Anesthesia and Postoperative Cognitive Dysfunction (POCD)

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Abstract: POCD describes a decline in cognitive function after surgery with a predominance in the elderly patient. Although there is general agreement that POCD is likely to be multifactorial, it remains unclear whether its occurrence is a result of the effects of surgery or general anesthesia. This review provides a synopsis of the available clinical and preclinical data and summarizes recent research relevant to the occurrence of POCD and possible pharmacologic algorithms for its prevention and treatment.

1. DEFINITION AND DIAGNOSIS

Although perioperative morbidity and mortality in surgery and anesthesia have been dramatically improved over the last decades, adverse cognitive outcome presents an almost unchanged postoperative complication with serious effects on patients' quality of life as well as on overall health care costs [1].

Cognitive dysfunction is characterized by changes in perception, recognition, thinking and memory. Although several terms have been used synonymously for this syndrome, they describe different entities. As an attempt to differentiate these entities, the **central anticholinergic syndrome** (development immediately after cessation of general anesthesia) should be distinguished from **postoperative delirium** (peak at the second and third postoperative day), which is further differentiated as a harbinger for long lasting **postoperative cognitive deficits (POCD)**.

The central anticholinergic syndrome is a complication observed following general anesthesia with central manifestations ranging from excitatory symptoms such as agitation to central nervous system depression such as stupor, coma and respiratory depression. The incidence varies between 1 and 40 %. This wide variation is due to the fact that precise diagnostic criteria for the central anticholinergic syndrome are not fully characterized and diagnosis is mainly confirmed by rapid recovery of the symptoms with the administration of physiostigmine following the exclusion of other contributing factors [2, 3]. The etiology has not been fully elucidated so far, but it is assumed that drugs used for general anesthesia blocking central cholinergic transmission result in a relative lack of acetylcholine in the brain, which is essential for learning and memory. Drugs affecting the cholinergic system are atropine, scopolamine, opioids, benzodiazepines, ketamin, H_2-blocker, volatile anesthetics, propofol, etomidate and nitrous oxide [3].

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Delirium is a well-known mental disorder, which was already described in the medical writings of Hippocrates 2500 years ago and is characterized by an acute decline in attention and cognition. Following surgery and anesthesia the incidence varies between 0 and 73% dependent on the type of surgery and on the studied patient population [4]. Due to the clinical importance of delirium, its association with a higher incidence of mortality and extended hospital stay with an increase in hospital costs, an immediate and accurate diagnosis is essential. This diagnosis is primarily based on clinical examination and careful bedside observation of key diagnosis features described in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM IV).* These features are described by acute onset, fluctuating course, altered sleep-wake cycle, inattention, altered level of consciousness, disorganized thinking, cognitive deficits, perceptual, psychomotor and emotional disturbances [5]. Delirium itself presents heterogeneously as a hyper- or a hypoactive subtype. Hyperactive forms associated with agitation tend to be clinically obvious and may be dangerous for patients in the early postoperative period compromising both surgical outcome and hemodynamic stability, especially in the elderly. In contrast, the hypoactive form often goes unrecognized or misdiagnosed as dementia or other psychiatric illness. Therefore, formal cognitive testing using certain instruments like the confusion assessment method [6] or the mini mental state examination [7] should be performed on a routinely basis. An interdisciplinary approach between psychiatrist, surgeon, anesthetist and nurse is required to provide an efficient therapy, which seems to be important as an untreated postoperative delirium is associated with a longer lasting cognitive decline [8].

POCD is characterized by a persistent decline in cognitive function following anesthesia and surgery, identified by preoperative and postoperative cognitive testing [9, 10]. This testing requires a sensitive and comprehensive neuropsychological test battery assessing a variety of cognitive domains. However, the investigation and diagnosis of POCD is hampered by the absence of a consensus regarding the tests to be used as well as the operational definition of POCD [11]. Consequently, the comparison between studies investigating POCD is difficult, as different test instruments have

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been utilized at different time points using varying statistical methods to define cognitive decline. Therefore, future investigations of POCD are recommended to use a standardized test battery and defined diagnosis criteria as well as to include a control group, which is essential to allow correction for practice effects and variability between follow-up sessions [12, 13]. The incidence of POCD depends on the type of surgery, on the age of patients studied, as well as on preexisting diseases and the preoperative cognitive performance. The largest international multicenter POCD study to date investigating 1218 elderly patients undergoing major non-cardiac surgery was published by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group. In this study POCD was present in 26% of the patients after one week, persisting in 10% after three months and only in 1% after two years [14]. In contrast, POCD has been demonstrated in 53% of patients within the first week following cardiac surgery utilizing cardiopulmonary bypass (CPB) and was still present in 42% of the patients five years later [15]. These long-lasting effects might suggest that POCD may present a more chronic and persistent disorder and therefore blur the distinction to dementia. In this context, Lee and colleagues reported an increased risk for the emergence of Alzheimer disease following coronary artery bypass graft surgery compared to a group of patients in whom percutaneous transluminal angioplasty has been performed [16]. Further, recent studies have assumed a relationship between delirium, POCD and dementia due to the following observations [17-19]: first, a preoperatively impaired cognitive performance is an important risk factor for the development of postoperative delirium; second, delirium is discussed as a harbinger for POCD and dementia and third, recent studies have postulated comparable underlying mechanisms for both delirium and dementia especially in terms of cholinergic deficiency and inflammation. However, the pathophysiology of all three, delirium, POCD and dementia, remains poorly understood, rendering their distinction difficult. Consequently one could only speculate if delirium itself leads to long-term cognitive deficits (called POCD or dementia) or if it merely unmasks a preexisting reduction in cognitive reserve [20]. Consequently, preclinical as well as clinical studies are required to further elucidate the mechanisms leading to delirium, POCD and dementia and therefore clarify potential interrelationships between these entities.

