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Original Article

Effects of Anesthetic Agents on Blood Brain Barrier Integrity: A Systematic Review

Abanoub Aziz Rizk[1], Eric Plitman[2], Pooja Senthil[3], Lashmi Venkatraghavan[4] and Tumul Chowdhury[4]

[1]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, [2]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [3]Faculty of Science, McMaster University, Hamilton, Toronto, Ontario, Canada and [4]Department of Anesthesia and Pain Management, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

ABSTRACT: ***Background:*** The blood brain barrier (BBB) is a highly selective permeable barrier that separates the blood and the central nervous system. Anesthesia is an integral part of surgery, and there is little known about the impact of anesthetics on the BBB. Therefore, it is imperative to explore reversible or modifiable variables such as anesthetic agents that influence BBB integrity. We aimed to synthesize the literature pertaining to the various effects of anesthetics on the BBB. ***Methods:*** MEDLINE, Embase, and Cochrane were searched from inception up to September 2022. ***Results:*** A total of 14 articles met inclusion into the review. The articles included nine randomized control studies (64.3%) and five quasi-experimental studies (35.7%). Twelve studies used volatile anesthetics, one study used fentanyl intravenously, and one study used pentobarbital or ketamine intraperitoneally. BBB structural deficits following the administration of an anesthetic agent included ultrastructural deficits, decreases in tight junctions, and decreases in BBB components. BBB functional deficits included permeability increases following exposure to volatile anesthetics. However, two studies found decreased permeability after fentanyl, pentobarbital, or ketamine exposure. Moreover, the impact of anesthetics on the BBB seems to be related to the duration of exposure. Notably, study findings also suggest that changes following anesthetic exposure demonstrate some reversibility over the short-term. ***Conclusion:*** Overall, our systematic review highlights interesting findings pertaining to the impact of anesthetic agents on BBB integrity in previously healthy models. These findings and mechanisms should inspire future work to aid practitioners and healthcare teams potentially better care for patients.

RÉSUMÉ : Effets des anesthésiques sur l'intégrité de la barrière hématoencéphalique : résultats d'une synthèse. ***Contexte :*** La barrière hématoencéphalique (BHE) est une structure perméable, très sélective, qui isole le système nerveux central de la circulation sanguine. L'anesthésie fait partie intégrante de la chirurgie, et on en sait peu sur l'influence des anesthésiques sur la BHE. Aussi est-il impérieux d'étudier les variables réversibles ou modifiables, par exemple les anesthésiques, qui influent sur l'intégrité de la BHE. L'étude visait donc à dresser une synthèse de la documentation médicale sur les différents effets des anesthésiques sur la BHE. ***Méthode :*** Une recherche a été effectuée dans les bases de données MEDLINE, Embase et Cochrane, depuis leur constitution jusqu'à septembre 2022. ***Résultats :*** Au total, 14 articles respectaient les critères de sélection de l'étude en vue de la synthèse : 9 d'entre eux (64,3 %) faisaient état d'études comparatives à répartition aléatoire et 5 (35,7 %), d'études quasi expérimentales. Dans douze études, on avait administré des anesthésiques volatils; dans une, du fentanyl par voie intraveineuse; et, dans une autre, du pentobarbital ou de la kétamine par voie intrapéritonéale. Les failles structurales de la BHE observées après l'administration des anesthésiques comprenaient des faiblesses ultrastructurales, un relâchement des jonctions serrées et une diminution des composants de la BHE. Parmi les troubles fonctionnels de la BHE, il y avait une augmentation de la perméabilité à la suite de l'exposition aux anesthésiques volatiles. Par contre, une diminution de la perméabilité avait été observée, dans deux études, après l'administration de fentanyl, de pentobarbital ou de kétamine. De plus, les effets des anesthésiques sur la BHE semblaient liés à la durée d'exposition. Point digne de mention : d'après des études, il se produirait, à court terme, une certaine réversibilité des modifications consécutives à l'exposition aux anesthésiques. ***Conclusion :*** Dans l'ensemble, les résultats de la revue systématique font ressortir des changements intéressants, liés à l'action des anesthésiques sur l'intégrité de la BHE chez des sujets antérieurement en bonne santé. Les constations et les mécanismes qui s'en dégagent devraient donner lieu à d'autres travaux de recherche dans le but d'aider les praticiens et les équipes de soins de santé à améliorer potentiellement les soins aux patients.

