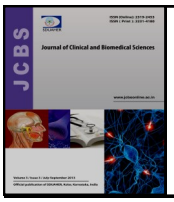

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Guest Editorial

How Safe are General Anaesthetics to Brain Itself ?

Mechanisms of General anaesthesia remain incompletely understood. It has been assumed that anaesthetics have minimal or no persistent effects after emergence from anaesthesia. Currently anaesthesia is conceptualized by its core features of amnesia, unconsciousness and immobility (in the order of decreasing potency), each mediated by pharmacological effects on specific neuronal networks of CNS. The molecular targets of these region- and dose-specific actions have not been defined for most anaesthetics. These could be ligand-gated ion channels involved in inhibitory (GABA and glycine) or excitatory (NMDA and AMPA glutamate receptors) of synaptic transmission, ion channels conducting Na+, Ca2+ and K+ that regulate neuronal excitability and chemical transmission, and pleiotropic intracellular signalling pathways.[1] So it should come as no surprise that this diversity of potential targets increases the probability of both positive and negative non-anaesthetic effects,that range from beneficial to detrimental.Evidence is accumulating to question safety of general anaesthesia at the extremes of age.[2]

While the actions of the intravenous (i.v) anaesthetics like Propofol and Etomidate, can often be ascribed primarily to one or a few targets, the inhaled anaesthetics (ethers and alkanes) appear to be less potent (<100), interacting less selectively with larger number of many functionally important targets, both in the nervous system and in other organs. The developing brain has several significant differences from the adult brain that provide a physiological basis for enhanced vulnerability to anaesthetics.

Developing or Young Brain

1. Early in development the number of neurones formed is significantly greater than in adult mammals

2. At the same time, there is an exuberant burst of synapse formation (synaptogenesis). It has been hypothesized that perinatal exposure to anaesthesia suppresses neurogenesis. proliferation with delayed -onset deficits in fear conditioning and spatial reference tasks.

3. Programmed cell death, or apoptosis, is responsible for the elimination of 50–70% of developing neurones under normal circumstances and has both physiological and pathological roles. It is difficult to determine the extent or impact of apoptosis after anaesthesia involves cells that were already destined to die, or whether anaesthesia induces excessive apoptosis in viable cells that might negatively impact maturation of the nervous system.[3] In immature rodents a surgical plane of anaesthesia for 6 hours by cocktail of Isoflurane, Ketamine, Midazolam and Nitrous oxide was created.[4] Immediately after exposure, the rat pups developed excessive neuronal apoptosis throughout the brain, including the hippocampus and cerebral cortex. This apoptotic effect was significant both physiologically, with impairment of learning and memory and behaviorally, with impairment of spatial reference memory even as they grew into juveniles. Equipotent exposure of neonatal mice to Desflurane, Isoflurane and Sevoflurane produced similar increases in apoptotic cell death. In vivo or in vitro data suggest increased neuronal cell death after neonatal animal exposure to Midazolam, Diazepam, Clonazepam, Propofol, Pentobarbital, Nitrous oxide and Xenon. Hence concerns that derangements of physiological homeostasis secondary to anaesthesia might contribute to neurodegeneration are valid.

4. It has been proposed that anaesthetic suppression of spontaneous neuronal activity might lead to insufficient neurotrophic factor secretion in the developing nervous system, rendering them more susceptible to apoptosis.

5. One significant difference between immature and mature mammalian brain with neuropharmacological implications is the developmentally regulated reversal of the transmembrane chloride gradient. This is relevant to anaesthetic effects as many anaesthetic agents enhance the activity of GABA and glycine receptor. Increase in chloride permeability associated with GABA or glycine receptor activation leads to hyperpolarisation resulting in suppression of neuronal activity in adults whereas in imma-

