



Negative effect of general anaesthesia on the human brain – mechanism and methods of prevention

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Abstract

Introduction and Objective. General anesthesia is an integral part of many medical procedures. Its main premise is that it is completely reversible and has no effect on the human brain. Unfortunately, a number of scientific findings report potential effects of anaesthetics on the human nervous system. The aim of this review is to present the negative impact of sevoflurane (inhalation anaesthetic) and propofol (intravenous anaesthetic) on the human brain with an analysis of its mechanisms and factors, and possible methods of preventing this phenomenon.

Review Methods. A review was undertaken of the most current literature using PubMed and Google Scholar databases, on the mechanism of action and the negative effects of sevoflurane and propofol on the brain and methods of its prevention. Included are both original works, reviews and case reports from Poland and worldwide.

Brief description of the state of knowledge. Post-operative cognitive dysfunction affects 10–65% of patients. Sevoflurane and propofol have potentially damaging effects on the human brain. This occurs mainly through induction of neuronal cell apoptosis and disruption of synaptogenesis by affecting receptor proteins, cell organelles (mitochondria, endoplasmic reticulum) and signaling pathways (apoptotic and trophic) of neurons. However, this effect depends on the drug dose and patient-dependent factors (age, diseases, cognitive status before anaesthesia).

Summary. Anaesthetics have potentially harmful effects on the human brain, although only in large and repeated doses. One should also not forget the much more notable effect of mechanical damage to tissues during surgery. In order to prevent cognitive dysfunction, both a detailed preoperative assessment of the patient's condition and the use of additional pharmacological and non-pharmacological measures during surgery are important.

Key words

brain, central nervous system, anaesthesia

INTRODUCTION AND OBJECTIVE

By the standards of modern medicine, many surgical procedures could not be performed without general anaesthesia which is generally regarded as one of the greatest discoveries in medicine. General anaesthesia (referred to as anaesthesia) is a procedure involving the induction and maintenance of the patient in a state of unconsciousness with to eliminate pain by the use of an appropriate combination of intravenous and inhaled agents [1]. The word 'anaesthesia' comes from the Greek language (*an* – 'without', and *aisthesis* – 'sensation'), a translation that defines its main components which, depending on the type and dose of the anaesthetic used, include: loss of consciousness, pain relief, skeletal muscle relaxation, loss of motor and autonomic reflexes, to potentially harmful stimuli, and retrograde amnesia [2].

The most important assumption of general anaesthesia is its complete reversibility, i.e. it has no lasting effect on the central nervous system (CNS). Unfortunately, many

studies on animal models have shown a direct damaging effect of anaesthetics on the CNS. This led to a change in the perception of the safety and excellence of general anaesthesia and the search for their negative impact on the human CNS, especially in relation to the developing brain of small children and the deterioration of cognitive functions in the elderly [3, 4].

The aim of this review is to present the negative impact of sevoflurane (inhalation anaesthetic) and propofol (intravenous anaesthetic) as two important representatives of their groups on the human brain in different phases of life, together with an analysis of the mechanisms and factors that determine it and possible methods of preventing this phenomenon.

REVIEW METHODS

A review was undertaken of publications from 2014–2023 on the negative impact of anaesthetics on the human brain was made. The review was conducted on 20 January – 20 March 2023 using the PubMed and Google Scholar online databases of scientific publications. Initially, a list of relevant titles and abstracts was compiled, and after further