Keywords: Anesthesia; Animal models; Blood brain barrier; Cognitive impairment; Permeability; Structure

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Corresponding author: Tumul Chowdhury MD, DM, FRCPC, Consultant Anesthesiologist, Department of Anesthesia and Pain Management, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada. Email: Tumul.Chowdhury@uhn.ca

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Background

The blood brain barrier (BBB) is a highly selective permeable barrier that separates the blood and the central nervous system.[1,2] The normal functioning of the BBB is required to control the extracellular environment of the central nervous system.[3,4] The neurovascular unit (NVU) is an important and closely related structure, composed in part of neural cells, glia, extracellular matrix, and endothelial cells with tight junctions contributing to the BBB. [3,4] The NVU plays a critical role in regulating cerebral blood flow, along with the regional delivery of nutrients and oxygen.[3,4] Dysfunction of the anatomic components or physiologic processes within the NVU may contribute to BBB disruption.[3,4] BBB disruption has been described to occur through various mechanisms affecting both its structure, such as decreased production of its components and ultrastructural alterations, and its function, as observed through various markers of increased permeability.[2,5–8] BBB breakdown has been implicated in the pathophysiology of several neurologic diseases, including stroke and multiple sclerosis, among others, through a variety of purported pathophysiologic processes, including neuroinflammation, edema, and ion dysregulation.[9]

Anesthesia is an integral part of perioperative management of patients with a neurological condition. The impact of anesthesia on the integrity of the BBB and its structure and function is an evolving area of investigation. Given the potential implications for important clinical outcomes such as postoperative cognitive function (POCD),[10] a comprehensive understanding of the influence of anesthetic exposure on the BBB is required, including any potential modifiable variables such as choice of anesthetic agent. The present systematic review aims to synthesize all literature pertaining to the effects of anesthetics on BBB.

Methods

Search Strategy and Selection Criteria

The literature search was conducted on the electronic databases MedlineALL, Embase, and Cochrane to identify relevant articles from 1978 to 2022. The database search strategies were generated with assistance from M.E., librarian. The search involved MESH and keyword searches, titles, and abstracts of the following words: anesthetics, anesthesia, general anesthesia, volatile anesthetics, intravenous anesthetics with blood brain barrier, BBB, with disruption, damage, and permeability. The search was limited to include only human and animal studies published in the English language. No sex restrictions were placed. Reference lists of relevant articles were also searched manually.

Inclusion and Exclusion Criteria

This systematic review was designed utilizing the PRISMA-P methodology flowchart. Two independent reviewers (AAR and EP) evaluated the search results to identify eligible studies that met the predefined inclusion and exclusion criteria; a third author (TC) was involved to make the final decision in the event of a discrepancy. Primary laboratory animal research, case series, case reports, randomized control trials, and letters were considered for inclusion. Studies were included if the sample comprised previously healthy adult human subjects and/or animal models, and the primary aim of the study was to measure changes in BBB integrity (i.e. structure or function), following the administration of any anesthetic agent (general anesthesia, spinal anesthesia, conscious sedation, or combination) without the context of a surgical procedure. Articles that not only analyzed BBB permeability but also discussed secondary findings (e.g. cognitive impairment) were included. Studies that employed an experimental model that produced BBB disruption (e.g. iatrogenic, osmotic, medications, surgery) were excluded so as to examine only the pure effect of anesthetics on BBB instead of a synergistic effect. Articles for which the full text was not accessible were excluded.

Data Extraction and Quality Assessment

Several key indices were obtained from all included studies: first author, year of publication, study design, sample size, sample characteristics (species, age, gender), anesthetic agent (type, molecule, concentration, dose), measures of BBB integrity, and results. Quality assessment was performed using the Newcastle–Ottawa Scale.[11]

Results

Our database-advanced search yielded a total of 1050 articles (MedlineALL, Embase, and Cochrane) (Figure 1) and search development strategies are described in detail in the supplementary material. A total of 121 articles were screened and out of those, 14 articles were finally included in the study (Table 1).[2,5–8,12–20] Nine reports were of level II evidence and five were of level III evidence.[21] The articles included nine randomized control studies (64.3%) and five quasi-experimental studies (35.7%). Out of 14 articles, 3 studies utilized mice as their study models ($n = 206$ mice), and 11 articles used rat models ($n = 265$ rats).

