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THEME ISSUE: MECHANISMS OF ANESTHESIA

Inhibition of learning and memory by general anesthetics
Inhibition de l'apprentissage et de la mémoire par les anesthésiques généraux

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Abstract

Purpose *Today's general anesthetics were developed empirically according to their ability to produce memory blockade, analgesia, immobility, and unconsciousness. Thus, a major outstanding question remains: How do anesthetics produce their desirable behavioural end points at the molecular level? Understanding the mechanisms underlying memory blockade is of particular importance, because some patients experience the unexpected recall of events during anesthesia while others experience persistent memory deficits in the postoperative period. This review provides a brief summary of the acute memory-blocking properties of general anesthetics and the neuronal substrates that most likely contribute to memory loss.*

Principal findings *Studies in human volunteers and laboratory animals have shown that the memory-blocking properties of general anesthetics depend on the specific drug, the dose, the type of memory, and the experimental paradigm, as well as the species and age of the experimental subject. The cellular substrates of memory blockade include an increase in neuronal inhibition by γ-aminobutyric acid subtype A receptors, a decrease in excitatory glutamatergic neurotransmission, and alterations in synaptic plasticity.*

Conclusions *Anesthetics target different receptors and brain regions to modify the various forms of memory. In the hippocampus, extrasynaptic γ-aminobutyric acid subtype A receptors may play a particularly important role. Knowledge regarding the molecular basis of memory blockade may help to address memory disorders associated with the anesthetic state.*

Résumé

Objectif *Les anesthésiques généraux actuels ont été mis au point empiriquement en se fondant sur leur capacité à bloquer la mémoire ainsi qu'à provoquer l'analgésie, l'immobilité et l'inconscience. En raison de ce développement empirique, une question cruciale demeure sans réponse: comment les anesthésiques produisent-ils leurs effets désirables sur le comportement au niveau moléculaire? La compréhension des mécanismes sous-jacents au blocage de la mémoire est particulièrement importante, étant donné que certains patients se souviennent de manière imprévue d'événements ayant eu lieu pendant qu'ils étaient sous anesthésie, alors que d'autres souffrent de troubles de mémoire persistants en période postopératoire. Ce compte-rendu présente brièvement les propriétés des anesthésiques généraux sur le blocage aigu de la mémoire ainsi que les substrats neuronaux qui contribuent très probablement à la perte de mémoire.*

Constatations principales *Les études réalisées chez des volontaires humains et des animaux de laboratoire ont montré que les propriétés des anesthésiques généraux sur le blocage de la mémoire sont dépendantes du médicament en question, de sa dose, du type de mémoire, du paradigme*

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expérimental, ainsi que de l'espèce et de l'âge du sujet soumis à l'expérience. Les substrats cellulaires de blocage de la mémoire comprennent une augmentation de l'inhibition neuronale des récepteurs de l'acide γ-amino-butyrique de type A ($GABA_A$), une diminution de la neurotransmission glutamatergique excitatrice, et des modifications de la plasticité synaptique.

Conclusion *Les anesthésiques ciblent différents récepteurs et régions du cerveau pour modifier les diverses formes de mémoire. Dans l'hippocampe, les récepteurs extrasynaptiques de l'acide γ-amino-butyrique de type A pourraient jouer un rôle particulièrement important. Des connaissances concernant la base moléculaire du blocage de la mémoire pourraient nous permettre de mieux comprendre et traiter les troubles de la mémoire associés à l'état d'anesthésie.*

To facilitate an understanding of the memory-blocking properties of anesthetics, we begin with a brief overview of the terms that describe the various forms of memory and their underlying anatomic regions. We then describe the concentration-dependent effects of anesthetics on memory in more detail. Finally, we describe how anesthetics act to modify the function of receptors that regulate the synaptic plasticity in the hippocampus, which is thought to be a molecular substrate for long-term memory.