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verification, the authors analyzed the full texts of selected publications. Original articles, review papers and case reports were accepted for review. Studies conducted on both animal models and less available descriptions of clinical trials were analyzed. Abstracts, posters and editorials were rejected. The country of origin of the study and the language of the article were not criteria for inclusion. When describing some mechanisms or phenomena, works published before or after the specified dates were used in order to accurately present the problem. The publications were analyzed using the non-systematic review method, with the intention of producing a short synthesis of the available information, and not a comprehensive description of the entire literature on the subject.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Molecular mechanism of action. The mechanism of action of anaesthetics is not fully understood, nor is the effect of these agents on the human nervous system. Sevoflurane acts mainly on the ionotropic receptors GABA_A (γ-aminobutyric acid binding receptor) and NMDA (N-methyl-D-aspartate receptor), and additionally on nicotinic cholinergic receptors and voltage-gated sodium and potassium channels [5, 6]. Propofol, on the other hand, acts on glycine, GABA_A and nicotinic receptors [7]. The GABA_A receptor is a chloride channel in which, after ligand binding, the channel opens and Cl⁻ ions enter the nerve cell. This causes hyperpolarization of the neuron's cell membrane and a decrease in its excitability and impulse conduction [6]. The NMDA receptor is characterized by a completely different action – its stimulation causes the conduction of sodium and calcium ions inside the cell and potassium ions outside, which causes the depolarization of the cell membrane and its activation. The antagonistic effect of anaesthetics on this receptor results in the inhibition of the generation of nerve impulses [8]. The nicotinic receptor is an ion channel through which sodium and potassium ions flow in the same way as in the NMDA receptor, and its activation also leads to depolarization of the cell membrane and impulse flow [9]. Moreover, the nicotinic receptor is one of the main ones mentioned in the pathogenesis of neurodegenerative diseases, including Alzheimer's or Parkinson's disease; therefore, the interaction of anaesthetics with these receptors could be a risk factor for neurological diseases [10]. It is also assumed that anaesthetics may affect the transmission between the cerebral cortex and the thalamus and hypothalamus, mainly through the dopaminergic and histaminergic systems; however, there is insufficient *in vivo* evidence for this [5]. Both compounds have an inhibitory effect on the CNS, resulting in the desynchronization of nerve impulses, leading to disturbances in signal conduction in the areas of the cerebral cortex responsible for the states of sleep and wakefulness [7].

Negative effects of anaesthetics on the human CNS. The mechanism of the negative effect of anaesthetics on the human CNS is not fully understood. It is assumed that it consists in the induction of apoptosis and depletion of the synaptic network by generating neurogenic inflammation, stimulating neuronal autophagy and inhibiting neurogenesis and synaptogenesis. It is also suspected that it affects proteins crucial for the CNS (receptors, ion channels), organelles inside

cells (endoplasmic reticulum, mitochondria, lysosomes) and pathways controlling the life cycle of neurons (trophic factors, apoptosis pathways) [4].

Post-operative cognitive dysfunction (POCD) is a type of cognitive disorder that occurs after surgery with the use of general anaesthesia, in the form of impaired thinking, memory, concentration, or even executive and motor functions [11]. It affects up to 10–65% of patients, depending on their age, gender, level of education, comorbidities and the type of surgery performed [12]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), POCD occurs from the 30th day to the 12th month after anaesthesia, while in the period of several hours to several days after surgery, such disorders are classified as post-operative delirium (POD) [13]. Neuropsychological scales are used to assess these disorders, in particular: the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), Verbal Fluency Test (VFT), performed before and after the procedure. Biochemical exponents of POCD may also be useful, including primarily: tau protein, amyloid protein Aβ, calcium-binding protein β (S100β), neutrophil-specific enolase (NSE), or parameters of inflammation: C-reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin 1, 6 and 7 (IL-1, IL-6, IL-7) [14, 15]. The study of cognitive performance in rats during experimental studies is mainly based on the orientation test in the Morris water maze [20].

Sevoflurane. The neurotoxicity of sevoflurane has been proven in animal models, mainly by stimulating neurogenic inflammation and apoptosis of brain cells. It has been shown to increase the synthesis of caspase-3 in hippocampal cells, which disrupts the life cycle and stimulates the death of neurons in this region of the brain, which is crucial for cognitive functions [16]. In addition, it is assumed that sevoflurane enhances the death of nerve cells by disturbing the release of calcium ions from the endoplasmic reticulum and increasing their intracellular concentration, which leads to an increase in the concentration of caspase-3 and subsequent induction of apoptosis [17]. These ions also determine the disorder of neurotransmitter secretion, indirectly influencing the modulation of synaptic transmission, which is necessary in the processes of learning and remembering. Disorders associated with calcium accumulation in neurons can be at least partially reversible by using nimodipine – a drug that blocks slow calcium channels [16].

It is also worth noting the increased concentration of inflammatory factors. It has been proven that sevoflurane significantly increases the concentration of IL-6, IL-8 and TNF-α, regardless of inflammation induced by stress associated with surgical tissue damage [16, 18]. Intensification of the inflammatory process in the CNS, evidenced by the increased level of these markers, reduces the survival of nerve cells. Sevoflurane also causes an increase in the formation of reactive oxygen species (ROS), which cause mitochondrial degradation which, in turn, contributes to a decrease in the level of adenosine triphosphate (ATP) and, as a result, to cell death [19].

