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An update on anesthetics and impact on the brain

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Abstract

Introduction: While anesthetics are indispensable clinical tools and generally considered safe and effective, a growing concern over the potential neurotoxicity of anesthesia or specific anesthetic agents has called into question the safety of general anesthetics, especially when administered at extremes of age.

Areas covered: This article reviews and updates research findings on the safety of anesthesia and anesthetics in terms of long-term neurotoxicity, with particular focus on postoperative cognitive dysfunctions, Alzheimer's disease and dementias, developing brain, post-operative depression and autism spectrum disorder.

Expert opinion: Exposure to general anesthetics is potentially harmful to the human brain, and the consequent long-term cognitive deficits should be classified as an iatrogenic pathology, and considered a public health problem. The fact that in laboratory and clinical research only certain anesthetic agents and techniques, but not others, appear to be involved, raises the problem on what is the safest and the least safe anesthetic to maximize anesthesia efficiency, avoid occurrence of adverse events, and ensure patient safety. New trends in research are moving toward the theory that neuroinflammation could be the hallmark of, or could have a pivotal role in, several neurological disorders.

Keywords

Alzheimer's disease; anesthesia; autism spectrum disorder; developing brain; neuroinflammation; neurotoxicity; postoperative cognitive dysfunctions; safety.

Article highlights

- Anesthetics are indispensable clinical tools and generally considered safe, but there is growing concern about long-term potential neurotoxicity.

- Postoperative cognitive dysfunctions, a decline in cognitive functions and temporary memory problems occurring after surgery and anesthesia, can persist for days to months and, in some cases, longer.

- There is a possible link between general anesthetics and induced changes in molecules known to be involved in the pathogenesis of Alzheimer's Disease.

- Exposure of children up to 3 years of age to general anesthetics may affect CNS development, resulting in long-lasting cognitive and behavioral deficiencies, such as learning and memory deficits.

- In recent years, scientists have also addressed the potential role of general anesthesia in the development of post-operative depression and autism spectrum disorder.

- Neuroinflammation activation, due to surgery and anesthesia, could be a key factor in the pathogenesis of neurotoxicity.

1. Introduction

In the last few decades, anesthesia management has clearly shown major advances in technology and drug development, permitting improvement of surgical techniques and the possibility of performing complex and prolonged surgical operations, even in the very elderly and the critically ill. As a consequence, the evolution of anesthesia procedures has been considered to be amongst the greatest achievements in medicine [1].

Anesthetics are pharmacological agents that target specific central nervous receptor systems that, once they bind to the brain receptors, modulate remote brain areas and eventually interact with global neuronal networks, leading to a controlled, reversible loss of consciousness. General anesthesia is usually adopted to safely induce a reversible brain state, allowing the performance of surgery under optimal conditions, but, far from shutting down all brain activity, anesthetics lead to a shift in the brain state to a distinct, highly specific and complex state [2].

While anesthetics are indispensable clinical tools and generally considered safe and effective, in some situations there is growing concern about the potential neurotoxicity of these agents [3]. Recent studies have called the safety of general anesthetics into question. An increasing number of clinical and experimental observations have suggested that anesthetic drugs, especially when administered at the extremes of age, can trigger long-term morphological and functional alterations, and adverse effects in the brain [4, 5, 6, 7, 8]. With roughly 234 million people each year worldwide undergoing surgery, diagnostic, therapeutic and surgical procedures requiring administration of anesthetic agents, it remains imperative that any potentially deleterious effects of anesthetics should be investigated and addressed [6].

The purpose of this review is to summarize and update key recent studies and thoughts on the potential role of general anesthesia and certain anesthetic agents on long-lasting brain adverse effects.

2. Postoperative Cognitive Dysfunction

Despite technological advances in surgery and anesthesia during the last few decades, postoperative cognitive dysfunction (POCD) remains a relatively common important complication in surgical patients, especially in the elderly [9].

It is defined as a decline in cognitive functions and temporary memory problems (or aggravation of pre-existing memory disorders) occurring after a surgical operation and related anesthesia: it may persist for days to months [10, 11]. In some cases, cognitive dysfunctions may persist longer and may be a precursor for further deterioration [12].

2.1 Etiology, risk factors and mechanism of POCD

Etiology and mechanism of POCD are poorly understood and probably largely still to be determined, however, important progress has been made in the last decade.

Generally, risk factors considered for the occurrence of postoperative memory disorders include advanced age, low education level, intellectual comorbidity, onset of dementia and other neurodegenerative disorders, and also immobilization, existing sleep disorders, sleep deprivation, unfamiliar surroundings, medication errors and the experience of postoperative pain [13, 14].

Other implicated factors include surgical stress, which could induce cognitive impairment. However, it is unknown how surgical stress and psychological stress affect postoperative learning and memory function in geriatric patients [15].

The possible role of anesthetics has also been recognized. Postoperative impairment of cerebral functions may appear immediately after general anesthesia: therefore, interactions of anesthetic agents and different targets have been studied at the molecular, cellular and structural anatomical levels [12]. For example, depression of brain function during anesthesia is attributed primarily to increased activity of gamma-aminobutyric acid type A receptors (GABA(A)Rs), a receptor linked to memory deficits after anesthesia, but it is assumed that once the anesthetic has been eliminated, the activity of GABA(A)Rs rapidly returns to baseline and these receptors no longer impair memory [10].

In laboratory studies, the inhaled anesthetic isoflurane demonstrated the property of triggering a persistent increase in tonic current and cell-surface expression of alpha5GABA(A)Rs: thus, alpha5GABA(A)R function does not return to baseline after the anesthetic is eliminated, suggesting a mechanism to account for persistent memory deficits after general anesthesia [10].