Demographic Characteristics

The studies included a total of 354 male (75.2%), 60 female animals (12.7%), and 57 unknown sex (12.1%). In addition, though many exact ages were not reported, mice ranged from 8 weeks in age to models described as "adults," $n = 18$ (8 weeks of age), not specified ($n = 145$).

Primary Findings (Table 2)

Diagnostic modalities utilized across studies included: transmission electron microscopy ($n = 4$ studies), western blots ($n = 4$ studies), immunohistochemistry ($n = 4$ studies), immunofluorescence ($n = 3$ studies), 14C-alpha-aminoisobutyric acid ($n = 3$ studies), 14C-iodoantipyrine ($n = 2$ studies), Evans Blue albumin extravasation ($n = 2$ studies), UV spectroscopy ($n = 1$ studies), 14C-glucose ($n = 1$ study), scanning electron microscopy ($n = 1$ study), and fluorimetry ($n = 1$ study).

Twelve studies used volatile anesthetics, of which three used sevoflurane, six used isoflurane, one used sevoflurane and isoflurane, one used nitrous oxide, and one used pentobarbital and halothane. One study used fentanyl intravenously. One study used pentobarbital or ketamine intraperitoneally.

Primary findings can be further categorized into BBB structure and BBB function leading to BBB disruption and permeability changes. BBB structural deficits following the administration of an anesthetic agent included ultrastructural deficits, decreases in tight junctions, and decreases in BBB components such as F-actin, occludin, claudin-3, claudin-5, and VE-cadherin.[2,5–8,12,17] Primary findings commenting on BBB function also suggest

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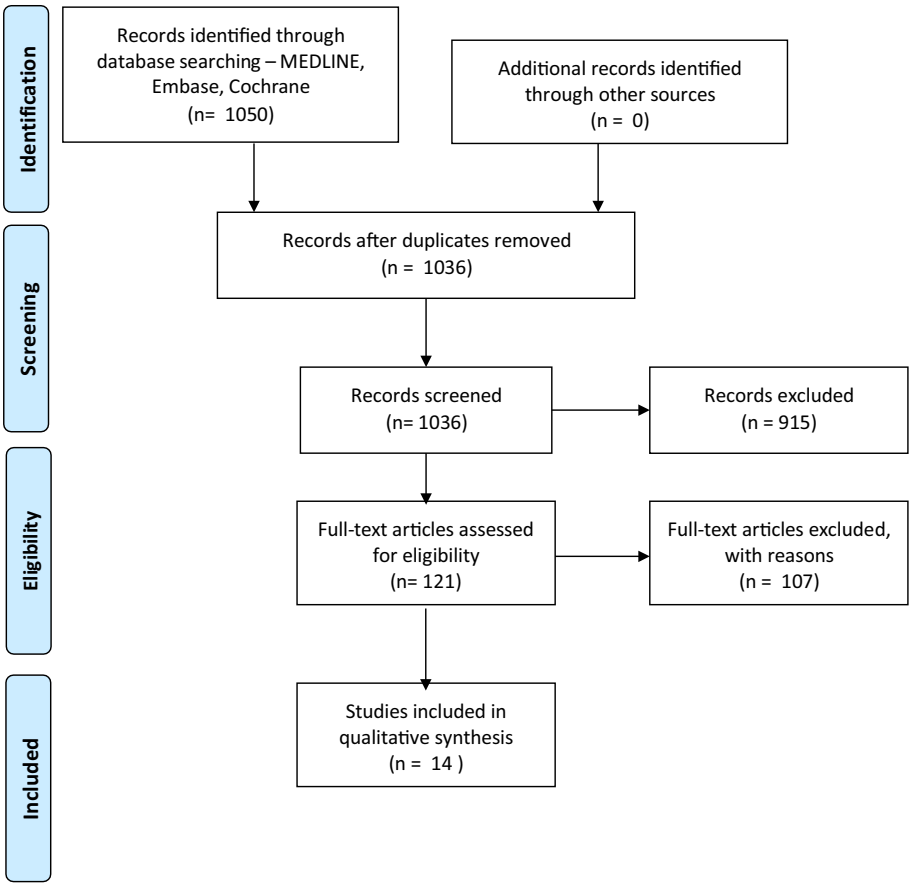