Learning and memory

Learning is the process of acquiring new information, skills, or thought patterns that either add to or override existing learned items.[1] Memory is the capacity to retain and revive impressions or to recall or recognize experiences.[2] Memory has been characterized as having three distinct temporal stages: encoding, consolidation, and retrieval.[3] Encoding occurs when sensory stimuli are converted into memory and knowledge is acquired. Consolidation of memory occurs when a permanent trace or "engram" is formed and stored through the reorganization of neural circuits. The final stage, retrieval, occurs when information is brought out of storage to be recalled.[3]

The two major forms of memory are explicit (or declarative) memory and implicit (or non-declarative) memory (Fig. 1). Explicit memory is accessible to the conscious state and, thus, can be confirmed as facts and events. In contrast, implicit memory relates to skills and habits that are unavailable in the conscious state yet influence a person's behaviour and mental life.[4,5] Explicit memory has been further subcategorized into episodic memory and semantic memory.[6] Memory for particular

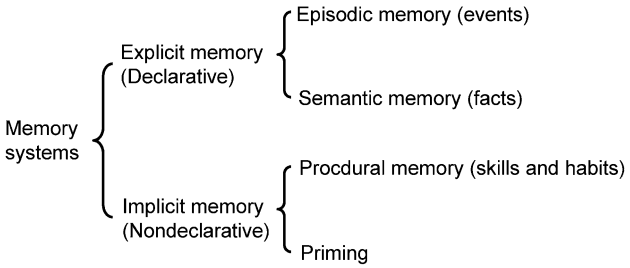

Fig. 1 Taxonomy of memory systems

events, times, and places is called episodic memory, whereas semantic memory includes memory for facts about concepts or meanings that have been acquired over the course of a person's life.

Implicit memory, which occurs in the absence of conscious recognition, has been subdivided into procedural memory and priming.[7,8] Memory for how to do things is called procedural memory. It can be retrieved automatically to assist in the execution of procedures that require both cognitive and motor skills, such as riding a bike or typing. Priming is a change in the ability to identify an item as a result of a previous encounter with that item.[3]

Memories are not formed instantly but rather develop through time-dependent processes that involve multiple neuronal circuits.[9,10] On the basis of the time interval between the learned event and its recall, memory has been further categorized into short-term memory (that occurs in the timeframe of seconds to an hour after the initial stimulus), intermediate memory (60-90 min), and long-term memory (longer than 90 min).[9-11]

Memory blockade has also been categorized as being either anterograde or retrograde.[12] Anterograde memory blockade (or amnesia) is the loss of the ability to create new memories after an event that caused the memory loss. This condition leads to an inability to recall events that occurred after the onset of amnesia, whereas long-term memories for events that occurred before onset remain intact. Retrograde amnesia is the inability to recall events that occurred before the occurrence of the memory-blocking event.

Structures in the medial temporal lobe are particularly important for establishing long-term explicit memory. Specifically, the hippocampal formation and its adjacent cortices are essential for the formation, reorganization, and consolidation of memory during the period after learning.[5,13] These structures also play a role in the storage of memories.[4] The increasing importance of the cortical regions for the storage of memory as time passes after learning has recently been demonstrated.[14-16] Damage to the hippocampus and related structures typically impairs recent memory yet spares remote memory in a temporally graded manner. Recent memories are more likely to be affected, and remote memories are less likely to be

affected.[17-20] In laboratory animals, lesions to the hippocampus, entorhinal cortex, or fornix typically impair memory for material learned up to 30 days before the lesion was introduced.[17] In humans, damage to the hippocampus generally impairs memory for material that was learned a few years before the damage occurred.[20,21]