2. NEURONAL PHYSIOLOGY AND PATHOMECHANISMS

Memory phenomena have been categorized as explicit or implicit memory function. Explicit memory function (declarative memory) involves the hippocampus–medial temporal lobe system whereas implicit memory function (non-declarative memory) includes basic associative learning and memory from the cerebellum, amygdala, and other systems [21]. Most, if not all, cognitive tests, which were chosen for the assessment of POCD explore more or less the performance of declarative memory after surgery. This memory is formed through life experience and includes acquisition of input information (learning), consolidation and recall, and use of stored information (memory retrieval). The retrieval of declarative memory in humans is, by definition, the conscious recall of stored information and, important for clinical studies concerning POCD, the memory storage can only be tested by its retrieval. It now seems relatively clear that the hippocampus and related cortical structures, e.g., perirhinal, parahippocampal, and entorhinal cortex are critical for declarative memory [22]. Lesions including all of these structures produce the most profound amnesia and research on declarative memory in rodents has concerned the role of the hippocampus in spatial memory.

Long-term potentiation (LTP), whereby brief high-frequency stimulation of a neural pathway can induce long-lasting increases in synaptic efficacy, has several features that make it suitable as a molecular and cellular storage mechanism (for review see [23]) and provides an experimental analogue of the postulated learning-induced changes in synaptic connectivity. The best studied synaptic pathway for LTP is the Schaffer-collateral CA1 synapse in the hippocampus, which uses glutamate as its transmitter for activation of NMDA (N-methyl-D-aspartate) receptors and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors. NMDA receptor channels are only activated in the presence of a local strong depolarization induced by strong AMPA receptor activation and concurrent GABAergic disinhibition via feedback effects of $GABA_A$ and $GABA_B$ autoreceptors. As a result, the Mg^{2+} blockade of NMDA receptors is transiently fully relieved allowing Ca^{2+} to flow into the postsynaptic neuron. This Ca^{2+} influx triggers a cascade of secondary messengers that ultimately activate a number of enzymes such as phosphokinase C (PKC), phospholipase A2 (PLA2), phospholipase C (PLC) and Ca^{2+}/calmodulin-dependent protein kinase II (CaM kinase II). Consequently, these processes lead to fixation of changes in postsynaptic AMPA receptors such as an increase in their affinity and/or number and, possibly through retrograde signals (arachidonic acid, nitric oxide), modulate presynaptic glutamatergic terminals influencing transmitter release. A large body of evidence has now been gathered demonstrating that LTP and memory in rodents and humans are supported by similar molecular mechanisms (for review see [21, 24]). LTP is affected by a lot of genetic and/or pharmacological interference, and such alterations might be causally related to memory dysfunction. Since NMDA and AMPA receptors are playing a crucial role in CA1-dependent LTP and memory (for review see [23]), blockade of these receptors with antagonists impairs learning in rodents in a variety of hippocampus-dependent memory tasks [25]. Consequently, anesthetics which attenuate NMDA and AMPA receptor-mediated depolarization may also induce cognitive deficits, e.g., Xenon and N_2O directly affect NMDA receptor activity, and intravenous and volatile anesthetics mainly increase $GABA_A$ receptor function (see section 4).

However, the crucial role of NMDA and AMPA receptors triggering the Ca^{2+} signal, important for learning processes, is a double-sided sword. Physiologically, NMDA and AMPA receptors are transiently activated in the presence of glutamate in millimolar concentrations [26] following strong depolarization of the postsynaptic membrane which rapidly causes the release of magnesium with the subsequent reversal of its voltage-dependent blockade of NMDA receptors [27], whereas, under pathological conditions, e.g., ischemia, NMDA and AMPA receptors are activated by lower concen-

trations of glutamate but for a much longer time [28]. As a result, the excessive activation of NMDA receptors destabilizes intracellular Ca^{2+} homeostasis producing cognitive dysfunction and even cell death [29]. This cell death, ascribed to an excessive activation of glutamate receptors, has been termed "excitotoxicity" and seems to occur in acute ischemia such as stroke and trauma [25], but also in chronic neurodegenerative diseases such as Alzheimer's disease (AD; [30]). The voltage-dependency of the divalent cation Mg^{2+} is so pronounced that it also leaves the NMDA channel upon moderate depolarization under pathological conditions, i.e. in the presence of tonically mildly elevated glutamate levels and moderate membrane depolarization due to energy deficits or ischemic conditions which may occur during surgery. Under such ischemic conditions, temporally uncoordinated, continuous stimulation of NMDA and AMPA receptors produces enhanced "synaptic" noise, decreasing the probability of detecting the relevant signal (e.g. inducing LTP or learning new facts) once it arrives [25]. This produces a progressive decline in cognitive functions, which might be reflected in an impairment of acquisition and encoding of new memory. Furthermore, prolonged Ca^{2+} influx may also trigger apoptosis of post-mitotic cells and late neuronal death. The regulation of apoptosis has been investigated extensively and the reader is referred to the literature [31]. In brief, the accumulation of intracellular Ca^{2+} and generalized ionic imbalance are major mediators of late cell death. Thus, Ca^{2+} imbalance is intimately connected to programmed cell death pathways and, as a consequence, might produce chronically dementia-related neuronal dysfunction.

