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Review Article

Anesthesia Awareness: Pharmacological Interventions to Stabilize the Anesthesia Level

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Abstract

Anesthesia awareness is a clinical paradox that can help us in studying both consciousness and memory during general anesthesia. The aim of this brief review is an attempt to analyze the theoretical basis of the explicit and subliminal learning, focusing on the possibility of memory modulation under anesthesia. After this introduction we also report some data about general anesthetics targets, as well as pharmacological interventions that could be used to stabilize the anesthesia level.

Keywords: Anesthesia awareness; Consciousness under general anesthesia; Memory modulation

Introduction

Through the analysis of the memorization process and the relationship between Anesthesia Awareness (AA) and memory, we can assume that the AA is, paradoxically, a model that can help us in studying the consciousness during anesthesia. AA can be defined as a sensory perception with a memorization process during anesthesia. Two items are identified in its genesis: perception, which alone seems to be insufficient, and the memorization of perceived events.

In addition to the explicit and implicit memory, examples of long-term memory, some concepts of sensory memory and primary memory or short-term memory have been identified. According to the Modal Model of Atkinson-Shiffrin also called multi-store model process-any stimulus perceived during anesthesia for a sudden and not identifiable emergence of the anesthetic plan, composes the sensory memory [1].

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This process, however, is completely outside of conscious control and therefore does not necessarily imply that our patient opens his eyes oris capable of interacting with the operator to show us the performance of the first phase of the program.

According to the classic explanation of the AA genesis, the information is transferred from the sensory memory to the short-term memory through the process of attention, a cognitive process that consists in concentrating selectively on one aspect of a context, ignoring the other surrounding elements.

The information in short-term memory is available for a short period of time (usually from 10 to 15 seconds, or sometimes up to a minute) and is destined to disappear forever, unless the engrams are transferred to the next phase of maintenance, the long-term memory.

This step poses a big obstacle to Atkinson's model. While this system provides that consolidation-necessary for establishing long term memory-requires motivation, personal reference, interest and attention, it is well known that transferring of information to long term memory doesn't necessary require the presence of consciousness. Implicit memory (and the phenomenon of the awareness without recall) 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 [2]. However, the mechanism of unconscious memory under GA is very efficient with clinical relevance; indeed Sanders et al., [3] showed that the incidence of awareness without explicit recall 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 [4], 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 [5]. Therefore, cognitive processes can occur in the absence of awareness, arguing for a dissociation of consciousness and many high-level cognitive functions [6]. The serial parallel independent model of Tulving [7] represents a more recent attempt to explain memory processing. It provides dynamic information processing with interactions among different memory systems rather than static classification of different types of memories [2]. In this model there are three memory systems representing the Perceptual Representation System (PRS), the semantic, and the episodic memory. While the information processing is serial, storage of memories is parallel in each system, offering the possibility of an independent recovery. As a consequence, during anesthesia it is possible that any sensation (PRS) would be stored in secondary sensory association cortices in the absence of consciousness or in a specific moment of consciousness fluctuations. The neurophysiological background is the linkage between consciousness and memory. Although dissociable cognitive processes-indeed, the doses of anesthetic required for

unconsciousness are higher than the doses required for amnesia [8] they are both integrate functions. So, their parallel paths may include phases of intersection, involving AA with/without a really episode of consciousness.

Memory Modulation Under Anesthesia

Is it possible a memory modulation under GA? A controversy regards the timing for memorization processes, even during GA. This may involve both subliminal learning and conscious memory. According to available evidence, a 30-second emergence from the anesthesia is sufficient for consolidation to occur [9]; therefore, 30 seconds could be the time at our disposal to find the necessary counter measures to correct errors in the technique of anesthesia or to exploit the backward action of the amnesia activity of Benzodiazepines (BZDs) [10]. This is a singular practical aspect. Although we have always used BZDs as anxiolytics for the preoperative preparation, however we should assess especially their amnesiceffect in order to interrupt the memorization circuit in the suspicion of an unexpected emergence from the anesthesia status [11]. 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 midazolam dose to avoid the risk of AA, but also to prevent the induction of PD. The general anesthetics cause amnesia, and it is one of the core desirable endpoints of GA. Nevertheless, the exact mechanisms for this action are unclear. Propofol produces anterograde amnesia through a complex mechanism involving an obstacle in the hippocampal memory consolidation. However, as demonstrated by Pryor et al., this anesthetic does not interfere with the amygdalar activation [12]. 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 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. 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 [13,14], 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 [15]. 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 [16]. 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., [17] 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 [18].

