Review Article
Effect of general anesthesia drugs on GFAP/Iba-1 expression: a meta-analysis

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Abstract: Glial fibrillary acidic protein (GFAP) is a marker associated with astrocyte activation and plays a role in various pathologic processes, including traumatic brain injury, stroke, and neurodegenerative diseases. Interacting boson approximation (Iba-1) is a marker protein for microglia, which are important in neuroinflammatory responses. This meta-analysis aimed to investigate the impact of general anesthetics on the expression of GFAP and Iba-1 in animal models. A meta-analysis was conducted using databases such as PubMed, EMBASE, Springer, and Web of Science. The quality of the selected publications was estimated using the SYRCLE guidelines to ensure credibility and consistency of the research. Continuous variables were measured using mean difference or standardized mean difference (SMD), with a 95% confidence interval (CI) calculated. Ten randomized controlled animal experiments were included in this analysis, utilizing different general anesthetics such as sevoflurane and propofol compared to untreated control groups. The results consistently demonstrated a significant increase in GFAP (SMD = 0.41, 95% CI: 0.09, 0.72, P = 0.01) and Iba-1 (SMD = 0.43, 95% CI: 0.04, 0.83, P = 0.03) expression in the general anesthetic-treated groups, suggesting a neuroinflammatory response induced by these agents. Assessment of publication bias revealed no significant bias in the included studies. This meta-analysis highlights the impact of general anesthetics on GFAP expression in animal models, emphasizing the importance of understanding the neuroinflammatory response associated with anesthesia administration. Further research is warranted to elucidate the underlying molecular pathways and explore possible therapeutic interventions to mitigate adverse effects associated with anesthesia administration.

Keywords: Glial fibrillary acidic protein, Ionized calcium-binding adapter molecule, general anesthetics, astrocytes

Introduction

General anesthetics are used to induce unconsciousness and loss of sensation for surgical procedures [1]. They can have various effects on the central nervous system (CNS), including altering neuronal excitability, influencing synaptic transmission, and affecting glial cell function [2]. Studies have suggested that general anesthetics can modulate glial fibrillary acidic protein (GFAP)/interacting boson approximation (Iba-1) expression in microglia [3]. Recent research has shown that exposure of astrocytes to anesthetics such as isoflurane, sevoflurane, and propofol can lead to changes in GFAP expression levels [4, 5]. These alterations in GFAP expression may be linked to changes in astrocyte morphology, function, and signaling pathways [6]. Another study found that sevoflurane, a commonly used volatile anesthetic, increased the expression of GFAP in astrocytes isolated from rat cerebral cortex [7]. This increase in GFAP/Iba-1 expression was associated with changes in the glial cell cytoskeleton and altered cell morphology, suggesting that anesthetics can affect glial cell structure and function [8]. However, some research indicated that exposure to volatile anesthetics did not change the expression of GFAP in primary cultured rat astrocytes [9]. Therefore, the effects of general anesthetics on GFAP expression remain uncertain.

GFAP is an intermediate filament protein that is specifically expressed in the non-neuronal cells of the CNS, including astrocytes, ependymal

cells, and oligodendrocytes [10]. It is a major component of the glial intermediate filament network and plays an essential role in maintaining the structural integrity and mechanical strength of the glial cell cytoskeleton [11]. Iba-1 is a marker protein of microglia, which are important for the neuroinflammatory response [12]. Upon activation, microglia release cytokines and other substances that can cause neuroinflammation [13]. Therefore, GFAP and Iba-1 play crucial roles in macroglial and microglial cells, respectively.

To investigate the role of general anesthetics in the expression of GFAP/Iba-1, this study conducted a meta-analysis of experimental publications in English. The findings of this study may provide a theoretical foundation for resolving the contradictory results regarding the effects of general anesthetics on GFAP/Iba-1 expression.

Methods

This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and conformed to SYRCLE (Systematic Review Center for Laboratory animal Experimentation) guidelines. The meta-analysis was registered at INPLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols, 2024-40002).

Selection criteria

The inclusion criteria were defined in accord with the PICO tenets. Publication design: Experimental studies published in English. Participants (P): All animals. Intervention (I): The experimental group was administrated with general anesthetic drugs. Comparison (C): The control group served as a negative control without any intervention. Outcome (O): The main outcome indicators in the tissues were the expression levels of GFAP and Iba-1. Immunohistochemistry, western blot, and RT-qPCR were used to determine the expression of GFAP and Iba-1.