It should be stressed that any dysfunction of postsynaptic neurons leading to weakened blockade by Mg^{2+}, e.g. due to partial depolarization as a consequence of an energy deficit or ischemic conditions, may also trigger excitotoxicity and structural (neuronal loss) deficits [32].

Memory processes and LTP are not only blocked at the time of their initiation by antagonists of NMDA receptors, but also by an enhancement of $GABA_A$ receptor function (for review see [33]) demonstrating that compounds (e.g. many anesthetics) which increase the activity of the GABAergic system may induces memory deficits. It is well known that the augmented $GABA_A$ activity by benzodiazepine administration induces episodic memory deficits in rodents and humans [34, 35]. Several studies in animals in a wide variety of tasks and species have provided evidence that the impairment induced in memory processing by increasing GABA receptor activity clearly concerns the acquisition of information [36]. Similar findings have also been found for human subjects [37].

Nevertheless, it should be considered that decreasing glutamate receptor and increasing GABA receptor activity provides neuroprotection (for review see: [25]) and is effective against acute ischemia [38]. GABA may protect neurons not only by directly inhibiting neurons [38], but also by exerting an inhibitory influence on glutamate-mediated neuronal activity [39]. In agreement with this hypothesis, it has been shown that the $GABA_A$ agonist muscimol inhibits NMDA-induced neurotoxicity in primary cell cultures [40].

As already stated above, excessive NMDA and AMPA receptor stimulation is also a hallmark of excitotoxicity-related diseases. The pharmacological intervention of NMDA and AMPA receptor function by antagonists or modulators has been shown to exert excellent neuroprotective properties in several models of cerebral ischemia, neuronal injury and neurodegenerative diseases. These neuroprotective effects have been intensively studied. However, a detailed description would be beyond the scope of this review and the reader is referred to the literature (see: [25, 41]).

3. RISK FACTORS

The etiology leading to POCD is still poorly understood and is most likely multifactorial. Risk factors for POCD are either present already preoperatively including the patient's comorbidities and baseline cognitive function, are generated during surgery or are developed in the postoperative period mainly as complications. The identification of the patient's risk profile is important as it may help to optimize perioperative treatment in terms of utilizing neuroprotective strategies and consequently to improve postoperative cognitive performance.

3.1. Preoperative Risk Factors

The majority of studies to date have reported advancing age as a risk factor for the development of POCD [14, 42]. Particularly older patients with a history of alcohol abuse present an increased risk for postoperative cognitive impairment compared to a control group [43]. Several studies pointed out that a lower level of education is associated with an adverse cognitive outcome following surgery [14, 15]. Patients with pre-existing cognitive dysfunction and depression are often excluded from POCD studies, although they are at high risk to develop or to aggravate cognitive dysfunction [44]. Diabetes mellitus does not only contribute to the development of coronary heart disease but also increases the risk for an impaired cognitive outcome following cardiac surgery [45]. During the last years genetic polymorphisms have been more elucidated in order to better understand the pathomechanism and to obtain a suitable tool for identification of patients at high risk for the development of POCD. These genetic differences among patients may explain the wide variation in the susceptibility to POCD. The apolipoprotein ε4 genotype (APOEε4) has been shown as one of the first genetic variants to be associated with POCD [46, 47], however recent studies have questioned the impact of APOE on the development of POCD, speculating that APOE is only one of multiple genetic variants altering cognitive outcome [48]. More recently, genetic variants in P-selectin and C-reactive protein have been linked with post-cardiac surgery cognitive dysfunction [49].

3.2. Intraoperative Risk Factors

Studies have shown that both, duration and type of surgery - with an increased risk for vascular, orthopedic and cardiac surgery - are associated with a higher incidence of POCD [14, 50].

POCD following vascular and orthopedic surgery is discussed to be in part due to cerebral emboli, however, studies

failed to show new lesions in the diffusion weighted imaging following carotid endarterectomy [51] or to demonstrate an association between cerebral emboli detected with transcranial Doppler and cognitive dysfunction following orthopedic surgery [52].

