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Review of preclinical studies on pediatric general anesthesia-induced developmental neurotoxicity

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ABSTRACT

Thousands of infants and children undergo complicated surgical procedures that require prolonged periods of anesthesia and/or sedation each year. A growing body of preclinical research suggests pediatric anesthetics are harmful to the developing brain; yet, the extent to which these effects generalize to the clinical setting remains unclear. As there will be a continuing need for surgical and other interventions requiring sedation and/or anesthesia during the neonatal period, it seems clear that research efforts should focus on determining the extent to which general anesthetics can affect the developing brain as well as determining strategies for preventing or ameliorating the adverse effects associated with exposure to such agents. The purpose of this paper is to provide a review of the preclinical literature examining the effects of general anesthesia on brain and behavioral development. This paper will detail the effects of different anesthetic agents on various indices of neurotoxicity and functional outcomes as well as provide a review of potential protective compounds and suggestions for areas of future research.

1. Introduction

In 2014, approximately 1 of every 10 infants (9.57%) in the United States was born preterm (Hamilton et al., 2015). Fortunately, continuing advances in pediatric medicine have resulted in an increased ability to keep premature infants and otherwise compromised neonates alive. Part of this success lies in the increased number of complicated surgical procedures and other interventions that are brought to bear in this already at-risk population (Tzong et al., 2012). However, many of these procedures are carried out under various forms of anesthesia and/or sedation, often in combination with other therapeutics that can impact the central nervous system (CNS) and often for protracted periods (de Graaf et al., 2011). Concerns over the potential adverse effects of these kinds of exposures have prompted the need for studies to address this issue (Olney et al., 2004). A large body of preclinical research has demonstrated that general anesthetics and sedatives, administered during critical periods of development, can have neurotoxic effects on the developing brain (Creeley and Olney, 2013). Nevertheless, the ability of these agents to induce neurotoxicity in pediatric patients has not been confirmed (Mann and Kahana, 2015). The purpose of this paper is to provide a review of the preclinical literature examining the effects of general anesthesia on neurobehavioral development, including a review of potential protective compounds and suggestions for areas of future research. This information will be critical for the review of new anesthetic agents and for developing best practice guidances.

2. History

Interest in the effects of general anesthesia on neurodevelopment increased greatly after the finding that blockade of *N*-methyl-D-aspartate (NMDA) receptors for a few hours in the neonatal rat during the brain growth spurt causes robust increases in apoptotic cell death (Ikonomidou et al., 1999). This seminal work revealed that the NMDA receptor antagonists, (+) MK801, phencyclidine (PCP), ketamine, and carboxypiperazin-4-yl-propyl-l-phosphonic acid (CPP), all trigger similar apoptotic cell death and neurodegeneration in the postnatal day (PND) 7 rat brain, suggesting that excitatory glutamate activity at NMDA receptors plays a central role in neuronal survival (Ikonomidou et al., 1999).These findings were subsequently extended to γ-aminobutyric acid $(GABA)_A$ receptor agonists and were also shown to occur after exposure to the dual NMDA receptor antagonist and $GABA_A$ receptor agonist, ethanol, which was already a well-established teratogen, known to cause reproducible neurotoxic effects (West et al., 1986; Jones et al., 1973; Clarren et al., 1978; Bauer-Moffett and Altman, 1977). Ikonomidou et al. (2000) demonstrated that the benzodiazepines, diazepam and clonazepam, the barbiturates, phenobarbital and pentobarbital, and ethanol all produced widespread apoptotic cell death when administered to the PND 7 rat. Nevertheless, administration of agents that act as either agonists or antagonists at dopamine receptors, block voltage-gated ion channels, or block kainic acid or muscarinic

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cholinergic receptors did not produce widespread apoptotic cell death in the PND 7 rat brain, suggesting that this effect was specific to $GABA_A$ receptor agonists and NMDA receptor antagonists (Ikonomidou et al., 2000). These results were consistent with prior investigations into the mechanisms of ethanol-induced developmental neurotoxicity that demonstrated manipulation of NMDA receptors during critical stages of development can disrupt normal brain development (Brooks et al., 1991; Thomas et al., 1997; McDonald and Johnston, 1993).

These findings are not surprising given the critical roles that the glutamatergic and GABAergic systems play during development. The L-amino acid neurotransmitters glutamate and GABA have been shown to regulate neuronal survival and migration, axonal and dendritic structure, and synaptogenesis and plasticity (Komuro and Rakic, 1993; McDonald and Johnston, 1990; Lujan et al., 2005). The involvement of these neurotransmitters and receptors in normal development, therefore, has raised speculation that the developing infant brain is likely to be much more sensitive to the adverse effects of agents that affect NMDA and $GABA_A$ receptor function than the adult brain. If NMDA and $GABA_A$ receptors are critical to brain development, it is only logical that significant disruption of their normal function should adversely impact the developing brain. Thus, the potential risks posed by NMDA antagonists [e.g., ketamine and nitrous oxide (N_2O)] and $GABA_A$ agonists (e.g., diazepam, propofol, sevoflurane, isoflurane, and halothane) that are commonly used during pediatric medical procedures (Olney et al., 2000; Ikonomidou et al., 2001) need to be fully understood.

