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The Impact of Anesthetics Drugs on Memory and Memory Modulation under General Anesthesia

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Abstract

A significant endpoint of general anesthesia is the loss of memory, indeed a terrible complication of narcosis is the anesthesia awareness (AA), a rare condition that occurs when surgical patients can recall their surroundings or an event related to their surgery while they are under general anesthesia (GA). During GA the amnesia is mostly achieved with general anesthetic drugs (endovenous and inhaled), nevertheless different classes of drugs administered can impact the memory. Starting from a brief description of the recent knowledge on the AA phenomenon, this work focuses on the relationship between GA and memory, the pharmacodynamic mechanisms of amnesia induced by anesthetic drugs, as well as the possibility of memory modulation during GA. Benzodiazepines (BDZs) are a complex class of drugs with significant effects on anterograde memory, however in this paper we also discuss on a their hypothetical effect on retrograde memory, even in anesthetized patients.

Introduction

General anesthesia (GA) is an induced, temporary state with unconsciousness, amnesia, analgesia and paralysis. While analgesia and muscle relaxation are respectively obtained with narcotic and neuromuscular-blocking drugs, general anesthetics are used in order to render the patient unconscious. A significant endpoint of GA is the loss of memory, indeed a terrible complication of GA is the anesthesia awareness (AA), a rare condition that occurs when surgical patients can recall their surroundings or an event related to their surgery while they are under general anesthesia. Starting from a brief description of the recent knowledge on the AA phenomenon this work focuses on the relationship between GA and memory, the mechanisms of amnesia of anesthetic drugs, as well as the possibility of memory modulation during GA.

Memory and anesthesia. The AA phenomenon

The AA is a dangerous and fascinating phenomenon in which there is a strong link between consciousness and memory, that are dissociable cognitive processes, as well as both integrate functions. Thus, the actions of anesthetics to make the patient unconscious and amnesic run on different neuronal paths. Yet, it is well known that the doses of anesthetic required for unconsciousness are higher than the doses required for amnesia [1]. An episode of AA may concern the explicit or the implicit memory. The first is the conscious, intentional recollection of previous experiences and information. In a right anesthesia status with unconsciousness is not possible the working of the conscious recollection of a never happened event. Contrarily, explicit memory can work in case of insufficient depth of hypnosis or in the event of a sudden recovery from the anesthesia, for example because of an accidental interruption of the administration of inhalation or intravenous anesthetics. Much more complicated is the linkage between GA and implicit memory. This latter is a type of memory in which previous experiences aid the performance of a task without conscious awareness of these previous experiences [2]. In other words, this type of memory is completely outside of conscious control and therefore does not necessarily imply that our anesthetized patient opens his eyes or is capable of interacting with the operator. Implicit memory is an example of unconscious memory formation during anesthesia. This subliminal learning during GA is a complex phenomenon involving many neurophysiological factors, yet to be elucidated [3]. However, the mechanism of unconscious memory under GA is very efficient with clinical relevance; indeed Sanders et al. [4]

showed that the incidence of awareness without explicit recall (type of AA in which the implicit memory may not be consciously recalled, but may affect behavior or performance at a later time) is significantly higher than the incidence of awareness with recall. Recently many studies focus on this neurophysiological topic and the anatomical basis of unconscious memory. Although the hippocampus is needed to encode new conscious, however according to Henke [5], it now appears that the hippocampus also participates in processes independent of conscious awareness. Studies in healthy sedated participants suggest that the activation of specific primary cortical regions and even limited reactivity in association cortices can occur in the absence of consciousness [6]. Therefore, cognitive processes can occur in the absence of awareness, arguing for a dissociation of consciousness and many high-level cognitive functions [7]. All these brain structures are targets for drugs that are commonly used during GA.