Pharmacological Interventions to Stabilize the Anesthesia Level

The possibility to stabilize the anesthesia level is closely related to the complex mechanisms of neuromodulation that determine the transition consciousness/unconsciousness during the induction of the GA, and vice versa at the emergence. The interactions between anesthetics and consciousness is a fascinating field of study, so several ligand channels and neuronal pathways are studied as molecular targets to explain the action of the general anesthetics. It is well known that the neurotransmitter-gated ion channel Gamma-aminobutyric acid.

(GABA) type A receptor is responsible for the majority of fast inhibitory neurotransmission in the central nervous system, and intravenous anesthetics (like propofol) act mainly on theses inhibitory pathways [19]. GABAA receptor subunits are subject to the action of different ligands, like kinases, structural proteins, and neurosteroids which are the principal endogenous modulators of GABAA receptors. However, although BZDs are the main chance for enhancing the GABA inhibitory transmission, the risk of postoperative cognitive disorders restricts their use for this proposal. Another ion-inhibitory channel that produces its effects through chloride current is the glycine channel, while Glutamate receptors: N-methyl-D-aspartate (NMDA), α-Amino-3-Hydroxy-5-Methyl-4-isoxazolepropionic Acid (AMPA), and kainate receptors, are responsible fora large portion of excitatory neurotransmission in the mammalian nervous system. While N_2O, xenon, cyclopropane, and ketamine have little or no effect on GABAA receptors, these anesthetics potently inhibit NMDA receptors. Many other receptors mediate the excitatory and inhibitory actions of the anesthetics and they could represent hypothetical targets to stabilize the anesthesia level. For example, potassium channels modulate neuronal excitability, pre- and postsynaptically [20]. They have five subunits (TREK-1, TREK-2, TASK-1, TASK-3, and TRESK) that can homo and heterodimerize. All five subunits can be modulated by halothane, but they are insensitive to clinically relevant concentrations of intravenous anesthetics. Other receptors are sensitive to anesthetics like the Hyperpolarization-activated Cyclic Nucleotide-gated (HCN), a family of channels that gives rise to pacemaker currents with rhythmic or oscillatory activity regulating the dendritic excitability and the neuronal respond to synaptic input. Come into play also voltage-gated Na^+ and Ca^{2+} channels critical to excitability and synaptic transmission. Recently many studies have been conducted on the pharmacology of G-Protein-Coupled Receptor (GPCR) signaling [21]. Metabotropic glutamate receptors carry transmembrane segments similar to other G-protein coupled receptor. These ligand-receptors are other possible targets for anesthetics, because some anesthetics inhibit the functions of Gq-coupled receptors, including muscarinic acetylcholine M1, metabotropic type 5glutamate, 5-hydroxytryptamine 2A, and substance P receptors. John et al., investigated on the Hypotalamichistaminic neuromodulation, and its role in the sleep/awake transition in dogs [22]. They hypothesized that during cataplexy; connectedness is maintained by a tonic histaminergic signaling. It could be another important field of research, because there are many molecules capable of interfering with the histaminergic pathways. There is increasing interest in adrenergic pathways involved in the mechanisms of consciousness and unconsciousness. For these reasons, today the greatest scholars of AA propose the use of adrenergic agonists, such as clonidine, for premedication [3]. One of these drugs is dexmedetomidine: it

produces anti-nociceptive, sedative and hypnotic actions, binding the central α2-Adrenergic Receptors (α2-AdRs). It is very interesting that the activation of spinal α2-AdRs involves anti-nociceptive effects, while α2-AdRs in locus ceruleus mediate sedation. This latter action has suggested to some authors that dexmedetomidine could reduce the drug requirement during a BIS-guided anesthesia [23]. Akeju et al., [24] studied EEG patterns during sedation with dexmedetomidine using spectral and coherence analysis and they found that dexmedetomidine determines a different EEG patterns compared to propofol. This important piece of data proves that the sedation mechanisms interfering with adrenergic pathways are different from those that operate the transition from consciousness to unconsciousness and vice-versa. The practical consideration of this observation is that adrenergic agonists may potentiate the effect of general anesthetic drugs acting on different paths but their isolated use (e.g., for sedation) may expose the patient to the risk of AA [25].

Conclusion

The AA phenomenon, when not results from medical errors, is the consequence of our limitations in both precise knowledge of the anesthesia mechanisms and our inability to accurately assess the level of anesthesia with brain monitoring. Scientific research is enabling the development of new technologies for cerebral monitoring. In this regard, we are witnessing a rapid evolution of the brain monitoring techniques EEG based. However, another route is the clinical and pharmacological research that could provide us new knowledge about the relationship between memory, consciousness, and anesthesia, as well as strengthening our pharmacological equipment.

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