Similarly, keeping in mind the functions of the central muscarinic cholinergic system and its multiple interactions with drugs of general anesthesia, it seems possible to hypothesize that the inhibition of muscarinic cholinergic receptors could have a pivotal or partial role in the pathogenesis not only of post-operative delirium but also the more complex phenomena of post-operative cognitive dysfunction [16, 17, 18]. Furthermore, several individuals may have altered essential cellular processes, such as intra-neuronal signal transduction and second messenger system, which play an important role in neurotransmitter synthesis and release.

Moreover, clinical aspects of POCD mimicking other psychiatric and neurological pathologies highlighted the conviction of a plausible link among possible anesthetic effects during general anesthesia, the central cholinergic system and the molecular pathological mechanism of Alzheimer's disease [12, 16].

Serum brain-derived neurotrophic factor (BDNF) levels are associated with neurotransmission and cognitive functions. A study including 50 male patients demonstrated that different anesthesia techniques have different effects on serum BDNF levels: serum BDNF levels are significantly lower ($p < 0.01$), and cortisol and glucose levels higher ($p < 0.05$ and $p < 0.01$) in patients receiving spinal anesthesia when compared to those receiving general anesthesia, but it also suggests that general anesthetics have an effect on serum BDNF levels independent of stress response [19].

New trends in research are moving toward the theory that neuroinflammation could be the hallmark of, or have a pivotal role in, several neurological disorders. An exaggerated pro-inflammatory response is generally considered to be a key cause of POCD. [20]: microglia activation, inflammatory cytokines, brain-derived neurotropic factor impairments, and cognitive dysfunction were found up to two weeks after surgery [21].

While neuroinflammation is a critical neuropathological process for POCD, not all anesthetic agents have similar effects: surgery under desflurane anesthesia may have reduced neuroinflammation and cognitive impairment compared with surgery under isoflurane anesthesia. P2X7 receptors may mediate neuroinflammation and cognitive impairment after surgery [22].

Young adult mice demonstrated profound hippocampus microglia activation, however insufficient to impair spatial reference memory, from 6 to 24 hours after surgery [21], in accordance with the clinical evidence that POCD impairs cognitive dysfunction in old, but not in young, adults [23].

Finally, pain might be associated with cognitive impairment after surgery despite the fact that, in humans, characterization of such effects in a preclinical model and investigation of the underlying mechanisms still remain largely to be determined, calling however for further investigation to determine the role of pain in cognitive function [24].

2.2 Surgical procedures and risk factors for POCD

A systematic review of 24 studies, average patient age 68 years, determined incidence of post-operative cognitive dysfunction 3 months after non-cardiac surgery in adults: pooled incidence of post-operative cognitive dysfunction at 3 months was 11.7%, with increasing age being the most consistent risk factor, especially in patients over 60 years old [11].

In opposition, a multicenter prospective cohort study of 1040 patients concluded that, at 3 and 12 months, cognitive impairment after major non-cardiac surgery and critical illness is not associated with surgery and anesthesia exposure but is predicted by baseline education level and in-hospital delirium [25]. However, limitation of study, as well as difference in the type of anesthesia and length, anesthetics and drugs administered, and possible bias related to the fact that patients were

enrolled in ICU, and therefore not reproducing the common postoperative clinical setting, could limit the clinical application of these results [25].

Nevertheless, there is general consensus on the fact that, because of incidence, cardiac and orthopedic surgery have been indicated as the most “at risk” surgical procedures for POCD. Cognitive dysfunction is well documented after cardiac surgery, with incidence related to the use of cardiopulmonary bypass as high as 70-90%, attributed to the adverse effects of surgery-related trauma, microembolisation, temperature changes, levels of mean arterial pressure used, or modification in jugular bulb oxygen saturation with bypass [12]. Coronary artery bypass grafting (CABG) procedure is also considered a high risk for POCD, with an approximate incidence of 67% of patients suffering before discharge, and 20% of patients experiencing cognitive and quality of life deterioration one year after operation [12].

In a randomized trial, high-dosage of remifentanil (a short-acting opioid used during general anesthesia) during pump-assisted CABG, patient pre-conditioning was shown to play a protective role in brain damage, possibly through inhibition of oxidative stress response: it could therefore offer a promising possibility of reducing cognitive derangement closely linked to cardiac surgical procedures [26].

Orthopedic surgery has also been described as a high-risk procedure for POCD, with impressive incidence after hip fractures in subjects > 75 years old [12]. In addition, a review of current literature has recently associated arthroscopic shoulder surgery (patient in the beach-chair position) under general anesthesia at risk for postoperative neurocognitive complications and deficits, suggesting that intraoperative monitoring of cerebral perfusion, alternative techniques to general anesthesia, and prudent use of intraoperative blood pressure control could improve patient safety [27].

Finally, a systematic review of eighteen studies on POCD in liver transplant recipients (time of testing ranging from 0.5 to 32 weeks) identified a "more than expected" postoperative deterioration in cognitive domains, including short-term and long-term memory, mood, consciousness and circadian rhythm, occurring in up to 50% of liver transplant recipients [28].

3. Anesthesia and Alzheimer’s Disease

Aggregation of amyloid beta peptide into senile plaques, and hyperphosphorylated tau protein into neurofibrillary tangles in the brain are the pathological hallmarks of Alzheimer's disease [29]. Accumulating clinical and epidemiological evidence has highlighted the potential adverse consequences of general anesthesia and a possible link with anesthesia induced changes in molecules known to be involved in the pathogenesis of AD, as well as persistent cognitive deficits

meeting clinical criteria of amnestic mild cognitive impairment or AD [1, 30]. However, while some of these retrospective studies have discounted the notion that general surgery and anesthesia can induce or exacerbate AD, others have demonstrated a correlative link between anesthesia exposure and AD [30].

