Basic Science of Anesthetic-Induced Developmental Neurotoxicity

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Millions of newborn and infants receive anesthetic, sedative and analgesic drugs for surgery and painful procedures on a daily basis. Recent laboratory reports clearly demonstrate that anesthetic and sedative drugs induced both neuroapoptosis and neurocognitive deficits in laboratory models. This issue is of paramount interest to pediatric anesthesiologists and intensivists because it questions the safety of anesthetics used for fetal and neonatal anesthesia.\(^1,2\) In an attempt to summarize the rapidly expanding laboratory-based literature on anesthetic-induced developmental neurotoxicity (AIDN), this review will examine published reports on the characterization, mechanisms and alleviation of this phenomenon.

Characterization of AIDN

The Olney group reported accelerated neurodegeneration in rat pups exposed to N-methyl-D-aspartate (NMDA) antagonists and g-aminobutyric acid (GABA) agonist drugs and heralded that CNS depressant agents can be toxic to the developing brain.\(^3\) It is known that the immature brain undergoes some degree of neurodegeneration by apoptotic processes as part of normal development and the initial response from the scientific community was that anesthetic and anticonvulsant drugs and ethanol accelerate this normal “pruning” or apoptotic process. However, this notion was dismissed by a report that demonstrated both decrements histological parameters and behavioral and locomotor performance, in mature rats that were exposed to isoflurane and midazolam during infancy.\(^4\) AIDN appears to be both dose and duration dependent in both in vivo and in vitro experimental paradigms in rats and monkeys. Rat pups receiving ketamine continuously for nine hours exhibited poor feeding behavior and increased neurodegeneration. Whereas single doses of ketamine did not affect weight gain and neurodegeneration,\(^5,6\) Increased neurodegeneration and subsequent cognitive deficits also occur in fetal and postnatal day 5 rhesus monkeys exposed to ketamine or isoflurane.\(^7,9\) These findings confirmed that anesthetic dose and duration both play important roles in AIDN. However, several reports in neonatal mice clearly show that a single dose of ketamine and propofol induces neurodegeneration.\(^10,11\)

Anesthetic and sedative drugs also affect the development of dendritic spines and differentiation of neuronal precursor cells. Ketamine- and propofol-treated primary neuronal cell cultures exhibited blunted dendritic growth and arborization.\(^12,13\) Isoflurane also reduced dendritic spines in neonatal mice.\(^14\) Although neuronal cell death and changes in dendritic arborization did not occur in juvenile rodents exposed to both injectable and inhaled anesthetics. However, these drugs increased dendritic spine density.\(^15,16\) Neuronal precursor cells derived from neonatal, not aged, rats have a reduced capacity to proliferate in the presence of isoflurane.\(^17\) Taken together, these findings demonstrate age-specific effects of anesthetic exposure have the potential to regulate synaptic modeling and plasticity. The spinal cord is also susceptible to AIDN. Isoflurane not only leads to AIDN in the brain, but in the spinal cord as well.\(^18\) Intrathecal and epidural drugs have the potential of neuroapoptosis in the spinal cord. Intrathecal ketamine induces apoptosis in neonatal rat spinal cords, but morphine does not.\(^19,20\) Spinal bupivacaine had no effect on neuronal apoptosis and locomotor activity in rats.\(^21\)

The developing central nervous system is exquisitely sensitive its internal milieu. Peak synaptogenesis occurs between the 3rd and 7th post-natal week in rats, which is equivalent to the period between 25 gestational week and 1 year of age in humans.\(^22\) Therefore, non-physiologic exposure to various drugs and stressors (painful stimuli, maternal deprivation, hypoglycemia, hypoxia and ischemia) during this critical window, can lead to neurodegeneration. These findings beg the question of whether other confounding variables are involved in this process. It is well known that MAC of inhaled anesthetics is age-dependent. The potency of isoflurane also increases with the duration of exposure in neonatal rats but not in aged rats.\(^23\) Prolonged exposure to isoflurane also increases with the duration of exposure in neonatal rats but not in aged rats.\(^24\) However, neuronal density and a battery of neurobehavioral tests did not appear to be altered when the isoflurane-exposed mice were assessed at adulthood.\(^25\) Finally, a comparison of the neurotoxic effect of equipotent concentrations commonly used volatile anesthetics reveals that similar neurotoxic profiles were detected in neonatal mice.\(^26\)