According to recent discoveries (Zhang et al., Lv et al. Dong et al.), sevoflurane also inhibits peroxisome proliferator-activated receptor γ (PPAR-γ), thereby indirectly stimulating the activity of nuclear factor-kappa B (NF-κB), a transcription factor of the apoptotic pathway. In addition to intensifying

the death of neurons, sevoflurane also affects the processes of plasticity and synaptogenesis. It reduces the concentration of brain-derived neurotrophic factor (BDNF), the deficiency of which leads to reduced cell survival, neurogenesis and synaptogenesis. A reduced level of BDNF is a proven exponent of many neurodegenerative diseases, including Alzheimer's disease, hence its influence in disorders such as POCD is estimated [20]. Disturbances in the release of neurotransmitters – dopamine, serotonin, epinephrine, acetylcholine and GABA, induced by sevoflurane and other inhalation anaesthetics have also been demonstrated [21]. Electroencephalographic features of epilepsy have also been observed during the use of sevoflurane [14]. Both of these phenomena prove the effect of sevoflurane on the desynchronization of neural signaling between the cerebral cortex, thalamus and hypothalamus, which may lead to dysfunction of the higher levels of the CNS. Researchers have also indicated the induction or progression of Alzheimer's disease in predisposed mice subjected to sevoflurane anaesthesia (especially in cardiac and abdominal surgeries), which also raises concerns about the possible impact of this agent on the occurrence of dementia in humans [22]. The development of neurodegenerative diseases could be particularly visible in people predisposed due to age, gender and burdened personal and family history [22].

An interesting observation is also the neuroprotective effect of sevoflurane and isoflurane, by improving the blood supply to the brain, even leading to the reduction of infarct foci and the activation of microglia and its participation in regeneration processes. This effect has been noted with pathologies of young brains in a rat model. However, under the same research conditions, the brains of old but healthy rats showed a clear neurotoxic effect of these agents, practically in the same mechanism – activation of microglia and subsequent induction of inflammation due to its immunological properties [23]. Therefore, the negative impact of inhalation anaesthetics may also probably be observed in humans, depending on the functional and somatic state of the CNS. In studies of cognitive functions using the MMSE scale, it was proved that after anaesthesia with sevoflurane or desflurane, there is a decrease in efficiency in this area by at least two points to the same extent. In most patients, the result returned to normal within a maximum of three days after surgery [24,25]. However, there are no studies that would verify the condition of patients for more than a month after surgery. Therefore, the long-term impact of the use of inhalation anaesthetics on people's cognitive functions is unknown. A comparison of the mechanisms of neurotoxicity of inhalation anaesthetics is presented in Table 1.

Propofol. This agent, although widely used, presumably has a negative effect on the state of the CNS under certain conditions. In addition to the direct effect on ionotropic receptors, propofol also causes the depolarization of the mitochondrial membrane, contributing to the reduction of the amount of ATP produced. With the inhibition or lack of appropriate compensatory mechanisms, it may impair the metabolic processes of nerve cells. This effect depends on the concentration and elimination time of propofol – it occurs at high, longer-lasting concentrations; therefore, it is difficult to relate the results of *in vitro* studies to *in vivo* use [33]. Increased levels of A β proteins (lower than sevoflurane) and tau (higher than sevoflurane) have been demonstrated

Table 1. Neurotoxicity mechanisms of inhalation anaesthetics [14–32]

Effects on neurons	Sevoflurane	Isoflurane	Desflurane
Induction of caspase-3 synthesis	✓	✓	✓
Influence on neurotransmission	✓	✓	✓
Increase in Ca ²⁺ secretion from the ER	✓	✓	✓
Increased influx of Ca ²⁺ into the cell	X	✓	X
Increase in A β protein synthesis and accumulation	✓	✓	X
Increased sensitivity of the cell to A β	X	X	✓
Increase in BACE-1 protein synthesis	X	✓	X
Increased neurogenic inflammation (IL-6, IL-8, TNF- α)	✓	✓	?
ROS formation	✓	✓	X
Apoptosis induction by NF- κ B	✓	✓	✓
Apoptosis induction by Bax/Bcl2	X	✓	X
lowering BDNF concentration	✓	✓	?