We excluded articles that met the following criteria: 1) lack of outcome indicators (as mentioned above); 2) duplicate articles; 3) case report, conference literature, review articles; 4) absence of a control group; and 5) lack of exploitable information.

Retrieval strategy

The search was conducted on PubMed, EMBASE, Springer, and Web of Science (publications until Feb 29th, 2024). The key words used included: general anesthetics, anesthesia, sevoflurane, propofol, isoflurane, Xeon, N_2O, etomidate, dexmedetomidine, fentanyl, desflurane, barbiturates, GFAP and Iba-1.

Publication screening and data extraction

Two researchers rigorously screened the literature based on the predetermined inclusion and exclusion criteria, using EndNote X9 for literature management. Disagreements were resolved through discussion or consultation with a third investigator. After initially reading the titles and excluding obviously irrelevant literature, abstracts and full texts were further examined to determine inclusion. The extracted data included the first author, animals, groups, detection methods, baseline information for all groups, and outcome indicators (GFAP and Iba-1 expression levels).

Quality assessment

A quality assessment was conducted to exclude studies with low quality or potential bias to minimize their impact on the overall results and conclusions. The SYRCLE was used to evaluate the quality of 10 articles identified in this meta-analysis. SYRCLE is a set of guidelines and tools specifically designed for meta-analyses in animal research. Its bias analysis tool helps assess potential biases, as well as the credibility and consistency of research. This assessment aimed to ensure methodological quality and reduce bias across the included studies.

Data analysis

Review Manager 5.4 software was used for meta-analysis of the included literature.

We measured continuous variables using mean difference or Standardized Mean Difference (SMD) as the effect size and calculated 95% Confidence Intervals (CI) for these measurements. During our comprehensive analysis of the literature, we performed a heterogeneity test to assess the variability between studies. Based on our findings, a fixed-effects model

Figure 1. Flow chart of screening and including publications.
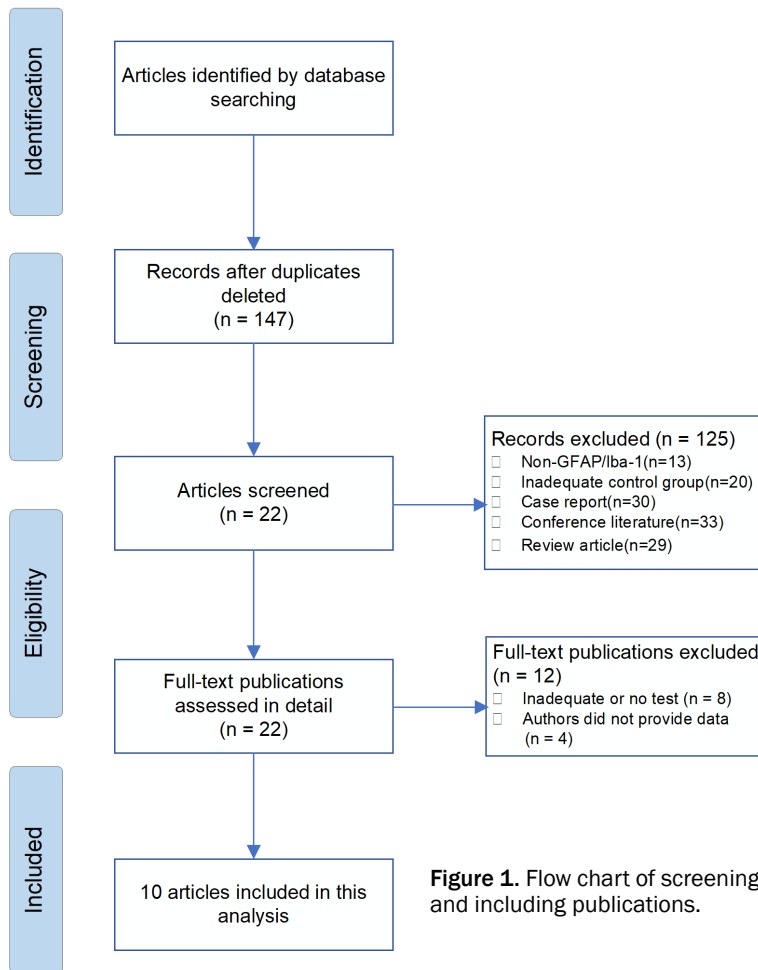
obtained. After reading the full text, 12 articles were excluded, leaving 10 articles that met inclusion and exclusion criteria, as shown in **Figure 1**.