The expression patterns of several biochemical markers of neural activity support the importance of the cortical regions in long-term memory storage.[22,23] The expression of activity-related genes, such as *c-fos* and *Zif268*, gradually decreased in the hippocampus after learning, whereas there was a parallel increase in gene expression in the cortical regions, such as the prefrontal, frontal, anterior cingulate, retrosplenial, and temporal cortices.[22] Neuroimaging studies using functional magnetic resonance imaging show that gradual changes in neocortical connectivity allow for the establishment of stable long-term memory.[15] As these changes occur, the role of the hippocampus (which initially interacts with the neocortex to support long-term storage of memories) declines. The long-term storage of associative memories is thought to be distributed to the relevant encoding sites of the neocortex.[15]

The cerebellum and the striatum are two of several brain regions that support implicit memory. One of the most studied examples of implicit memory in vertebrates is the classical eyeblink response, which depends on the cerebellum.[24] The eyeblink response is a Pavlovian classical conditioning paradigm where the animal is exposed to an auditory or visual stimulus (the conditioned stimulus) that is subsequently paired with an eyeblink-eliciting unconditioned stimulus, such as a mild puff of air to the cornea.[25,26] After many pairings of the conditioned (tone) and unconditioned stimuli (air puff), a learned eyeblink or conditioned response occurs that precedes the onset of the unconditioned stimulus.[27]

The striatum is also important for the gradual feedback-guided learning that results in the acquisition of habits.[28] Neuroimaging functional magnetic resonance imaging studies of human volunteers showed that the caudate nucleus in the striatum is active when subjects acquire a habit task that can be learned only gradually by trial and error because of its probabilistic structure.[29] Interestingly, patients with lesions of the hippocampus were able to learn gradually by trial and error within a given test session but could not recall the task or instructions from one session to the next.[30] The learning occurred in the absence of any conscious recall at the beginning of each new test session of the previous experience. The striatum-based neural circuits have broad relevance, not only for habit learning but also for species-specific behaviours, such as birdsong learning, and for more extreme forms of acquired repetitive learned behaviours, such as addictive behaviours and neuropsychiatric conditions, including Tourette's syndrome.[31,32]

The midbrain has been strongly implicated in implicit memory. In particular, reward-based learning depends on dopamine neurons in the substantia nigra and ventral tegmental area of the midbrain that project to the striatum and signal information about the value of a reward.[33,34] The learned response to a reward is the strongest when the reward is most unexpected and instructive, and it is absent when the reward is fully predicted. The striatum receives both sensory and motor input from the neocortex as well as reward signals from the midbrain. These inputs may allow the stimuli and responses to become associated and consequently to guide behaviour.

Emotional learning, such as learning associated with fearful stimuli, involves the amygdala. Ablation or deactivation of the amygdala can prevent both the learning and expression of fear.[35-41] In addition, the amygdala modulates fear-related learning in other brain structures, such as the cortex and hippocampus.[42-45] Some types of fear conditioning, including the contextual and trace fear conditioning, also involve the hippocampus.[46-51] Unlike the hippocampus, the amygdala is necessary for the acquisition of fearful memories and their long-term storage and retrieval.[38,52-54]

In summary, explicit memory requires structures in the medial temporal lobe, such as the hippocampal formation and several cortical regions. Implicit memory involves a number of diverse brain regions, including the cerebellum, striatum, and midbrain. The amygdala is necessary for the acquisition of fearful memories as well as their long-term storage and retrieval.

Blockade of memory by general anesthetics in humans and laboratory animals

The memory-blocking properties of general anesthetics have been investigated in some details. Briefly, low concentrations of isoflurane (at about one-fifth of the dose required for immobilization, i.e., 0.2 minimum alveolar concentration [MAC]) suppressed learning and explicit memory of verbal cues in healthy volunteers.[55] Sub-sedative doses of isoflurane (0.3%) and nitrous oxide (20%) also impaired immediate and delayed word recall.[56] Memory for emotional encounters was blocked by sub-anesthetic concentrations of sevoflurane (0.25%), desflurane (1.5-2 times MAC-awake), and propofol (1.5-2 times MAC-awake).[57,58] At MAC-equivalent concentrations, some anesthetics are more effective than others at preventing memory. For example, both isoflurane and nitrous oxide suppressed memory in a dose-dependent manner, although isoflurane was more effective than MAC-equivalent concentrations of nitrous oxide.[59] The intravenous anesthetic, ketamine, administered to human volunteers at sub-anesthetic doses