Mechanisms of amnesia of anesthetic drugs

During GA the amnesia is mostly achieved with general anesthetic drugs, nevertheless different classes of drugs administered can impact the memory, such as benzodiazepines (BZDs). The exact mechanisms whereby intravenous and inhaled anesthetics cause amnesia are still unclear. Perhaps the mechanisms are different depending on the substance. Propofol is one of the most commonly used intravenous drugs employed to induce and maintain GA; it produces anterograde amnesia through a complex mechanism involving an obstacle in the hippocampal memory consolidation. One brain region important in verbal encoding is the left inferior pre-frontal cortex; moreover, according to Veselis et al. [8] low dose of propofol- induced amnesia is not linked to a failure of memory encoding in this cortical area. Yet, as demonstrated by Pryor et colleagues, this anesthetic does not interfere with the amygdalar activation [9]. Thus, a propofol regimen (i.e Target Control infusion) could strengthen the amnesia, nevertheless, it does not completely protect against the memorization of any emotional components perceived during an inadequate anesthesia plan. In other words, in case of a hypothetical event of intraoperative awakening during GA, propofol could interfere with its explicit recall, but not with the implicit consolidation of the emotional components related to the episode [10]. Thiopental and methohexital, are ultra-short-acting barbiturates used to induce and maintain anesthesia. These class of drugs have poor amnesic action. An old fascinating study showed that thiopental has mild memory effects compared with propofol and BZDs [11]. The same considerations can be applied for methohexital, although a clinical study showed no clinically significant differences in amnesia compared with propofol [12]. Administration of etomidate is used for rapid sequence intubation. As Zarnowska and colleagues showed, the amnesic effects of etomidate are mediated by the GABAA receptors that contain the extrasynaptic alpha5 subunit (GABAARs) [13]. This data confirm the results of previous study in which was well demonstrated that GABAARs mediate amnesic but not sedative-hypnotic effects of etomidate [14]. The importance of these studies is the possibility of explain the effects of an anesthetic on different cognitive functions (memory and consciousness) through the interaction with subtype of receptors. Ketamine is a dissociative anesthetic with several pharmacodynamic properties; indeed it can be used to induce anesthesia, sedation, analgesia, and amnesia. The cellular mechanisms for its amnesic proprieties are not clear. Maybe the amnesia is due to the inhibition of α4β2 neuronal nicotinic acetylcholine receptors [15,16], which modulate synaptic release of neurotransmitters in the hippocampus. Recently, some researchers have hypothesized that the glycogen synthase kinase (GSK)3β/β-catenin signaling may play a role in ketamine-induced retrograde amnesia [17]. Inhalational anesthetics of significant clinical interest include volatile anesthetic agents such as isoflurane, sevoflurane and desflurane, as well as certain anesthetic gases, such as nitrous oxide and xenon. This latter is a rare gas belonging to the noble gases of the periodic table with anesthetic properties due the noncompetitive inhibition of N-methyl-D-aspartate receptors [18]. According to Haseneder et al. [19] xenon could have a significant amnesic effect. In a study using murine brain slices they reported inhibition of both glutamate receptors N-methyl-D-aspartate and quisqualate receptors in amygdala neurons. This data suggests, the role of the gas on the modulation of emotional components of memory. Also isoflurane, halothane and nitrous oxide have amnesic proprieties, maybe interfering on the hippocampal θ-rhythm, a synchronized rhythmic oscillation at 4-12 Hz, involved in memory formation [20]. BZDs enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. For these actions these drugs can be used for sedation before [21] or after surgery, as well as to induce and maintain GA. The four benzodiazepines, widely used in clinical anaesthesia, are the agonists midazolam, diazepam and lorazepam and the antagonist flumazenil, this latter used in reversing benzodiazepine-induced sedation [22]. Midazolam is the most commonly prescribed by the anesthesiologists for this use because of its strong sedative actions and fast recovery time, as well as its water solubility, which reduces pain upon injection. The amnestic effects of the BDZs have been extensively studied [23,24]. While lorazepam has particularly marked amnesic properties that may make it more effective when amnesia is the desired effect, however a recent clinical trial showed that lorazepam premedication was associated with modestly prolonged time to extubation and a postoperative cognitive disorders [25]. The pharmacodynamics of the anesthethic-opioid association is even more complex to explain. Although it may seem logical that a low-dose opioid anesthetic regimen would enhance implicit memory, Lequeux et al. [26] demonstrated that there is no difference on implicit or explicit memorization under propofol/remifentanil anesthesia either with a low or a high-dose opioid anesthetic regimen. This is a further proof of our gaps in the knowledge of the complex relationship between anesthesia (and anesthetics drugs), memory and consciousness [27].