Interestingly, a synergistic effect of anesthesia exposure, surgery and presence of the APOE epsilon4 allele in the cognitive decline and neuropathologic changes underlying Alzheimer's disease has recently been highlighted. A retrospective cohort analysis of two prospective longitudinal aging studies, to assess the relationship between surgical/anesthetic exposure, APOE genotype, and rate of change in measures of cognition, function and brain volumes, assessed that a surgical group of 182 patients experienced a more rapid rate of deterioration compared with a nonsurgical group of 345 subjects in several cognitive, functional, and brain magnetic resonance imaging measures. It demonstrated a significant synergistic effect of anesthesia/surgery exposure and presence of the APOE epsilon4 allele in the decline of multiple cognitive and functional measures, finally providing insight into the role of surgical exposure as a risk factor for cognitive and functional decline in older adults [31].

3.1 The Multifactorial Mechanism

Several studies have accounted for the close relationship between AD and the central cholinergic system, suggesting that a dysfunction in the brain of neurons containing acetylcholine contributes significantly to the cognitive deficit of individuals with AD [32]. Indeed, AD is associated with a loss of cholinergic neurons resulting in profound memory disturbances and irreversible impairment of cognitive function.

The central cholinergic system is involved in the action of general anesthetic agents. The anesthetic modulation of cholinergic transmission has profound effects on brain function via a cascade of synaptic and postsynaptic events by binding both nicotinic and muscarinic receptors: during general anesthesia, decrease in acetylcholine release and depression of cholinergic transmission facilitates the desirable effects of general anesthetics, such as loss of consciousness, pain, voluntary movements and memory [33].

Increasing evidence also supports an extensive interrelationship between the cholinergic system and thyroid hormones, that *per se* negatively regulate expression of the amyloid-beta protein precursor (AbetaPP), which plays a key role in the development of AD [34].

Uncontrolled production, oligomerization and deposition of amyloid beta peptide, with subsequent development of amyloid plaques, are fundamental steps in the generation of Alzheimer's disease. Recent *in vitro* nuclear magnetic resonance spectroscopy studies have shown that several

anesthetics act on the oligomerization of Abeta (Aβ) peptide [12]. Smaller molecular sized anesthetics (e.g., halothane, isoflurane, etc.) also play a direct leading role in Aβ oligomerization. It has been demonstrated that the presence of smaller molecular sized anesthetics at clinically relevant concentrations promote

Aβ oligomerization even when co-administered with a larger sized anesthetic (e.g. diazepam)[35, 36]**.**

The inhaled anesthetics isoflurane and desflurane induce Aβ oligomerization by inducing chemical shift changes of the critical amino acid residues (G29, A30, and I31), reinforcing the evidence that perturbation of these three crucial residues indeed plays an important role in oligomerization. These findings support the hypothesis that several commonly used inhaled anesthetics could be involved in neurodegeneration, as well as being risk factors for accelerating the onset of AD [37]. Aβ peptide is naturally present in the central nervous system (CNS), and is found at higher tissue concentrations in the elderly: administering certain general anesthetics to elderly patients may worsen Aβ peptide oligomerization and deposition and thus increase the risk of developing POCD (Table 1) [7, 12, 35, 36, 37].

A large and growing body of evidence also shows that neuroinflammation participates in the development of neurodegeneration associated with Alzheimer's disease, especially early in the pathogenesis [38]. Misfolded and aggregated proteins bind to pattern recognition receptors on microglia and astroglia, and trigger an innate immune response characterized by release of inflammatory mediators, which contribute to disease progression and severity [39].

The peripheral inflammatory response elicited by surgery itself appears to provoke a mutual neuroinflammatory response, which enhances ongoing neurodegeneration in some models, whereas anesthetics have both anti- and pro-inflammatory effects depending on the agent given and its concentration [38].

Both Aβ peptides, associated with Alzheimer disease, and tumor necrosis factor-alpha (TNF-alpha), a proinflammatory stress-related peptide, impair the synaptic function in rat hippocampus. Brief exposure to inhaled anesthetic isoflurane prevents rather than impairs the decrease in hippocampus synaptic function, caused by Aβ 1-42; in contrast, isoflurane has no effect on synaptic impairment caused by TNF-alpha or a combination of TNF-alpha and Aβ. Although this was seen in an *in vitro* study and translation to clinical medicine requires additional work, the interactions of isoflurane, Aβ, and TNF-alpha revealed could have implications for patients with Alzheimer disease or perioperative neuroinflammation [40].

Multiple anesthesia exposures of the commonly used inhalation anesthetic sevoflurane induces neuroinflammation and cognitive impairment in young mice, but anesthesia with a single exposure

to sevoflurane does not [41]. In mice, anesthesia with 3% sevoflurane two hours daily for one day increased the levels of P-GSK3beta(ser9) and P-AKT(ser473), but anesthesia with 3% sevoflurane daily for three days decreased them. At the same time, an *in vitro* experiment performed in H4 human neuroglioma cells shows that treatment with 4% sevoflurane for two hours increased, but treatment with 4% sevoflurane for six hours decreased, levels of P-GSK3beta(ser9) and P-AKT(ser473). These studies have established that the anesthetic sevoflurane might induce a dual effect (increase versus decrease) on the activation of the AKT/GSK3beta signaling pathway [41].

Critically ill patients with severe inflammation often exhibit heightened sensitivity to general anesthetics; however, the underlying mechanisms remain poorly understood. Inflammation increases the number of gamma-aminobutyric acid type A (GABAA) receptors expressed on the surface of neurons, which supports the hypothesis that inflammation increases up-regulation of GABAA receptor activity by anesthetics, thereby enhancing behavioral sensitivity to these drugs [42].