(0.27 mg kg^{-1} over the first ten minutes then 0.12 mg kg^{-1} over the next 50 min) reduced memory performance for explicit word recall. At low doses, ketamine interfered primarily with early consolidation of memory, reducing the delayed recall of words presented immediately before but not during infusion of the drug.[60]

Different doses of anesthetics have different effects on the time-dependent types of memory. Generally, low doses of anesthetics leave very short-term memory intact, such that patients can carry on a conversation and appear to be lucid. However, long-term memory of events that occurred during the low-dose exposure (such as a conversation) is missing, possibly because memory for the events have not been transferred into intermediate-term memory.[1] A gradual increase in the drug dose produces the progressive impairment of short-term memory until events occurring even one or two seconds earlier cannot be remembered.[61,62] A further increase in the dose of anesthetic is associated with loss of consciousness.[55,63] This deeper state of anesthesia prevents the proper encoding of sensory information, even for short-term memory, presumably because an increase in inhibitory processes blocks sensory transmission.[64,65] General anesthetics generally do not impair long-term memories that have already been consolidated into long-term storage in the cortex.[66,67]

The brain regions involved in memory blockade have been studied using imaging techniques. Functional magnetic resonance imaging studies in human volunteers have shown that sevoflurane (0.25 MAC administered for 25 min) can depress memory-related regions in healthy volunteers, including the visual cortex, thalamus, hippocampus, and supplementary motor area.[68] The primary visual cortex and other cortices with higher-order associations are particularly sensitive to memory-blocking concentrations of anesthetics.[68]

As evidenced by animal studies, the potency for memory blockade differs between different anesthetics. The relative potencies of five inhalational anesthetics (desflurane, sevoflurane, isoflurane, halothane, and nitrous oxide) used most commonly for a classical Pavlovian conditioning paradigm are summarized in Fig. 2.[69] The behavioural assay used to measure and compare anesthetic potency was the inhibitory avoidance task. In this task, rats were trained to remain in a starting "safe" compartment for 100 consecutive seconds by administration of a foot shock (0.3 mA) each time the animals entered an adjacent unsafe or "shock" compartment. The ability to learn to avoid the shock compartment was impaired by relatively low concentrations of sevoflurane (0.3%) and halothane (0.15%) and by higher doses of desflurane (1%). Surprisingly, memory in this paradigm was not impaired by isoflurane at doses up to 0.3% or by nitrous oxide at doses up to 60%.

The potency of anesthetics for memory blockade also depends on the type of learning. Suppression of fear conditioning to tone required approximately twice the dose of isoflurane (half-maximal effective dose or $ED_{50} = 0.47$ MAC) than that required to suppress fear conditioning to context ($ED_{50} = 0.25$ MAC). Thus, relatively higher concentrations of isoflurane (>0.5 MAC) were needed to suppress fear-conditioned learning to both tone and context.[70] The effects of anesthetics on memory are also age-dependent. For example, in a reversal learning paradigm, an animal or a human is trained to respond differentially to two stimuli (e.g., approach and avoidance) under reward and punishment conditions. The subject is then re-conditioned where the reward values are reversed.[71] The isoflurane-sensitive memory deficits for reversal learning became more pronounced as the animals grew older.[72] Finally, in surprising contrast to the results summarized

