Early Human Development xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

The effect of anaesthesia on the infant brain

Andrew Davidson MBBS MD FANZCA

Melbourne Children's Trials Centre, Murdoch Children's Research Institute, Australia
Department of Anaesthesia, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria 3052, Australia

ARTICLE INFO

Available online xxxx

Keywords:
General anaesthesia
Neurotoxicity
Paediatrics
Apoptosis

ABSTRACT

Pre-clinical studies have consistently found that most general anaesthetics produce accelerated apoptosis in the developing brain. The effect has been seen in species ranging from the nematode to the non-human primate. A variety of other effects are also seen. There is also some evidence that animals exposed to anaesthesia are at increased risk of deficits in memory and learning. The effects are only seen with prolonged exposure. There are numerous problems in translating these findings to human clinical scenarios. Several human cohort studies have found an association between surgery in infancy and increased risk of poorer neurobehavioural outcome; however the possibility of confounding factors such as co-morbidity and surgery itself make it impossible to determine if these associations are due to anaesthesia toxicity. A recent trial and cohort studies suggest that an exposure of less than an hour does not increase the risk of poor outcome.

Contents

1. Introduction

There is considerable controversy around the lasting effect of anaesthesia on the brain [1–4]. Previously it was assumed that anaesthesia effects were transitory and merely related to suppressing neural traffic. Increasingly it is recognised that the brain continually adapts to its state and that the anaesthetised state could result in lasting changes in morphology. This may be reflected in triggering cell death or by more subtle changes such as changes in dendritic morphology or synaptic density. The changes are most apparent in the developing brain. The clinical relevance of these changes is very uncertain.

2. Animal data

There is a large amount of preclinical evidence describing how many general anaesthetics alter brain development in young animals. The effects of anaesthetics on the developing brain were first noted by a group originally investigating the effects of alcohol and antiepileptic medication. A seminal study in 1999 found widespread apoptosis following exposure to NMDA antagonists in rat pups [5]. In the following years accelerated apoptosis was observed after exposure to most general anaesthetic and sedative agents including benzodiazepines, nitrous oxide, desflurane, halothane, isoflurane, sevoflurane thiopentone, propofol and ketamine [6]. There are now hundreds of papers describing accelerated apoptosis after exposure to anaesthesia in many species including nematodes, rodents, piglets and non-human primates.

The changes are greatest after longer exposures. Accelerated apoptosis is usually only seen after several hours of exposure. Effects are also greatest in younger animals; in rats the effect is greatest at day 7 [5],

E-mail address: Andrew.davidson@rch.org.au.

http://dx.doi.org/10.1016/j.earlhumdev.2016.09.006
0378-3782/

and in primates during late gestation or the neonatal period [7,8]. There is also some suggestion that combinations of agents may be more deleterious. The area of the brain affected varies and includes the superficial cortex, thalamus, amygdala and hippocampus. The mechanism is unclear. The agents may have a direct toxic effect or the changes may be triggered by a change in neuronal activity or even the lack of neuronal traffic that often characterises the anaesthetised state.

Apoptosis is not the only effect seen. Other effects include alterations to dendrite architecture [9], effects on neurogenesis, a decrease in trophic factors [10], destabilisation of the cytoskeleton [11], abnormal re-entry into the cell cycle [12] and degeneration of the mitochondria [13]. It is unclear if this variety of effects is linked though a common mechanism.

Neuro-behavioural effects have also been detected although the results from the studies are often inconsistent and often defects were seen in only some very specific domains. In rodents, most often the deficits are seen in tests of learning and memory [6,14–16]. The most important studies are those which have demonstrated long term altered behaviour and impaired learning in non-human primates [17]. It is not known if the neurobehavioural changes are correlated with the morphologic changes. There are examples of where accelerated neuroapoptosis is not associated with any neurobehavioural defect.

In summary from preclinical data:

- Many general anaesthetics have a variety of effects on the developing brain; including apoptosis.
- The effects and regions affected vary with *dose*, *agent* and *age* of exposure.
- The strongest evidence for morphologic change is for agents that are *GABA agonists* or *NMDA antagonists*.
- The changes are greatest in *young* animals and with *longer* and *repeated* exposure.
- There are multiple mechanisms described.
- There is mixed evidence for long term neurodevelopmental changes in rodents and *non-human primates*.

3. Problems in translation

There are many problems translating the preclinical data from animal models to human clinical scenarios.