Figure 1: Prisma flowchart.

evidence of BBB permeability increases following exposure to volatile anesthetics, as characterized by IgG, NaF, fibrinogen, and Evans Blue markers.[2,5–8,14,17] However, one study found decreased BBB permeability as captured by [14C]alpha-aminoisobutyric acid after pentobarbital or ketamine exposure.[20] Other BBB function alterations reported within the literature include increased glucose transport across the BBB, Ki changes, and cerebral blood flow changes.[15,16,19]

Further, three studies explored the effect of anesthetic dose on the BBB. Hu et al demonstrated that exposure to 3.6% sevoflurane for 6 hours downregulated expression of BBB components and increased fibrinogen deposition at 24 hours after treatment, while animals exposed to lower doses (2.4% or 3.2% sevoflurane) did not have such changes.[7] Contrarily, Chi et al found that there was no significant difference in transport across the BBB in any brain region between groups exposed to 1 or 2% isoflurane, and groups exposed to low-dose fentanyl (25 μg/kg) and high-dose fentanyl (100 μg/kg).[15,19]

Two studies investigated the effect of duration of anesthetic exposure. Cao et al identified that after 2 or 4 hours of isoflurane exposure, progressive changes occurred in the BBB ultrastructure morphology, but this did not occur after 30 minutes or 1 hour of isoflurane exposure.[5] The authors also reported that increased BBB permeability, as detected by NaF content and IgG immunoreactivity, was only observed after 4 hours of isoflurane exposure, and not after 30 minutes, 1 hour, or 2 hours of isoflurane exposure. Sun et al found that the BBB opened gradually with increasing duration of sevoflurane exposure.[12] The authors found that exposure to sevoflurane for shorter durations (30 minutes) did not induce any long-term effects.

Of the studies that identified BBB changes, 10 employed inhalational (i.e. volatile) agents and 2 employed intravenous/intraperitoneal agents (Table 2).[2,5–8,12,14–17,19,20] Each of the 10 studies examining inhalational agents identified BBB disruption and/or increased BBB permeability,[2,5–8,12,14–17] while the 2 studies examining intravenous/intraperitoneal agents, Chi et al and Saija et al, indicated decreased BBB permeability using fentanyl and pentobarbital/ketamine, respectively.[19,20]

Three studies reported upon reversibility of BBB changes following anesthetic exposure. Cao et al found that the BBB ultrastructure morphological changes that occurred after 2 and 4 hours of isoflurane exposure gradually resolved at 24, 48, and 72 hours after exposure.[5] Also, the expression of occludin, a BBB component, which was decreased after 4 hours of isoflurane exposure, recovered to normal levels within 72 hours. Moreover, the authors found that BBB permeability returned to normal by 48 hours after isoflurane exposure as assessed by NaF content, and by 24 hours after isoflurane exposure as assessed by IgG immunoreactivity. Acharya et al found that increased BBB permeability, as assessed by IgG immunoreactivity, was not completely resolved at 24 hours after 3 hours of sevoflurane or isoflurane exposure.[2] The authors found that the extent of reversibility after 24 hours following exposure may have been influenced by age, as morphological changes as assessed by scanning electron microscopy were more comparable to untreated controls in young and middle-aged animals, than in older animals. Sun et al reported that 48 hours after sevoflurane

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Table 1: Study and demographic characteristics

