PERIOPERATIVE NEUROCOGNITIVE DISORDERS IN GERIATRIC PATIENTS: A REVIEW OF NEURONAL PATHOPHYSIOLOGY

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ABSTRACT

Introduction: With the ageing population, elderly patients are overrepresented among surgical patients, and experience an increased variety of postoperative complications. Of these complications, perioperative neurocognitive disorders significantly jeopardize patients' postoperative outcomes. Risk factors for perioperative neurocognitive disorders include age, depth of anesthesia, preoperative cognitive function, and surgical procedure type. However, the underlying pathophysiological mechanisms are still not well understood and have been the focus of multiple previous studies. This narrative review aimed to define the possible pathophysiological pathways of perioperative neurocognitive disorders from different cellular perspectives.

Method: A literature search was conducted using the following keywords: perioperative neurocognitive disorders, delirium AND synaptic dysfunction, neuroinflammation, and pathophysiology, focusing on studies published within the last 10 years. All studies written in English, reporting perioperative neurocognitive disorders and its pathophysiological mechanisms in adults undergoing elective surgery were included.

Results: A total of 516 studies were assessed and 182 studies were selected. Among the 182 studies, 60 most relevant to the research question regarding the cellular mechanisms of perioperative neurocognitive disorders were included.

Conclusion: Perioperative neurocognitive disorders are important perioperative complications, and early recognition, prevention, and treatment of high-risk patients are crucial. Neurocognitive tests are commonly used to identify and assess perioperative neurocognitive disorders. However, new biomarkers are required to better understand the pathophysiology. Furthermore, defining the underlying molecular mechanisms and related pathways, which could possibly serve as predictive tools and possible targets for treatment, is important to better delineate the risks especially in the elderly population.

Keywords: Neurocognitive Disorders; Perioperative Period; Synapse; Neuroinflammatory Diseases; Geriatrics.

INTRODUCTION

Perioperative neurocognitive disorders (PNCD) are characterized by reductions in cognitive performance, impaired memory, information handling, attention, executive ability, verbal memory, and visuospatial attention, and have become one of the most common and important complications encountered during the perioperative period (1). The prevalence of PNCD is as high as 25–40% within the geriatric population, resulting in decreased quality of life as well as disability, morbidity, and occasionally mortality (2). Recent studies have focused on the mechanism of neuroinflammation caused by surgery and anesthesia in the pathogenesis of PNCD (3,4). Surgery results in an increased release of inflammatory factors, especially at the surgical site, whereas anesthesia causes inflammation throughout the body as well as the brain. This neuroinflammation may be a trigger for cognitive decline (1).

Postoperative cognitive impairment related to surgery and anesthesia was first described in 1887 with nitrous oxide and elaborated to anesthesia and surgical injury in 1955 (5,6). Since then, a substantial number of studies have focused on the pathophysiology of perioperative cognitive conditions, including delirium, dementia, and aggravation of pre-existing cognitive problems (7-9). One major study involving 1218 perioperative patients aged ≥ 60 years emphasized the association between surgery, anesthesia, and perioperative cognitive disorders in non-cardiac surgery (10). Several risk factors for PNCD have been identified, including age, level of education, duration of surgery, and anesthesia exposure (11). Numerous studies have also aimed to define the specific effect of anesthesia on cognition. However, neither the type of anesthesia (general versus loco-regional) nor the various anesthetic drugs used could be defined as major triggers for PNCD (12-15).

In light of these results, the Fifth International Perioperative Neurotoxicity Working Group has developed recommendations to safeguard postoperative brain health (16). Recommendations for intraoperative management include avoidance of hypotension, maintenance of normothermia, and careful monitoring of anesthetic depth. In addition, the importance of a multidisciplinary team approach, thorough preoperative baseline cognitive assessments with neuropsychiatric tests, and postoperative follow-up with similar tools have been highlighted (17). Despite the well-recognized definition of PNCD and its risk factors, the molecular pathophysiology of PNCD remains controversial. This article reviewed studies related to the risk factors and pathophysiology of PNCD, with the goal of discussing the pathophysiology of PNCD from different cellular aspects.

MATERIAL AND METHODS

Design and selection of eligible studies

A literature search was conducted according to narrative review guidelines (18). PubMed was searched for titles and abstracts using the following keywords: PNCD, delirium AND synaptic dysfunction, neuroinflammation, pathophysiology, and risk factors. Searches were conducted for studies over the last 10 years. All studies written in English reporting PNCD and its risks in adults (≥18 years) undergoing elective surgery were included in this review. All articles with data on both PNCD and synaptic dysfunction were evaluated for inclusion. Additionally, the reference lists of any review articles that were found during the search were screened for further original articles related to the subject. Any type of surgery, definition of PNCD, and length of follow-up were qualified as the inclusion criteria. Articles for which full text was unavailable and articles not written in English were excluded.