Memory modulation during GA

As described above anesthetics have also amnesic proprieties with different effect depending on the class and type of molecule. Starting from this assumption, is it possible a memory modulation under GA, for example in case of sudden awakening due to an error in anesthetics administration? A controversy regards the timing for memorization processes, even during GA, for both subliminal

learning and conscious memory. According to available evidence, a 30-second emergence from the anesthesia is sufficient for consolidation to occur [28]; therefore, 30 seconds could be the time at our disposal to find the necessary countermeasures to correct errors in the technique of anesthesia or to exploit the backward action of the amnesia activity of drugs, such as BZDs [29]. This is a singular practical aspect. Although we have always used BZDs as anxiolytics for the preoperative preparation, however we should assess especially their amnesic effect in order to interrupt the memorization circuit in the suspicion of an unexpected emergence from the anesthesia status [30]. While the use of BZDs has been limited because of the risk of postoperative confusion and cognitive problems, including postoperative delirium (PD), the main challenge is not only finding the appropriate BZDs dose to avoid the risk of AA, but also to prevent the induction of PD. We can only assume that there are a range of doses, whereby the effect on retrograde memory (when this can be demonstrated) occurs at different doses (higher or lower) than those interfering with the anterograde memory. Earlier sleep-laboratory studies on lormetazepam suggested that the amnesic effects depend on the dosage and type of substance [31]. These observations were confirmed by recent experimental studies demonstrating the complex mechanisms that link the areas involved in memory consolidation, including the hippocampus and substructures of the wider medial temporal lobe, and the rapidly working memory of the prefrontal cortex [32]. The capacity of the BZDs to produce amnesia is not only dependent by the substances, because a number of conditions may potentiate their receptorial or functional effects, such as the simultaneous administration of drugs or a history of alcohol abuse. This evidence makes the effect less predictable. Studies of comparisons between the classes of drugs that positively modulate the GABAA receptor have provided evidence that there may be important differences among them in terms of their capacity for causing amnesia; so, the modulation of GABAA receptors through the various allosteric sites is a very complex pharmacodynamic phenomenon [33]. This data is supported by the results of behavioral studies on rats [34], monkeys [35] and humans [36].

BZDs, memory interfering and postoperative cognitive disorders

The effect of BZDs on anterograde memory is well known. Therefore, when we use midazolam as a premedication, we protect the patient (or at least we try!) from the possibility that sensorial data can be consolidated into the long-term memory - explicit or implicit - on the occurrence of intraoperative awakening during general anesthesia, for example in case of selection of inadequate anesthetic dose. Based on pharmacological data, it is safe to assume that we can use midazolam not only prophylactically in premedication, but also rapidly to attempt to prevent consolidation in the event of an unexpected emergence from surgical status during GA. This strategy is based on the capacity of the BZDs of interfering with retrograde amnesia. In truth, this effect has never been exactly demonstrated despite it being sought in several investigations. However, several scientific data do not completely exclude this possibility, justifying their clinical use for that purpose. The main challenge is to not only find the appropriate BZDs dose to avoid the risk of AA, but also to prevent the induction of postoperative cognitive disorders. For example Hardman et al. asserted that the administration of midazolam 5 mg i.v. may reduce postoperative recall [37]. Moreover, although midazolam is a therapeutic choice, it should not be used at an arbitrary dosage. Thus, as directions for further studies it would be of interest to investigate the effects of several midazolam doses on provoked recall during GA, for instance in experimental rat models.

Conclusion

The study of memory during GA is a fascinating interdisciplinary link between pharmacology, cognitive neuroscience, and psychology and behavioral sciences. In this direction, the research on BZDs is not the only significant field of study on this topic, because it is possible to import neurophysiological acquisitions and pharmacological studies, from other fields of research. Thus, the next step is collecting this data to draw studies particularly finalized to investigate on memory modulation during GA, using not only anesthetics or BZDs. For instance, contributions on the effects of drugs and environmental factors on hippocampal function are very significant. Indeed, the possibility on interfering with the storage of long-term memory using specific drug, like tropomyosin receptor kinase B agonist [38] may provide further treatment options to be used in AG. On the other hand, several interesting molecules, like cannabidiol, can impact the non-hippocampal short-term memory [39], while glucocorticoids influence the beta-adrenoceptor (cAMP system) in the basolateral amygdala influencing memory consolidation [40].

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