No.	Study ID.	Type of study	Level of evidence	Study subjects	Age (years)	Gender	Anesthetic agent studied	Sample size (n) Agent: control
1	Sun Z et al. (2019)	Randomized Control Trial	II	Mice	8 weeks	M and F	Sevoflurane	18: N/S
2	Wang B et al. (2017)	Randomized Control Trial	II	Mice	N/S	M	Isoflurane	81: 27
3	Johansson BB et al. (1978)	Quasi-experimental	III	Rats	N/S	M	Nitrous Oxide	37: no control
4	Chi OZ et al. (1992)	Randomized Control Trial	II	Rats	Adult	M	Isoflurane	20:17
5	Nemoto EM et al. (1978)	Quasi-experimental	III	Rats	N/S	F	Pentobarbital and Halothane	N/S
6	Cao Y et al. (2018)	Randomized Control Trial	II	Rats	Adult	M	Isoflurane	12:6
7	Chi OZ et al. (1992)	Randomized Control Trial	II	Rats	Adult	M	Fentanyl	20:14
8	Acharya et al. (2015)	Quasi-experimental	III	Rats	Three groups: 3–5 months 10–12 months 17–19 months	N/S	Sevoflurane, Isoflurane	14:13:12
9	Cao et al. (2015)	Randomized Control Trail	II	Rats	20 months	M	Isoflurane	8:4
10	Zhu et al. (2018)	Randomized Control Trial	II	Mice	18 months	M	Isoflurane	60:20
11	Hu et al. (2016)	Quasi-experimental	III	Rats	20 months	M	Sevoflurane	8:8
12	Zheng et al. (2017)	Randomized Control Trial	II	Rats	4 months	M	Sevoflurane	6:6
13	Saija et al. (1989)	Quasi-experimental	III	Rats	N/S	M	Pentobarbital and Ketamine	N/S
14	He et al. (2012)	Randomized Control Trial	II	Rats	22–23 months	F	Isoflurane	45:15

N = Number; M = Male, F = Female, N/S = Not specified.

exposure, the percentage of capillaries that were destroyed decreased to 29%, as compared to 47% at 24 hours after exposure.[12]

Discussion

Our systematic review highlights findings pertaining to the impact of anesthetic agents influencing BBB integrity in previously healthy models (Figure 2). Overall, our study showed that volatile anesthetics increase BBB permeability in previously healthy animal models. One study showed an increase in BBB permeability in older animals treated with sevoflurane but not isoflurane.[2] Electron microscopy showed marked flattening of the luminal surfaces of brain vascular endothelial cells leading to such a permeability effect.[2] Similarly, even with neonate models, 2% sevoflurane caused BBB disruptions in their hippocampus that was increased with exposure time.[12] This study not only showed the potential vulnerability of the developing brain to sevoflurane exposure but also highlighted the importance of duration of anesthesia and concentration.[12] Another study looking at nitrous oxide anesthetic explains that protein extravasation takes place in most rats when MAP exceeds 170 mmHg, suggesting a potential correlation to blood pressure changes in the intraoperative setting.[14] This is in line with another study that showed extreme hypertension and extreme hypotension, in combination with vasodilators may alter BBB permeability.[15] Interestingly, this study found that isoflurane significantly decreased the transfer of small hydrophilic molecules across the BBB.[15] This may be explained by a reduction in the perfused capillary surface area or as suggested in the paper, a potential direct effect of BBB disruption by isoflurane.[15]

Our study findings were equivocal with respect to the impact of anesthetic dose on the BBB. While one study reported that down-regulation of BBB components occurred only after exposure to a high dose of sevoflurane and not with lower doses,[22] two other studies did not observe any difference in transport across the BBB with exposure to higher or lower doses of isoflurane and fentanyl, respectively.[15,19] By contrast, our study is more supportive of the notion that the impact of anesthetics on the BBB is related to the duration of exposure. Both studies investigating this question demonstrated that longer anesthetic exposure resulted in more significant BBB disruption, and that shorter durations of anesthetic exposure (e.g. 30 minutes) did not lead to significant BBB changes.[5,12] These observations are hypothesis generating, and the influence of dose and duration of anesthetic exposure on the BBB is a clinically relevant topic that warrants further investigation.

