



Elucidating a correlation between general anesthesia and post-operative depression

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Abstract

Post-operative depression is a condition in which a person develops new or worsening depressive symptoms after undergoing surgery. Depression is characterized by persistent feelings of sadness, loss of interest in previously enjoyed activities, changes in sleep or appetite, fatigue, difficulty concentrating, and feelings of hopelessness. When these symptoms persist and interfere with daily functioning, they can affect a person's recovery and overall quality of life. Although the underlying causes of post-operative depression are not fully understood, several factors may contribute to its development, including the physiological stress of surgery, pain, and medications administered during the surgical process (Borsook et al., 2010). One factor of particular interest is general anesthesia, as it produces significant changes in brain activity and may influence physiological pathways associated with depression. Here, we examine the potential relationship between general anesthesia and post-operative depression by exploring how different anesthetic agents may influence neurotransmitter activity, inflammation, neuroimmune signaling, and neural pathways involved in mood regulation. We also consider how factors such as age, type of surgery, and anesthetic type may influence post-operative depressive symptoms and patient outcomes. Understanding this relationship may help identify potential risk factors for post-operative depression and guide future research into strategies that support patients' mental health and recovery following surgery.

Introduction

General Anesthetic Agents and Their Molecular Targets

General anesthesia is a medically, reversible induced state of unconsciousness that allows patients to undergo surgery or other invasive procedures without experiencing pain, awareness, and memory of the operation (Bao et al., 2023). General anesthesia agents are typically propofol, sevoflurane, ketamine, and dexmedetomidine and are usually administered using inhaled anesthetic gases, intravenous medication, or a combination of both (Borsook et al., 2010; Bao et al., 2023). Although these agents produce a similar clinical outcome, they are structurally and pharmacologically different and act on different molecular targets within the nervous system. For example, propofol primarily enhances the activity of γ -aminobutyric acid type A (GABA-A) receptors, increasing inhibitory signaling and reducing neuronal activity (Tang & Eckenhoff, 2018). Sevoflurane, a volatile inhaled anesthetic, acts on multiple targets, including GABA-A and glycine receptors, while also reducing excitatory signaling through receptors such as NMDA (Kira et al., 1998; Hollmann et al., 2001). In contrast, ketamine primarily blocks N-methyl-D-aspartate (NMDA) receptors, which normally mediate excitatory signaling through the neurotransmitter glutamate, producing dissociative anesthesia and analgesia (Vadivelu et al., 2016). Dexmedetomidine acts predominantly on α 2-adrenergic receptors, reducing norepinephrine release and activity in neural pathways involved in arousal (Liu et al., 2021). Therefore, although these anesthetics differ in their molecular structures and receptor targets, their combined effects on inhibitory and excitatory neurotransmission disrupt the neural networks responsible for consciousness, awareness, memory, and pain perception similarly.