A summary of recent, established effects and emergent safety issues linking AD with anesthetics or neuroinflammation is presented in Table 2 [41, 42, 43, 44, 45, 46, 47]**.**

The growing number of elderly having surgery, combined with expanding life expectancy, indicates the potential of this interaction having considerable public health implications, and calls for further research, especially in humans [38].

4. Anesthesia and the developing brain

Every year in the United States, approximately six million children, including 1.5 million infants, undergo surgery with general anesthesia [48]. Surgical procedures are often difficult and extensive: providing anesthesia to neonates is not easy and the physiology of neonates makes respiratory and cardiovascular problems more frequent and life-threatening [49]. Frequently, premature infants need multiple surgical procedures[50].

A number of recent animal and clinical studies now indicate that anesthetic exposure could cause toxicity and neuronal apoptosis in the developing brain, potentially influencing long-term neurodevelopmental outcome [51]. It means that exposure to general anesthetics may affect CNS development, resulting in long-lasting cognitive and behavioral deficiencies, such as learning and memory deficits, as well as abnormalities in social memory and social activity [48, 52].

Nearly all general anesthetics tested have been shown to cause abnormal brain cell death in animals when administered during periods of rapid brain growth (children up to 3 years) [53].

In 2007 and 2011, the Food and Drug Administration (FDA) mobilized the scientific community for additional research to understand the long-term cognitive implications for children exposed to

prolonged anesthesia, in accordance to alarmist laboratory data [54]. A summary of recent, established and emergent safety issues on neurotoxicity in the developing brain is presented in Table 3 [55, 56, 57, 58, 59, 60].

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4.1 Mechanisms of neuronal degeneration in the developing brain

Anesthetics primarily modulate two major neurotransmitter receptor groups, either by inhibiting N-methyl-D-aspartate (NMDA) receptors, or conversely by activating gamma-aminobutyric acid (GABA) receptors. Both of these mechanisms result in the same effect of inhibiting excitatory activity of neurons: in the developing brain, which is more sensitive to disruptions in activity-dependent plasticity, the transient inhibition may have long-term neurodevelopmental consequences [48].

Other anesthesia-related neurotoxicity studies focused on the role of mitochondrial dysfunctions. The results evidenced that general anesthesia can cause mitochondrial dysfunction via complex pathways, including oxidative stress, electron transport chain dysfunction, mitochondrial dynamics, calcium homeostasis, and the mitochondrion-dependent apoptotic pathway [61, 62].

The molecular processes of mitochondrial dysfunction warrant additional research to develop novel strategies to prevent or mitigate anesthesia-induced neurotoxicity and provide neuroprotection for the developmental CNS [61] .

4.2 Laboratory and Clinical studies

In animal studies, the majority of commonly used anesthetic agents induce widespread neuronal degeneration in the developing mammalian brain.

Isoflurane induces neuronal apoptosis in a dose-dependent manner and modulates oxidative stress within forebrain mitochondria, whereas carbon monoxide (CO), a gas that exerts biological activity in the developing brain at low dose exposures, has the potential to provide neuroprotection [62]. In a recent work, low concentration CO exposures limited isoflurane-induced neuronal apoptosis in a dose-dependent manner in newborn mice and modulated mitochondrial oxidative stress: as infants and children are routinely exposed to low levels of CO during low-flow general anesthesia, such anti-oxidant and pro-survival cellular effects could result in prevention of anesthetic toxicity in the immature brain [62].

Both isoflurane and propofol caused significant apoptosis in the seven-day-old mouse developing brain, with isoflurane being more potent. Compared to controls and propofol, isoflurane significantly increased levels of the plasma neurodegenerative biomarker S100beta; however, these

neurodegenerative effects of isoflurane and propofol in the developing brain were not associated with inflammation or with cognitive dysfunction in later life [59].

In humans, epidemiologic studies have been unable to sufficiently address neuronal degeneration in the developing brain, in part due to reliance on group-administered achievement tests, inability to assess brain structure, and limited control for confounders [63].

In a neurocognitive assessment including the Oral and Written Language Scales, the Wechsler Intelligence Scales (WAIS) and brain structural T1-weighted MRI scans, healthy students aged 5 to 18 years who had undergone surgery with anesthesia before 4 years of age were compared with unexposed peers [63]. Compared with control subjects, the previously exposed children scored significantly lower in listening comprehension and performance IQ, which were associated with lower gray matter density in the occipital cortex and cerebellum. It suggests that general anesthesia for a surgical procedure in early childhood may be associated with long-term diminution of language abilities and cognition, as well as regional volumetric alterations in brain structure [63].

A retrospective matched cohort study compared 4,470 children less than 4 years of age exposed to general anesthesia (3,850 exposed to a single and 620 exposed to two or more general anesthesias) to 13,586 nonexposed children. Single exposure between 2 and 4 years of age was associated with deficits, most significant for communication/general knowledge (estimate, -0.7; 95% CI, -0.93 to -0.47; $P < 0.0001$) and language/cognition (estimate, -0.34; 95% CI, -0.52 to -0.16; $P < 0.0001$) domains, whereas multiple anesthesia exposure at the age of 2 to 4 years did not confer greater risk than single general anesthesia exposure [64].

In an ongoing international assessor-masked randomized controlled equivalence trial, infants younger than 60 weeks postmenstrual age and born at more than 26 weeks' gestation, and who had inguinal herniorrhaphy were randomly assigned to receive either awake-regional anesthesia or sevoflurane-based general anesthesia [65]. The primary outcome of the trial was to be the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years, but Authors also published the research results of a secondary outcome "the composite cognitive score of the Bayley Scales of Infant and Toddler Development III, assessed at 2 years". Outcome data were available for 238 children in the awake-regional group and 294 in the general anesthesia group. The median duration of anesthesia in the general anesthesia group was only 54 min. In the as-per-protocol analysis, the cognitive composite score (mean) was 98.6 (14.2) in the awake-regional group and 98.2 (14.7) in the general anesthesia group. There was equivalence in mean between groups (awake-regional minus general anesthesia 0.169, 95% CI -2.30 to 2.64) coming to the conclusion, for this secondary outcome, that there is no evidence that

just less than 1 h of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anesthesia [65].