Given that the effect is seen in such a wide range of species, there is no reason to expect that the effect would not be seen in humans if given at a sufficient dose, for a sufficient duration in the age most susceptible. What we don't know is what dose, duration and age are required for there to be any morphologic effect in humans, and more importantly, we do not know if the morphologic changes would have any clinical correlates.

The human brain is obviously far more complex than a rodent or non-human primate brain. It is plausible that any morphologic change could be of no consequence given the prolonged period of complex development. The human response to brain "injury" depends on the timing of the injury, the nature of the injury, as well if it is diffuse or focal, and the site if focal. Lastly any effect can be substantially modified by the environment or genetic makeup of the child. Given that the nature of injury in preclinical studies remains poorly defined and varies with age and dose, it is unlikely that there will be a single obvious phenotype in humans.

The doses required to produce anaesthesia in animals may vary considerably compared to humans. While the concentration of volatile anaesthetic required to produce immobility is remarkably constant across species, the mg/kg dose of ketamine and other injectable agents may be up to 50 times higher in animals. The duration of exposure needed for injury is also difficult to translate. A five hour exposure in a rodent represents an exposure for a significant proportion of the animal's neurodevelopment, while for a human this is a relatively fleeting period of time. The timing of exposure is difficult to interpret. While a day 7 rat may "represent" a late gestation or neonatal human in some aspects of neurodevelopment, it is naïve to attempt to too closely correlate particular periods of animal development to humans as trajectories of different aspects of development differ across species.

A very considerable problem with translation is the other physiologic impact of anaesthesia. Infant rodents are difficult to anaesthetise safely. Some studies report high mortality due to respiratory and cardiovascular events. It is plausible that some of the changes seen may be due to hypoxia etc. In contrast human neonates are monitored very carefully during anaesthesia and there is considerable effort to ensure that physiologic homeostasis maintained. Thus the animal data that is most relevant to humans are the non-primate studies where conditions more closely resemble human anaesthesia.

Lastly few animal studies are done in the context of surgery. It is unclear if the effect of surgery may compound any effect from anaesthesia.

In summary for translation:

- There is no reason to suggest the changes in animals would not occur when the developing human brain is exposed to sufficient doses of general anaesthetics.
- But, there are precedents for animal models being irrelevant to humans.
- It is hard to predict what age, or at what dose, children are at risk.
- We have incomplete data on which neurological domains in humans are likely to be affected, if any.
- We don't know the impact of surgery.
- There are many modifying factors when translating animal to humans.

4. Human data

There are numerous cohort studies examining the association between exposure to anaesthesia in early childhood and neurodevelopmental outcome. The cohort studies have found conflicting evidence for an association between exposure to anaesthesia and adverse long-term neurodevelopmental outcome [18–27]. Most cohort studies have found an increased risk of poor neurodevelopmental outcome following anaesthesia [18,19,21–23,28]. Small cohort studies looking at children who have had repair of congenital diaphragmatic hernia, oesophageal atresia, or congenital heart disease, laparotomy for necrotising enterocolitis and hernia repair in very premature infants have all shown an association with increased risk of poorer neurodevelopmental outcome [29–33]. Several larger cohort studies have been performed to specifically address the issue of anaesthesia neurotoxicity. One study looking at children after hernia repair fund weak evidence for an association between hernia repair and a later diagnosis of a behavioural or developmental disorder [23,34]. Another study found an association between exposure to anaesthesia in children less than 2 years of age and later learning disability [21,35]. Both these studies found a greater effect with multiple anaesthetic exposures and little evidence after a single exposure. Several studies have looked at school grades. They found evidence for an increased risk of marginally worse school grades in children that had anaesthetics in infancy however there was little or no evidence for any association when adjusted for various known confounding factors [25,36]. Interestingly children that had anaesthetics were at greater risk of not attaining the level of school when the tests were performed. Three relatively small studies have examined specific psychometric tests in older children and found evidence for an association between exposure to anaesthesia and worse scores in cognitive, memory, listening comprehension and language tests [19,28,37–39]. Although these associations are in line with preclinical animal data, it could also be explained by the confounding effects of surgery, pathology, or co-morbidity. Infants and young children who receive anaesthesia inevitably undergo surgery or a

Please cite this article as: A. Davidson, The effect of anaesthesia on the infant brain, Early Hum Dev (2016), http://dx.doi.org/10.1016/j.earlhumdev.2016.09.006