Basic characteristics of the included studies

A total of 10 randomized controlled animal experiments were included. The effects of general anesthetics on the expression of GFAP/Iba-1 were assessed. The animals in the experimental groups were administered with various general anesthetics. The control groups were blank control animals without any treatment. The experimental animals included SD rats (7 studies), Wistar rats (2 studies), and SD neonatal pups (1 study). Eight studies included male animals, 2 studies included both male and female animals. The 10 papers did not demonstrate adverse animal reactions. The basic characteristics of included studies are exhibited in **Table 1**.

was chosen to manage possible variability among the studies to ensure the reliability of our analysis. To further validate the results, we conducted sensitivity analyses by systematically excluding individual studies. Consistent results before and after removing studies would indicate the robustness of our findings, while inconsistent results would suggest instability that should be interpreted with caution. To investigate publication bias, we created a funnel plot and employed Egger's test in Stata 12.0 software.

Results

Study retrieval results

A total of 513 related articles were obtained from the databases. After removing duplicates, 147 publications remained. Upon reading the titles and abstracts, 22 publications on the effects of general anesthetics on the expression of GFAP/Iba-1 in animal models were

Quality assessment

The methodological quality of the 10 included articles was assessed, with the risk of bias assessment results exhibited in **Figure 2**. The majority of publications demonstrated high methodological quality.

Meta-analysis of general anesthetics and GFAP

All the 10 included studies described the effect of general anesthetics on GFAP expression. GFAP expression was enhanced in the general anesthetic administered groups compared to that of the control groups (SMD = 0.41, 95% CI: 0.09, 0.72, P = 0.01) (**Figure 3**). Furthermore, 2 articles used western blot to evaluate the effect of general anesthetics on the protein expression of GFAP. Their results showed that the protein expression of GFAP in the general anesthetic groups was significantly enhanced compared to that of the controls (SMD = 0.68, 95% CI: 0.10, 1.25, P = 0.02) (**Figure 4**).

Table 1. Characteristics of the included studies

Reference	Animals	Groups	Method	Indicators
Sun et al. [25]	Adult male SD rats	Control group (n = 18) Model group (n = 18) Propofol + Dex group (n = 18)	Immunohistochemistry	GFAP/Iba-1
Feng et al. [26]	Adult male SD rats	Control group Propofol group Lidocaine + Etomidate group	Immunohistochemistry/ Western Blot	GFAP
Morax et al. [27]	Adult male Wistar rats	Sham-propofol (n = 11) Sham-sevoflurane (n = 11) SAH-propofol (n = 16) SAH-sevoflurane (n = 13)	Immunohistochemistry	GFAP
Jiang et al. [28]	Adult male Fischer 344 rats	Control group (n = 15) Propofol group (n = 15) Model group (n = 18)	Immunohistochemistry	GFAP/Iba-1
Yang et al. [29]	Adult male SD rats	Control group (n = 13) Propofol 50, 75, 100, 150 mg/kg (n = 13 for each)	Immunohistochemistry	GFAP
Wang et al. [30]	Adult male SD rats	Saline treatment model group Propofol treatment model group Saline treatment sham-operation group Propofol treatment sham-operation group	Immunohistochemistry	GFAP
Zhu et al. [31]	Adult SD rats	Control (Con), 2% Sev, 5% Sev	Immunohistochemistry	GFAP
Liao et al. [32]	Adult male SD rats	Control, Sev, DM, DM + Sev, DM + Sev + Cel	Immunohistochemistry	GFAP/Iba-1
Li et al. [11]	Adult male Wistar rats	Control (Con), 2% Sev, 3.5% Sev	Western Blot	GFAP
Tian et al. [33]	Adult male SD rats	NS + O_2, NS + sev, Aβ + O_2, and Aβ + sev	Immunohistochemistry/ Western Blot	GFAP/Iba-1