However, the data published seem to show important limits, and trial findings have very limited application for pediatric anesthetic care. In fact, the trial does not fit the FDA specific requests on the possible long-term cognitive effects of prolonged anesthesia; in addition, awake-regional anesthesia has a high failure incidence in infancy, and general anesthesia using only sevoflurane is uncommon in pediatric operating theatres.

Finally, an inattentive reader might get the impression that authors come to the definitive conclusion that the use of sevoflurane is safe in children, a conclusion which is totally unjustified by trial findings. The title of the related introductory editorial "Anesthetics, infants, and neurodevelopment: case closed?" [66] adds reinforcement to the impression of definitive findings.

5. Post-Operative Depression

While most patients recover uneventfully from the effects of anesthesia and surgery, for a small percentage of patients the immediate postoperative period can be a period of significant physiological stress [67]. Depression is a well-documented adverse effect after surgical procedures, which may lead to further morbidity and mortality [68].

Depression after surgery and anesthesia may result in significant increases in post-operative complications [68]: 1) The suppression of the immune system in depressive disorders may expose the patients to increased rates of postoperative infections and increased mortality; 2) Depression is commonly associated with cognitive impairment, which may be exacerbated postoperatively; 3) There is evidence that acute postoperative pain causes depression and depression lowers the threshold for pain; 5) In patients with depression, general postoperative mortality is increased.

Moreover, a close link between depression and postoperative pain has been described: patient reporting pain intensity immediately after surgery can be associated with underlying depression, and depression lowers the threshold for pain increasing the intensity of postoperative acute pain leading, in conclusion, to a vicious circle between intensity of pain and postoperative depression [68, 69, 70, 71]. Depression is also a strong predictor of chronic post-surgical pain [68], whereas persistent postoperative pain intensity is potentially useful in detecting hidden depression symptoms [71].

Anesthesia related to surgery has been indicated as a possible cause of post-operative depression, but post-surgical traumatic stress syndrome, soreness and pain, antibiotics and other medications given to treat pain could play an important role in the development of this disease.

Finally, the inflammation/neuroinflammation activation related to surgery and anesthesia, bridging immune activation and metabolic danger signals due to stress exposure, is considered a key factor in the pathogenesis of depressive disorder [72]. In accordance, levels of some inflammatory cytokines correlate with pain and depression [73].

5.1 The patient at risk for post-operative depression

There is a risk of depression after all types of operations, but there are certain specific surgical sub-specialties that are more prone to promoting post-operative depression. Strong correlations exist between postoperative depression and heart surgery, bariatric surgery, plastic surgery procedures, brain surgery, hip replacement surgery, mastectomy, radical prostatectomy, hysterectomy, cancer resection and vision-correction surgery [68]. After general thoracic surgery, postoperative depression and psychiatric disorders are reported in 11% of patients [74]. Moreover, a patient is more prone to experience post-operative depression if single, a smoker, with high cholesterol, or with high levels of anxiety caused by the surgery. Other causative factors in the development of post-operative depression are older age, longer operation time, abnormal serum chemistry values of sodium, potassium, calcium and glucose, hypoalbuminemia, the presence of postoperative respiratory distress, infection and blood transfusion ($p<0.05$) [74].

5.2 Onset of symptoms, diagnosis and outcome

A common denominator factor characterizing many of the cases of post-operative depression is the occurrence, in the process of awakening, of a state of agitation and/or panic and the patient reporting an exaggerated feeling of intense pain, even in the presence of suitable analgesic treatment [71].

In the successive period (months to years), symptoms of post-operative depression vary with each person, but commonly include changes in appetite and energy levels (patient is always fatigued), apathy or irritability, difficulty making decisions, feelings of hopelessness and despair, insomnia or sleeping more than usual, unexpectedly crying many times during the day, and a loss of interest in activities they used to enjoy.

The best way to make a diagnosis of whether a patient is depressed after surgery is to run through a brief checklist of specific depression signs at the patient's follow-up visits. Patients with less severe depression symptoms should be able to wait a few weeks to see whether symptoms persist before

seeking treatment. Patients having destructive thoughts should be referred to a mental health provider immediately.

Healthcare professionals are encouraged to administer two widely used depression screening instruments: the Zung self-rating depression Scale, a brief depression screening handout that patients can self-administer [75], and the Patient Health Questionnaire (PHQ-9), commonly used to monitor the severity of depression and response to treatment [76].

Most patients experiencing post-operative depression typically recover within six months after the operation, but during those six months they may need medical or psychological treatment, and decidedly need support.

6. Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is the fastest growing neurodevelopmental disorder in the world [77] and is described as an heterogeneous developmental disorder characterized by impaired social interaction and communication skills, and restricted and repetitive behavior that usually begins before a child is three years old [78]. Researchers have shown that prevalence rates in the U.S. may be as high as 1 in 68.52 [79].

Despite little being known about the possible effects of anesthetic agents on social-behavioral functioning, in the last few years, scientists have addressed the potential role of general anesthesia in the development of autism spectrum disorder.

Neonatal mice (P6-7) were exposed to a titrated dose of sevoflurane for 6 h and evaluated with multiple behavioral assays for autism-like behaviors, general activity, anxiety level, and long-term memory: sevoflurane-exposed mice did not exhibit autism-like features in any of the following assays: social interaction (three-chamber test, caged social interaction), social communication (ultrasonic vocalization test), or repetitive behavior (self-grooming test, digging), with the conclusion that sevoflurane did not induce autism-like features [80].

