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Should we be anesthetizing young children?

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In 2007, the FDA advisory committee on anesthesia recommended that «children less than 3 years of age not undergo elective procedures» because of concerns regarding anesthetic toxicity[1]. The vast majority of the evidence upon which that recommendation was based on young rodents and primates. These studies implicated virtually every available anesthetic as a cause of apoptosis in the young. However, the positive predictive value of evidence from animals for apoptosis in humans is exceedingly small, 10-20%. In addition, socializing and exercise appear to mitigate the damage in young brains, possibly explaining why the gross anatomical changes in the brains of young animals are inconsistent with the experience in humans. Perhaps more importantly, interventions including preconditioning and caspase-3 inhibitors have substantially reduced the injury in these young animals. In this lecture, we review the available evidence that demonstrates that anesthetics (and other compounds) cause neuroapoptosis and neurocognitive dysfunction in young animals, address the limited external validity of these data and present strategies that prevent or limit anesthetic-associated injury in vulnerable animals.

WHAT ARE THE HISTOPATHOLOGICAL EFFECTS OF ANESTHETIC-ASSOCIATED INJURY?

The first pathological finding of anesthetic–induced brain injury was a dramatic increase in neuroapoptosis in newborn rodents who received NMDA receptor antagonists[2]. Although neuroapoptosis during rapid synaptogenesis and brain growth is a normal phenomenon, with loss of up to 50% of cells during the period of brain development, exposure to anesthetics (that antagonize NMDA receptors or stimulate $GABA_A$ receptors) increased the severity of the apoptosis dramatically. The maximum damage in rodents occurred on postnatal day 7, with a corresponding interval in humans of the 3rd trimester of gestation to 3 years of age[3]. Furthermore, the severity of the apoptosis increased with combinations of drugs compared with individually administered drugs as well as with the duration of exposure[4,5]. The second notable finding was the special distribution of the neuroapoptosis. The apoptosis did not occur uniformly throughout the brain and differed among animal subspecies[6-9]. For example in newborn mice, apoptosis was detected after ketamine and midazolam in the cerebral cortex and caudate/putamen regions, in newborn rats in the frontal cortex, thalamus, and putamen, in guinea pigs in layers IV/V of the cortex and in monkeys in the cortex. Several different markers have been used to identify and quantify the apoptosis but the final common pathway has been caspase 3 levels as well as fluoro-Jade C and silver staining[10,11]. More recent evidence has further complicated these findings, noting that apoptosis peaks in some regions of the brain in adolescence, not neonatal rodents[12]. This raises questions regarding the period of vulnerability suggesting that perhaps it is greater than previously appreciated and involves many more areas of the brain than previously thought to be the case.

Not only is neuroapoptosis a significant concern after exposure to anesthetics, but anesthetics also appear to interfere with other facets of brain growth including the arborization of dendrites[13], development of the neurocytoskeleton, neurogenesis and lastly, changes in mitochondrial function[14].

The mechanism by which anesthetics induce apoptosis is poorly understood. How $GABA_A$ agonists and NMDA receptor antagonists trigger apoptosis remains an area of active investigation. Currently, we know that neural cells undergo apoptosis by either the intrinsic or extrinsic pathway, the former dependent on mitochondrial pathways and the latter dependent on surface receptor activation[3,15]. These may be complements by involvement of neurotrophic factors and a neuronal cell dependent pathway[16]. During brain cell remodeling, cells that are active survive whereas those that are

recognized as being inactive undergo apoptosis[14]. Similarly, synaptic development and dendritic growth are linked to the activity levels of the cells, resulting in a similar effect. It is possible that anesthetics induce a state of neuronal inactivity, rendering the cells vulnerable to self-destruction or apoptosis.

WHICH ANESTHETICS/DRUGS ARE INVOLVED AND HOW ARE THEY INVOLVED?

