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REVIEW ARTICLE

Genetic Markers for Anesthesia-induced Neurotoxicity

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Abstract

This comprehensive review article delves into the intricate genetic basis of individual variability in anesthesia sensitivity and the associated neurotoxic effects of specific anesthetics. Investigating the interplay between genetic factors and neurotoxic responses, we explore key aspects shaping the landscape of personalized anesthesia care. The article meticulously outlines the diverse neurotoxic effects of certain anesthetics, shedding light on their implications for cognitive function and neurodevelopment. Through an in-depth analysis of gene variants linked to these neurotoxic responses, such as those within the *APOE* and *BDNF*, the review synthesizes current research findings to provide a holistic understanding of the intricate relationship between genetics and anesthesia-induced neurotoxicity. By bridging gaps in knowledge, this article aims to pave the way for future investigations and innovations in personalized anesthesia strategies, optimizing patient outcomes and minimizing potential risks.

Keywords: Anesthesia, anesthesia-induced neurotoxicity, genetic and anesthesia

Introduction

Anesthesia-induced neurotoxicity has been a growing concern in the medical community, mainly due to its potential long-term consequences on cognitive function and neural development (Fodale et al., 2017). With an increasing number of surgical procedures performed on young children and infants, understanding the genetic factors that contribute to anesthesia-induced neurotoxicity is of paramount importance (Vutskits & Davidson, 2023). This paper aims to explore the current state of knowledge about genetic markers associated with anesthesia-induced neurotoxicity and discuss the implications of these findings for clinical practice and future research directions.

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Anesthesia-Induced Neurotoxicity: A Brief Overview

This issue has gained significant attention in recent years as research findings have indicated that exposure to anesthesia during critical periods of brain development can lead to long-term cognitive and behavioral changes (Liu et al., 2020).

The most commonly studied anesthetic agents associated with neurotoxicity are volatile anesthetics, such as isoflurane and sevoflurane, and intravenous agents such as propofol and ketamine (Andropoulos, 2023). Various hypotheses have been proposed, including disrupting neuronal homeostasis leading to apoptosis, inhibiting neuronal plasticity, oxidative stress, and inflammation. Several factors can influence the risk of anesthesia-induced neurotoxicity (Yang et al., 2024). These include the type, duration and dosage of anesthetic exposure, the specific type of anesthetic used, the age at exposure (with neonates and young children being particularly susceptible), and any pre-existing neurological disorders (Loepke & Soriano, 2020).

Individual Variations in Response

It allows healthcare professionals to administer anesthesia more safely and effectively, by considering each patient's unique characteristics and predispositions (Flexman et al., 2020). This could reduce complications and a smoother recovery following surgical procedures (Bernstein et al., 2020). Secondly, acknowledging these differences in response can contribute to developing personalized medicine, enabling clinicians to tailor anesthesia management plans specifically for individuals rather than a one-size-fits-all approach. This may optimize treatment outcomes and minimize unwanted side effects (Kaye et al., 2018). Finally, studying individual variations can increase our comprehension of the underlying mechanisms behind them. This knowledge could potentially unveil new therapeutic targets or intervention strategies to mitigate the risk of neurotoxic effects associated with anesthesia exposure (Johnson et al., 2018). It also paves the way for future research into genetic and epigenetic factors that may influence a person's susceptibility to anesthesia-induced neurotoxicity. This information can aid in risk assessment and developing more effective, targeted therapies (Vutskits & Davidson, 2023).

Neurotoxicity in Anesthesia

A. Anesthesia-induced neurotoxicity

Anesthesia-induced neurotoxicity refers to potential adverse effects on the developing nervous system, particularly in the brains of infants and young children, due to exposure to specific anesthetic agents (Ji et al., 2019). Researchers have suggested that prolonged or repeated exposure to anesthesia during critical periods of brain development may lead to neurotoxic effects, causing cognitive and behavioral impairments, which is particularly concerning for vulnerable populations such as infants, young children, and older people (Graham, 2017; Kamat et al., 2019; Sekimoto et al., 2017). (Montana & Evers, 2017; Zanghi & Jevtovic-Todorovic, 2017).