SD: Sprague-Dawley; PND: perioperative neurocognitive disorders; HCN: hyperpolarization-activated cyclic nucleotide-gated; DM: diabetes mellitus; Sev: sevoflurane; NS: normal saline; Aβ: amyloid-β.
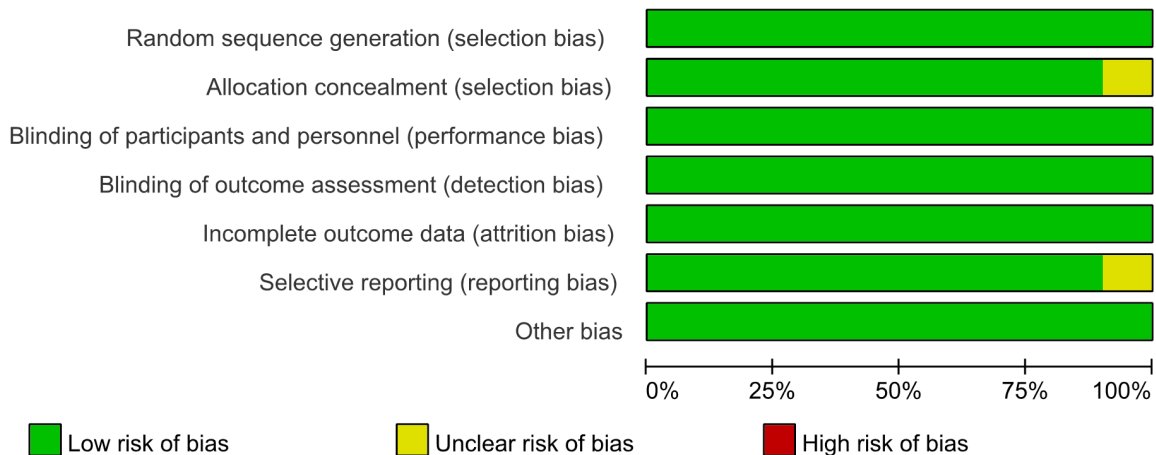

Figure 2. Risk of bias diagram.

Meta-analysis of general anesthetics and Iba-1

Four included studies described the effect of general anesthetics on Iba-1 expression. Results indicated a significant increase in Iba-1 in the groups administered general anesthetics compared to the controls (SMD = 0.43, 95% CI: 0.04, 0.83, P = 0.03) (**Figure 5**).

Publication bias

The funnel plot analysis showed a uniform scatter of results, suggesting no publication bias.

Egger's test implied no indication of publication bias about GFAP expression (t = -1.85, P = 0.316), GFAP protein expression (t = -1.46, P = 0.513), or Iba-1 expression (t = -2.25, P = 0.058) (**Figure 6**).

Sensitivity analysis

The sensitivity analysis was carried out for GFAP. The data of all the 10 publications were scattered consistently from the center line and no marked deviation was found. Consequently,
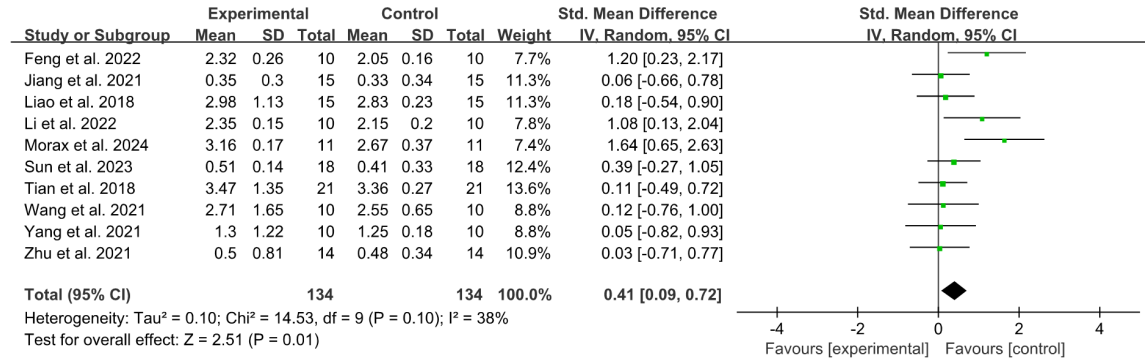
Figure 3. Forest plot reveals the effect of general anesthetics on GFAP expression in experimental and control groups.
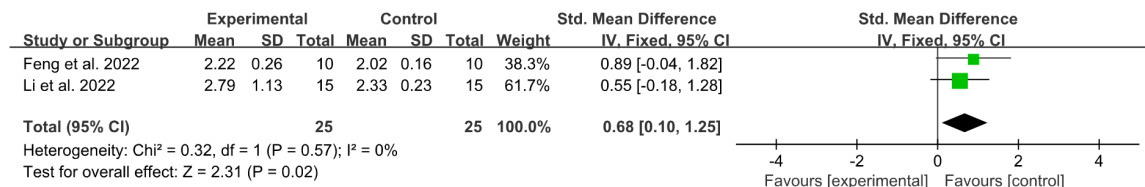