In a retrospective population based cohort study, the association between exposure to anesthesia either in uterus, during the first years of life, or later and development of ASD was determined. Of the 262 patients with ASD, 99 had exposure to anesthetics before diagnosis, while in the non-ASD population (253 children), 110 had exposure to anesthesia, demonstrating no statistically significant association between both groups ($p = 0.2091$) [79].

A retrospective matched-cohort study from the National Health Insurance Research Database of Taiwan, from 2001 to 2010, was designed to investigate the association of exposure to general anesthesia/surgery with autistic disorder. The primary endpoint was the diagnosis of autistic disorder after a first exposure to general anesthesia and surgery. No differences were found in the

incidence of autistic disorder between the exposed group (0.96%) and the unexposed controls (0.89%) (P = 0.62). Therefore, exposure to general anesthesia and surgery before the age of 2 years at first exposure, and number of exposures were not associated with the development of autistic disorder [81].

Exposure to N_2O, even at non-toxic doses, may modulate central neurotransmission and target many neural substrates directly implicated in neurodevelopmental disorders, including the glutamatergic, opioidergic, cholinergic, and dopaminergic systems, concluding that neurodevelopmental impairment found in conditions like ASD may be due to exposure to the increasing air pollutant, N_2O [82].

Increased risk of autism has been shown in neonates delivered by C-section. In neonates delivered vaginally, by C-section with regional anesthesia (RA), and by C-section with general anesthesia (GA), a mean follow-up of 4.3 years shows an incidence of autism higher in neonates delivered by C-section with GA than in neonates delivered vaginally, with an adjusted risk of 1.52 (95% confidence interval 1.18-1.94). However, the adjusted risk of autism in neonates delivered by C-section with RA and in neonates delivered vaginally was not significantly different [83].

Therefore, any association of exposure to anesthesia with subsequent ASD disorders remains to be determined.

7. Conclusion

Accumulating clinical and epidemiological evidence has highlighted a long-term effect of general anesthesia (or specific anesthetic agents) on expression of various molecular targets. It has been implicated in mediating potentially long-lasting adverse effects, generating fear in patients, relatives and population, especially with regard to potentially significant detrimental impacts on the developing brains of young children, and cognitive decline in the elderly [1, 5].

Other issues, questioning the safety of general anesthetics, have been emerging in the last few years, but their knowledge is still restricted to a limited number of care givers.

The choice of anesthetic agent may often appear irrelevant. In designing the anesthetic plan for patients undergoing surgery, the use of a technique or a drug in most cases depends on which one the anesthesia care provider is familiar with [84].

The accumulating evidence calls not only to identify the at-risk patient scheduled to undergo surgery, but also to understand the relative degree of safety, toxicity, negative effects and protection provided by various anesthetics agents and anesthesia techniques daily used, and with these objectives in mind, to improve our decision-making regarding the most appropriate perioperative care for the patient [84, 85, 86].

8. Expert opinion

Exposure to general anesthetics is potentially harmful to the human brain, and the consequent long-term cognitive deficits are an iatrogenic pathology authoritatively brought to the attention of the international scientific community by Bedford in *The Lancet* more than sixty years ago: *"It is well known, too, that in elderly people transitory confusional states often follow operations under general anesthesia; but it is not so widely appreciated that minor dementias and even permanent catastrophic mental impairment may occasionally be the aftermath. Evidence is presented which indicates that this complication in its lesser degrees of severity is not rare"* [87].

This postoperative cognitive impairment, today considered a public health problem, appears to involve the extreme ages of life; young children under 3 and the elderly.

Regarding postoperative cognitive derangement in the elderly, the most critical and impressive evidence is the changes seen in the brain of aged patients after general anesthesia, similar to the morphological, molecular and biomarker changes occurring in Alzheimer's disease, which are considered responsible for a decline in cognitive status or a worsening of pre-existent dementia.

The fact that in laboratory and clinical research only certain anesthetic agents and techniques, but not others, appear to be involved, raised the problem regarding what is the safest and the least safe anesthetic, and the existential questions "which anesthesiological technique should I choose and which should I avoid if I undergo surgery and anesthesia"?

From this point of view, a selection of appropriate anesthesia drugs and protocol is mandatory, especially to maximize anesthesia efficiency, avoid occurrence of adverse events, and ensure patient safety. Moreover, individuals with pre-existing CNS disorders, AD or mild cognitive impairment (a pre-Alzheimer's condition), characterized by a compromised neuronal transmission, represent particular cases in which the wrong choice of anesthesia drugs may have a negative effect on postoperative outcome.

The data presented in this paper, but also in previous research, have outlined the fact that other factors, indirectly correlated to anesthetics and surgery, could have a central role in the pathogenetic development of POCD and derangement.

Inhaled anesthesia and anesthetics have demonstrated the properties of promoting and activating the most important steps of AD cascade at a molecular level. Recently, the commonly used, modern anesthetic agent sevoflurane has evidenced the capability of inducing neuroinflammation, at least after multiple anesthetic exposures.

Intravenous anesthesia and anesthetics are considered safer, relative to postoperative cognitive derangement in the aged: the intravenous hypnotic agent propofol offers more guarantees, appears to induce a natural-sleep type of anesthesia and prevents/does not affect neuroinflammation; remifentanil, unlike other opioids (morphine, etc.) does not disrupt cholinergic neurotransmission, a disruption known to cause post-operative delirium and impaired memory function (POCD), and raises new hope for the potential safe use of remifentanil in aging patients and subjects with dementia and AD with cholinergic neurotransmission dysfunction. However, the intravenous anesthesia is not an anesthesiological technique which can be used with the aging patient because of hemodynamic instability, and especially in those with cardiovascular disease.

Regional anesthesia and anesthetics offer considerable advantages: they do not act directly on the brain, have less immunosuppressive effects, and potentially reduce the proinflammatory cytokine response.