Animal studies have demonstrated changes in synaptic structure, neurotransmitter systems, and neuronal cell death associated with anesthesia exposure (Hao et al., 2020; Ramirez-Lee et al., 2023; Wenzel et al., 2021). However, it's important to note that the exact mechanisms and extent of these effects in humans are still under investigation, and the clinical significance of anesthesia-induced neurotoxicity remains a topic of ongoing research and debate.

B. Types of neurotoxic effects associated with certain anesthetics

The types of neurotoxic effects associated with certain anesthetics can be categorized into several groups:

1. Excitatory Effects: Certain anesthetics can cause excessive neuronal excitation, leading to seizures, tremors, and hyperexcitability. These effects are often associated with drugs such as ketamine and some volatile anesthetics (Stratmann, 2011).

2. Inhibitory Effects: Some anesthetics can cause neurotoxic effects by excessively inhibiting neuronal activity. This can lead to reduced neural function, delayed recovery after anesthesia, and even cognitive impairment. Examples of such anesthetics include propofol and barbiturates (Bosnjak et al., 2016; Karmarkar et al., 2010).

3. Apoptosis and Neuronal Degeneration: Certain anesthetics have been shown to induce apoptosis, a programmed cell death process, in neurons. This can lead to long-term damage to the central nervous system, particularly in the developing brain of infants and young children. Inhaled anesthetics such as isoflurane and sevoflurane have been linked to this type of neurotoxic effect (Loftis et al., 2012; Mete et al., 2015; Yang & Wei, 2017).

4. Oxidative Stress: Anesthetic compounds can generate reactive oxygen species (ROS), harmful substances that damage cellular components like proteins, lipids, and DNA. This oxidative stress can lead to inflammation in the nervous system and may contribute to neurological disorders like Alzheimer's disease or Parkinson's disease (Alavuk Kundović et al., 2020; Koo et al., 2021; Kovacic & Somanathan, 2012; Levy, 2017; Nishimura et al., 2021).

5. Neuroinflammation: Some anesthetics have been shown to cause neuroinflammation by activating immune cells such as microglia within the brain or spinal cord. The inflammatory response can damage neurons and contribute to postoperative cognitive dysfunction (POCD) (Baud & Saint-Faust, 2019; Useinovic et al., 2022).

6. Impaired Synaptic Plasticity: Certain anesthetics have been found to interfere with synaptic plasticity, which is the ability of synapses to strengthen or weaken over time in response to changes in activity. Disruption of synaptic plasticity may impair learning and memory processes (Hudson & Hemmings, 2011).

Genetics in Neurotoxic Response

A. Genetic markers for anesthesia-induced neurotoxicity

Research has focused on identifying possible genetic markers associated with a higher risk of anesthesia-induced neurotoxicity. Such genetic markers can help predict patients' risk profiles and enable physicians to tailor anesthetic management accordingly (Alharbi et al., 2024). Additionally, understanding the connection between these genetic factors and neurotoxic events may contribute to developing new prevention strategies and targeted therapies (Stone & DeAngelis, 2016). As research continues to elucidate potential mechanisms involved in anesthesia-induced neurotoxicity, clinicians can better understand how to mitigate cognitive risks during surgery (Apai et al., 2021; Belrose & Noppens, 2019). Several significant genetic markers linked to anesthesia-induced neurotoxicity and cognitive risks comprise the following:

1. *BDNF* (Brain-Derived Neurotrophic Factor) - *BDNF* plays a pivotal role in the survival, growth, and differentiation of neurons. Alterations in *BDNF* expression have been associated with anesthesia-induced neurotoxicity. (Lu et al., 2006; C. Wu et al., 2020; J. Wu et al., 2016). One example of a reported polymorphism in the *BDNF* gene is the single nucleotide polymorphism (SNP) *rs6265*, also known as the Val66Met variant. This polymorphism involves a substitution of the amino acid valine (Val) with methionine (Met) at position 66 in the *BDNF* protein. The Val66Met polymorphism has been implicated in various neurological and psychiatric conditions and may influence *BDNF* function and expression levels. Studies have investigated its potential role in modulating the susceptibility to anesthesia-induced neurotoxicity and its impact on cognitive outcomes (Xie et al., 2020; Giarratana et al., 2019).

