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Editorial

Emerging Model in Anesthetic Developmental Neurotoxicity: Human Stem Cells

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EXPERIMENTAL EVIDENCE OF ANESTHETIC-INDUCED DEVELOPMENTAL NEUROTOXICITY FROM ANIMAL MODEL

It is well known that the prolonged exposure of developing animals such as rodents and non-human primates to general anesthetics can induce widespread neuronal cell death followed by long-term memory and learning disabilities [1-7]. The field of anesthetic neurotoxicity research is rapidly evolving and expanding, allowing for contribution to a better understanding the underlying molecular and cellular mechanisms and developing preventive strategies.

Anesthetic-induced neurotoxicity may depend on the following variables

1. Anesthetic dose, exposure duration, and numbers of exposures [8-10]. Repeated exposures to propofol potentiated neuroapoptosis in neonatal rats [10].

2. The receptor type being activated or inactivated [1-11]. The vast majority of general anesthetics are N-methyl-D-aspartate receptor (NMDAR) antagonists (ketamine and nitrous oxide) and/or gamma-aminobutyric acid types A receptor ($GABA_AR$) agonists (isoflurane and propofol). Transient blockade of NMDAR or excessive activation of $GABA_AR$ during the brain growth spurt period triggers neuroapoptosis. For instance, withdrawal of ketamine induced the compensatory upregulation of NMDAR expression followed by a toxic influx of calcium into neurons, leading to the elevated reactive oxygen species (ROS) generation and neuronal cell death. Administration of the antisense of NMDAR1 attenuated the ketamine-induced neuronal death [12-17]. Isoflurane was found to induce neurotoxicity in the cultured hippocampal neurons via a $GABA_AR$-mediated increase in intracellular calcium concentration [18-19]. Its appears that more profound neurodegeneration is induced if both NMDAR and $GABA_AR$ are simultaneously altered. Combining a nontoxic concentration of NMDA antagonist N_2O with GABA mimetic agents (isoflurane and midazolam) induced a much more severe and widespread pattern of neurodegeneration than either drug category by itself, even at substantially higher doses [1].

3. Brain development stage [11-20]. Isoflurane-induced neurodegeneration was only observed in young rats, but not in adult rats [20]. Intravenous administration of ketamine for 24 h caused an increase of cell death in the cortex of rhesus monkeys at 122 days of gestation and postnatal day 5 (P5) [16]. Following exposure to ketamine for 5 h, less amount of neuroapoptosis was observed in neonatal brains than in fetal brains [11]. Anesthesia neurotoxicity appears to only affect young animals. The window of the greatest vulnerability of the developing brain to anesthetics is restricted to the period of rapid synaptogenesis or the so-called brain growth spurt. This vulnerable period for anesthesia neuroapoptosis is very brief in animals occurring in rodents primarily during the first two weeks after birth. For rhesus monkeys this period ranges from approximately 115-day gestation to P60. In humans, rapid synaptogenesis period starts from the third trimester of pregnancy and continues until two to three years following birth [11]. However, one recent study indicates that vulnerability to anesthetic neuroapoptosis is dependent on the age of the neurons, but independent of the age of the mice. In this study, the effects of anesthetic exposure on the neurons in newborn (P7), juvenile (P21), and adult mice (P49) were examined. The authors identified a critical period of cellular development during which neurons were susceptible to anesthesia-induced apoptosis. This neurotoxicity could extend into adulthood in brain regions with ongoing neurogenesis, such as dentate gyrus and olfactory bulb. However, whether this anesthesia neurotoxicity in adult mice causes abnormal functions of brains remains uncertain [21].

The underlying mechanisms of anesthesia neurotoxicity in animal models are complex and just beginning to be

understood. In addition to a direct influence on NMDAR- and $GABA_AR$-mediated intracellular desregulation and elevated ROS production [12-19]. As it was reported that anesthetic-induced neuroinflammation contributed to neurotoxicity. Anesthesia with 2 h of 3% sevoflurane daily for 3 days only induced cognitive impairment and neuroinflammation (e.g., increased interleukin-6 levels) in the developing mice but not in adult mice. Anti-inflammatory treatment (ketorolac) attenuated the sevoflurane-induced cognitive impairment [22]. Alterations in the levels of a variety of neurotrophins have also been implicated to be involved in anesthesia neurotoxicity in developing rodent brains [23,24]. It was observed that exposure of rat pups to propofol induced a significant decrease in the level of nerve growth factor, a protein that is critical in the survival and growth of neurons, in the thalamus [24]. Additionally, mitochondria appear to play important roles in anesthesia neuroapoptosis [25]. One recent study showed that ketamine increased mitochondrial fission in stem cell-derived human neurons [26]. A similar observation that was also reported by Dr. Jevtovic's group. They noted mitochondrial fission/fusion balance in neonatal rat brains was impaired after a sedative dose of midazolam followed by combined nitrous oxide and isoflurane for 6 h. Increased translocation of the main fission protein, dynamin-related protein 1, from the cytoplasm to mitochondria, and increased oligomerization on the outer mitochondrial membrane might cause increased mitochondrial fission [27]. Collectively, the underlying mechanisms are complex. The anesthetics might also have other detrimental effects on the developing brains such as causing abnormal neuronal plasticity, circuitry organization, and functional connectivity, remaining further investigation.