Figure 4. Forest plot demonstrates the effect of general anesthetics on the protein expression of GFAP in experimental and control groups.
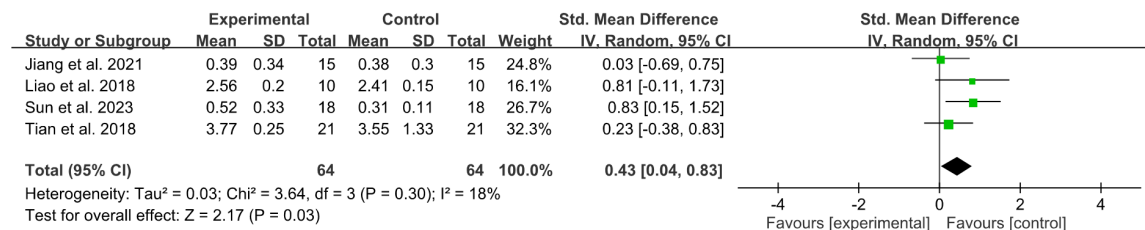

Figure 5. Forest plot demonstrates the effect of general anesthetics on Iba-1 expression in experimental and control groups.

there appears to be no individual publication influencing the combined results. Furthermore, sensitivity analysis was also performed for Iba-1. The data from 4 publications consistently scattered around the center line, indicating no significant deviation. Similarly, it was shown that no single publication has a significant influence on the combined results.

Discussion

This meta-analysis provides valuable insight into the proposed neuroinflammatory effects of general anesthetics on the brain. The findings, which are based on 10 relevant studies published between 2018 and 2023, suggest that these anesthetics may trigger a neuroinflam-

matory response within the brain. This response is characterized by an amplified expression of two key biomarkers, GFAP and Iba-1, in the brain cells of animals treated with general anesthetics. GFAP and Iba-1 are markers of glial cell activation, with GFAP being predominantly expressed in astrocytes and Iba-1 in microglia. Astrocytes and microglia are the primary immune cells of the CNS and play a crucial role in maintaining CNS homeostasis [14, 15]. Under normal conditions, these cells respond to tissue damage or infection by activating and producing pro-inflammatory cytokines and chemokines to initiate repair and defense mechanisms [16, 17]. However, chronic or excessive activation of these cells can lead to neuroinflammation, which is a key pro-
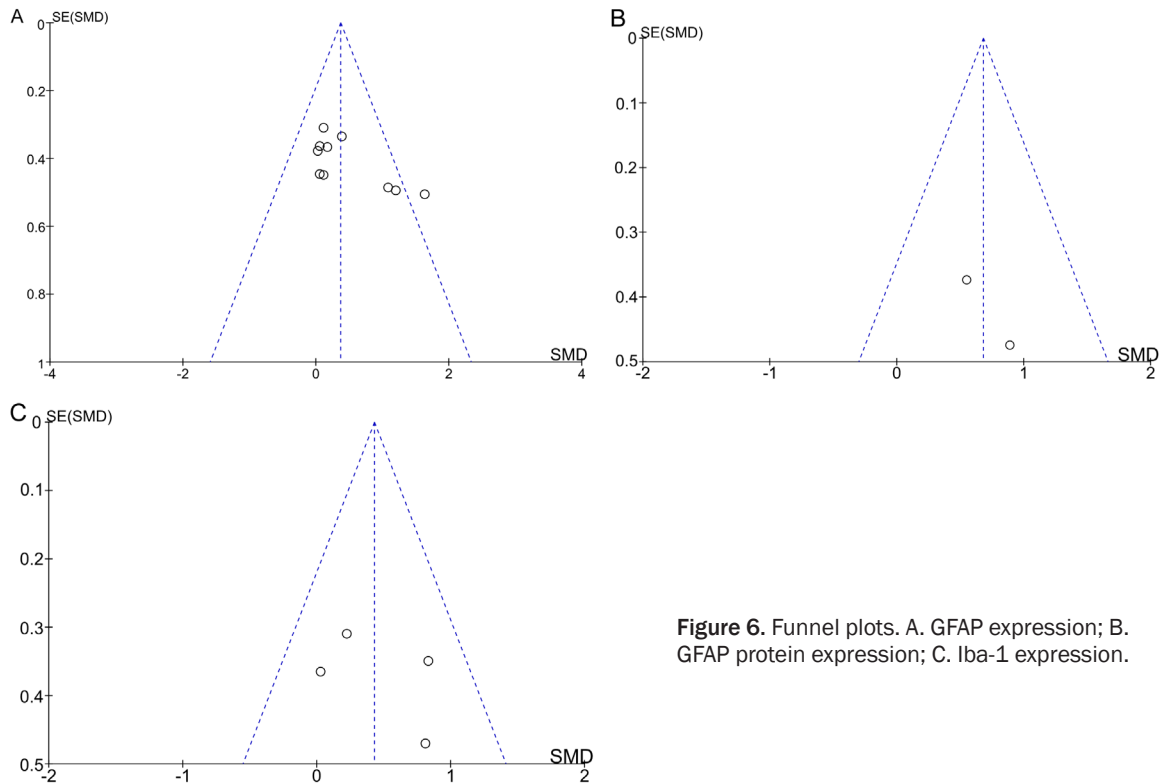
Figure 6. Funnel plots. A. GFAP expression; B. GFAP protein expression; C. Iba-1 expression.