Data extraction

From qualifying studies, we extracted data on the incidence, clinical presentation, and risk factors

of PNCD. Data related to neuroinflammation and the pathophysiological aspects of PNCD were also extracted. Since the aim of this review was to discuss PNCD from a cellular-synaptic approach, we particularly preferred studies performed at the cellular level.

RESULTS

A total of 516 studies were found between 2011–2022. Initial title and abstract screenings were performed. Studies focusing only on the clinical assessment and management of PNCD were excluded. Finally, 182 studies were selected. Of the 182 studies, 60 were relevant to the research question regarding the cellular mechanisms of PNCD and were included in this review.

DISCUSSION

Currently, we understand that loss of consciousness is a crucial component of anesthesia, although its dose, timing, and management remain controversial given a wide variety of possible complications. The primary effects of anesthesia are well known from a clinical perspective; however, effects on the brain at the cellular level remain unclear. PNCD is a major postoperative complication at the neural-tissue level. The wide distribution and heterogeneous set of conditions named PNCD from the early postoperative period presented as delirium to the late presentation as postoperative neurocognitive dysfunction emphasized a need for further studies at the cellular level in order to identify mechanisms underlying the development of such conditions (19).

Epidemiologically, a large number of risk factors for PNCD have been identified, including cardiac surgery, advanced age, pre-existing neurodegenerative disorders, and chronic inflammatory states such as diabetes and atherosclerosis (20-23). The European Society of Anesthesiology published evidence- and consensus-based guidelines on postoperative delirium to define the risk factors, such as advanced age, comorbidities (e.g., stroke, diabetes, depression, anxiety disorders, cardiovascular diseases, anemia, and chronic pain), preoperative fluid fasting and dehydration, hyponatremia or hypernatremia, anticholinergic drugs, alcohol-related disorders, surgical site, intraoperative bleeding, duration of surgery, and pain (24). They recommended controlling preventable risk factors and monitoring all patients for postoperative delirium for prompt diagnosis and treatment.

Neuroinflammation

At the cellular level, pre-existing inflammatory states and acute neuroinflammation secondary to perioperative processes, such as anesthetic exposure and surgical trauma, are still important areas of research. In several animal studies, the upregulation of inflammatory cytokines, such as TNF alpha, IL-1, and IL1 beta following anesthetic exposure and surgery has been reported (25-26). Additionally, pre-existing inflammation was shown to increase the incidence and severity of PNCD in rat models (27-28).

Neuroinflammation is one of the primary mechanisms of PNCD. Inflammation caused by surgical trauma in the peripheral tissue leads to disruption of the blood-brain barrier and neural activity. While several studies have defined different neuroinflammatory mechanisms in the perioperative period as inciting factors for PNCD, the isolated effect of anesthesia or surgery cannot be defined (29); thus, a synergistic effect between anesthesia, surgery, and even the preoperative inflammatory state of the patients is suspected. Neuroinflammatory steps are defined as the disruption of the blood-brain barrier and migration of inflammatory mediators and macrophages in the brain parenchyma. A proinflammatory state also stimulates microglial cells, which further amplifies inflammation. Several

cellular mechanisms have been described for this inflammatory cascade, leading to synaptic dysfunction and cellular death (30).

Synaptic dysfunction

The most important function of the central nervous system is information processing, a highly organized function performed via dynamic communication between neurons. The crucial components of this network are the synapses (31). Synaptic development underlies the formation of functional neural networks during brain growth in children, and synapse formation and elimination are crucial for adult neural plasticity (32-33). Synapse formation is called synaptogenesis, and the related neural circuitry assembly is dependent on the balance between excitatory and inhibitory (E/I) signaling (34). Disruption of this balance has been shown to result in neurodevelopmental disorders (35-37).

General anesthesia, which is a powerful modulator of GABAergic and glutamatergic neurotransmission, may also influence the E/I balance, synaptogenesis, and network formation. Therefore, these effects may lead to the modulation of synaptic plasticity. Animal studies have shown that the administration of general anesthetic drugs during central nervous system development impairs dendritic arbor development and decreases synaptic density, and that these changes have led to functional deficits in learning and behavior (38-40). In addition, Lunardi et al. demonstrated with a morphometric analysis that anaesthesia-exposed rodents had a loss of excitatory and inhibitory synapses (41).