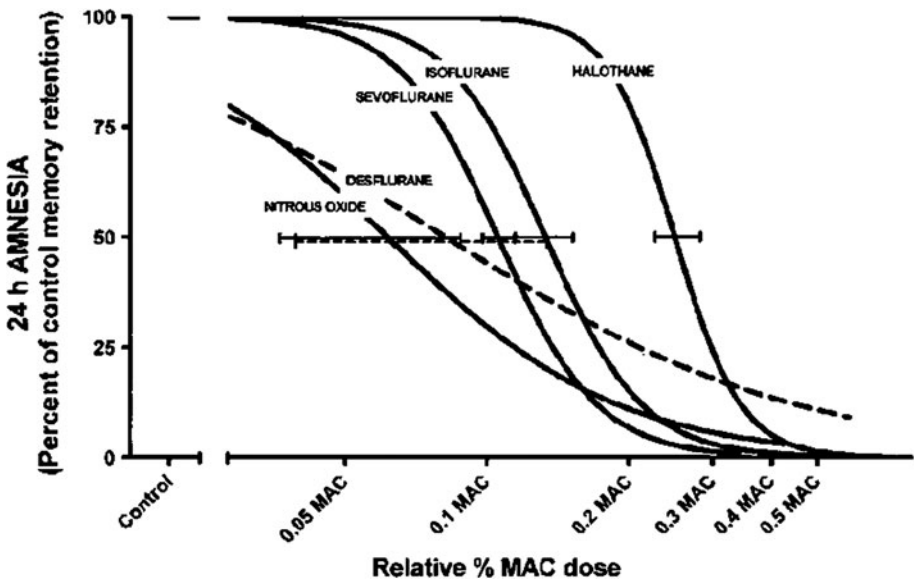

Fig. 2 Dose-response curves for memory impairment with five inhalation anesthetics plotted on a common logarithmic scale of relative minimum alveolar concentration (MAC). Memory retention over 24 hr is most potently suppressed by nitrous oxide and least potently inhibited by halothane. The order of amnestic potency is nitrous oxide > desflurane > sevoflurane > isoflurane > halothane. Reproduced with permission from *Alkire MT, Gorski LA*. Relative amnesic potency of five inhalational anesthetics follows the Meyer-Overton rule. Anesthesiology 2004, 101: 417-29

above, a few studies have suggested that low doses of some anesthetics might actually enhance memory. It was reported that sevoflurane (0.1 MAC, ≥45 min) enhanced aversive memory formation in rats.[73] Interestingly, lesions in the basolateral amygdala significantly reduced the anesthetic-enhanced memory performance in these animals.

Taken together, studies of human volunteers and laboratory animals have shown that the memory-blocking properties of anesthetics depend on the specific drug, the dose administered, and the memory paradigm under consideration.

General anesthetics and the neural substrates of memory

The molecular mechanisms by which some forms of short-term memory are converted to long-term memory in the hippocampus have been the subject of intense investigation.[10,74-76] At the circuit level, explicit short-term memory is thought to result from the strengthening of pre-existing synaptic connections and the covalent modification of pre-existing proteins.[77] Long-term memory requires the synthesis of new proteins and the growth of new synaptic connections[78,79] through processes that depend on specific signalling pathways involving protein kinase A, mitogen-activated protein kinase, and cyclic adenosine monophosphate response element binding protein-1 and -2.[80-82] These protein systems, together with others, induce morphological changes at synapses, such as an increase in synaptic size and spine density, that are thought to stabilize long-term memory.[83,84]

Long-term memory appears to involve a change in the brain at the level of the synapse called synaptic plasticity.[85-89] At the molecular level, several factors are known to contribute to synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse and the response of the postsynaptic neuron to those neurotransmitters.[87,90-93] Long-term potentiation (LTP), one of several phenomena underlying synaptic plasticity, is widely considered to be one of the major cellular mechanisms involved in learning and memory.[86,94] Long-term memory and LTP of synapses share many similar properties, as both are triggered rapidly and depend on the synthesis of new proteins, and they can last for many months.[94-96] Long-term potentiation may account for many types of learning, from the relatively simple classical conditioning that occurs in all animals[97-99] to the more complex higher-level cognition observed in humans.[94,100] The opposite process, long-term depression of synaptic strength, is also necessary and is normally involved in memory storage.[101,102] Both the strengthening and weakening of synapses between neurons are involved in the reshaping of the neural network and the encoding of a novel engram.[103]