However, research has pointed out that other factors may contribute significantly to neurotoxicity, including the length and repetitiveness of anesthesia, or the hypoxia and hypothermia faced by patients during the surgical procedure.

These last considerations call to identify specific perioperative management for aged patients, with particular attention for those affected by AD, other dementias and mild cognitive impairment, who are scheduled to undergo surgery.

Current clinical data addressing the safety of these pharmaceutical agents on the developing human brain are limited as research is very difficult in this population, and it is not clear if the laboratory findings and local retrospective clinical data can be fully applied to humans or to daily worldwide clinical practice. The updated data indicate that a single brief anesthetic seems to be safe in infants, whereas multiple anesthetic and surgical exposures are not.

Moreover, certain anesthetic agents (i.e. propofol), considered neuroprotective and not dangerous in adults and in the aging, have demonstrated neurotoxic properties in the developing brain in terms of long term cognitive effects.

Given the number of neonates, infants, and young children anesthetized annually worldwide, neurotoxicity alert over anesthetics for the developing brain (children up to 3 years) is a global public health issue. The call of the Food and Drug Administration (FDA) to the scientific community for additional research to understand the long-term cognitive implications for children exposed to prolonged anesthesia, in accordance to alarmist laboratory data, is a worldwide request for independent studies, not overshadowed by the participation of companies in a clear conflict of interest.

In the last few years, the huge number of patients receiving surgical operations and related anesthetic care have allowed the detection of other long-term complications that have severe effects on patient health and quality of life, as well as post-operative depression and ASD.

Depression is a well-documented adverse effect of many surgical procedures, but diagnosis of primary depression (patient with pre-existent depressive symptomatology or developed outside of medical cause, such as surgery or anesthesia) or secondary (depression follows medical or psychological condition) is often not possible because doctors, surgical and anesthesiological facilities do not routinely screen patients for depression before and after surgery. Post-operative depression usually does not begin to show itself until after the patient has returned home from hospital, or it is even considered as an unfortunate side-effect since there are many conditions and diseases known *to be per se* precursors of depression. Surgeons who are informed by relatives or caregivers during patient follow-up about a switch toward a depressive status after an operation should refer the patient to screening for postoperative depression. Often, most post-operative depression cases seen are left undiagnosed and untreated.

With regard to autism spectrum disorder (ASD), due to the small amount and ambiguity of available research, it appears truly impossible to address the potential role of general anesthesia in the development of ASD. Therefore, any association of exposure to anesthesia with subsequent ASD disorders remains to be determined.

Finally, regarding the anesthetic neurotoxicity issue, it is necessary to point out the following general aspects:

1) A critical appraisal of the research done in this field shows unsolvable weaknesses and limits, essentially represented, on the one hand, by numerous problems in translating the value of animal model findings into human clinical scenarios, and, on the other, the impossibility of designing or conducting a single study without confounding factors such as comorbidity, surgery, or other drugs given, as well as the impossibility of administering only anesthesia without surgery, making it impossible to determine, without bias and beyond any reasonable doubt, if any associations are due to anesthesia toxicity.

2) The ultimate goal in this field should be not merely to demonstrate the neurotoxicity of anesthesia and if the case, as best solution, to restrain surgery and anesthesia in children and/or the elderly, but to identify underlying pathomechanisms, patient risk factors, and the use of the least provocative drugs and techniques, to minimize the incidence of neurotoxicity and neurodegenerative disorders, given that surgery and anesthesia in the extremity of ages are often mandatory or for emergency procedures.

3) The biggest challenge to be overcome is to search, in humans, for a potential neurological phenotype of anesthesia-related neurotoxicity, to understand why, despite millions of patients receiving anesthesia and surgery, only a few face these long-term notable complications.

4) There is a particular area of research of interest at present that would appear to be the common denominator among all the above mentioned adverse effects and bodes well for the future: neuroinflammation. A growing body of evidence shows that neuroinflammation is involved in cognitive dysfunction symptoms and in the development of neurodegeneration associated with Alzheimer's disease. Certain anesthetics have anti- and pro-inflammatory modulatory effects, depending on the drug and concentration.

In conclusion, long-term anesthesia effects and impact on the brain continue to be undervalued, whereas this knowledge must be taken seriously into account. Even today, despite being able to choose among different anesthesia protocols thanks to the wide development of regional anesthesia techniques, there are still many procedures requiring general anesthesia, and many surgical subspecialties where general anesthesia continues to retain the monopoly.

The man in the street, the frightened parents or relatives, and the confused surgeon deserve clear answers, not only politically correct responses. In particular, a clear answer is imperative for the anesthetist, who, every day, meets the frightened glance of a human being who is receiving general anesthesia.

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TABLE 1. Several anesthetics play a direct leading role in Aβ oligomerization. Smaller molecular sized inhaled anesthetics (halothane, isoflurane and sevoflurane) at clinically relevant concentrations promote Aβ oligomerization by inducing chemical shift changes of the critical amino acid residues (G29, A30, and I31). In contrast to inhaled anesthetics, bigger molecular sized intravenous anesthetics (propofol, thiopental and diazepam) have no effect on Aβ oligomerization at clinical concentrations. Propofol promotes Aβ oligomerization at very high concentrations [7, 12, 35, 36, 37].