A series of experiments were performed in young rodents in which they received one or more anesthetics including ketamine, midazolam, propofol, inhalational anesthetics, and nitrous oxide *(Table I)*[4-6,17-20]. All of these anesthetics are $GABA_A$ receptor agonists and/or NMDA receptor antagonists, although some are non-anesthetics (eg., dexamethasone). In fact, all anesthetics cause apoptosis and neurocognitive dysfunction when given in large enough doses for long enough periods except the alpha2 agonists (eg., dexmedetomidine), muscle relaxants and possibly opioids. Investigators confirmed that as in the case of alcohol toxicity, maximum apoptosis occurred in postnatal day 7 (PND 7) young rodents, although there is recent evidence that older rodents may develop apoptosis in other parts of the brain, heretofore not the focus of previous investigations[12]. Most investigations have involved newborn rats or mice, although a number have studied fetal animals including non-human primates[21,22]. The severity of the apoptosis after propofol in fetal monkeys is comparable with that in the newborn monkey[22].

Combinations of anesthetics cause more apoptosis than individual anesthetics. In fact, N_2O does not cause apoptosis alone, but the combination such of N_2O and ketamine resulted in apoptosis in specific parts of the brain that exceeded the additive effects of apoptosis by the individual anesthetics[23]. Hence, it appears that combinations of anesthetics augment the severity of the apoptosis to a greater extent than that explained by the sum of the apoptosis of the individual anesthetics. Several anesthetics have been shown to be anti-apoptotic *(Table I)*. Lithium, melatonin, dexmedetomidine and clonidine prevent apoptosis-induced by other agents. Indeed, they have been shown to prevent ketamine-induced neuroapoptosis in the newborn rodent models[24,25].

Table I. Anesthetics anti-apoptotic.

Pro-apoptotic:
• Isoflurane, sevoflurane, desflurane, N_2O, ± xenon
• Propofol, thiopental, ketamine, midazolam, diazepam, $MgSO_4$, dexamethasone
• CO_2, acetaminophen
Anti-apoptotic:
• Lithium, melatonin, clonidine
Non-apoptotic:
• Dexmedetomidine, acute exposure to opioids
Unknown:
• Muscle relaxants

Beyond the histopathology associated with administering anesthetics to young infants, administering an anesthetic impairs neurocognitive development in these young animals. The evidence is unequivocal that the neurocognitive development in young animals exposed to anesthetics is impaired compared to those not exposed and that the dysfunction is not transient but continues into adulthood[26-28]. A variety of cognitive tests including memory, spatial orientation and learning are impaired suggesting substantially impaired cognitive function.

Numerous editorials and letters suggested that methodological errors limit the external validity of the data. Although subsequent studies confirmed reasonably normal physiologic conditions, blood gases and glucose concentrations, the effects of other factors such as pain and surgery remained conflicting.

Current animal evidence points to a direct effect of anesthetics on the immature brain resulting in neuroapoptosis, changes in brain development and long-term cognitive impairment in newborn animals. Most anesthetics that we use today have been implicated in this pathology, although some have been shown to confer anti-apoptotic or no apoptotic properties. Exercise and socializing and several specific drugs and interventions have been shown to attenuate both the histopathological impairment associated with anesthetic exposure in newborn animals[29]. However, what is the positive predictive value of animal data to humans? The answer is ~10%. Hence, we can continue to perform animal studies but until there is confirmation in humans, these data remain of interest in animals only.

Studies have attempted to link the above animal data to humans. To what end has a link been found? First, a host of retrospective, flawed studies have been published, most of which claimed that a link exists between anesthetic exposure multiple times before the age of 3 years and subsequent learning disabilities and other deficits[30]. A large database in identical twins in Denmark however found no difference in school-tested performance in twins who were discordant for anesthetics[31]. Second, two prospective studies now have failed to identify any difference in cognitive function between general anesthetic exposure in young children and precise neurocognitive testing at a later age[32,33]. These two recent studies are consistent with our decades of anecdotal observations as a collective pediatric anesthesia body that general anesthetics are UNLIKELY to induce cognitive dysfunction in children. Additional studies will assist in closing the door on this interesting roller coaster ride of questioning the safety of anesthesia in children.

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