EPIDEMIOLOGICAL STUDY

The evidence of anesthesia-induced developmental neurotoxicity from animal studies raises the serious concern about the safety of pediatric anesthesia [28-31]. However, similar studies in humans are not feasible. It is also impossible to determine anesthesia neurotoxicity using primary cultures of neonatal human neurons due to the limited access to human tissue. So far, there is no direct clinical evidence showing any such effect in pediatric populations. Considerable controversy remains as to whether the findings from animal studies are relevant to humans partially due to the interspecies differences in development and brain plasticity [32-34]. Several epidemiological studies in humans have implicated that children exposed to anesthesia in early life have a higher incidence of learning disabilities later in life [32-39]. The study of a population-based, retrospective birth cohort showed that children that had received two or more anesthetic exposures were at an increased risk for learning disabilities than the children that had received one anesthetic exposure, or none at all [39]. However, others did not find an association between timing of surgery and neurobehavioral outcome. For instance, monozygotic twins discordant for having received anesthesia showed no significant difference in learning outcomes [40]. There were no differences in educational outcomes at 15 to 16 years of age between 2,500 children with or without inguinal hernia repair [41]. It is very difficult to interpret the discrepancy in the results of the epidemiological studies. Confounding factors in the investigated patients such as surgery procedure, inflammatory, and disease conditions may influence outcome. So far, we cannot draw any conclusions regarding the confirming or ruling out the relationship between anesthesia and neurobehavioral changes. There is a considerable ongoing effort to more fully understand clinical significance of anesthetic neurotoxicity. The US Food and Drug Administration and the International Anesthesia Research Society have formed a unique public-private partnership called SmartTots (smarttots.org) and several retrospective and prospective human studies are underway. In addition, the discrepancy of the results from clinical data also highlights the need of an alternative human model by which to study anesthesia developmental neurotoxicity.

STEM CELL MODEL

Each year, up to 2% of pregnant women in North America undergo anesthesia during their pregnancy for surgery unrelated to the delivery of a fetus. In addition, it is estimated that 4 million children are exposed to anesthetics every year in the United States and throughout the world. Currently, there is no sufficient evidence to determine whether these findings from animal and epidemiological studies are translatable to the millions of young children receiving anesthesia each year. In addition, there is no direct clinical evidence showing any such effect in fetuses, infants, or children at any dose. As for the clinical practice, more evidence is clearly needed to guide clinical decision-making on the safety of anesthesia during pregnancy as well as pediatric anesthesia. Thus, it is imperative to find a reliable mechanistic model to study whether or not clinically relevant doses of anesthetics induce developmental toxicity in human neurons. As we described earlier, the greatest vulnerability of developing brain to anesthetics occurs at the time of the brain growth spurt period. Many developmental events, including neural stem cell (NSC) proliferation, neurogenesis, and cell migration, formation of axons and dendrites, and synaptogenesis occur within this period. Thus, in addition to the induction of neuroapoptosis anesthetics may perturb individual neural development process [42,43]. With the development of stem cell technology, we are able to recapitulate the neurogenesis from human stem cells *in vitro,* allowing the investigations of anesthetic-induced developmental neurotoxicity which is difficult to perform in humans.

Stem cells have two characteristics, proliferation and differentiation. Among various types of stem cells, both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) are able to replicate indefinitely and differentiate into virtually every cell type found in the adult body [44,45]. hESCs are derived from the inner cell mass of human blastocysts. iPSCs are reprogrammed from somatic cells such as skin fibroblasts and blood cells by transferring pluripotency factors (e.g., Oct4, Klf4, Sox2 and cMyc). iPSCs are similar to hESCs in cell morphology, pluripotent marker expression (e.g., Oct4 and SSEA4), proliferation, and differentiation potential [45]. Despite the significant advances in hESC biology, issues such as ethical controversies with hESCs limit their utility. iPSCs can be generated from any patient including those with heritable diseases and,

therefore, carry the genotype of the patient they were derived from. For instance, iPSCs obtained from the patients with long QT syndrome recapitulate the long action potential phenotype features of inherited arrhythmias in the context of the patient's genetic background in cellular culture [46,47]. Thus, development of iPSC technology provides an alternative pluripotent cell source and offers the unique possibility of investigating the cellular consequences influenced by genetic vs. environmental factors in a human model and the underlying mechanisms.