Anesthetics	**Aß Oligomerization**	
Halothane	+++	
Isoflurane	++	
Sevoflurane	+	
Desflurane	+	
Propofol	+ high concentrations	- low concentrations
Thiopental	-	
Diazepam	-	

TABLE 2. Anesthetics, neuroinflammation and Alzheimer's Disease

Anesthetic	Effects	Clinical Significance	Ref
Neuroinflammation	Male 18-mo-old Wistar rats that had experienced infection before surgery exhibited a more generalized and exacerbated postoperative cognitive impairment compared with healthy surgery rats, as well as a prolonged increase in systemic cytokine levels and increased microglial activation in the hippocampus and prefrontal cortex.	These findings support the hypothesis that an infection before surgery under general anesthesia exacerbates POCD.	[45]
General anesthesia	In cultured hippocampal and cortical neurons, inflammation increases sensitivity of neurons to general anesthetics. This increase in anesthetic up-regulation of GABAA receptor activity *in vitro* correlates with enhanced sensitivity for GABAA receptor-dependent behavioral endpoints *in vivo*.	Critically ill patients with severe inflammation often exhibit heightened sensitivity to general anesthetics. Inflammation increases the number of gamma-aminobutyric acid type A receptors thereby enhancing drug behavioral sensitivity.	[42]
Dexmedetomidine	In aged mice, anesthesia alone caused weak cognitive dysfunction on the first day after general anesthesia. Cognitive function in mice with splenectomy (increased the expression of IL-1beta, TNF-alpha, Bax and caspase-3 in hippocampus) under general anesthesia was significantly exacerbated at the first and third days after surgery, and was significantly improved by dexmedetomidine administration.	Hippocampal inflammatory response and neuronal apoptosis may contribute to POCD, and selective alpha 2 adrenal receptor excitation plays a protective role.	[46]
Isoflurane	Isoflurane might induce DNA damage,	Isoflurane induces DNA	[43]

	as represented by increased gammaH2A.X level, via induction of oxidative stress and inhibition of the repair of DNA damage through the p53 signaling pathway.	damage.	
Isoflurane	Exposure for 2 h to1.4% isoflurane causes Zn-deficient potential neurotoxicity, exacerbated learning and memory impairment, and neuropathology in mice, which is tolerated to some extent in Zn-adequate APP/PS1.	Isoflurane exposure markedly indicating that AD patients with Zn deficiency may be more vulnerable to volatile anesthetic isoflurane.	[44]
Isoflurane Sevoflurane	Old rats (17-19 months) were anesthetized with sevoflurane or isoflurane for 3h. Quantitative immunohistochemistry revealed increased BBB permeability in older animals treated with sevoflurane, but not isoflurane, thereby contributing to POD.	In the elderly, exposure to some inhaled anesthetics can cause BBB compromission that disrupts brain homeostasis, perturbs neuronal function and thereby contributes to POD that may progress to postoperative cognitive decline and later dementia.	[47]
Sevoflurane	Six day-old wild-type mice were exposed to 3% sevoflurane two hours daily for one or three days. Sevoflurane can induce a dual effect (increase versus decrease) on the activation of AKT/GSK3beta signaling pathway that is involved in neurotoxicity and neurobehavioral deficits.	Anesthesia with multiple exposures of commonly used inhalation anesthetic sevoflurane induces neuroinflammation and cognitive impairment in young mice, but anesthesia with a single exposure to sevoflurane does not.	[41]

TABLE 3. Anesthesia and developing brain

Anesthetic	Effects	Clinical Significance	Ref
Sevoflurane	6-day old monkeys received sevoflurane anesthesia for 5 h. Sevoflurane also did not affect the learning and memory of the monkeys when they were assessed from the age of 7 months.	Exposure of neonatal monkey to sevoflurane may not affect cognition, behavior and neuronal structures in childhood, indicating the safety of sevoflurane anesthesia in children.	[55]
Sevoflurane	Neonatal rhesus monkeys (postnatal day 5 or 6) were exposed for 8 h to 2.5% sevoflurane. 1 day after exposure showed that sevoflurane exposure increased -FEPPA uptake in the frontal lobe from 0.927 +/- 0.04 to 1.146 +/- 0.04, and in the temporal lobe from 0.859 +/- 0.05 to 1.046 +/- 0.04 (mean +/- SE, $P < 0.05$).	Sevoflurane-induced general anesthesia during development increases glial activation, which may serve as a surrogate for neurotoxicity in the nonhuman primate brain.	[56]
Sevoflurane	In exposed PND7 pup brain maturation in neonatal rodents is impeded by sevoflurane anesthesia.	Potentially clinically relevant because 1HMRS can be applied across species and may be useful in providing evidence of neurotoxicity in the human neonatal brain.	[57]
Sevoflurane	Infant monkey exposition to 2.5% sevoflurane for 9 h, resulted in a broad identification of differentially	Generally, sevoflurane-induced neuronal damage was also	[58]

	expressed genes associated with nervous system development, function, and neural cell viability. Critical lipid components were significantly downregulated.	associated with changes in lipid content and composition, or both, providing insights into the molecular mechanisms underlying anesthetic-induced neurotoxicity.	
Propofol Isoflurane	Mice received 6 h of 1.5% isoflurane or propofol. Isoflurane significantly increased plasma S100beta levels compared to controls and propofol. Both isoflurane and propofol significantly increased caspase-3 levels in the cortex and hippocampus, though isoflurane was significantly more potent than propofol. However, there were no significant differences in the inflammatory biomarkers in the cortex or in subsequent learning and memory between the experimental groups.	Both isoflurane and propofol caused significant apoptosis in the mouse developing brain, with isoflurane being more potent. Isoflurane significantly increased levels of the plasma neuro-degenerative biomarker, S100beta. These effects in the developing brain were not associated with effects on inflammation or with cognitive dysfunction in later life.	[59]
General anesthesia	Seventy-six patients aged between 3 to 14 (median 5 years). Anesthesia with midazolam, fentanyl, propofol and sevoflurane. In all the patients, serum S100B protein levels increased after general anesthesia.	The concentration of serum S100B protein (serum marker of cerebral damage) increased significantly after general anesthesia, indicating	[60]

		that general anesthesia may cause brain damage.	

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