In response to this concern, Jevtovic-Todorovic et al. (2003) assessed in the PND 7 rat the effects of a 6 h exposure to a cocktail of drugs (midazolam, N_2O, and isoflurane) commonly used in the pediatric setting for general anesthesia. This drug cocktail produced widespread apoptotic neurodegeneration in many regions of the developing brain (See Fig. 1). Further, when the sensitivity of the rat brain to the neurotoxic effects of this anesthetic cocktail was assessed as a function of age (1, 3, 7, 10, and 14 d), it was demonstrated that sensitivity was greatest at the peak of synaptogenesis (PND 7) and lowest at the end of synaptogenesis (PND 14) (Yon et al., 2005). Many rodent studies now typically incorporate exposures on PND 7 to target the period of maximal synaptogenesis. This is done primarily to maximize the likelihood of observing an effect, not to target or model a specific developmental stage in humans.

3. Neurotoxicity in Rodents

These findings by Ikonomidou et al. (2000) have since been replicated and extended by many others. A variety of general anesthetics including sevoflurane (Fang et al., 2012; Zheng et al., 2013a), isoflurane (Liang et al., 2010; Wei et al., 2008), N_2O (Savage and Ma, 2014), desflurane (Kodama et al., 2011), propofol (Yu et al., 2013; Ponten et al., 2011; Pearn et al., 2012; Zou et al., 2013), and ketamine (Scallet et al., 2004; Young et al., 2005; Liu et al., 2013a; Zou et al., 2009a) all produce a similar pattern of neuronal damage in neonatal rodents. Many different indices of neurotoxicity have also been described. In addition to inducing apoptotic cell death (Zhang et al., 2008; Zhou et al., 2011; Zhao et al., 2016), general anesthetics have been shown to disrupt mitochondria integrity and function (Zhang et al., 2010; Boscolo et al., 2013a; Sanchez et al., 2011), impair glial development and function (Ryu et al., 2014; Lunardi et al., 2011), alter dendritic spine morphology and density (Xiao et al., 2016; Ju et al., 2016; De Roo et al., 2009; Crosby et al., 2010; Briner et al., 2010; Briner et al., 2011), alter synaptic morphology and induce synaptic loss (Amrock et al., 2015; Lunardi et al., 2010), impair neurogenesis (Fang et al., 2012; Zhu et al., 2010; Stratmann et al., 2009a; Dong et al., 2012; Dong et al., 2014), and inhibit long-term potentiation (LTP)(Jevtovic-Todorovic et al., 2003; Xiao et al., 2016; Kato et al., 2013; Gao et al., 2014). Moreover, the neurotoxic effects associated with developmental exposures to general anesthetics have been seen in many brain regions, including the cerebral cortex (Zou et al., 2009a; Yang et al., 2011), hippocampus (Zheng et al., 2013a; Yu et al., 2013), thalamus (Zhang et al., 2008; Loepke et al.,

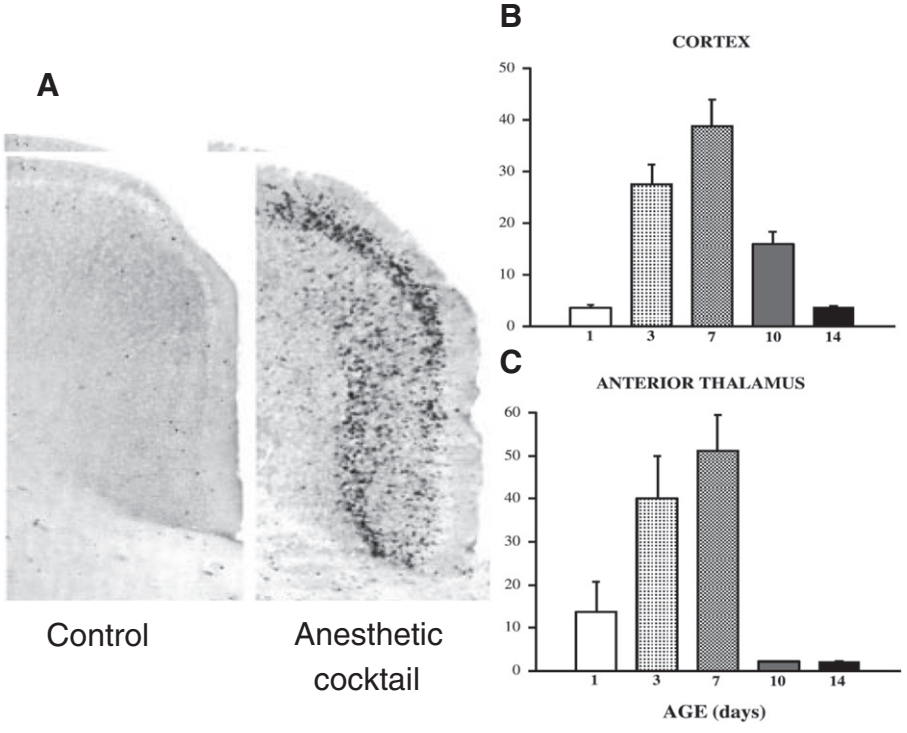

Fig. 1. (A) Silver staining of posterior cingulate/retrosplenial cortex from Jevtovic-Todorovic et al. (2003). A single 6 h exposure to a triple anesthetic cocktail of midazolam, nitrous oxide, and isoflurane on PND 7 induces significant apoptotic neurodegeneration (right) in comparison to control (left). Overall sensitivity of the cortex (B) and anterior thalamus (C) to neurodegeneration induced by the anesthetic cocktail when administered at different ages in development (Data from Yon et al. (2005)). A robust increase in damage occurred at PND 3 and PND 7.