Although the majority of research in this field had focused on cardiac surgery the etiology of POCD in these patients is not fully elucidated so far. It is discussed to be most likely multifactorial including mainly the effects of cerebral hypoperfusion, cerebral emboli and systemic inflammatory reaction [53]. Cerebral emboli could be generated during surgery either as solid emboli by separation of atherosclerotic plaques during aortic clamping, or as gaseous emboli mainly during open chamber procedures or as an effect of perfusionist interventions [54]. The amount of emboli determined with the transcranial Doppler is thereby associated with the incidence of POCD eight weeks after coronary artery bypass graft surgery [55]. The inflammatory cascade is specifically activated during CPB via several pathways: the contact activation by the foreign surface of the circuit, surgical trauma as well as the effect of ischemia-reperfusion injury and endotoxemia [56, 57]. Human studies examining the impact of systemic inflammatory reaction as determined by cytokine levels on cerebral outcome following CPB have revealed conflicting results [58]. However, the preoperative immunity seems to play an important role, as it has been shown that reduced preoperative endotoxin immunity is a risk factor for the development of POCD after cardiac surgery, particularly in the elderly [56]. Recent studies questioned these mechanisms to be responsible for POCD. At first, van Dijk and colleagues showed no difference between patients undergoing off-pump and on-pump procedures with regard to the incidence of POCD five years following coronary artery bypass grafting (CABG) [59]. Another study showed that cognitive decline in patients six years following CABG was comparable to patients of similar age with coronary artery disease but who have not undergone cardiac surgery [60]. Whether cognitive decline in older patients after cardiac surgery is more related to vascular risk factors than to surgery itself requires further studies with inclusion of an appropriate control group.

3.3. Postoperative Risk Factors

The postoperative period has been almost neglected as origin or modulator for the development of POCD until recent studies have highlighted its importance. In this context patients following total knee replacement in which POCD was found demonstrated an accentuated likelihood for postoperative complications compared to patients without cognitive deficits [61]. These complications included cardiac and pulmonary dysfunction next to bleeding. A most recent study has shown that older patients after non-cardiac surgery who experienced POCD were more likely to demonstrate moderate pain compared to patients without any cognitive deficits. Additionally, adequate pain management in this study seems to play an important role as orally administered analgesia was related to a lower risk for POCD compared to patients with intravenous patient-controlled analgesia. However, the treatment was not randomized in this study, which means that oral analgesia may be only a marker for a less painful state and the assessment of cognitive function was restricted to the first and second postoperative day and therefore might have been compromised by the sedating effect of the opioids [62]. A recent review stated that intravenous and epidural analgesia techniques do not influence postoperative cognitive performance differently, although more studies, sufficiently sized and with standardized methods to define outcome, are required to confirm these results [63].

Hyperthermia during the early postoperative period has also been associated with cognitive decline six weeks following cardiac surgery [64]. However, whether the elevated temperature itself is responsible for the cognitive dysfunction or whether hyperthermia presents a marker for ongoing infection has not been investigated so far.

4. INFLUENCE OF ANESTHESIA

Anesthetic agents are widely used in clinical medicine and provide pain relief, immobility and unconsciousness. Although considerable progress has been made in understanding how anesthetics affect CNS function, most of the molecular and neuronal substrates are still a matter of debate (for review see: [65]). The relative non-selectivity and low potency of anesthetics has made it difficult to identify which targets are pharmacologically relevant and which are not (for review see: [66]). Research on anesthetic mechanisms has mainly focused on ion channels that are located in the membrane of nerve cells. Ion channels that are sensitive to anesthetics at clinical effective concentrations include AMPA receptors, NMDA receptors, $GABA_A$ receptors, glycine receptors, $5\text{-}HT_3$ (5-hydroxytryptamine, type 3) receptors and nicotinic acetylcholine receptors [67]. Voltage-gated ion channels for sodium, potassium and calcium are also sensitive to some anesthetics, albeit usually at concentrations higher than those used clinically [65]. Strong evidence exists that anesthetics particularly affect the glutamatergic and GABAergic system [68] which is considered to be responsible for the reversible depression of CNS function during anesthesia. AMPA and NMDA receptor-mediated responses are depressed by intravenous [69], volatile [70, 71] and gaseous anesthetics [72]. Whereas xenon and nitric oxide have no effects on $GABA_A$ receptors [66, 73], volatile and intravenous anesthetics potentiate $GABA_A$-activated currents subunit-dependent in recombinant receptors (for review see [66]) and in rat hippocampal neurons *in vitro* [74-76].

Beside these effects on neurotransmission, it is known that anesthetics can induce the expression of several genes belonging to the class of immediate-early genes (IEGs) and alter mRNA expression of nitric oxide synthase [77, 78]. Furthermore, on the protein level, Futterer *et al.* [79] showed that desflurane induces an alteration of several intracellular proteins, which are e.g. important for the endocytosis of neurotransmitter receptors. Furthermore, the expression levels of several receptor subunits in different brain areas have been investigated recently [80]. 24h after isoflurane anesthesia NR2B subunits of the NMDA receptors were selectively up regulated in hippocampal neurones, whereas NR2A subunits were selectively down regulated in the medial prefrontal cortex. All other receptor subtypes investigated (GluR1, GluR6/7, α_2-$GABA_AR$ and β_2 nicotinic acetylcholine receptors) were not altered.

GABAergic mechanisms of anesthetics may contribute to cognitive dysfunction after general anesthesia as enhancement of $GABA_A$ receptor-mediated hyperpolarizing responses will reduce the activation of the voltage-sensitive NMDA receptors [81] and voltage-gated calcium channels, prerequisites for the induction of alterations in synaptic strength. In addition, some anesthetics cause hyperpolarization and diminished excitability of neurons by enhancing the activity of background potassium channels (for review see [82]). The direct antagonism at NMDA and AMPA receptors, as has been reported for the gaseous anesthetics xenon and N_2O [72, 83], may also affect the induction of LTP and produce memory deficits.