ER – endoplasmic reticulum; BACE-1 – beta-site APP cleaving enzyme 1; ROS – reactive oxygen species; BDNF – brain-derived neurotrophic factor

in patients undergoing propofol anaesthesia. Increased levels and accumulation of these proteins in the CNS are observed in the course of neurodegenerative diseases. After administration of propofol, the results of the MMSE test in the operated patients were significantly lower than before the operation, but in most cases they returned to normal on the 7th post-operative day [34]. In a prospective trial, Goswami et al. proved that propofol impaired cognitive functions, in particular memory, to a greater extent than sevoflurane in the period immediately after the procedure [35]. Another study showed that even after three and twelve months there were cases of lowering in the the MMSE score after administration of this agent, but without a significant difference between propofol and sevoflurane [36]. In studies in mouse and rat models, it has been proven that propofol, administered repeatedly in high doses, contributes to the synthesis of pro-apoptotic (caspase-3 and Bax) and pro-inflammatory factors (IL-1 β , IL-6 and TNF- α), and increases the concentration of A β protein in the hippocampus, which causes permanent cognitive impairment (spatial memory, learning), especially in young animals at the stage of CNS development and genetically susceptible to Alzheimer's disease [37, 39]. However, this effect was observed under typical laboratory conditions, with the use of high doses of propofol for a sufficiently long time, which is not adequate to the time and doses that are used in humans during single surgical procedures. Presumed strong neurotoxic effects would be observed after repeated repetitions of anaesthesia with relatively high doses of the agent, in patients predisposed to neurological disorders due to age or personal history.

Prevention of negative effects of anaesthetics on the brain.

In addition to pharmacological methods that can reduce the negative impact of anaesthetics on the brain, the anaesthetist should inform the patient about potential harm, so that he/she can make an informed decision before the procedure and plan or prepare for such effects after the operation. Such conversations should ideally take place months before the planned operation so that the patient can learn about these risks in a stress-free environment, and have time to calmly analyze and ask comprehensive questions on this issue [39].

Prior to surgery, especially elective surgery, attention should be paid to the patient's cognitive ability, and anaesthesia should be adjusted accordingly. This can be achieved by short screening tests performed in the clinic before the procedure, contributing to the identification of patients most at risk of post-operative complications. Such patients should then be referred for more detailed and specialized examinations, analogous to the cardiac stress tests ordered by anesthesiologists in a certain group of patients before surgery. The simplest quick tests with which a doctor of any specialization should have no problems performing and analyzing, are, among others, attempt to draw a clock, the Verbal Fluency Test (TFS), Minicog, MoCA and MMSE [40].

Ideally, at-risk patients should self-implement measures to minimize post-operative side-effects, such as improving sleep and eating habits, avoiding certain medications, and involving their immediate families. Such actions can reduce the risk of post-operative neurocognitive complications by up to 40% [39].

Despite the fact that there is no unequivocal evidence that individual inhalation anaesthetics are associated with a variable intensity of post-operative side-effects, every anaesthesiologist should note that there are differences in patients' sensitivity to anaesthesia depending on their age. The minimum alveolar concentration (MAC) decreases by about 6% per decade after the age of thirty. Inhalation anaesthetics have one of the narrowest therapeutic indexes, therefore constant monitoring of the patient's MAC fraction will help to minimize the side-effects associated with the administration of too high a dose of anaesthetic [41].

Another concept is the administration of regional anaesthesia or a nerve block with a reduced dose of general anaesthesia, which would also contribute to reducing post-operative neurocognitive complications. However, there is no unequivocal evidence or recommendations regarding the combination of regional and general anaesthesia yet [39].

Increasing attention is also paid to the EEG response to the anaesthetic administered to the patient during the procedure. Recent studies have shown a lower frequency of post-operative cognitive impairment when the anaesthetic was administered based on data from the Bispectral Index (BIS) monitor – a processed EEG monitor. However, currently, the downside of such a monitor is the lack of adaptation to the elderly and possible display of false values. This may prompt the anaesthesiologist to administer too much anaesthetic; consequently, the practical use of this method for each age group is currently under investigation. This does not alter the fact that more and more circles are willing to administer anaesthesia based on EEG [42].

An important role is also played by drugs administered by an anesthesiologist which, especially in people over sixty-five, may contribute to post-operative neurocognitive disorders. This group includes, among others, atropine, first generation antihistamines, antispasmodics (scopolamine) and anti-emetics of the phenothiazine type, due to their central anticholinergic effect. Benzodiazepines, first- and second-generation anti-psychotics, H₂-receptor antagonists and glucocorticoids also carry a risk of subsequent cognitive impairment. In the elderly, an anaesthesiologist should avoid these drugs, and if there is no alternative, to use them with caution and limit the dose to a minimum [39].