Anesthetics modify a wide variety of neurotransmitter systems that influence synaptic plasticity, including the glutamatergic, GABAergic, cholinergic, and serotonergic neurotransmitter systems, among others.[65,104-108] Anesthetics generally reduce or prevent LTP-inducing memory formation and the production of memory-associated proteins primarily by altering the kinetics, conformation, gating, or catalytic properties of neuronal membrane-bound proteins. A strong association has been demonstrated between blockade of LTP by anesthetics and memory impairment.[109-111]

Many anesthetic-sensitive proteins are critical to establish and maintain the synaptic changes that underlie intermediate and long-term memory. These targets include the excitatory glutamate receptors and the inhibitory γ-aminobutyric acid (GABA) receptors.[106-108] Ionotropic glutamate receptor subtypes, including N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and kainate receptors, are involved in fast excitatory synaptic transmission, synaptic plasticity, and higher cognitive functions.[112,113] Inhibitory GABA receptors, specifically the $GABA_A$ receptors, are also well characterized targets for most general anesthetics.[106-108,114] The $GABA_A$ receptor is a ligand-gated ion channel that mediates the inhibitory neurotransmission in the brain. It is a pentameric receptor that selectively conducts anions, particularly chloride ions. The activation of $GABA_A$ receptors generally causes hyperpolarization of the neuron and shunting inhibition,[115-117] which diminishes the chance of a successful firing of action potentials.[118,119]

Different anesthetics preferentially target different neurotransmitter receptors. At clinically relevant concentrations, nitrous oxide, cyclopropane, ketamine, and the noble gas, xenon, potently inhibit NMDA receptors but have little or no effect on $GABA_A$ receptors.[120-122] Unlike $GABA_A$ receptors and NMDA receptors, the AMPA and kainite subtypes of glutamate receptors are not key targets for most general anesthetics,[65,106] although barbiturates inhibit AMPA and kainate receptors.[123-125] Intravenous anesthetics, including etomidate, propofol, and barbiturates, enhance the $GABA_A$ receptor function, and this effect contributes to hypnosis, immobility, and memory blockade.[105,108,111,114,126,127] The halogenated volatile anesthetics (isoflurane, sevoflurane, and desflurane) also enhance $GABA_A$ receptor function, although these drugs appear to be less selective for $GABA_A$ receptors than most intravenous anesthetics.[105,128] Studies using site-directed mutagenesis suggest that $GABA_A$ receptors are not the sole