4.1. Synaptic Plasticity and Learning

In general, synaptic plasticity is defined as the ability of a synapse to produce short-term or long-term changes in its strength. The two major forms of synaptic plasticity, LTP and long-term depression (LTD), are long-lasting modifications of synaptic transmission that provide the best experimental model for a cellular mechanism underlying learning and memory in the vertebrate CNS. Due to this pharmacological profile, an additional important target for anesthetics may be the modulation of LTP. However, despite the importance to know more about the mechanisms how general anesthetics affect synaptic plasticity, only few data are presently available.

4.1.1. Acute Effects of Anesthetics

The intravenous anesthetic etomidate, acutely applied, suppresses LTP of field excitatory postsynaptic potentials (fEPSPs) in the CA1 region of the hippocampus through modulation of $GABA_A$ receptors [84]. Using transgenic α_5 null mutant mice ($\alpha_5^{-/-}$), Cheng *et al.* [84] could demonstrate that LTP and memory for spatial and non-spatial hippocampal-dependent learning tasks were impaired in wild type, but not in $\alpha_5^{-/-}$ mice. The α_5 subunit is of particular interest in memory processes, because it is predominantly expressed in the hippocampus [85], and reduced expression of α_5 is associated with better performance of hippocampal-dependent learning tasks [86]. Similar results were obtained with propofol, which, at low concentrations (20mg/kg; i.p.), facilitates the development of LTD and impairs the maintenance of LTP in the CA1 region of anesthetized rats [87]. *In vitro* experiments elucidate that the application of propofol (30-50μM) inhibits CA1 LTP induction via a $GABA_A$, but not NMDA, receptor-mediated mechanism [88]. However, there is a discrepancy between the *in vivo* and *in vitro* studies with regard to the effect of propofol on LTD. Propofol facilitates LTD *in vivo*, but not in slices [88]. This discrepancy is probably due to differences between the experimental systems and propofol doses (rat *in vivo*: 20mg/kg or 11 μg/g tissue versus mouse slice preparations: 50μM or 27.5 μg/g). Propofol-induced memory loss is said to require a serum propofol concentration of 3.5 μM [89] yielding 1.9 μg/g in tissue. This concentration is approximately 14-fold lower than that required to inhibit LTP, as applied in the *in vitro* experiments.

The effects of volatile anesthetics have first been measured by Maclver *et al.* [90], who found a reduced probability of LTP induction in CA1 pyramidal neurons with halothane (1.2 Vol%), but not with methoxyflurane (0.16 Vol%). Clinically relevant concentrations of isoflurane (0.2-0.3mM), acutely applied, block the induction of LTP and LTD [70]. This study provides strong evidence for $GABA_A$ receptors to be crucially involved in the blocking effect of isoflurane on the induction of LTP, since a blockade of $GABA_A$ receptors prevented the effect of isoflurane.

The noble gas xenon is thought to be an ideal anesthetic with analgetic properties [91]. The effects of xenon were tested in anesthetized rats on spinal C-fiber-evoked potentials and on the induction of LTP in the superficial lumbar spinal cord in response to electrical stimulation of the sciatic nerve. Xenon (100 μL/mL) did not affect evoked potentials, but blocked the induction of LTP. These results suggest that xenon revealed no antinociceptive, but preventive, action in spinal pain pathways.

The effects of anesthetics on memory, when present during the learning procedure, have also been studied *in vivo*. Using classical conditioning in rabbits El-Zahaby *et al.* [92] studied the effects of N_2O and isoflurane on learning of the nictitating membrane responses. The authors could show that learning was impaired and that both anesthetics interact additively on the suppression of learning. Similar results have been obtained with rats when testing working memory performance under N_2O exposure in a two-trial recognition task [93]. Working memory was dose-dependently and selectively impaired for acquisition and retention and, as a compensatory effect, also slowed the acquisition processes.

In another study, rats were exposed to isoflurane (0-0.75 MAC) during the training phases of fear conditioning paradigms for freezing to context (hippocampus-dependent) and freezing to tone (amygdala dependent). Suppression of fear-conditioning to tone required approximately twice the isoflurane concentration that suppresses fear conditioning to context [94]. These results suggest that brain regions, necessary for learning show a different sensitivity to isoflurane. In contrast, a memory-enhancing effect of aversive memory formation has been found by Alkire *et al.* [95], when rats underwent a single trial inhibitory avoidance training during the exposure to low doses of volatile anesthetics. Halothane (0.10 Vol%) and sevoflurane (0.11 Vol%), but not desflurane (0.77 Vol%) or isoflurane (0.12 Vol%), significantly enhanced 24h retention performance. However, halothane-induced hyperalgesia during learning questioned the enhanced retention performance solely as a memory consolidation effect. This study suggests that the risk of aversive memory formation may be enhanced during exposure to low-dose sevoflurane.