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Table 2: Main findings

No.	Study ID	Anesthetic exposure	Diagnostic modality	Procedure	Primary findings	Possible mechanism	Details and secondary findings
1	Sun et al. (2019)	2% sevoflurane	Transmission electron microscope	Brain tissue study	2% sevoflurane exposure caused BBB disruption in the hippocampus of mice at POD6	BBB disruption	After 2 hr of sevoflurane exposure, ultrastructural integrity was locally collapsed After 4 hr, 64% of capillaries were destroyed and perivascular spaces were enlarged After 6 hr, 78% of capillaries were destroyed BBB disruption was reversible
2	Wang et al. (2017)	1.5–2% isoflurane	Western blot UV Spectroscopy Transmission Electron Microscopy	N/A	N/A	N/A	N/A
3	Johansson et al. (1978)	70% Nitrous Oxide	Evans Blue albumin (EBA) extravasation	N/A	Under nitrous oxide anesthesia pharmacologically induced hypertension (MAP >170 mmHg) caused increased permeability and blood flow	BBB permeability	Increased permeability with protein leakage was also seen lower MAP especially in hypercapnic rats
4	Chi et al. (1992)	1 and 2% isoflurane	14C-alpha-aminoisobutyric acid: blood brain transfer coefficient (Ki) 14C-iodoantipyrine: regional cerebral blood flow (rCBF)	N/A	Ki was less in both the 1 and 2% isoflurane groups compared to controls	BBB permeability	No significant difference between 1 and 2% isoflurane in any brain region 2% isoflurane did not affect rCBF in 9 of 13 brain regions
5	Nemoto et al. (1978)	Pentobarbital 60 mg/kg Halothane 1.5–2.0%	H2O/14C-D-Glucose soluble indicator	N/A	Increased diffusional transport of glucose across the BBB with Halothane processes	BBB permeability	At normal glucose concentrations (5 nM), total brain glucose influx was unaltered by pentobarbital Halothane inhibits BBB glucose transport by competing for the glucose carrier and by altering affinity of the carrier for glucose Halothane attenuated glucose transport capacity from 1.9 to 0.4 μmol/g min^{-1} and increased diffusional transport
6	Cao Y et al. (2018)	1.5% Isoflurane	Immunofluorescence staining: HIF-1a and VGEF	N/A	IgG leakage was significantly increased after 4 hr isoflurane exposure (IOD ratio: 26.39 ± 8.03, $p < 0.05$) compared with the control group (IOD ratio: 8.12 ± 5.35)	BBB disruption and BBB permeability	4 hr isoflurane exposure enhanced expression of HIF-1α and its downstream effector VEGF in the hippocampus of aged rats Isoflurane disrupted the BBB ultrastructure *via* activation of the HIF-1α/VEGF pathway leading to degradation of tight junction protein and collagen type IV in brain blood vessels Hippocampal HIF-1α/VEGF signaling seems to be mechanism of isoflurane-induced cognitive impairment and YC-1 pre-treatment significantly attenuated isoflurane-induced cognitive deficits in the Morris water maze task
7	Chi et al. (1992)	Fentanyl low dose (25 ug/kg) and high dose (100 ug/kg)	C-cr-aminoisobutyric acid; blood brain transfer coefficient 4C-iodoantipyrin; regional cerebral blood flow	N/A	Fentanyl decreased the transfer of small hydrophilic molecules across the BBB	BBB permeability	Blood brain barrier permeability was lower in 9 out of 13 brain regions Decrease in K, decreased permeability and capillary surface area despite a lack of significant change in the average cerebral flow with fentanyl It may be related to reduced cerebral metabolism

(*Continued*)

Table 2: (*Continued*)