cess in the pathophysiology of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [18].

The expression of GFAP and Iba-1 was observed to be augmented in the groups treated with general anesthetics, indicating that these drugs may trigger a neuroinflammatory response in the brain. This finding is significant as it suggests that general anesthetics not only induce unconsciousness and immobility, but also have the potential to impact the brain's immune response and cellular integrity. The mechanisms by which general anesthetics may cause neuroinflammation and neuronal damage are complex. One possibility is a direct toxic effect of the anesthetics on neurons and glial cells. Anesthetics have been found to disrupt neurotransmitter balance, alter membrane integrity, and interfere with mitochondrial function, all of which can result in cellular damage [19]. The upregulation of GFAP and Iba-1 observed in the studies can be interpreted in two main ways. First, it may represent a cellular stress response to the insult caused by the anesthetics. Glial cells, especially astrocytes and microglia, become activated in response to injury or insult, leading to an increase in

GFAP and Iba-1 expression as part of a protective or repair mechanism. This upregulation may help to protect the CNS from further damage and promote tissue recovery [20].

The neuroinflammatory effects of general anesthetics may also be attributed to the immune response and oxidative stress induced by anesthesia. It has been shown that anesthetics disrupt the balance of neurotransmitters, alter membrane integrity, and interfere with mitochondrial function, which can lead to cellular damage [21]. Additionally, anesthetics can induce immune response within the CNS, resulting in the release of pro-inflammatory cytokines and chemokines, which can exacerbate inflammation [22]. The increased expression of GFAP and Iba-1 may reflect the brain's attempt to repair itself. After anesthetic-induced neuroinflammation, the CNS may mount a response aimed at restoring normalcy [23]. This could involve the recruitment of glial cells and immune cells to the site of injury to remove debris and promote the formation of new neural connections [24]. It is also possible that the upregulation of these biomarkers is an adaptive response to the chronic neuroinflammatory environment that persists following anesthesia. This could have long-term implica-

tions for brain health. Therefore, understanding the mechanisms by which general anesthetics affect GFAP and Iba-1 expression, and how they contribute to neuroinflammation, is crucial for improving patient outcomes. This is particularly important for individuals at risk for or already affected by neurodegenerative diseases. Further research is needed to elucidate these mechanisms and develop strategies to mitigate potential harms of general anesthesia on brain health.

The meta-analysis of this study does have some limitations. First, the number of publications included in this meta-analysis was relatively small. This limited number of included studies is a common limitation in meta-analyses. It can impact the overall reliability and generalizability of the findings and increase the risk of chance findings. Therefore, these results should be interpreted with caution. Additionally, the limited number of studies also limits the ability to draw strong conclusions from the findings. Overall, while this meta-analysis provides valuable insight into the relationship between general anesthesia, biomarkers, and neuroinflammation, further research is needed to validate and expand upon these findings.

In conclusion, the findings of this meta-analysis underscore the ability of general anesthetics to induce neuroinflammatory response in the brain, with implications for neuronal damage and long-term outcomes. Further research is needed to clarify the mechanisms by which anesthetics affect the CNS and to develop strategies to mitigate these adverse effects. Ensuring patient safety and optimizing outcomes in the context of anesthesia requires a deep appreciation of the complex interplay between anesthetics, the brain, and the immune system.

Disclosure of conflict of interest

None.