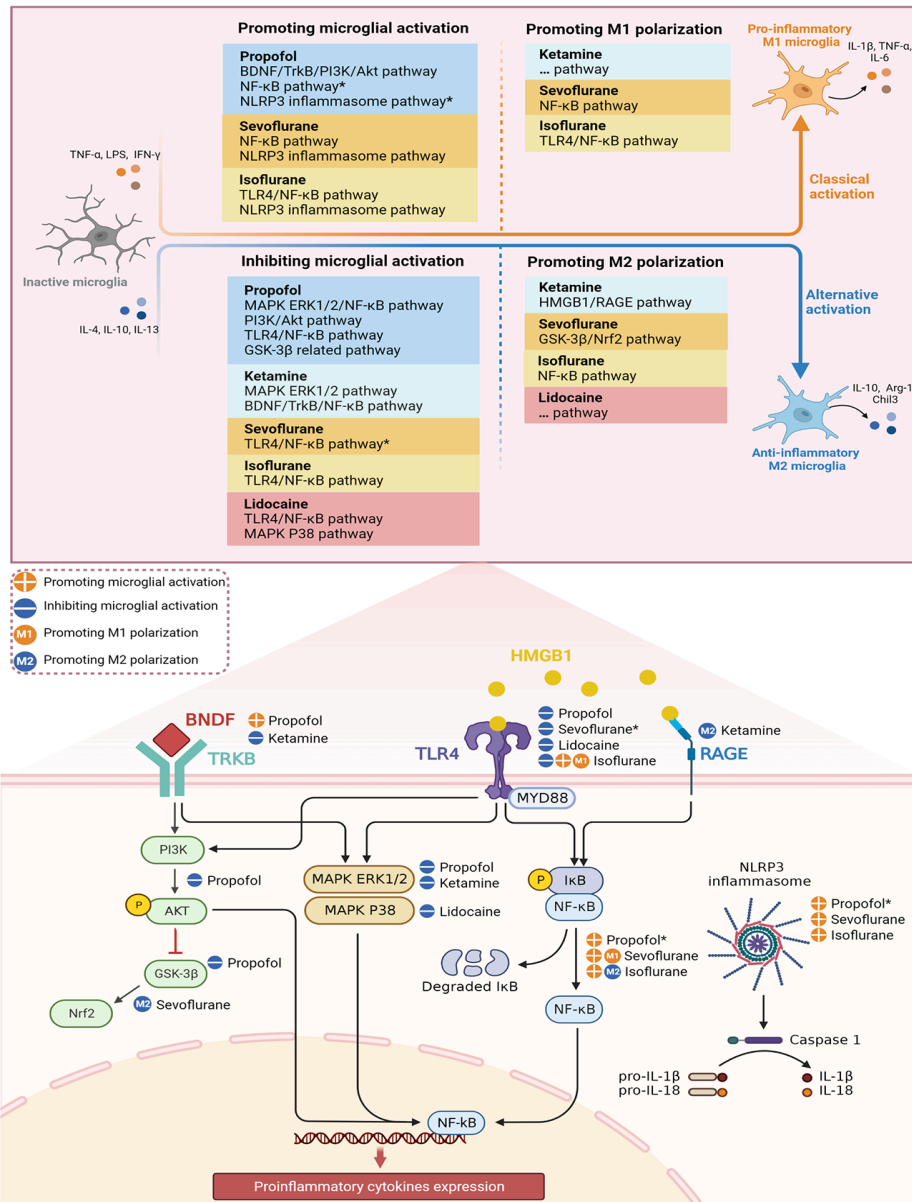


Figure 2. Functional alterations of microglia after exposure to general anesthetic agents. Reproduced from Yang et al. (2024), Figure 1, under the Creative Commons Attribution (CC BY) license. <https://doi.org/10.14336/AD.2023.1108>

Physiological Changes Associated With Anesthesia and Surgery

General anesthesia itself induces reversible changes in brain activity to produce unconsciousness, but the combination of anesthesia and surgical trauma also triggers systemic inflammation and activation of the hypothalamic-pituitary-adrenal (HPA) axis, the body's primary stress-response system that regulates the release of cortisol (Hollmann et al., 2019; Besnier et al., 2017). During surgery, the stress response can activate the HPA axis, leading to the release of cortisol and other stress hormones that help the body respond to the physical stress of

surgery (Besnier et al., 2017). Importantly, these physiological responses do not require conscious awareness, as the body can detect tissue injury and activate hormonal and inflammatory pathways even while a patient is unconscious under general anesthesia. Although general anesthesia suppresses consciousness and awareness, it does not completely eliminate the body's physiological responses to surgical stress. However, prolonged or dysregulated activation of this system may affect brain function and interact with inflammatory and neuroimmune pathways involved in mood regulation (Borsook et al., 2010; Beurel et al., 2020). In addition to HPA axis activation, surgery and anesthesia can trigger oxidative stress, which occurs when the production of reactive oxygen species (unstable molecules that can damage cells) exceeds the body's ability to neutralize them (Stevens et al., 2019). These physiological changes may influence several neurological processes described below that are associated with postoperative depression.