No.	Study ID	Anesthetic exposure	Diagnostic modality	Procedure	Primary findings	Possible mechanism	Details and secondary findings
8	Acharya et al. (2015)	1–3% Sevoflurane, 1–3% Isoflurane	Scanning electron microscopy Immunohistochemistry	3 hr of anesthesia Sacrificed immediately and after 24 hr	Increased BBB permeability in older animals treated with sevoflurane but not isoflurane BBB ultrastructure morphological damage in anesthetic-treated rats	BBB disruption and BBB permeability	BBB permeability increases and luminal surface topology of brain vascular endothelial cells flattened Extravasated IgG showed selective affinity for pyramidal neurons
9	Cao et al. (2015)	1.5% Isoflurane	Transmission electron microscopy Western blot analysis Fluorimetry Immunohistochemistry	Isoflurane for 4 hr Assessments performed at 30 mins, 1, 2, and 4 hr during exposure and 24, 48, and 72 hr after exposure	Increased BBB permeability after 4 hr of isoflurane exposure in aged rats Reversible time-dependent hippocampal BBB ultrastructure morphological damage in isoflurane-treated rats	BBB disruption and BBB permeability	BBB ultrastructure morphological damage- collapsed basal lamina, swollen astrocyte foot processes, dilated mitochondria, open tight junctions, and angioedema Decrease in occludin expression and increased BBB permeability Isoflurane exposure led to cognitive impairments in the Morris water maze test
10	Zhu et al. (2018)	2% Isoflurane	Evans Blue test Western blot analysis Immunofluorescence assay	Isoflurane for 4 hr	Increased BBB permeability in POCD mice compared to control and non-POCD groups Decrease in BBB component production in hippocampus of POCD mice compared to control and non-POCD mice	BBB disruption and BBB permeability	4 hr exposure was found to be the optimal condition for POCD mouse model Increased BBB permeability was due to decreases in expression of claudin-5 and occludin Using flow cytometry, CD4+ T and NK cell expression higher in the hippocampus of POCD mice compared to control and non-POCD mice
11	Hu et al. (2016)	3.6% Sevoflurane	Western blot analysis Immunofluorescence	Sevoflurane for 6 hr Assessments performed at 6, 12, and 24 hr after exposure	Increased BBB permeability at 24 hr after anesthetic exposure Decrease in BBB component production	BBB disruption and BBB permeability	Decreased expression of tight junction proteins (occluding, claudin-3, VE-cadherin), F-actin and cytoskeleton protein Decreased expression of Annexin A1 at 24 hr after exposure Pre-treatment with Annexin A1 attenuated BBB disruption and prevented sevoflurane-induced cognitive decline
12	Zheng et al. (2017)	2% Sevoflurane	Immunohistochemistry	Sevoflurane for 2 hr Analyses performed 24 hr after exposure	No difference in BBB permeability between sevoflurane and control groups	BBB permeability	
13	Saija et al. (1989)	Pentobarbital (54 mg/kg) and ketamine (150 mg/kg)	Unidirectional blood-to-brain constant for the circulating tracer [14C] alpha-aminoisobutyric acid	N/A	Decreased BBB permeability during anesthesia with pentobarbital and ketamine	BBB permeability	Neurogenic or direct interaction of the anesthetic with elements of the microvasculature Pentobarbital was associated with a widespread decrease in cerebral glucose utilization Ketamine was associated with increased cerebral glucose utilization in the striatum and hippocampus, and a decrease in the cerebellum and brainstem
14	He et al. (2012)	2% Isoflurane	Immunohistochemistry Transmission electron microscopy	Isoflurane for 2 hr	Increased BBB permeability at day 1 after exposure to isoflurane compared to naïve rats. Minor changes in BBB ultrastructure after exposure to isoflurane	BBB disruption and BBB permeability	Ultrastructure changes: mild and localized swelling, expanded perivascular space Increases in TNF-alpha, IL-1β, HMGB1, and RAGE mRNA and protein levels at day 1 following anesthesia exposure Morris water maze latency impaired at day 1 following anesthesia exposure

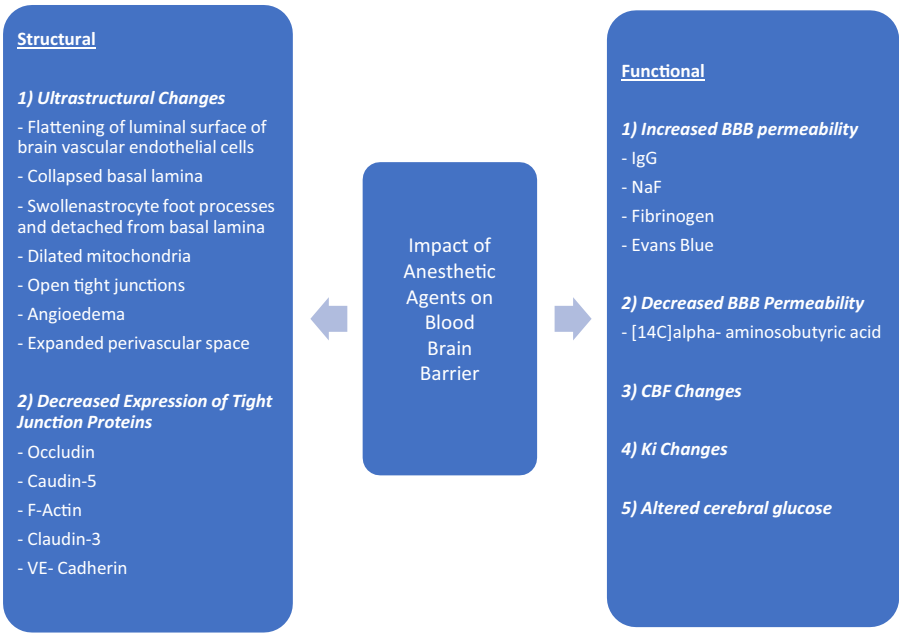

Figure 2: Plausible mechanisms for impact of anesthetic agents on blood brain barrier.

