Anaesthesia and the developing brain

Jansie Prozesky*

Department of Paediatric Anaesthesia, Penn State Hershey Medical Center, Hershey, Pennsylvania, USA
*Corresponding author, email: jprozesky@hmc.psu.edu

Increasing concern about the effect of anaesthesia on the infant and young child is being raised by healthcare practitioners, as well as the public. Immature neurons exposed to anaesthesia may lead to apoptosis and long-term neurobehavioural deficits in animals. The majority of anaesthetic agents work by influencing the gamma-aminobutyric acid or N-methyl-D-aspartate receptors and may induce animal neuroapoptosis. The search for neuroprotective strategies to reverse or counteract the effect of anaesthesia has not been very successful so far. Dexmedetomidine is an α2-adrenergic receptor and may have neuroprotective effects. Available human studies have failed to prove any long-term neurobehavioural deficiencies caused by anaesthetic exposure. Large international prospective studies are currently underway that may change the practice of paediatric and obstetric anaesthesiologists in the future.

Keywords: GABA, neurobehavioural deficits, neurodevelopmental, neurogenesis, NMDA, plasticity, synaptogenesis

Introduction

For more than 150 years of anaesthesia practice, it was believed that once the anaesthetic wore off, the brain returned to the same state as before.1 With emerging evidence from animal studies on long-term neurobehavioural deficits after anaesthesia exposure, including extensive neuroapoptosis,1 the question: “Can anaesthetic agents cause any long-term neurological development deficits?” is often posed by parents, parents to be and surgical colleagues. What is the evidence? How can this be prevented from occurring or is it reversible?

To answer these questions, it is necessary to consider how the brain develops, and how anaesthetic drugs influence it. From this understanding, better choices can be made in terms of planning the timing of elective surgery in pregnancy, as well as that with respect to the neonate or young child. And if surgery is prudent, what anaesthetic drugs are the safest?

Brain development in the human

The development of the human nervous system consists of consecutive steps. Neurogenesis starts in the foetus with differentiation and neuronal migration, followed by the establishment of synaptic connections, i.e. synaptogenesis, which continues postnatally.2,3 By birth, most neurons have migrated to their final location in the brain.2 The formation of the synapses is dependent on electrochemical activity, and involves the activation of calcium channels.4 Neurogenesis and synaptogenesis are activity dependent: “Neurons that fire together, wire together.”6 The peak period of myelination occurs during the first two years after birth, during which period the brain structure drastically changes its biochemical composition.4 The brain's ability to learn, remember, forget, recover from injury and reorganise is called cerebral plasticity.7 The developing brain has the greatest potential for recovery from any injury because of an overproduction of neurons in the foetus and the overproduction of synapses after birth.8

Cerebral plasticity not only helps the brain to recover from injury, but may also lead to abnormal adaptation and therefore abnormal structural changes.2 Adverse experiences, e.g. repetitive pain during early brain development, can modify neuronal activity patterns and may permanently alter the functional wiring of the immature neurons.1 This may lead to behavioural and emotional problems in childhood, altered pain responses, anxiety, depression or suicidal tendencies.2 Apoptosis is also a part of normal growth and development,6 and approximately 1% of mammalian brain neurons that are dysfunctional are normally pruned in this process to maintain normal functioning pathways.7 Brain development is not a uniform process, but consists of spurts of increased development, followed by periods of lesser brain development which occur in different areas of the brain. Neurogenesis and neuronal migration accelerate and reach a peak during and after the second trimester of pregnancy.5

Mechanism of action of anaesthetics on the brain

The majority of anaesthetic agents work by two basic mechanisms in the brain: an increase in inhibition via the gamma-aminobutyric acid (GABA) receptors, e.g. benzodiazepines, barbiturates, propofol, etomidate, isoflurane, enfurane and halothane, and a decrease in excitation through the N-methyl-D-aspartate (NMDA) receptors, e.g. ketamine, nitrous oxide (N2O) and xenon.9,10 Dexmedetomidine is the exception to these mechanisms. The drug is a potent α2-adrenergic receptor agonist that has eight times higher affinity for the α2-adrenergic receptor than clonidine. Dexmedetomidine has sedative, analgesic and anxiolytic properties.11 Recent findings indicate that drugs that act by inhibition of either the GABA or the NMDA receptors induce widespread neuronal apoptosis in the immature rat brain when administered during synaptogenesis.12 Apoptosis is increased if the neurons are exposed to a combination of GABA agonists and NMDA antagonists.7 Neuronal exposure to anaesthetics during a critical the neurodevelopmental period triggers an unknown chain of events, causing the translocation of BCL2-associated X protein to mitochondria, followed by mitochondrial membrane disruption and permeability, resulting in the leakage of cytochrome c into the cytosol.7

The evidence

Animal studies

In analysing the literature, it is important to understand the animal model. The lifespan of a rodent is approximately three years, and synaptogenesis occurs mainly after birth.2 Therefore, the neuron lifespan of a rodent is a maximum of three years, in comparison with the human neuron lifespan, which may be over 100 years.1 It is important to recognise that the anaesthetic exposure of a rat is
The underlying mechanism of the potential intrauterine anesthetic drug-induced neurological changes during pregnancy is not fully understood. It seems that since GABA is a trophic factor for the developing brain, use of GABA-stimulating agents during critical brain development periods can lead to neural connectivity injury. Reduced synaptic activity and neuroapoptosis in the developing brain can be triggered, even by short exposure to commonly used anesthetics, such as propofol, ketamine, N₂O, isoflurane, sevoflurane, barbiturates and benzodiazepines. A combination of anesthetic drugs can increase the severity of neuroapoptosis.