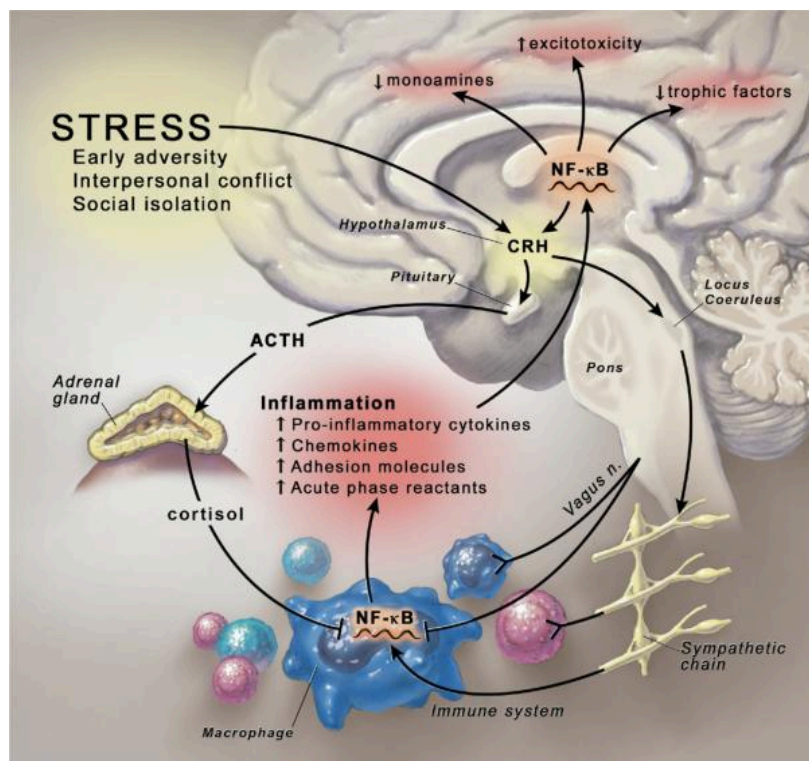


Figure 2. Stress-induced activation of the inflammatory response. Reproduced from Miller et al. (2009), Figure 2, in *Biological Psychiatry*, 65(9), 732–741. <https://doi.org/10.1016/j.biopsych.2008.11.029>

Microglial Activation and Neuroinflammation

Microglia are immune cells that reside in the central nervous system and help protect the brain by responding to injury, infection, and cellular damage (Wang et al., 2022). In contrast, neurons are specialized nerve cells that transmit electrical and chemical signals, allowing different parts of the brain to communicate and regulate functions such as mood, memory, and behavior. While neurons primarily process and transmit information, microglia help maintain the brain's environment and respond to potential threats that may disrupt normal neuronal function.

Microglial activation occurs when these cells detect signals of stress or damage and transition into an active state, releasing inflammatory molecules such as cytokines (Wang et al., 2022; Yang et al., 2024). Excessive or prolonged microglial activation can contribute to neuroinflammation, which may affect neuronal function and communication between brain cells (Wang et al., 2022). Because surgery produces tissue injury and systemic inflammatory responses, these processes may contribute to microglial activation and subsequent changes in brain function (Subramaniyan & Terrando, 2019).

Neurotransmitter Systems and Mood Regulation

Neurotransmitters are chemical messengers that allow neurons to communicate with one another and regulate processes such as mood, motivation, cognition, sleep, and stress responses (Kato et al., 2013). Inflammation, HPA axis dysregulation, and microglial activation may alter neurotransmitter systems, including serotonin, dopamine, glutamate, and GABA (Miller et al., 2009; Sperner-Unterwieser et al., 2014; Kato et al., 2013). These changes can interfere with neural circuits involved in mood regulation and may contribute to depressive symptoms following surgery (Miller et al., 2009; Beurel et al., 2020). For example, human research has found that higher postoperative levels of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) predicted depressive symptoms three months after total knee replacement surgery, providing evidence that the inflammatory response following surgery may be associated with subsequent depressive symptoms (Cremins-Smith et al., 2009). Therefore, the inflammatory and stress responses associated with surgery and anesthesia may influence mood not only through inflammation itself but through changes in neuronal communication as well.