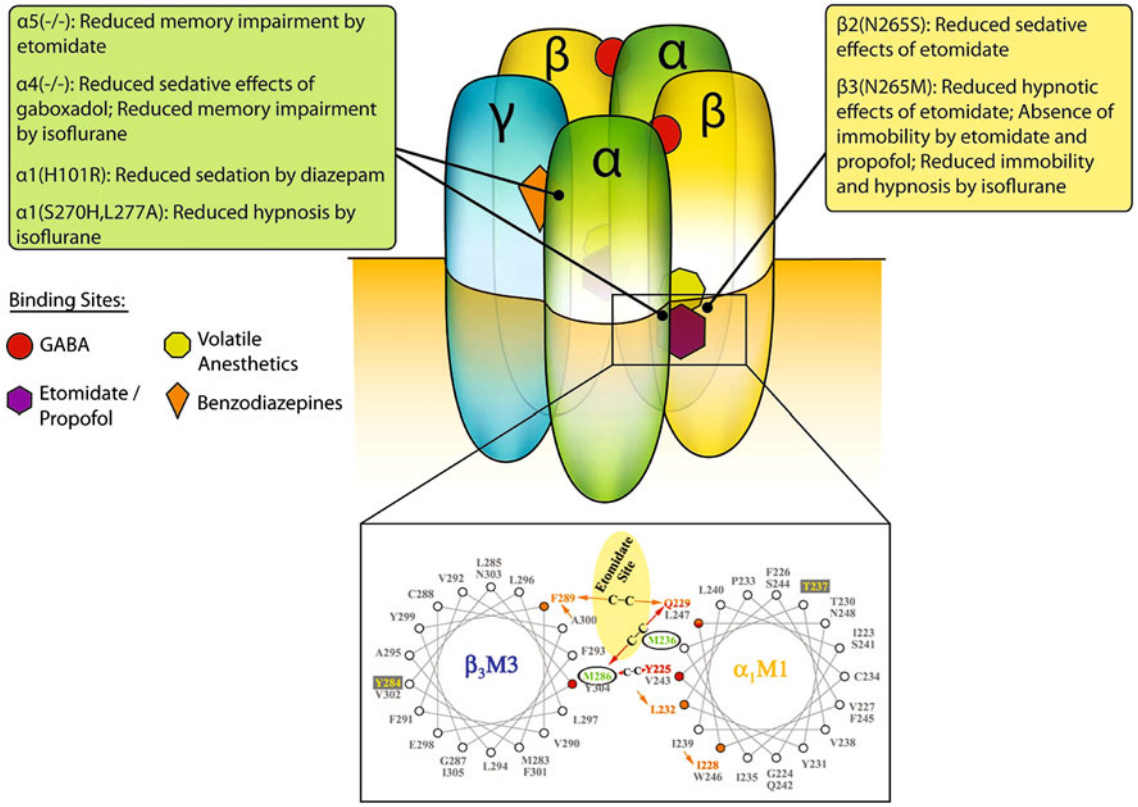

Fig. 3 Anesthetic binding sites on the γ-aminobutyric acid $(GABA)_A$ receptor. The $GABA_A$ receptor is a site of action for many general anesthetics and neurodepressive drugs. The approximate binding sites for several anesthetics on the $GABA_A$ receptor are indicated in the cartoon. Anesthetic action at selective receptor isoforms may produce several of the behavioural end points associated with the anesthetic state, such as amnesia or hypnosis. The evidence for this is provided largely through the genetic deletion of specific $GABA_A$ receptor subunits or through the study of mutant $GABA_A$ receptors that are insensitive to anesthetics. The mutations can reduce or eliminate some behavioural effects of anesthetics, and the effects of these genetic manipulations on anesthetic action are indicated in the boxes. Inset: Etomidate is proposed to interact with a common anesthetic binding pocket at the interface of the $GABA_A$ receptor and β subunits. Image reproduced from *Li GD, Chiara DC, Cohen JB, Olsen RW.* Neurosteroids allosterically modulate binding of the anesthetic etomidate to γ-aminobutyric acid type A receptors. J Biol Chem 2009, 284: 11771-5

mediators of volatile anesthetics.[129] Current data suggest that volatile anesthetics act at several molecular targets, including AMPA[130-132] and kainate[133,134] receptors, to produce the essential neurodepressive effects.

The transmitter-gated ion channel that has gained the most attention as a target for memory blockade is the $GABA_A$ receptor. The $GABA_A$ receptor is a heteropentameric complex composed of five different subunits (Fig. 3). At least 19 mammalian genes encoding different $GABA_A$ receptor subunits and their isoforms (α1-6, β1-3, γ1-3, δ, ε, φ, π, and ρ1-3) have been identified.[135] The most common combination of subunits is α, β, and γ in a ratio of 2:2:1 (Fig. 3). Changes in the subunit composition can dramatically alter the biophysical properties of the receptors and their sensitivity to anesthetics.[136,137] Several components of the anesthetic state, including etomidate-induced sedation, amnesia, and immobility, have been strongly attributed to drug-receptor interactions at specific $GABA_A$ receptor subtypes (Fig. 3). Generally, anesthetics increase the potency of GABA and increase the activation of $GABA_A$ receptors, which usually leads to hyperpolarization of the cell membrane. Representative agents that have been identified as increasing the activity of this inhibitory receptor include propofol, etomidate, benzodiazepines, barbiturates, isoflurane, sevoflurane, and neurosteroids.[114,118,138,139]