4.1.2. Effects After the Removal of Anesthetics

Besides this acute effect on memory, anesthesia also interferes with memory performance, depending on age and learning task, when animals were first tested after the exposure to anesthetics. Unfortunately, the results are scarce and less consistent. In an early work from 1993, Komatsu *et al.* [96] exposed mice for 120 min to a halothane, enflurane or isoflurane anesthesia and tested them on posttraining memory in an avoidance task. 22 hours after anesthesia all mice

showed facilitation in memory function. An unimpaired learning has been shown in rats after a single bolus propofol (15-20mg/kg i.v.) anesthesia. Training five to seven mins after anesthesia resulted in normal retention of the swim-to-platform task and demonstrates that the ability to learn recovers rapidly after propofol application [97]. Similarly, a recent study shows that spatial memory, assessed for 14 days using a 12-arm radial maze, is intact in 14-month-old rats after propofol anesthesia [98]. Acquisition of new memory and performance improvement on an already-learned spatial memory task was impaired in aged (18-20-month-old) rats, up to 2 weeks after a 2h isoflurane/nitrous oxide (1.2 Vol%/70%) anesthesia [99, 100]. Rats, anesthetized without nitrous oxide showed the same weak performance in the 12-arm radial maze [99]. Adult rats (6 months), however, showed an impaired acquisition of new memory only when tested 2 days, but not 2 weeks after anesthesia and even improved spatial memory performance [100, 101]. Bekker *et al*. [102] assessed working memory of mice in a control (oxygen 21%) and anesthetized (oxygen 21% + iso 1.2 Vol%) group by use of a Y maze. One hour exposure to isoflurane 1.2% administered with room air marginally impaired mice's performance ($P = 0.04$; [102]). When the behavior of adult mice was assessed 28 h after anesthesia in a T-maze, mice anesthetized with 1% isoflurane had a significantly poorer performance than mice anesthetized with 2% isoflurane, which was not statistically different from that of the control group [103]. In contrast, anesthesia with 1 MAC (1.3 Vol%) isoflurane reversibly induces a hippocampus-specific elevation of NR2B subunit composition, improved hippocampal-dependent cognitive performance in the modified hole board test and enhanced *in vitro* LTP in CA1 neurons in 4-month-old mice [80].

Studying the effect of general anesthesia on cognitive outcome in humans remains difficult, as the effect of surgery can be excluded and appropriate control groups are missing. To overcome at least the latter limitation patients undergoing regional anesthesia are classified as control group and compared to patients subjected to general anesthesia, presuming that the use of regional anesthesia instead of general anesthesia for the same type of surgery results in a reduced incidence of POCD. The largest trial to date investigating the effects of general versus regional anesthesia on cognitive performance up to three months following cardiac and major non-cardiac surgery reported no difference between the two techniques [104]. This finding has been confirmed by Williams-Russo and colleagues studying the effects of general and epidural anesthesia following elective total knee replacement [105]. Not even patients at very high risk to develop POCD like those with preexisting cognitive dysfunction or depression have demonstrated some benefits of regional anesthesia compared to general anesthesia after orthopedic surgery [44]. Taken these studies together it is very unlikely that general anesthetics per se cause POCD.

4.2. Neuroprotection

In contrast to the hypothesis that anesthesia may worsen postoperative cognitive outcome, the hypothesis that anesthesia may be neuroprotective has been proposed. The neuroprotective potential of anesthetics probably results from their pharmacological properties contributing to the decrease or inhibition of neuronal excitability and enhancing $GABA_A$ receptor function. A detailed discussion about neuroprotective effects of anesthetics is beyond the scope of the present review and the reader is referred to the literature, e.g. [106, 107]. However, for the sake of completeness we provide a short summary. Beirne *et al*. [108] found that halothane antagonizes NMDA excitotoxicity in primary neuronal culture. Isoflurane has been shown to reduce excitotoxic injury mediated by NMDA and AMPA *in vivo* in rats [109, 110]. It also reduces $GABA_A$ receptor-dependently the frequency of spreading depression-like transient depolarization during focal ischemia in organotypic hippocampal cultures [111]. The influence of anesthetics on sympathetic tone has also been proposed as a possible mechanism of volatile anesthetic-mediated neuroprotection [112]. Volatile anesthetics further activate TWIK (transient weak inwardly rectifying K^+ channel)-related potassium channels [113]. Activation of those channels has been shown to be neuroprotective in models of both global cerebral ischemia and kainate-induced seizure activity [114]. In addition, beneficial effects on neuronal outcome have been shown for xenon, propofol and pentobarbital [115-117] (for review see [118]).

Surprisingly, preclinical *in vitro* studies suggest that general anesthetics may also exert neurodegenerative effects in different cell lines [119]. One plausible explanation for these divergent pharmacological properties of anesthetics might be the existence of synaptically and extrasynaptically located NMDA receptors [120, 121]. Under physiological conditions mainly synaptic NMDA receptors are activated, and blocking these receptors has a neurotoxic effect. However, under pathological, ischemic conditions, the increased glutamate levels open also extrasynaptic, mainly subunit 2B-containing NMDA receptors. Antagonizing these receptors mediates neuroprotective effects.

Another concept of neuroprotection, introduced about 21 years ago [122] (for review see [123]), is ischemic preconditioning, in which brief episodes of sub-lethal ischemia produce a robust protection against the deleterious effects of subsequent, prolonged, lethal ischemia [122, 124]. It has been shown that similar preconditioning effects can also be achieved with the volatile anesthetics isoflurane, sevoflurane, desflurane and halothane [125-127] (for review see [128]), whereby the potency of this effect is linearly correlated with their anesthetic potency [127].