ture developing brain, the receptor activation leads to depolarization, with resultant excitation. Hyperexcitation in human neonates evident by electroencephalography has been reported with Sevoflurane, Isoflurane and Propofol anaesthesia. Observation of seizures in neonatal rats exposed to Sevoflurane and the finding that both seizure activity and apoptosis could be mitigated by co-administration of Bumetanide (chloride transport inhibitor) suggest that apoptosis after anaesthesia could be secondary to excitotoxicity rather than to the withdrawal of trophic factors. It remains to be seen whether perturbation of the neonatal chloride gradient can rescue neurones from apoptosis under other conditions.[5] The most robust neurotoxicity data available in primates were obtained by exposure of rhesus monkey fetuses and newborns to 24 h of Ketamine anaesthesia. This produced neurodegeneration assessed using biomarkers for apoptosis both neonatal and older primates. It is possible that there is an exposure threshold or minimum dose, exposure time for neurodegeneration. Information regarding the minimal neurotoxic dose and duration in humans would be extremely useful in defining the margin of neurological safety for specific anaesthetics. But it will be impossible to reliably obtain such data until specific non-- invasive biomarkers for apoptotic neurodegeneration are developed. It is difficult to compare data from rodents and primates. Anaesthetic neurotoxicity is probably most significant for the premature human fetus rather than term neonates or infants. There is a paucity of human data to support or refute the clinical extrapolation of these animal data.

6. It is likely that early exposure to anaesthesia can, under certain circumstances, lead to long term cognitive deficits in humans. Children who underwent hernia repair before 3 yr of age were more than twice as likely than age-matched controls to have a developmental or behavioural disorder. The longterm cognitive effects of early anaesthetic exposure is a matter of study for the SmartTots programme by FDA, GAS study, PANDAS, etc. Further studies are essential to determine the relative toxicity of specific agents and the possibility of concomitant administration of neuroprotective drugs to counteract the pro-apoptotic effects of anaesthetics.

Old Brain

The elderly appear to be at increased risk of prolonged post-operatve cognitive dysfunction (POCD) after surgery/ anaesthesia.[6]

1. With ageing, rates of neurogenesis and synaptogenesis decrease, the total number of neurones decline, and potentially toxic by-products accumulate leading to a gradual loss of reserve, increasing vulnerability to insults, including exposure to perioperative stressors. Current theories for anaesthetic contributions to POCD include direct toxic effects, like alterations in calcium homeostasis, systemic inflammatory effects of surgical insult, age-sensitive suppression of neuronal stem cell function and acceleration of ongoing endogenous neurodegenerative processes.

2. *Alzheimer's Disease vis-à-vis Anaesthesia:* Alzheimer's disease is a chronic neurodegenerative process associated with diffuse atrophy of the cerebral cortex, deposition of characteristic plaques of amyloid β (Aβ) peptide. Isoflurane, Isoflurane with nitrous oxide, Sevoflurane and Desflurane with hypoxia[induce apoptosis and increase Aβ formation. Volatile anaesthetics enhance aggregation of Aβ in vitro,[7] providing another potential interaction between anaesthesia and Alzheimer's pathology. However, choice of drug, exposure duration, dose, and interval to testing might all matter. Multiple anaesthetic agents can also promote hyperphosphorylation when associated with hypothermia.

3. Several studies suggest a potential neuroprotective preconditioning effect with lower exposures.

4. Several studies have attempted to study the effect of systemic inflammation from a surgical insult on neuro-inflammation, neurogenesis and postoperative cognitive function. Increased levels of TNF-α, IL-6, and IL-1β have been reported in neuroinflammatory response to surgery which is attenuated by an IL-1 receptor antagonist or peripheral TNF-α blockade and hence modified the associated postoperative cognitive decline.[8]

5. Data linking Alzheimer's disease pathophysiology to anaesthesia exposure in humans are contradictory in mean cumulative duration of general anaesthesia in a 1–5 yr window preceding the onset of Alzheimer's disease. Recent evidence suggests that the severity of POCD might have been overestimated. A relatively recent retrospective cohort study by Avidan and colleagues found no long -term cognitive decline in annual assessments that could be independently attributed to illness or surgery and neither illness nor surgery appeared to speed progression to dementia, although pa-

tients who had initial dementia declined more rapidly over the course of the study than those who did not.[9]

Clinical Corollary

The clinical impact of these preclinical findings has not been established owing to difficulties in designing definitive studies and the significant delay between exposure and testing. Clearly further investigations, both experimental and epidemiological, are warranted to establish the clinical relevance and possible neuroprotective strategies for these untoward effects. It is unlikely that definitive clinical studies absolving general anaesthetics of neurotoxicity will become available in the near future. Alternatives to surgery and general anaesthesia are usually not available and pain itself can cause long -term neurodevelopmental deficits. As current data do not support significant changes in practice other than avoiding purely elective procedures, anaesthesiologists should strive to minimize unnecessary exposure to general anaesthetic agents and other factors that might potentiate toxicity in extremes of age.

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