While cultured in chemically defined medium, both hESCs and iPSCs can undergo neurogeneis. This *in vitro* neurogenesis system mimics basal processes of brain development. Multiple sequential steps are involved in hESC or iPSC-neurogenesis and include 1) differentiation of hESCs or iPSCs into NSCs with proliferation and differentiation potential; and 2) differentiation of NSCs into multiple neuronal lineages including neurons, astrocytes, and oligodendrocytes. hESC-derived neurons expressed neuron-specific marker β-tubulin III and synaptic protein synapsin-1 [26]. In addition, differentiated neurons exhibited functional synapse [48]. The differentiation efficiency of NSCs into neurons reached over 90% [26]. This *in vitro* human stem cell model is promising for high throughput examination of developmental neurotoxicity based on the following advantages of this experimental model in addressing the critical issues relevant to anesthetic neurotoxicity.

1. Providing unlimited number of human NSCs, neurons, and other neuronal cell lineages.
2. High throughput screening the neurotoxic effect of various anesthetics under controlled conditions (e.g., dose, duration and frequency of drug exposure).
3. Allowing the dissection of the toxic effects of varying anesthetics on the neuronal cells at various developmental stages and the underlying molecular mechanisms.
4. Investigating the potential preventive strategies to avoid this toxic effect.
5. Eliminating the need for a large number of animals.

Ethanol, an NMDA antagonist, has long been recognized to be neurotoxic to the developing brain [49,50]. Using stem cell approach, ethanol was shown to induce a complex mix of phenotypic changes, including an inappropriate increase in human NSC proliferation and loss of trophic astrocytes [51]. Recently, this *in vitro* human stem cell neurogenesis approach has been used by several groups to examine the effect of anesthetics on NSCs and stem cell-derived human neurons [26,52]. They found that both ketamine and isolfurane influenced neuronal developmental progress including NSC proliferation, neurogenesis, and/or neuronal viability described as follows [26,53]. Different doses and exposure durations of anesthetics resulted in varied effects on the proliferation and neurogenesis of NSCs. A low concentration (0.6%) of isoflurane increased proliferation of these NSCs; a clinically relevant concentration (1.2%) of isoflurane had no effect; and a high concentration of isoflurane (2.4%) caused an increase in proliferation [53]. Ketamine also caused an increase of NSC proliferation after 6 h of exposure [26]. In addition, shorter exposure (1 h) to a high dose of isoflurane (2.4%) had no effect on the differentiation of NSCs into neurons and astrocytes. However, prolonged exposure (24 h) to the same concentration of isoflurane significantly suppressed neuronal differentiation and promoted glial differentiation [53]. This toxic effect may be attributed to differential regulation of calcium release through the activation of endoplasmic reticulum localized inositol-1,4,5-trisphosphate and/or ryanodine receptors. Pretreatment of NSC cultures with inositol-1,4,5-trisphosphate or ryanodine receptor antagonists (xestospongin C and dantrolene, respectively) mostly prevented isoflurane-mediated effects on the neuronal differentiation [53].

Anesthetic not only influenced NSC proliferation and neurogenesis, but also caused hESC-derived neuroapoptosis accompanied with the decreased mitochondrial membrane potential and the increased cytochrome c release from mitochondria, mitochondrial fission, and ROS production. Trolox, a type of ROS scavenger, significantly decreased ROS generation and attenuated cell death caused by ketamine [26]. Collectively, these findings from the *in vitro* stem cell model demonstrate for the first time that anesthetics interfere with neuronal development. Mitochondria were involved in ketamine-induced neuroapotosis that can be prevented by Trolox, suggesting that the *in vitro* hESC-neurogenesis model provides a simple and promising *in vitro* human model for addressing such important anesthesia-related issues. Importantly, this approach has a potential translational application because identification of the cellular mechanisms that underlie anesthesia neurotoxicity will allow targeting of the molecules that can prevent this toxic effect.

One of the major caveats with this *in vitro* stem cell study lies in the relevance of the *in vitro* model to a true *in vivo* system. Specifically, there are many cell types present in the human brain including neurons and glial cells, all of which interact extensively. Utilizing cultures of pure neurons may not allow for the accurate assessment of the effects of anesthetics on intact brains. Establishing an *in vitro* model of co-culturing of multiple types of neuronal cells is needed for mimicking *in vivo* brain environments. In addition, it will be necessary to confirm the *in vitro* findings in animal models.

In summary, development of research in the area of stem cell biology allows the recapitulation of neurogenesis from hESCs *in vitro,* providing a valuable and promising tool for the investigation of anesthetic-induced developmental neurotoxicity, which is very difficult to study in human patients. Utilizing this human model is a major stride toward advancing our understanding of anesthetic neurotoxicity and further assuring the safety of anesthetic agents in young children.

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