Unfortunately, despite these promising preclinical results, human trials, which have been conducted to guide clinical practice, can only considered to be preliminary. Recently, a study has shown that deeper isoflurane anesthesia determined with the bisprectal index is associated with a better cognitive outcome six weeks following surgery [129]. Another study investigating the effect of deeper anesthesia on one-year postoperative mortality observed an association of longer cumulative deep hypnotic time and longer periods of intraoperative systolic hypotension with a higher one-year postoperative mortality [130]. Intraoperative anesthetic management clearly influences the postoperative outcome. To determine the extent and evaluate the consequences, a wide variety of randomized trials will likely be needed to further elucidate the particular mechanisms still being discussed. One of the first anesthetic drugs studied for neuroprotective

properties was thiopental, which showed an improved cognitive outcome following cardiac surgery [131]. However, further studies were unable to confirm the positive effect of this barbiturate [132]. Also propofol has shown to be insufficient to improve cognitive outcome after cardiac surgery administered to achieve burst suppression EEG [133]. Over the last years, the NMDA receptor antagonists have received much attention in the field of neuroprotection, as these drugs may attenuate excitotoxicity as main reason for acute neuronal death. In this context, Arrowsmith and colleagues have performed a randomized, placebo-controlled study using the NMDA antagonist remacemide. This study showed that the perioperative administration of remacemide improved cognitive outcome eight weeks following coronary artery bypass grafting surgery [134]. S(+)-ketamine, another NMDA receptor antagonist, which is frequently used as an anesthetic, has been studied in 106 patients undergoing cardiac surgery. The ketamine group demonstrated only a trend towards an improved cognitive outcome ten weeks later, but the study was underpowered, therefore more trials would be needed to determine the effect of ketamine on cognitive outcome [135].

The desirable preclinical effects turned out to be beneficial also for volatile anesthetics, which provide major improvement in ischemic outcome. The dose required to obtain this protection is within a clinically relevant range, with higher doses potentially worsening outcome [136]. Kadoi and colleagues have compared sevoflurane to propofol anesthesia for cardiac surgery in a retrospective manner and have not found any difference between these two anesthetics regarding cognitive outcome [137]. The effect of the three volatile anesthetics isoflurane, desflurane and sevoflurane on cognitive outcome after cardiac surgery has been compared in a small pilot study including 42 patients. This study suggests that isoflurane is associated with a better cognitive performance compared to the others and that sevoflurane leads to the worst cognitive outcome, but these findings represent only preliminary data and more patients are needed to further identify any differential effect of the volatile anesthetics on cognitive outcome [138]. Volatile anesthetics protect against both focal (e.g. obstruction of flow distal to the circle of Willis) and global (e.g. complete cessation of blood flow to the brain or forebrain) ischemia. However, the improvement in outcome is transient in global ischemia [139], whereas it is persistent in focal ischemia [140].

Recently it has been reported that anesthetics may be neurotoxic for the developing brain with potential cognitive deficits in neonatal and young pediatric patients. Such neurotoxicity has now been demonstrated *in vitro* and *in vivo* for isoflurane, sevoflurane, ketamine, midazolam, diazepam, pentobarbital, thiopental, nitrous oxide, and propofol [141-144], for review see [145]. Although the discussion of this phenomenon is beyond the scope of the current review, the mechanism seems to be mediated by GABAergic and glutamatergic actions (for review see [145, 146]). NMDA receptors play a crucial role during synaptogenesis, and inhibition of these receptors in this critical period is detrimental to brain development. Volatile anesthetics, also associated with neonatal excitotoxicity, potentiate $GABA_A$ receptor activity. Normally, this would result in hyperpolarization and hence neuroprotection. However, in contrast to the adult, in the developing brain, especially during synaptogenesis, activation of $GABA_A$ receptor results in depolarization of the neuron [147]. Consequently, depolarization-mediated rise in intracellular calcium concentration reaches levels that can be harmful to the cell, suggesting that this excitotoxic action of GABA may contribute to neuronal injury.

In summary, several studies have shown that the choice of anesthesia technique (general versus regional) does not influence postoperative cognitive outcome, suggesting that general anesthesia per se does not contribute to POCD. In contrast, anesthetics used for general anesthesia like NMDA receptor antagonists have been shown to provide neuroprotective properties, however more studies are needed to confirm these findings.

5. CURRENT POSSIBILITIES OF POCD PREVENTION

5.1. Pharmacologic Neuroprotection

As we have outlined above, *in vitro* and *in vivo* experiments point to considerable neuroprotective potential for general anesthetics (for review see [106, 107]) and may therefore prevent putative cognitive decline after surgery. However, clinical studies cannot confirm these promising results to an equal degree. One explanation for this conflicting data may be that acute neurologic disorders (ischemic and hemorrhagic stroke, traumatic brain and spinal cord injury, brain damage after cardiac arrest) are characterized by early death mediated by excitotoxicity and by delayed cell death caused by apoptosis. Current evidence indicates that volatile agents, barbiturates, and propofol can protect neurons against ischemic injury caused by excitotoxicity. In the case of volatile agents and propofol, neuroprotection may be maintained if the ischemic insult is relatively mild; however, with moderate to severe insults, this neuronal protection is not sustained after a prolonged recovery period (see [106]). Apoptosis, which is a delayed form of cell death, is associated with slowly progressive conditions similar to Parkinson's disease, ALS and AD and may therefore be responsible for cognitive dysfunction months and years after surgery. For this reason, combining different neuroprotective strategies may be of advantage for sustained prevention of POCD.