Neuroplasticity

Neuroplasticity refers to the brain's ability to change and adapt by modifying connections and communication between neurons (Wang et al., 2022). Surgical stress, inflammation, and neuroimmune activation may interfere with these processes, potentially reducing the brain's ability to adapt to physiological stress and maintain normal emotional and cognitive function (Miller et al., 2009; Wang et al., 2022; Zhang & Yin, 2023). Research on microglia has provided evidence that inflammatory activation can alter neuroplasticity by affecting synaptic structure, connectivity, and the brain's ability to adapt following physiological stress (Wang et al., 2022). In the perioperative setting, surgery and anesthesia can activate peripheral inflammatory pathways and microglia, which may contribute to changes in synaptic function and neuroplasticity (Subramaniyan & Terrando, 2019; Zhang & Yin, 2023). These alterations in neuroplasticity may provide a link between perioperative inflammation and postoperative depression, as disruptions in the brain's ability to maintain and adapt neural connections could contribute to persistent changes in neuronal function following surgery. Impaired neuroplasticity has therefore been proposed as another mechanism that may contribute to postoperative depression.

Biological Pathways Associated With Depression

During general anesthesia and surgery, multiple physiological pathways are activated in response to both anesthetic exposure and surgical stress. However, the pathways involved can differ depending on whether they are primarily associated with the anesthetic drugs or the physical trauma and stress of surgery (Borsook et al., 2010; Yang et al., 2024; Subramaniyan & Terrando, 2019). Depression is associated with several biological pathways that may also be

affected by the physiological changes that occur during surgery and anesthesia. These pathways include inflammation, dysregulation of the HPA axis, microglial activation, alterations in neurotransmitter signaling, and changes in neuroplasticity (Miller et al., 2009; Beurel et al., 2020; Osimo et al., 2020). Because these pathways are involved in regulating brain function and responding to physiological stress, changes occurring during the perioperative period may contribute to alterations in brain function associated with postoperative depression. The following sections examine these pathways in greater detail, with particular attention to inflammation, neuroimmune activity, neurotransmitter signaling, and neuroplasticity.

Overlap Between Perioperative Responses and Depression

The overlap between these pathways provides a potential connection between the physiological effects of surgery and anesthesia and the biological mechanisms involved in depression. Surgical stress and anesthesia may create physiological conditions involving inflammation, HPA axis activity, oxidative stress, microglial activation, neurotransmitter alterations, and changes in neuroplasticity that overlap with pathways implicated in depressive symptoms (Borsook et al., 2010; Stevens et al., 2019; Subramaniam & Terrando, 2019; Yang et al., 2024). However, this overlap does not establish that general anesthesia directly causes postoperative depression. Surgical trauma, postoperative pain, pre-existing depression, medications, sleep disruption, and other perioperative factors may also contribute to these physiological and psychological changes (Borsook et al., 2010; Lee et al., 2024). Therefore, understanding the overlap between these pathways may help explain how postoperative depression can develop while recognizing that its underlying mechanisms are likely multifactorial (Borsook et al., 2010; Subramaniam & Terrando, 2019; Yang et al., 2024).

Inflammation and immune dysregulation in depression

Depression is associated with the activation of several biological pathways, such as those involved in inflammation and immune dysregulation (Beurel et al., 2020; Miller et al., 2009). Elevated levels of pro-inflammatory cytokines, which are small proteins released by immune and other cells that help regulate inflammation and immune responses, such as IL-6, tumor necrosis factor-alpha (TNF- α), and interleukin-1 beta (IL-1 β), along with increased CRP, have been consistently observed in individuals with depression (Miller et al., 2009; Beurel et al., 2020; Osimo et al., 2020). IL-6 is produced by immune cells and other tissues and helps coordinate inflammatory and immune responses; elevated IL-6 may influence neurotransmitter metabolism, HPA-axis activity, and neuroplasticity (Miller et al., 2009). TNF- α is produced primarily by immune cells such as macrophages and microglia and helps initiate inflammation, but excessive levels may disrupt neuronal signaling, neurotransmitter function, and Neuroplasticity (Miller et al., 2009; Wang et al., 2022). IL-1 β is also produced by activated immune cells and microglia and plays an important role in initiating inflammatory responses; increased IL-1 β may contribute to neuroinflammation and alter neurotransmitter and stress-response systems (Wang et al., 2022; Miller et al., 2009). Unlike these cytokines, CRP is an acute-phase protein produced mainly by the liver in response to inflammatory signals such as IL-6 and is commonly used as a blood marker of systemic inflammation (Osimo et al., 2020). Increased levels of these inflammatory mediators may influence neurotransmitter function, reduce neuroplasticity, impair neurogenesis, and contribute to the development and persistence of depressive symptoms (Miller et al., 2009; Beurel et al., 2020; Osimo et al., 2020).