Furthermore, 12 out of 14 studies included in the current review tested inhalational anesthetics. A consistent directionality toward BBB disruption and/or increased BBB permeability was reported amongst studies that employed such agents.[2,5–8,12–18] This was contrasted by studies employing intravenous or intraperitoneal agents, such as fentanyl, pentobarbital, or ketamine.[19,20] Despite there being a paucity of such studies included in the current work, there appeared to be a trend toward decreased BBB permeability subsequent to intravenous or intraperitoneal anesthetic exposure.[19,20]

Our study also suggests that BBB changes following anesthetic exposure demonstrate some reversibility over the short-term. Two of the studies found that both structural and functional changes in the BBB following anesthetic exposure gradually resolved over time, within 24, 48, or 72 hours following exposure depending on the finding in question.[5,12] However, it is possible that the extent of reversibility depends in part on factors such as the recovery time and patient age, as suggested by one study that found 24 hours to be insufficient for complete recovery of BBB changes, and that the extent of recovery was reduced in older animals.[2]

The impact of anesthesia on the BBB is particularly relevant to the phenomenon of POCD in older adults.[10] Unfortunately, the underlying causes of POCD have yet to be determined, and no definitive descriptions regarding mechanisms associated with the BBB disruption have been made.[13,22] Studies in animal models have suggested that exposure to agents such as sevoflurane is associated with BBB compromise, in an age-dependent manner.[2] One proposed mechanism is a decrease in expression of tight junction proteins such as occludin, causing increased leakage of molecules and mediating isoflurane-induced hippocampus BBB disruption.[5] Further, a study also proposed the involvement of specific danger-associated molecular patterns with a pivotal role in mediating acute damage response and causing BBB dysfunction during surgery.[8]

To the best of our knowledge, this is the first systematic review aiming to explore the pure effect of anesthetics on BBB integrity using data from healthy subjects. Notably, the present work identified a clear gap within the literature in that each of the included studies was in animal subjects. While our adopted inclusion criteria may have been too restrictive to draw upon human literature examining the impact of anesthetic on the BBB (i.e. healthy human subjects receiving anesthetics without surgical confounders), our review highlights the paucity of available human work related to this research question. Moreover, implications drawn toward the field are predominantly based on findings from preclinical studies employing volatile anesthetics; thus, additional studies including human subjects and utilizing intravenous anesthetics that test comparable research questions are warranted going forward.

Recommendations

This systematic review elucidated some potential findings and mechanisms that should inspire future work to aid practitioners and healthcare teams potentially better care for patients. It appears from our findings that a significant number of models with previously healthy brains suffered disruptions in BBB integrity following administration of different anesthetic agents. Therefore, in such a context, the risks and benefits of using particular sedative/opioid agents should be incorporated into the discussion. While the model studied in this review involved previously healthy models, it is plausible that greater post-surgical care and vigilance may be required for patients with previous neurological focal deficits prone to BBB disruption.

Limitations

There are several limitations to our systematic review. Overall, there was a limited number of studies looking at reversible or modifiable variables such as anesthetic agents that influence BBB integrity in previously healthy models. As a result, the conclusions regarding the impact of such agents on BBB integrity are limited. Subsequently, the results of this review should be considered preliminary, supporting the need for future prospective studies to examine effects on previously pathologic brains. In addition, attrition bias could not be eliminated due to heterogeneity in the study data. However, to the best of our abilities, we attempted to organize and standardize the information presented by each study. In addition, our review illustrated similar outcomes despite this variability.

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Conclusion

Our study elucidated interesting findings pertaining to potential mechanisms of BBB integrity changes in response to anesthetic agents. Although preliminary, we hope this study would inspire future work to explore this area of research further so we can collectively provide better healthcare to patients.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.319.

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