Unfortunately, the possible neuroprotective benefits of anesthetics for clinical use have not been sufficiently proven yet. Thus, the performance of representative, powerful clinical studies would be highly appreciated for resolving that discrepancy.

5.2. Non-Pharmacologic Neuroprotection

In addition to the neuroprotective properties of anesthetics several nonpharmacologic neuroprotective strategies like optimal temperature management, emboli reduction strategies and optimal cerebral perfusion hold promise to protect the brain during operation.

Hypothermia may provide neuroprotective effects most likely via multimodal actions and is intensively studied for cardiac surgery patients. The best-known effect of hypothermia is to decrease cerebral metabolism [148], but it also has been shown to reduce glutamate release [149], to de-

crease calcium influx [150], to lessen the formation of reactive oxygen species [151] and to prevent nitric oxide synthase activity [152]. Taken these effects it is surprising that convincing evidence for the neuroprotective effect of hypothermia employed during cardiac surgery is still missing [153, 154]. In contrast, it is without controversy that hyperthermia demonstrates a harmful effect on cerebral function when it occurs either intraoperatively or postoperatively [64, 155]. Some degrees of hyperthermia during re-warming may therefore explain the missing data about the neuroprotective effect of hypothermia during cardiac surgery. In this context, recent studies have demonstrated that slower re-warming strategies resulted in a better cognitive outcome following cardiac surgery compared to conventional fast re-warming most likely by avoiding peak cerebral temperatures [156].

Several studies have targeted the reduction of emboli load in order to improve postoperative cognitive outcome. In this context Hammon and colleagues showed that avoiding manipulation of the aorta during cardiac surgery can significantly reduce POCD [157] as the aorta represents an origin of injurious embolic load. Next to these solid emboli, gaseous emboli are discussed as contributing factors for postoperative cerebral injury leading to the attempt to flood the surgery field with CO_2 in order to improve resorption of the gaseous bubbles. However, CO_2 insufflation has not shown any benefit on postoperative cognitive function so far, but CO_2 concentration did not reach the anticipated levels in this study [158]. In patients undergoing carotid endarterectomy the risk for cerebral emboli was reduced by preoperative antiplatelet therapy using clopidogrel [159].

Although blood pressure can be easily controlled the optimal target mean arterial pressure during surgery especially in patients at high risk for cerebral injury has still to be defined. It is well accepted that a decrease in blood pressure during carotid endarterectomy should be avoided in order to maintain cerebral perfusion. But, in contrast, postoperative hyperperfusion lasting more than several hours could contribute to the potentially severe complication of cerebral hyperperfusion syndrome [160]. Gold and colleagues compared the impact of blood pressure management during cardiopulmonary bypass on cerebral outcome in 248 patients undergoing cardiac surgery. Combined cardiac and neurologic outcome was significantly better in patients of the high blood pressure group (80-100 mmHg) compared to the low pressure group (50-60 mmHg), although there was no difference in cognitive outcome six months after surgery[161].

Another parameter we are dealing with day-to-day is the hematocrit with the optimal range still being unknown. However, a recent study showed that profound hemodilution (haematocrit of 15 – 18%) during CPB in older patients was associated with a greater neurocognitive decline [162].

Recently, multidisciplinary literature documented the beneficial effect of physical activity on angiogenesis, synaptogenesis and neurogenesis in the brain. In this context, physical activity has been shown to improve cognitive performance in older, mildly cognitive impaired people [163]. Whether this beneficial impact of physical activity can also be used to improve cognitive function after surgery needs to be shown.

6. SUMMARY AND PROSPECTS

The precise mechanisms for POCD are still far from being clearly elucidated. Due to their pharmacological properties, the application of anesthetics *per se* induces acute effects which, on the one hand block LTP, a cellular correlate for learning and memory, and, on the other hand, exerts neuroprotective activities. These *in vitro* characteristics would exhibit a preferable profile of anesthetics: the patient is protected from undesirable memories and possible neurodegeneration, which might be induced during surgery. Unfortunately, as discussed in this review, there is clear evidence that a considerable proportion of people, dependent on risk factors, suffer from cognitive dysfunction described either as anticholinergic syndrome, delirium or POCD after surgery. At this point it should be stressed that the choice of anesthetic most probably does not influence the incidence of POCD and thus rather speaks in favor of a minor role for anesthesia in contributing to the development of cognitive impairment after surgery. Nonetheless, as we have seen, the interpretation of available data on POCD is accompanied by numerous methodological deficits. Overcoming those problems would imply the planning and performance of powerful clinical studies with comparable surgery, standardized neuropsychological tests and defined diagnosis criteria used to classify individuals as having POCD. Concomitantly, the availability of such meaningful data would be useful for the development and application of non-pharmacological and pharmacological neuroprotective strategies.

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