Surgical engagement of the immune system

Surgical trauma produces a more pronounced systemic stress and inflammatory response (Subramaniyan & Terrando, 2019). Tissue injury activates the HPA axis, leading to the release of cortisol and other stress hormones, while damage-associated signals stimulate the immune system and increase inflammatory markers such as IL-6, TNF- α , IL-1 β , and CRP (Borsook et al., 2010; Subramaniyan & Terrando, 2019). Surgical trauma can also contribute to microglial activation, in which microglia respond to inflammatory signals, injury, or changes in their surrounding environment (Subramaniyan & Terrando, 2019; Wang et al., 2022). Excessive or prolonged microglial activation can promote neuroinflammation through the release of inflammatory molecules, including IL-1 β , IL-6, TNF- α , and reactive oxygen species (Wang et al., 2022; Yang et al., 2024). This neuroinflammatory response can affect neurons, neurotransmitter signaling, neurogenesis, and synaptic plasticity, potentially contributing to changes in brain function and mood regulation (Miller et al., 2009; Wang et al., 2022; Zhang & Yin, 2023).

The relationship between these pathways is important when examining the potential connection between general anesthesia, surgery, and postoperative depression. Inflammatory cytokines and microglial activation can interact with the HPA axis, neurotransmitter systems, and neuroplasticity, meaning that activation of one pathway may influence several other processes involved in brain function (Miller et al., 2009; Wang et al., 2022; Zhang & Yin, 2023). Because many of these same pathways are implicated in depression, the physiological changes that occur during the perioperative period may contribute to depressive symptoms in some individuals (Beurel et al., 2020; Miller et al., 2009). However, these processes are influenced by multiple factors, including the surgical stress response, pain, anesthetic exposure, and an individual's underlying vulnerability, making postoperative depression a complex and multifactorial phenomenon (Borsook et al., 2010; Lee et al., 2024; Yang et al., 2024). Despite these connections, the specific relationship between general anesthesia and postoperative depression, particularly the biological mechanisms involved, remains unclear. This paper aims to examine this potential relationship by reviewing existing literature on how anesthetic agents may influence neurological pathways associated with depression and how factors such as age and surgery type may affect postoperative outcomes.

Methods

Here, a discussion of the results of a systematic literature review examining the potential connection between general anesthesia and postoperative depression. Research articles were identified using the PubMed database and selected using keywords and phrases including "inflammation," "general anesthesia," "MDD," "neuroinflammation," and "depression." The literature reviewed included systematic reviews, meta-analyses, randomized controlled trials, and other relevant review articles that examined biological pathways associated with depression, inflammation, anesthesia, and postoperative outcomes.

Results

The reviewed literature identified several biological pathways that may connect the perioperative period with postoperative depressive symptoms, although the extent to which these changes are caused by general anesthesia rather than surgery itself remains unclear. For example, Cremeans-Smith et al. (2009) examined inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), in relation to postoperative depressive symptoms following total

knee replacement. This finding is relevant because both markers have been associated with inflammatory processes implicated in depression. However, because this research involved patients undergoing surgery, the relationship does not establish that general anesthesia itself caused the observed depressive symptoms.

Other studies have examined the biological mechanisms that may help explain this relationship. Research on general anesthetic agents indicates that drugs such as propofol, sevoflurane, and ketamine act on different neurotransmitter receptors, altering inhibitory and excitatory signaling in the brain (Bao et al., 2023; Zhang & Yin, 2023). Research on neuroinflammation has also described how microglial activation and inflammatory cytokines may influence neuronal communication and contribute to changes in brain function (Subramaniam & Terrando, 2019; Wang et al., 2022). These findings provide possible explanations for how anesthesia exposure and surgical stress could affect pathways involved in mood regulation. Nevertheless, evidence that anesthetic agents alter these pathways does not necessarily demonstrate that those changes lead to postoperative depression.

Taken together, the literature suggests that inflammation, neurotransmitter activity, and neuroplasticity are relevant areas for investigating postoperative depression. However, differences in anesthetic agents, surgical procedures, patient characteristics, and follow-up periods make it difficult to determine whether particular anesthetics independently increase the risk of depressive symptoms. Further research comparing anesthetic agents and tracking patients' mood and biological changes throughout recovery is therefore needed to clarify these relationships.

