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Review article

Anesthesia, brain changes, and behavior: Insights from neural systems biology

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ABSTRACT

Long-term consequences of anesthetic exposure in humans are not well understood. It is possible that alterations in brain function occur beyond the initial anesthetic administration. Research in children and adults has reported cognitive and/or behavioral changes after surgery and general anesthesia that may be short lived in some patients, while in others, such changes may persist. The changes observed in humans are corroborated by a large body of evidence from animal studies that support a role for alterations in neuronal survival (neuroapoptosis) or structure (altered dendritic and glial morphology) and later behavioral deficits at older age after exposure to various anesthetic agents during fetal or early life. The potential of anesthetics to induce long-term alterations in brain function, particularly in vulnerable populations, warrants investigation. In this review, we critically evaluate the available preclinical and clinical data on the developing and aging brain, and in known vulnerable populations to provide insights into potential changes that may affect the general population of patients in a more, subtle manner. In addition this review summarizes underlying processes of how general anesthetics produce changes in the brain at the cellular and systems level and the current understanding underlying mechanisms of anesthetics agents on brain systems. Finally, we present how neuroimaging techniques currently emerge as promising approaches to evaluate and define changes in brain function resulting from anesthesia, both in the short and the long-term.

Contents

Abbreviation: AD, Alzheimer Disease; ASD, Autism Spectrum Disorder; AV, anterodorsal; BIS, Bispectral Index; BM, basomedial; CBF, Cerebral blood flow; CFA, Complete Freund's adjuvant; CSI, Cerebral state index; CVA, cerebral vascular accident; D, day; DGC, Dentate granule cell; DL, dorsolateral; DTI, Diffusion Tensor Imaging; EEG, Electroencephalogram; fMRI, functional Magnetic Resonance Imaging; fNRIS, functional Near-infrared Spectroscopy; GA, General anesthesia; GABA, y-aminobutyrate; GMR, Rate of glucose consumption; HbO, oxygenated hemoglobin; HbR, de-oxygenated hemoglobin; HbT, total hemoglobin; ICD, International Classification of Disease; ICU, intensive care unit; IQ, Intelligence quotient; IL, Interleukin; Kg, kilogram; LD, laterodorsal; MAC, Minimum Alveolar Concentration; MD, mediodorsal; Mg, milligram; MRI, Magnetic Resonance Imaging; MRS, Magnetic Resonance Spectroscopy; NAA, N-acetylasparate; NIRS, Near-infrared Spectroscopy; NMDA, N-methyl-D-aspartate; PET, Positron Emission Tomography; phMRI, pharmacological Magnetic Resonance Imaging; PND, postnatal day; POCD, Postoperative Cognitive Dysfunction; POD, Postoperative Delirium; RA, Regional anesthesia; rCBF, regional cerebral blood flow; TNF-α, Tumor necrosis factor-α; VM, ventromedial; Y, year; 1HMRS, proton Magnetic Resonance Spectroscopy.

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1. Introduction

Do anesthetics produce long-term alterations in brain function? From the beginning of anesthetic practice until recently, the actions of anesthetics on the brain were considered to have short-term consequences with a complete return to the initial state upon drug elimination, or in other words, the actions were completely reversible. However, as with many drugs that act on the central nervous system, there is now accumulating evidence that alterations in brain function occur beyond the initial anesthetic administration (Hudson and Hemmings, 2011).

Longer-term alterations in brain function, and consequently behavior, may occur following general anesthesia. Infants, young children and the elderly are particularly vulnerable populations (Hudson and Hemmings, 2011). In children, behavioral changes may include night terrors, increased anxiety, bedwetting, altered cognition, and altered sleep-wake cycles (Keaney et al., 2004; Perouansky and Hemmings, 2009). Moreover, although controversial, some studies have found in children an association between exposure to general anesthesia early in life and adverse long-term neurodevelopmental outcomes (for review see: Brambrink et al., 2012b; Lei et al., 2014; Lin et al., 2014; Loepke and Soriano, 2012). In adults, particularly the elderly, a state of confusion, memory loss, and alterations in executive functions are common days after surgery/anesthesia and may persist for months (Monk and Price, 2011; Silverstein and Deiner, 2013). Such postoperative behavioral disturbances have led to the concern that general anesthesia may induce long-term alterations in brain function, which may be more pronounced in vulnerable populations (Boxs 1 and 2,). Neuronal cell death, morphological changes and neurocognitive impairments after general anesthesia have been unequivocally demonstrated in laboratory animal models (Vutskits and Xie, 2016). This public health concern has prompted the Food and Drug Administration to issue a Drug Safety Communication *"warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains"* (Food and Drug Administration, 2016).

Preclinical animal studies have indicated that anesthetic agents can be neurotoxic by inducing central nervous system (CNS) changes at both the cellular and systemic levels in the juvenile and adult animal brain. Neurotoxicity is defined as structural or functional alteration in the nervous system resulting from exposure to a chemical, biological, or physical agent (Bittner et al., 2011). Alterations in dendritic complexity (sprouting or pruning) is a newer concept of the effects of anesthetics on brain structure and function, and is analogous to how antidepressants may alter neural connectivity (Castrén and Hen, 2013; Hudetz, 2012). Such alterations would form a basis of altered synaptic and therefore circuit function (Meyer, 2015). Recently, advances in brain neuroimaging have provided an opportunity to evaluate and define changes in brain function resulting from anesthesia.

In this article, we review the current evidence for the effects of exposure to general anesthesia on the developing and adult/aging brain in animals and humans. First, we briefly present the scope of the problem and the current debate in the literature regarding the accumulating experimental evidence for an association between exposure to general anesthesia and long-term deleterious effects on the CNS. In the section that follows, we review *Anesthetic effects*