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References

[1] Platholi J and Hemmings HC. Effects of general anesthetics on synaptic transmission and plasticity. Curr Neuropharmacol 2022; 20: 27-54.

[2] Bonvini JM. General anesthetics in cancer surgery: can anesthesiologists help the patient with more than a safe sleep. Medicina (Kaunas) 2022; 58: 1156.

[3] Guo CH, Bai L, Wu HH, Yang J, Cai GH, Zeng SX, Wang X, Wu SX and Ma W. Midazolam and ropivacaine act synergistically to inhibit bone cancer pain with different mechanisms in rats. Oncol Rep 2017; 37: 249-258.

[4] Li D, Sun J, Yu M, Wang Y, Lu Y and Li B. The protective effects of miR-128-3p on sevoflurane-induced progressive neurotoxicity in rats by targeting NOVA1. J Toxicol Sci 2022; 47: 51-60.

[5] Zhang ZL, Wang ZT, Shi J, Pu XP and Zhai SD. Tetrandrine attenuates SNI-induced mechanical allodynia by inhibiting spinal CKLF1. Neuropharmacology 2023; 238: 109673.

[6] Puthillathu N, Moffett JR, Korotcov A, Bosomtwi A, Vengilote R, Krishnan JKS, Johnson EA, Arun P and Namboodiri AM. Brief isoflurane administration as an adjunct treatment to control organophosphate-induced convulsions and neuropathology. Front Pharmacol 2023; 14: 1293280.

[7] Li X, Jiang X, Gao Q and Zhao P. FOXO3 regulates sevoflurane-induced neural stem cell differentiation in fetal rats. Cell Mol Neurobiol 2022; 42: 1777-1786.

[8] Zhang Y, Wu Z, Li X, Wan Y, Zhang Y and Zhao P. Maternal sevoflurane exposure affects differentiation of hippocampal neural stem cells by regulating miR-410-3p and ATN1. Stem Cell Res Ther 2020; 11: 423.

[9] Konnova EA, Deftu AF, Chu Sin Chung P, Pertin M, Kirschmann G, Decosterd I and Suter MR. Characterisation of GFAP-expressing glial cells in the dorsal root ganglion after spared nerve injury. Int J Mol Sci 2023; 24: 15559.

[10] Deng Y, Xie M and Zeng L. Autoimmune glial fibrillary acidic protein astrocytopathy. Neurol India 2023; 71: 1326-1327.

[11] Yetimler B, Tzartos J, Şengül B, Dursun E, Ulukan Ç, Karagiorgou K, Gezen-Ak D, Sezgin M, Papaconstantinou A, Tzartos S, Orhan EK, Ekizoğlu E, Küçükali Cİ, Baykan B and Tüzün E. Serum glial fibrillary acidic protein (GFAP)-antibody in idiopathic intracranial hypertension. Int J Neurosci 2021; 131: 775-779.

[12] Shi FJ, Xie H, Zhang CY, Qin HF, Zeng XW, Lou H, Zhang L, Xu GT, Zhang JF and Xu GX. Is Iba-1 protein expression a sensitive marker for microglia activation in experimental diabetic retinopathy? Int J Ophthalmol 2021; 14: 200-208.

[13] Gök E and Deveci E. Histopathological evaluation of IBA-1, GFAP activity in the brain cortex of rats administered cadmium chloride. Arch Ital Biol 2022; 160: 20-27.

[14] Xu S, Lu J, Shao A, Zhang JH and Zhang J. Glial cells: role of the immune response in ischemic stroke. Front Immunol 2020; 11: 294.

[15] Brenner M and Messing A. Regulation of GFAP expression. ASN Neuro 2021; 13: 1759091420981206.

[16] Neudecker V, Perez-Zoghbi JF, Martin LD, Dissen GA, Grafe MR and Brambrink AM. Astrogliosis in juvenile non-human primates 2 years after infant anaesthesia exposure. Br J Anaesth 2021; 127: 447-457.

[17] Cornet S, Carré D, Limana L, Castel D, Meilin S, Horne R, Pons L, Evans S, Lezmi S and Kalinichev M. Intraoperative abobotulinumtoxinA alleviates pain after surgery and improves general wellness in a translational animal model. Sci Rep 2022; 12: 21555.

[18] Dietz AG, Goldman SA and Nedergaard M. Glial cells in schizophrenia: a unified hypothesis. Lancet Psychiatry 2020; 7: 272-281.