However, it is very difficult to translate animal studies to humans. In contrast with rodents, where rapid brain growth (synaptogenesis) takes place after birth, the process starts in mid-gestation in humans and continues for a number of years after birth. Recent clinical studies suggest that major disability is unlikely with brief exposure to anesthesia in the older child. It is known that anesthesia-induced neurotoxicity is a real phenomenon in young rodents. Infants are rarely exposed to anesthesia in isolation. Also, many other factors can lead to neurotoxicity, e.g. untreated pain may induce significant, long-term harmful consequences. In addition, hypoxia has been associated with neuronal apoptosis in neonatal animals. Many confounding factors influence the results of human studies. Children who require more interventions and anesthetics usually have significant chronic illnesses that may, per se, contribute to learning disabilities. Another factor is that the majority of the studies did not comment on subtle neurobehavioural deficiencies. Environmental influences, e.g. a lag in psychosocial stimulation, resulted in lower intelligence quotients and memory scores and more behavioural difficulties in children.

Neuroprotective strategies
If anesthetic agents are possibly detrimental to neurobehavioural development in the unborn or young, are there any strategies or medications which could reverse or counteract their effects?

Erythropoietin, antidepressants and lithium are modalities that may enhance recovery after cerebral injury. Melatonin is worth mentioning. Melatonin was found to reduce anesthesia-induced neuronal apoptosis in rats in a dose-dependent way. It was previously shown that melatonin counteracts mitochondrial biochemical changes caused by anesthetics that lead to apoptosis. Melatonin causes the upregulation of the anti-apoptotic protein and a decrease in anesthesia-induced cytochrome c release into the cytoplasm. Also, melatonin causes a decrease in anesthesia-induced activation of caspase-3, an important step in the activation of deoxyribonuclease and the formation of apoptotic bodies. Another non-specific neuroprotective effect of melatonin may be the ability to decrease the requirement of anesthesia by inducing sleep and attenuating analgesia. Hypothermia has demonstrated neuroprotective effects in several neonatal studies, with hypoxic-ischaemic encephalopathy and improved neurological outcome. Hypothermia has its own harmful effect on newborn infants, and this is well described in the literature, e.g. impairment of the transition from the intrauterine to the extraterine circulatory pathways by increasing pulmonary vascular resistance.

Because dexmedetomidine is neither a GABAergic nor NMDA antagonist, it has been hypothesised that it is free of developmental anaesthetic toxicity. Dexmedetomidine improves neurocognitive deficit induced by a subanaesthetic dose of isoflurane by reducing neuronal apoptosis in a dose-dependent way. This was reversed through blocking the α₂-adrenergic receptor, indicating that the protective effect is mediated by this receptor. Unfortunately, at present, there are no convincing data to propagate the use of any of these agents in humans, with or after anesthesia exposure.
The future
With so many questions and so few answers, several international research groups are currently conducting research to better understand this very important concern. The research includes the following:

• General Anesthesia Study (GAS): This is an international, multisite, randomised controlled study investigating whether or not the long-term effects of spinal and general anaesthesia result in the same neurodevelopmental outcomes.

• Pediatric Anesthesia Neuro Development Assessment Study (PANDA study): The focus of this multicentre USA group is to compare the neurodevelopment of children exposed to anaesthesia with that of those not exposed to anaesthesia.

• The Oregon University Group: Angsar Brambrink, together with a multidisciplinary group, is investigating the long-term functional and morphological consequences of single versus triple anaesthesia exposure in infant non-human primates.

• National Center for Toxicological Research (NCTR): A group in the USA is conducting non-clinical studies in rodents and non-human primates to assess the mechanisms, long-term deficits and strategies to prevent or decrease neurotoxicity with respect to clinically relevant anaesthesia.

• The MASK study: This study is being conducted by the Mayo Clinic and the National Center for Toxicological Research. It compares the performance of children with no anaesthetic exposure to that of those with single or multiple exposure.

• Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots (SmartTots): This is a collaborative effort between the US Food and Drug Administration and the International Anesthesia Research Society to coordinate and fund some of the previously mentioned research programmes.

Conclusion
Research in animal studies indicates that anaesthetic exposure of the immature brain causes long-term anatomical and neurobehavioural deficits. The available limited data from prenatal animal studies indicate that the brain is vulnerable to anaesthesia exposure during pregnancy, especially in the second trimester onwards. All anaesthetic agents may be harmful and have an additive effect. No agent or modality has been proven to counteract or neutralise the anaesthetic effect on the brain.

Human studies are limited and lack evidence of detrimental effects on the neonatal and foetal brain. Currently, there is not sufficient evidence to warrant a change in paediatric anaesthesia practice, postponing necessary procedures or withholding the necessary analgesics, sedatives or anaesthetics from pregnant, as well as neonatal and young, patients. This is unethical and may lead to significant harm. Multicentre, international studies are underway, and will hopefully delineate the risk of anaesthesia exposure in the foetus and newborn baby.

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Received: 16-04-2014 Accepted: 03-07-2014