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 anesthesiologist 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 amnesia 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 properties 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)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 properties, maybe interfering on the hippocampal B-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 amnesic 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 anesthetic-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 lorazepam suggested that the amnestic 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].
References

1. Mashour GA, Avidan MS (2015) Intraoperative awareness: controversies and non-controversies. Br J Anaeth 115: i20-i26.

2. Schacter DL (1987) Implicit Memory: History and Current Status. Journal of Experimental Psychology: Learning, Memory, and Cognition 13: 501-518.

3. Veselis RA (2015) Memory formation during anaesthesia: plausibility of a neuropsychological basis. Br J Anaeth 115: i13-i19.

4. Sanders RD, Tononi G, Laureys S, Sleigh JW (2012) Unresponsiveness ≠ unconsciousness. Anesthesiology 116: 946-959.

5. Henke K (2010) A model for memory systems based on processing modes rather than consciousness. Nat Rev Neurosci 11: 523-532.

6. MacDonald AA, Naci L, Mac Donald PA, Owen AM (2015) Anaesthesia and neuroimaging: investigating the neural correlates of unconsciousness. Trends Cogn Sci 19: 100-107.

7. van Gaal S, de Lange FP, Cohen MX (2012) The role of consciousness in cognitive control and decision making. Front Hum Neurosci 6: 121.

8. Veselis RA, Pryor KO, Reinsel RA, Mehta M, Pan H, et al. (2008) Low dose propofol-induced amnesia is not due to a failure of encoding: left inferior prefrontal cortex is still active. Anesthesiology 109: 213-224.

9. Pryor KO, Root JC, Mehta M, Stern E, Pan H, et al. (2015) Effect of propofol on the medial temporal lobe: a functional magnetic resonance imaging study in human subjects. Br J Anaesth 115: i104-i113.

10. Deeprose C, Andrade J, Varma S, Edwards N (2004) Unconscious learning during surgery with propofol anaesthesia. Br J Anaesth 92: 171-177.

11. Veselis RA, Reinsel RA, Feshchenko VA, Wroński M (1997) The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology 87: 749-764.

12. Johns FR, Sandler NA, Buckley MJ, Herlich A (1998) Comparison of propofol and methohexitol continuous infusion techniques for conscious sedation. J Oral Maxillofac Surg 56: 1124-1127.

13. Zarnowska ED, Rodgers FC, Oh I, Rau V, Lor C, et al. (2015) Etomidate conscious sedation. J Oral Maxillofac Surg 56: 1124-1127.

14. Cheng VY, Martin LJ, Elliott EM, Kim JH, Mount HT, et al. (2006) Alpha5GABAA receptors mediate the amnestic but not sedative-hypnotic effects of the general anesthetic etomidate. J Neurosci 26: 3713-3720.

15. Friederich P, Dybek A, Urban BW (2000) Stereospecific interaction of ketamine with nicotinic acetylcholine receptors in human sympathetic ganglion-like SH-SY5Y cells. Anesthesiology 93: 818-824.

16. Forman SA, Chin VA (2008) General Anesthetics and Molecular Mechanisms of Unconsciousness. Int Anesthesiol Clin 46: 43-53.

17. Liu H, Xu GH, Wang K, Cao JL, Gu EW, et al. (2014) Involvement of GSK3β/β-catenin signaling in the impairment effect of ketamine on spatial memory consolidation in rats. Neurobiol Learn Mem 111: 26-34.

18. Jordan BD, Wright EL (2010) Xenon as an anesthetic agent. AANA J 78: 387-392.

19. Haseneder R, Kratzer S, Kochs E, Eckle VS, Ziegglansberger W, et al. (2008) Xenon reduces N-methylD-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated synaptic transmission in the amygdala. Anesthesiology 109: 998-1006.

20. Perouansky M, Rau V, Ford T, Oh SI, Perkins M, et al. (2010) Slowing of the hippocampal θ rhythm correlates with anesthetic-induced amnesia. Anesthesiology 113: 1299-1309.