Recently, there have been first reports that mild hypothermia has a protective effect on the anaesthetized brains of newborn

rhesus monkeys. The study showed that mild hypothermia (35 – 36.6°C) protected their brains from neuro- and oligoapoptosis induced by five-hour sevoflurane anaesthesia, as demonstrated by *post-mortem* immunohistochemistry. On the other hand, moderate hypothermia (<35°C) suppressed this effect. It remains to be further investigated whether mild hypothermia is neuroprotective also in relation to other anaesthetics, and under anaesthesia lasting longer than five hours. Due to the low degree of cooling, this phenomenon should also be more extensively studied on the human population [43].

While there has always been a strong belief in avoiding intra-operative hypotension, studies have recently begun to emerge suggesting contradictory evidence. So far, post-operative cognitive disorders have been associated with intraoperative hypotension. However, it is worth paying attention to each patient individually, and referring possible hypotension to the baseline value before the procedure. It is known that a large proportion of people over sixty-five are treated for hypertension, which also contributes to the shift to the right of the cerebral perfusion autoregulation curve. A useful method is near-infrared spectroscopy (NIRS), common in cardiac surgery, as a real-time continuous monitor of cerebral perfusion. It has been proven that the decrease in intraoperative NIRS values is associated with post-operative cognitive impairment in the patient. The first results showed that a longer time of regional brain oxygen saturation (rSO₂) at the level <60% was associated with the occurrence of cognitive impairment on the seventh post-operative day in elderly patients. However, these studies have been severely limited due to the short follow-up period and inconsistent results. Therefore, the administration of an anaesthetic based on EEG monitoring is currently more sensitive, contributing to a lower probability of neurocognitive disorders [44, 45, 46].

Among the anaesthetics there are also substances that may weaken post-operative neurocognitive disorders. This group includes, for example, ketamine, which has been proven to have a neuroprotective effect on patients undergoing cardiac surgery. In such situations, the administered dose of ketamine was 0.5 mg/kg (as much as it reduces systemic inflammation), therefore, it is assumed that its anti-inflammatory effect, consist in inhibiting the expression of nuclear factor κB which is involved in the transcription of genes encoding pro-inflammatory cytokines [47].

In the context of cardiac surgery, the cardioprotective effect of sevoflurane is also worth mentioning. A study by Lemoine et al. demonstrated that post-operative cTnI release and inotropic support were reduced in patients preconditioned with sevoflurane prior to coronary artery bypass surgery (CABG). In addition, in an *in vitro* study of isolated right atrial myocardium obtained from sevoflurane-exposed patients, increased contractile force recovery after hypoxia-reoxygenation was demonstrated. This suggests that sevoflurane triggered myocardial preconditioning in these patients [48].

Although it has long been known, or at least most of the medical community suspects, that intraoperative anaesthesia affects CNS complications to a greater or lesser extent, it has not yet been established who should take care of patients in the post-operative follow-up. The limitation here may be the fact that the anaesthesiologist sees the patient only one or two days after the operation, while hardly anyone pays attention to what happens with his/her cognitive functions months or years after the procedure. In addition, they are specialists

dealing mainly with intra- and early post-operative activities. At the moment, much more research is needed on how to prevent post-operative neurocognitive complications. They should focus on recommendations and risk assessment before surgery, procedures performed during surgery, appropriate follow-up, reconvalescence, and the appointment of an appropriate person who would typically deal with this scope of medical care [39,42].

SUMMARY

The results of the presented studies confirm the hypothesis that inhalation and intravenous anaesthetics are neurotoxic agents that have a negative impact on the human CNS. However, it should not be forget about other mechanisms acting on the patient's brain during surgery, much stronger than the anaesthetics themselves. These include physical stress associated with mechanical tissue damage and status of the patient's health (age, comorbidities, reason for the procedure). In addition, only one agent in a large, potentially neuronal-damaging dose is rarely used during anaesthesia. The appropriate combination of preparations allows reduction of the administered doses, and thus – side-effects. Numerous procedures can also be introduced to reduce the neurotoxic effects of anaesthetics, i.e. patient monitoring, both before, during and after the procedure, appropriate education, the implementation of pro-health behaviours, and the use of additional pharmacological agents.

A limitation of the presented review is the predominance of experimental studies on animal models, with a relatively small number of available neuropsychological or neuroanatomical studies proving the impact of these agents on the human CNS. This is an area that remains unexplored; therefore, further research is needed to clarify the cognitive state of patients both before and after anaesthesia, and the pharmacological properties of general anaesthetics themselves.

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