Mechanisms of AIDN

The reproducibility of the neurotoxic effects of commonly used anesthetic drugs in both in vivo and in vitro by independent laboratories cannot be denied. Therefore, an examination of the mechanism of AIDN is paramount in the development of strategies of ameliorating these problems and determining if it is clinically relevant.\(^27\) Anesthesia removes the input and suppresses normal neural traffic. Lack of physiologic activation of neuronal populations by anesthetic drugs decreases synaptogenesis and cell-to-cell interaction.\(^28\) Several potential mechanisms have been proposed. Prolonged antagonism of the NMDA receptor by ketamine results in upregulation of the NR1 subunit and accelerated neurodegeneration of the NMDA receptor in rodent and monkey primary neuronal cell cultures. Upregulation of the NMDA receptor by prolonged exposure to ketamine potentially leads to increase Ca\(^{2+}\) influx into the neuron. This leads to oxidative cell death by activation of both apoptotic and necrotic cell death pathways.\(^29\) Prolonged exposure to isoflurane and nitrous oxide modulates...
BDNF and AKT signaling and activates both the intrinsic and extrinsic apoptotic cell death pathways.\textsuperscript{30,31} BDNF activates the p75\textsuperscript{NTR} receptor and induces neuronal apoptosis. Blockade of this pathway attenuated AIDN in vitro.\textsuperscript{14} Experimental models of neurodegeneration have also implicated cell cycle–related proteins and cell cycle reentry as a potential mechanism for apoptotic cell death of the primary neurons. Ketamine has been shown to activate aberrant cell cycle reentry death pathway.\textsuperscript{32}

### Alleviation of AIDN

Anesthetic drugs have intrinsic neuroprotective effects. Anand and colleagues examined the effect of low (sedative) dose ketamine on P-7 rat pups subjected to repetitive inflammatory pain which accentuates neuronal excitation and cell death in developmentally regulated cortical and subcortical areas. Subanesthetic doses of ketamine attenuated cell death and provided some degree of neuroprotection.\textsuperscript{33} Furthermore, the co-administration of the xenon or dexmedetomidine prevents isoflurane-induced in neonatal rats.\textsuperscript{34,35} Other non-anesthetic drugs have been shown to also attenuate AIDN. These include lithium, melatonin, erythropoietin, and L-carnitine.\textsuperscript{36-39} A better understanding of the mechanisms of AIDN will certainly identify candidate drugs and techniques that will mitigate this phenomenon.

The Anesthesia and Life-Support Advisory Committee of the Food and Drug Administration convened an open public hearing on the Neurotoxic Potential of Anesthesia drugs on pediatric patients in March 27, 2007 (http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4285t1.pdf). The preclinical data and the extrapolation of these data to clinical practice were thoroughly discussed by investigators and regulatory officials. The statement “there are not adequate data to extrapolate the animal findings to humans” was posed to the committee and all uniformly agreed. The meeting concluded with the statement, “well-understood risks of anesthesia (respiratory and hemodynamic morbidity) continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing”. A follow-up public hearing will be conducted on March 10, 2011 and the transcripts of the proceedings will be made available to the public.

In light of the reports detailing the anesthetic-induced neurodegeneration and learning deficits, should anesthetic, analgesic and sedative drug be withheld, again, from neonates undergoing surgery and painful procedures? Certainly, no parent or anesthesiologist/intensivist would allow neonates or pregnant mothers to be exposed to a neurotoxin. Furthermore, methodological issues make the interpretation of results in rats questionable in the setting of the administration of anesthetic drugs to humans.\textsuperscript{40} The mechanism of anesthetic action has not been fully interrogated and most likely affects several signaling pathways.\textsuperscript{41} Therefore, uncovering the toxic effect of anesthetics on the developing CNS will involve a multitude of factors as well. Since a clinical manifestation or phenotype of anesthetic-induced neurodegeneration has not been identified, clinicians should continue administering but anesthetics during surgery and painful procedures in pediatric patients. However, the irrefutable findings in the neuroscience literature should prompt clinicians to be more aware of this issue and develop clinical studies to interrogate the potential long-term neurological sequelae of anesthetics.

### References