21. Kim D, Lee S, Pyeon T, Jeong S (2015) Use of triazolam and alprazolam as premedication for general anesthesia. Korean J Anesthesiol 68: 346-351.

22. Olkkola KT, Ahonen J (2008) Midazolam and other benzodiazepines. Handb Exp Pharmacol 335-360.

23. Lister RG (1985) The amnesic action of benzodiazepines in man. Neurosci Biobehav Rev 9: 87-94.

24. Lister RG, Weingartner H, Eckardt MJ, Linnola M (1988) Clinical relevance of effects of benzodiazepines on learning and memory. Psychopharmacol Ser 6: 117-127.

25. Maurice-Szamburski A, Auquier P, Viarre-Oreal V, Cuvillon P, Carles M, et al. (2015) Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. JAMA 313: 916-925.

26. Lequeux PY, Hecquet F, Bredas P (2014) Does anesthetic regimen influence implicit memory during general anesthesia? Anesth Analg 119: 1174-1179.

27. Pryor KO, Root JC (2014) Chasing the shadows of implicit memory under anesthesia. Anesth Analg 119: 1026-1028.

28. Dutton RC, Smith WD, Smith NT (1995) Wakeful response to command indicates Memory potential during emergence from general anesthesia. J Clin Moni 11: 35-40.

29. Semma K, Adachi N, Arai T (2005) Facilitation of serotonergic activity and amnesia in rats caused by intravenous anesthetics. Anesthesiology 102: 616-623.

30. Cascella M (2015) Anesthesia awareness. Can midazolam attenuate or prevent memory consolidation on intraoperative awakening during general anesthesia without increasing the risk of postoperative delirium? Korean J Anesthesiol 68: 200-202.

31. Roehrs T, McLenaghan A, Koshorek G, Zorick F, Roth T (1984) Amnesic effects of lormetazepam. Psychopharmacology 1: 165-172.

32. Fiebig F, Lansner A (2014) Memory consolidation from seconds to weeks: a three-stage neural network model with autonomous reinstatement dynamics. Front Comput Neurosci 8: 64.

33. Gerak LR, Stevenson MW, Winsauer PJ, Moerschbaecher JM (2004) Effects of pregnanolone alone and in combination with other positive GABA(A) modulators on complex behavior in rats. Psychopharmacology (Berl) 173: 195-202.

34. Leonard ST, Gerak LR, Delatte MS, Moerschbaecher JM, Winsauer PJ (2009) Relative potency and effectiveness of flunitrazepam, ethanol, and beta-CCE for disrupting the acquisition and retention of response sequences in rats. Behavioural pharmacology 20: 33-44.

35. Auta J, Faust WB, Lambert P, Guidotti A, Costa E, et al. (1995) Comparison of the effects of full and partial allosteric modulators of GABA(A) receptors on complex behavioral processes in monkeys. Behav Pharmacol 6: 323-332.

36. Bickel WK, Hughes JR, Higgins ST (1990) Human behavioral pharmacology of benzodiazepines: Effects on repeated acquisition and performance of response chains. Drug Development Research 20: 53-65.
37 Hardman JG, Aitkenhead AR (2005) Awareness during anaesthesia. Continuing Education in Anaesthesia, Critical Care & Pain 5: 183-186.

38 Armario A, Sanz-García A, Andero R (2015) How a traumatic stressor impact on spatial memory and the hippocampus: Possible protective effect of a TrkB agonist. Psychoneuroendocrinology 61: 19.

39 Morgan CJ, Schafer G, Freeman TP, Curran HV (2010) Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. Br J Psychiatry 197: 285-290.

40 Roozendaal B, Quirarte GL, McGaugh JL (2002) Glucocorticoids interact with the basolateral amygdala beta-adrenoceptor--cAMP/cAMP/PKA system in influencing memory consolidation. Eur J Neurosci 15: 553-560.