Synaptic plasticity is vital in maintaining neural circuit stability and therefore plays an important role in learning, memory, and cognitive function; as a result, several studies have been performed on brain-derived neurotropic factor (BDNF), a neurotrophic factor expressed in the central nervous system. The main functions of BDNF are to maintain neuronal survival and differentiation, facilitate synaptic transmission, enhance synaptic plasticity, and strengthen synaptic growth (42). Fan et al. demonstrated that a reduction in BDNF levels is involved in the pathogenesis of PNCD (43). In addition, Qui et al. showed that anesthesia and surgery induced disruption of BDNF signaling that led to cognitive impairment in mice (44). On the other hand, Xue et al. studied the correlation between PNCD and the ratio of BDNF to its precursor proBDNF, and showed that anesthesia and surgery-induced imbalance of BDNF/proBDNF expression deteriorated neuronal synaptic plasticity (45). Homeostatic changes lead to cognitive impairment and memory decline.

In another animal study, it was also shown that anesthesia exposure led to a significant decrease of mitochondrial profiles in presynaptic terminals, correlating with disturbed synaptic transmission (46). In addition, assuming that neuroinflammation is a major mechanism triggering PNCD, Yang et al. designed an experimental model to assess the site of inflammation that mediates neural damage in mice. In their study, they showed that surgery and anesthesia increased mitochondrial fragmentation, and that exposure to TNF in neuroinflammation also contributed to mitochondrial dysregulation (47); consequently, they suggested that these effects were related to the pathology of PNCD. This study supports the role of mitochondrial dysfunction in PNCD pathogenesis. These results suggest that general anesthetics may impair synaptogenesis by interfering with mitochondrial functions, thus disrupting neural networks and cognitive functions.

Cognitive dysfunction in elderly patients is partly explained by structural changes affecting plasticity, such as declines in neuron numbers, synapse numbers, and dendritic branching (48). Taking all data into consideration, we can partly explain the pathophysiology of PNCD via anesthesia-induced modulation of synaptic plasticity. Culley et al. studied the

net effect of inhalational anesthetic agents on cognitive function in the absence of surgical stimulus, and found that retrieval of consolidated memory tasks was affected (49). In another study, the acquisition of new tasks was impaired following anesthesia (50). These findings were confirmed in several studies, where inhalant-induced inflammatory cytokine expression and related cell injury were identified as underlying causes (51-52).

The role of MicroRNAs

Several animal studies on specific microRNAs (miRNAs) have also evaluated PNCD (53-54). MiRNAs are small non-coding RNAs 15-22 nucleotides in length, and they play an important role in the post-transcriptional regulation of gene expression by binding to the 3'-UTR regions of target mRNAs and inhibiting protein synthesis. Studies have shown that almost 50% of the human genome is regulated by non-coding RNAs. They are key players in important biological processes such as growth, apoptosis, and differentiation (55). miRNAs are thought to be potential biomarkers in the pathogenesis of many brain-related diseases because they can cross the blood-brain barrier and are easily detected in most body fluids. For example, miRNAs have been reported to be involved in neuropsychiatric disorders and cognitive function impairments (56). Several studies have also demonstrated that miRNAs are involved in the development of dementia, ischemic stroke, and Alzheimer's disease (56-59).

The association between miRNAs and PNCD has also been evaluated. Shan et al. demonstrated that anesthesia exposure significantly impaired recognition and spatial working memory in rats(60). This effect has been explained by an increase in neuronal apoptosis via proteins (GABA-A receptor alpha 5 subunit) in the hippocampus. The increase in these proteins involved in inhibitory neurotransmission has been shown to be regulated by miR-30a and miR-190a/b (60). In another study, Wang et al. showed that miRNA-320 could play a role in promoting PNCD in humans (61). However, the prognostic, diagnostic, and therapeutic values of miR-NAs are yet to be determined in humans.

CONCLUSION

With increased recognition and discussion of PNCD in the literature, new methods to predict and recognize cognitive dysfunction during the perioperative period have become increasingly important in clinical settings, especially for geriatric patients who are overwhelmingly affected by this condition. Neurocognitive tests, inflammatory markers, and patient characteristics are currently the most commonly used tools. However, new biomarkers to improve patient assessment and follow-up are needed in the field of PNCD. Furthermore, because the physiopathology of PNCD is still not fully understood and multifactorial risk factors are suspected, it is important to define underlying molecular mechanisms and related pathways that could be potential predictive tools and targets for treatment.

In light of these data, we can suggest that general anesthesia can have a long-term impact on cognition, particularly in elderly patients. The inflammatory effects of anesthetic drugs, as well as their modulatory effects on synaptogenesis and neuronal plasticity, are highly suspected in the pathogenesis of PNCD. Further studies are needed to identify potential therapeutic targets.

Conflict of Interest

The author has no financial conflict of interest.

Financial Disclosure: The author declares that there is no financial interest to report.

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