2. *ApoE* (Apolipoprotein E) - *ApoE* is a gene involved in the metabolism of lipids and cholesterol. The *ApoE* ε4 allele has been associated with an increased risk for cognitive decline following exposure to isoflurane, particularly in older adults (Ding et al., 2021; Dokkedal et al., 2020; Eun et al., 2022; Kim et al., 2021).

3. *TNF-α* (Tumor Necrosis Factor-alpha) - *TNF-α* is a pro-inflammatory cytokine that plays a vital role in immune system regulation and inflammation. Inhalational anesthetics like isoflurane have been studied in relation to TNF-α. Studies have shown that isoflurane can increase TNF-α production, which may contribute to cognitive dysfunction in certain individuals(Guo et al., 2018; Popić et al., 2015; Wu et al., 2012; Zhang et al., 2018). A specific SNP in the promoter region of the *TNF* gene, such as the -308G/A polymorphism, has been linked to variations in *TNF-α* levels. Individuals carrying the A allele may exhibit higher *TNF-α* expression, potentially increasing their risk of anesthesia-induced neurotoxicity (Baghel et al., 2014; Bessler et al., 2006).

4. *IL-1β* (Interleukin-1 beta) - *IL-1β* is a pro-inflammatory cytokine, encoded by a gene of the same name, essential for modulating the immune response within the central nervous system. An increased risk of cognitive impairment following anesthesia, particularly isoflurane and sevoflurane administration, has been linked to elevated levels of *IL-1β*. (Bessler et al., 2006; Guo et al., 2018; Haritha et al., 2023; Huang et al., 2021; Vosoughian et al., 2021). An example of a reported polymorphism associated with this gene is the *IL-1β*-511C/T polymorphism (Shi et al., 2010).

5. *CASP3* (Caspase 3) - The *CASP3* gene, crucial for apoptosis regulation, plays a significant role in cell death processes. Animal models exposed to sevoflurane have shown an upregulation of *CASP3* gene expression, resulting in heightened neuronal apoptosis and consequent cognitive dysfunction (Balasubramanian et al., 2018; Hofacer et al., 2013; Ling et al., 2017; Sarić et al., 2022). An example of a relevant polymorphism associated with *CASP3* gene is the *CASP3* -1337C/G polymorphism, which has been studied in various contexts, including cancer susceptibility and neurodegenerative diseases (Balasubramanian et al., 2021; Sarić et al., 2022).

The dysregulation of these genes may contribute to anesthesia-induced neurotoxicity, leading to potential cognitive risks following anesthetic exposure (Belrose & Noppens, 2019; Wu et al., 2019). Further research into these genetic factors could help improve our understanding of anesthesia-related complications and ultimately aid in developing personalized approaches to minimize associated risks.

Recommendations

In conclusion, the intricate interplay between genetics and anesthesia represents a dynamic field with significant implications for personalized patient care. Despite notable progress in understanding the genetic basis of anesthesia sensitivity and neurotoxic responses, challenges persist in translating this knowledge into routine clinical practice. This review underscores the importance of sustained research efforts and

collaboration between geneticists, anesthesiologists, and other healthcare professionals. A call for continued exploration of the genetic underpinnings of anesthesia response encourages the development of evidence-based guidelines for incorporating genetic information into anesthesia practice. By embracing these challenges and fostering interdisciplinary cooperation, the integration of genetics into anesthesia can usher in a new era of precision medicine, enhancing patient safety and individualizing anesthesia strategies for optimal outcomes.

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