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Neonatal anesthetic neurotoxicity: Insight into the molecular mechanisms of long-term neurocognitive deficits

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ABSTRACT

Mounting animal studies have demonstrated that almost all the clinically used general anesthetics could induce widespread neuroapoptosis in the immature brain. Alarmingly, some published findings have reported long-term neurocognitive deficits in response to early anesthesia exposure which deeply stresses the potential seriousness of developmental anesthetic neurotoxicity. However, the connection between anesthesia induced neuroapoptosis and subsequent neurocognitive deficits remains controversial. It should be noted that developmental anesthesia related neurotoxicity is not limited to neuroapoptosis. Early anesthesia exposure caused transient suppression of neurogenesis, ultrastructural abnormalities in synapse and alteration in the development of neuronal networks also could contribute to the long-term neurocognitive dysfunction. Understanding the mechanisms of developmental anesthetic neurotoxicity, especially by which anesthesia impairs brain function months after exposure, may lead to development of rational preventive and therapeutic strategies. The focus of present review is on some of those potential mechanisms that have been proposed for anesthesia induced cognitive decline.

Contents

1. Introduction

Advances in pediatric medicine have required widespread and prolonged administration of anesthesia to millions and thousands of neonates, infants and children for surgery and diagnostic procedure in operating rooms and intensive care units every year. Conventionally, anesthesia effects are thought to be fully reversible after anesthetic drugs are washed out from our human body. Even general anesthetics are assumed to have neuroprotection effects against to ischemia-reperfusion injury on central nervous system (CNS). However, overwhelming animal data have suggested that various general anesthetics could cause extensive neuroapoptosis and long-term neurocognitive deficits in the immature brain [1–4]. These preclinical data raised considerable concerns about whether potential risk exists in humans and prompted researchers to search for clinical evidence [5]. But the uncertainty of the relationship between neuroapoptosis and subsequent neurocognitive abnormalities add more obstacles on our way to extrapolate laboratory

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findings to clinical anesthesia [6]. The conventional concept is that anesthesia-induced neuroapoptosis is the direct cause of neurocognitive decline, but more and more researches have indicated that neuroapoptosis by itself is not sufficient to cause neurocognitive dysfunction [7]. It is now conceivable that neurocognitive outcome after neonatal anesthesia exposure is attributed to more mechanisms other than brain cell death [8]. To develop prevention strategies requires a clear understanding of the mechanisms of anesthesia induced neurocognitive abnormalities. The goal of the review is to provide a concise summary of proposed mechanisms for anesthesia induced cognitive decline (Table 1).

2. Neuroapoptosis and long-term neurocognitive deficits

Since the groundbreaking research implies that common anesthetic agents could cause widespread neuroapoptosis and persistent cognitive deficits [1], developmental anesthetic neurotoxicity has been duplicated by more and more investigators using several animal species [4]. In these studies, most of the vulnerable brain areas are involved in learning/memory, sensory information processing and cognitive function. It is possible that neuroapoptosis induced significant neuronal loss in these functional brain regions is able to produce adverse impact to fundamental development of neuronal networks, which lead to long-term neurocognitive decline. It is therefore seem to be plausible that a threshold level of neuroapoptosis must occur for cognitive deficits [9]. In other words, anesthesia exposure could induce apoptosis with several levels in the different regions of the immature brain, but behavioral effects only with the highest level of apoptosis in the important functional regions, for example, profound damages in hippocampus [10]. Accordingly, in the studies that obtained impaired learning/memory function, the cognitive deficits are largely hippocampal dependent and neuroapoptosis in the hippocampus is much more robust compare to other brain structures. This could explain why immediate neuroapoptosis is easily observed after anesthesia, while long-term neurocognitive impairment has only been verified in some, but not in all studies. But it is important to recognize that cognitive impairment is caused by cell death induced neuronal loss, but not cell death itself. So, only the detectable reduction in neuronal density in adulthood (when cognitive function is assessed) could support the premise that cognitive impairment is associated with neuroapoptosis [11]. Most preclinical studies focused on the timing and magnitude of anesthetic administration that necessary to induce neuroapoptosis and following cognitive impairment. However, little effort has gone into exploring the causal link of immediate neuroapoptosis and long-term neuronal density. Some studies have failed to establish the association between neuroapoptosis and long-term cognitive impairment, most of them attributed this disassociation to lower concentration, less exposure time and single anesthetic agent administration [12,13]. But without adult neuronal density quantification we can not exclude the possibility that even with lower concentration and less exposure time, single agent has already resulted in detectable neuronal deletion while not lead to long-term impairment in learning/memory task. That means neuroapoptosis may not be the direct cause of cognitive impairment.

There are a few points that need to be noted when scrutinizing the relationship between neuroapoptosis and neurocognitive deficits. First of all, increased cell death after anesthesia exposure in the immature brain does not inevitably lead to a significant reduction in neuronal density at adulthood. Programmed cell death (apoptosis) is a normal phenomenon that occurs as brain matures. During brain development, as many as 50–70% of the entire neuronal population will undergo natural cell death to maintain normal structure of the CNS [14]. Thus, it remains unclear that whether anesthesia accelerates apoptosis of neurons that were obliged to die due to physiological degeneration, or if it destroys health neurons that were not destined to die. Normal adult neuronal density may represent transiently hastened physiological apoptosis followed by a compensatory decrease in the rate of cell death as the brain matures. The net effect may be preserved adult neuronal density [11]. On the other hand, decreased adult neuronal density may present increased pathological cell death which beyond the compensatory capacity of the developing brain that lead to significant neuronal loss in adult [15]. Second, as a marker of neuroapoptosis, caspase-3 has been used in almost all the experimental researches regarding anesthetic neurotoxicity to demonstrate immediate brain cell death. But anesthesia induced neuroapoptosis might be (as yet undetected) delayed and progressive. It is possible that many caspase-3 negative neurons will activate cell death cascade and proceed to death before cognitive testing. On the other hand, some caspase-3 positive neurons may not complete the cell death cascade and survive [16]. It means that the actual neuroapoptosis may be underestimated or overestimated without long-term neuronal density quantification. Third, even caspase-3 stained cells in the immature brains met the morphological characteristics of neurons, we still can not clearly separate neuronal from non-neuronal cells. Increased cell death in the neonatal brain could just reflect the increased loss of non-neuronal cells that seldom lead to long-term cognitive abnormalities. Another concerned point is that anesthesia administration could cause severe physiological disturbances (lactoacidosis, hypercarbia and hypoglycemia) that also could lead to neuroapoptosis in the brain of neonatal animals [17,18]. Although most of preclinical studies have performed arterial

Table 1
Summary of representative preclinical studies related to mechanisms of anesthetic induced long-term neurocognitive deficits.

Agents	Species	Pathology	Tests	Neurocognitive outcome
Ketamine Thiopental Propofol [2]	Mice	Increased neuroapoptosis	Spontaneous behavior Radial arm maze Elevated plus maze	Disrupted spontaneous activity and learning
Isoflurane [9]	Rats	Decreased progenitor proliferation	Fear conditioning Water maze	Progressive and persistent deficit in fear conditioning and spatial learning/memory
Sevoflurane [29]	Rats	Reduced spine density and damaged synaptic ultrastructure	Water maze Novel-object recognition	Impaired spatial learning/memory and memory recall
Propofol [31]	Rhesus macaque	Increased apoptosis of oligodendrocytes	N/A	N/A
Propofol [33]	Rats	Increased neuroapoptosis and decreased neurotransmitter levels	Water maze	Impaired spatial learning/memory