[19] Baiardi S, Quadalti C, Mammana A, Dellavalle S, Zenesini C, Sambati L, Pantieri R, Polischi B, Romano L, Suffritti M, Bentivenga GM, Randi V, Stanzani-Maserati M, Capellari S and Parchi P. Diagnostic value of plasma p-tau181, NfL, and GFAP in a clinical setting cohort of prevalent neurodegenerative dementias. Alzheimers Res Ther 2022; 14: 153.

[20] Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, Blackburn KM, Turaga S, Binks S, Zitser J, Gelfand JM, Day GS, Dunham SR, Rodenbeck SJ, Clardy SL, Solomon AJ, Pittock SJ, McKeon A, Dubey D, Zekeridou A, Toledano M, Turner LE, Vernino S and Irani SR. Autoimmune encephalitis misdiagnosis in adults. JAMA Neurol 2023; 80: 30-39.

[21] Bharioke A, Munz M, Brignall A, Kosche G, Eizinger MF, Ledergerber N, Hillier D, Gross-Scherf B, Conzelmann KK, Macé E and Roska B. General anesthesia globally synchronizes activity selectively in layer 5 cortical pyramidal neurons. Neuron 2022; 110: 2024-2040.e2010.

[22] Little K, Llorián-Salvador M, Tang M, Du X, Marry S, Chen M and Xu H. Macrophage to myofibroblast transition contributes to subretinal fibrosis secondary to neovascular age-related macular degeneration. J Neuroinflammation 2020; 17: 355.

[23] Duan S, Sawyer TW, Sontz RA, Wieland BA, Diaz AF and Merchant JL. GFAP-directed inactivation of Men1 exploits glial cell plasticity in favor of neuroendocrine reprogramming. Cell Mol Gastroenterol Hepatol 2022; 14: 1025-1051.

[24] Deiner S, Baxter MG, Mincer JS, Sano M, Hall J, Mohammed I, O'Bryant S, Zetterberg H, Blennow K and Eckenhoff R. Human plasma biomarker responses to inhalational general anaesthesia without surgery. Br J Anaesth 2020; 125: 282-290.

[25] Sun L, Niu K, Guo J, Tu J, Ma B and An J. Dexmedetomidine attenuates postoperative spatial memory impairment after surgery by reducing cytochrome C. BMC Anesthesiol 2023; 23: 85.

[26] Feng Y, Liu J and Zhang WS. Etomidate-induced myoclonus correlates with the dysfunction of astrocytes and glutamate transporters in the neocortex of Sprague-Dawley rats. Eur Rev Med Pharmacol Sci 2022; 26: 6221-6235.

[27] Morax L, Beck-Schimmer B, Neff J, Mueller M, Flury-Frei R and Schläpfer M. Sevoflurane postconditioning protects from an early neurological deficit after subarachnoid hemorrhage: results of a randomized laboratory study in rats. Anesth Analg 2024; [Epub ahead of print].

[28] Jiang P, Jiang Q, Yan Y, Hou Z and Luo D. Propofol ameliorates neuropathic pain and neuroinflammation through PPAR γ up-regulation to block Wnt/β-catenin pathway. Neurol Res 2021; 43: 71-77.

[29] Yang Y, Yi J, Pan M, Hu B and Duan H. Edaravone alleviated propofol-induced neural injury in developing rats by BDNF/TrkB pathway. J Cell Mol Med 2021; 25: 4974-4987.

[30] Wang X, Yang X, Han F, Gao L and Zhou Y. Propofol improves brain injury induced by chronic cerebral hypoperfusion in rats. Food Sci Nutr 2021; 9: 2801-2809.

[31] Zhu Y, Lv C, Liu J, Shang S and Jing W. Effects of sevoflurane general anesthesia during early pregnancy on AIM2 expression in the hippocampus and parietal cortex of Sprague-Dawley offspring rats. Exp Ther Med 2021; 21: 469.

[32] Liao WT, Xiao XY, Zhu Y and Zhou SP. The effect of celastrol on learning and memory in diabetic rats after sevoflurane inhalation. Arch Med Sci 2018; 14: 370-380.

[33] Tian Y, Chen KY, Liu LD, Dong YX, Zhao P and Guo SB. Sevoflurane exacerbates cognitive impairment induced by Aβ (1-40) in rats through initiating neurotoxicity, neuroinflammation, and neuronal apoptosis in rat hippocampus. Mediators Inflamm 2018; 2018: 3802324.