties regarding pediatric anesthesia and to explore potential mechanisms of anesthesia-induced developmental problems. Experts in the field of general anesthesia-induced developmental neurotoxicity were invited to review currently available knowledge from recent publications and to provide new findings from laboratory experiments. Studies involving a wide variety of species – from *C. elegans* to rodents to primates – are included to emphasize the fact that the phenomenon has been observed in virtually all species examined, even though the duration, complexity and timing of synaptogenesis vary among them.

This Special Issue of *Neurotoxicology and Teratology* addresses the effects of clinically-relevant inhaled and intravenous anesthetics on different components of the nervous system, at several levels of analysis. Work in this issue shows that detrimental effects of general anesthetics occur in both neurons and glial cells, adding to the complexity of the interplay between the brain growth spurt, proper myelination and general anesthetic-induced developmental neurotoxicity. It also shows that anesthetics can affect neuronal synaptogenesis, receptor composition and neurogenesis, and that these effects depend to some extent on the genetics of the exposed animal. Behavioral analyses of exposed animals show that these effects on the nervous system can have long-term adverse consequences on cognitive functions as the animals mature. Finally, different therapeutic modalities that are thought to protect against general anesthesia-induced developmental neurotoxicity are presented.

The editors anticipate that this Special Issue will provide critical findings to support the development of research projects that will advance the field and guidance to improve “best practices” for the protection of our children's health, a goal also shared by a Public-Private Partnership between the US Food and Drug Administration and the International Anesthesia Research Society, SmartTots (<http://smarttots.org/>).