General Anesthetics and Neurotoxicity

How Much Do We Know?

Vesna Jevtovic-Todorovic, MD, PhD, MBA

KEYWORDS

• Learning and memory • Immature brain • Aging brain • Synaptogenesis • GABA • NMDA • Synaptic transmission

KEY POINTS

- The developing and aging brain could be vulnerable to anesthesia-induced neurotoxicity.
- An important mechanism for anesthesia-induced developmental neurotoxicity is widespread neuroapoptosis.
- An early exposure to anesthesia causes long-lasting impairments in neuronal communication and faulty formation of neuronal circuitries.
- Exposure to anesthesia during both extremes of brain age could result in long-lasting impairments in cognitive and behavioral performance in animals and potentially in humans.

INTRODUCTION

Over the past several decades, clinical anesthesiology has enjoyed an enormous growth with seemingly limitless ability to take care of patients in all age groups regardless of their health status. More than 300 million complex and very painful procedures are being performed annually. To achieve the level of unconsciousness and insensitivity to pain during various interventions, human brains are being subjected to a variety of general anesthetics, alone or in combinations. The long-term outcomes of this practice are being actively investigated and scrutinized in a variety of preclinical and clinical studies.

THE PHYSIOLOGY OF NEUROTRANSMITTERS AND THEIR RECEPTORS DURING BRAIN DEVELOPMENT

All key elements of neuronal development depend on a fine balance between various neurotransmitters. In particular, it has been known that 2 major neurotransmitters, glutamate and γ-aminobutyric acid (GABA), control all aspects of neuronal migration,

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Department of Anesthesiology, University of Colorado School of Medicine, Mail Stop B-113, Leprino Office Building 7th Floor, 12401 East 17th Avenue, Aurora, CO 80045, USA
E-mail address: VESNA.JEVTOVIC-TODOROVIC@UCDENVER.EDU

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differentiation, maturation, and synaptogenesis, the key components of mammalian brain development.[1] Synaptogenesis involves massive dendritic branching and formation of trillions of synaptic contacts between neurons thus enabling the formation of meaningful neuronal circuitries and orderly neuronal maps. The processes by which axonal and dendritic projections find the right "target" and the most appropriate pathways for growth are very complex and not within the scope of this article. However, it is worth mentioning that the synaptogenesis and the development of neuronal processes are based on activity-dependent remodeling, suggesting that neuronal firing and interneuronal communications are crucial for timely and proper synaptogenesis.[2,3] All aspects of developmental synaptogenesis are tightly controlled by glia, which actively participate in neuron-glia signaling while providing an appropriate milieu for neuron-neuron interaction.[4] The electrical activity and synaptic signaling are strategically important during synaptogenesis, so much so that the major inhibitory neurotransmitter, GABA, serves as an excitatory neurotransmitter during early stages of synaptogenesis.[5] Although synapses are very pliable and undergo constant remodeling whereby new synapses are being formed and others are being pruned away throughout one's life, the bulk of fundamental neuronal networks and synaptic contacts are formed during developmental synaptogenesis. In humans, that time period occurs during the last trimester of in utero life and the first few years of postnatal life, while being most intense during the first several months of postnatal life.[3]

UNPHYSIOLOGIC MODULATION OF THE NEUROTRANSMITTERS AND THEIR RECEPTOR SYSTEMS DURING BRAIN DEVELOPMENT MAY RESULT IN NEUROTOXIC DAMAGE TO THE IMMATURE NEURONS

The fact that neuronal activity and communication are crucial for proper formation of synaptic contacts and for the establishment of stable receptor structures, which form the foundation for cognitive and behavioral development, brings into focus general anesthetics, a class of drugs commonly used in modern anesthesia. Their main goal is unphysiologically "switching off" or "turning down" neuronal communication for the purpose of achieving amnesia, analgesia, and hypnosis. Both gaseous (eg, nitrous oxide, isoflurane, sevoflurane, desflurane) and intravenous (eg, benzodiazepines, barbiturates, propofol, etomidate) anesthetics are frequently used for the purpose of assuring patients' comfort during painful intervention.

General anesthetics are very potent and effective in transiently inhibiting neuronal communication.[6] However, despite their widespread use, the mechanisms of their anesthetic action are not fully understood. Based on the studies published over the last few decades, it appears that there are specific cellular targets through which general anesthetics act.[7] In general, enhancement of inhibitory synaptic transmission and/or inhibition of excitatory synaptic transmission have been reported. In particular, many intravenous anesthetics, among them barbiturates, benzodiazepines, propofol, and etomidate,[7,8] as well as inhalational volatile anesthetics such as isoflurane, sevoflurane, desflurane, and halothane,[9,10] promote inhibitory neurotransmission by enhancing $GABA_A$-induced currents in neuronal tissue. For this reason, they are often referred to as GABAergic agents. On the other hand, a small number of intravenous anesthetics (eg, phencyclidine and its derivative, ketamine)[11] and inhalational anesthetics, nitrous oxide and xenon,[12,13] inhibit excitatory neurotransmission by blocking *N*-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors.

Although general anesthetics are powerful modulators of GABA and glutamate and thus cause significant imbalance in their functioning, only recently has it been recognized that general anesthetics, given in clinically relevant concentrations and