Limitations found

Several limitations were identified across the literature. Some studies are observational, making it difficult to establish causation between depression and postoperative outcomes. Studies also differ in how depression, pain, inflammation, and postoperative outcomes are measured, which can make comparisons between studies difficult (Lee et al., 2024).

Additionally inflammation does not appear to affect every individual with depression in the same way. Differences between individuals, including biological and potentially sex-related differences, may influence inflammatory responses (Jarkas et al., 2024; Beurel et al., 2020).

Furthermore, the effects of anesthetic agents on microglia may depend on the specific anesthetic used, its dose, and the duration of exposure, making it difficult to generalize the effects of “general anesthesia” as one uniform exposure (Yang et al., 2024).

Future Directions

Further research is needed because the specific effects of different anesthetic agents on biological pathways associated with postoperative depression remain unclear, and the long-term relationship between these changes and depressive symptoms is not fully understood. Future studies should compare specific anesthetic agents to determine whether different agents have distinct effects on inflammatory signaling, neurotransmitter systems, microglial activity, and neuroplasticity (Yang et al., 2024; Zhang & Yin, 2023). Research should also examine these effects over longer periods of postoperative recovery to determine whether changes in these

pathways persist and whether they are associated with the development or duration of depressive symptoms.

More research is also essential to identify biomarkers that could help predict which patients may be at greater risk for postoperative depression. Examining inflammatory markers such as IL-6, TNF- α , IL-1 β , and CRP before and after surgery may help researchers determine whether changes in inflammation are associated with later depressive symptoms (Jarkas et al., 2024; Cremeans-Smith et al., 2009). Additionally, future studies should investigate why some individuals experience greater mood-related changes following surgery and anesthesia than others, including how factors such as age, type of surgery, anesthetic exposure, pre-existing depression, and individual inflammatory responses may influence outcomes.

Finally, more controlled research is necessary to distinguish the effects of general anesthesia from those of surgical trauma and other perioperative factors. Comparing patients receiving different anesthetic agents, as well as examining surgical patients alongside appropriate control groups, could help clarify whether anesthesia itself contributes to changes in neuroplasticity and other biological pathways associated with postoperative depression.

Discussion

Across the studies reviewed, a consistent pattern emerged showing that neuroinflammation and altered neural signaling may connect the perioperative period with biological pathways associated with depression. Elevated inflammatory markers, including IL-6, TNF- α , IL-1 β , and CRP, were repeatedly associated with depression, while HPA axis activation, microglial activation, oxidative stress, altered neurotransmitter activity, and changes in BDNF-mediated neuroplasticity were also identified in relation to perioperative and depressive processes (Miller et al., 2009; Osimo et al., 2020; Borsook et al., 2010; Yang et al., 2024; Zhang & Yin, 2023).

These findings are particularly relevant to the relationship between general anesthesia and postoperative depression because general anesthetic exposure can alter neural signaling, while anesthesia and surgical stress occur within the same perioperative period as inflammatory and neuroimmune changes. The overlap between these processes provides a possible explanation for how changes occurring during and after surgery could affect brain function during recovery. In particular, alterations in neuroplasticity may be important because the brain must adapt to the physiological stress associated with surgery and recovery. If inflammatory or neuroimmune activity interferes with normal neural adaptation, it may contribute to persistent changes in neuronal function that are associated with depressive symptoms (Subramaniyan & Terrando, 2019; Zhang & Yin, 2023; Wang et al., 2022).

However, the findings do not directly implicate that general anesthesia alone causes postoperative depression. The observed biological changes may result from the interaction of anesthetic exposure with surgical trauma, postoperative pain, inflammation, stress responses, and individual patient factors. Therefore, the relationship between general anesthesia and postoperative depression appears to involve multiple interacting pathways rather than a single mechanism. Overall, the evidence suggests that the relationship between general anesthesia and postoperative depression may involve multiple interacting biological pathways rather than a single mechanism. Further research is needed to determine whether specific anesthetic agents



contribute to postoperative depressive symptoms independently of surgical stress and other patient-related factors.

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