$GABA_A$ receptor-mediated inhibition occurs in two types: phasic inhibition, which is mediated by activation of postsynaptic $GABA_A$ receptors after synchronous release of presynaptic neurotransmitters, and tonic inhibition, which is generated by high-affinity slowly desensitizing extrasynaptic $GABA_A$ receptors that are activated by low ambient concentrations of GABA.[140] Phasic inhibition maintains high-fidelity neuronal communication and produces precise timing of action potentials and synchronization of neuronal populations.[141,142]

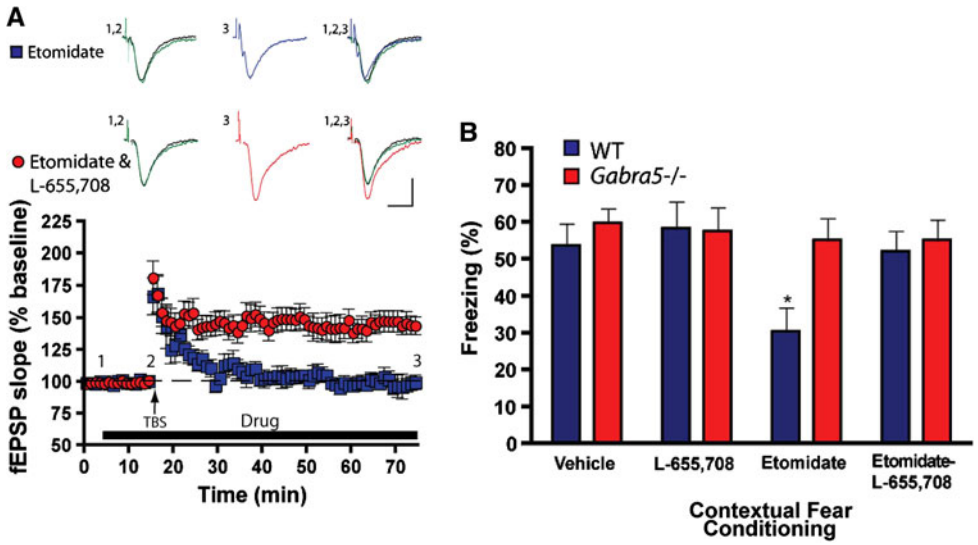

Fig. 4 Etomidate inhibits learning and memory processes through α5 γ-aminobutyric acid $(GABA)_A$ receptors. **A** Inhibition of long-term potentiation (LTP) by etomidate is mediated by α5$GABA_A$ receptors, since L655,708, an inverse agonist of α5$GABA_A$ receptors, reverses the inhibitory effects of etomidate on LTP. **B** Etomidate suppresses contextual fear-conditioning memory in wild-type (WT) mice but not in α5 knock-out mice (*Gabra5−/−*), and this effect can be occluded by L-655,708. fEPSP slope = slope of the rising phase of field excitatory postsynaptic potential. Reproduced with permission from *Martin LJ, Oh GH, Orser BA*. Etomidate targets α5 γ-aminobutyric acid subtype A receptors to regulate synaptic plasticity and memory blockade. Anesthesiology 2009, 111: 1025-35

Enhancement of phasic inhibition was widely thought to be the primary mechanism underlying the actions of many GABAergic drugs. However, extrasynaptic $GABA_A$ receptors have recently gained considerable attention as targets of several anesthetics at memory-blocking doses. In particular, α5 subunit-containing $GABA_A$ receptors (α5$GABA_A$ receptors) are predominantly expressed in the hippocampus where they are critically involved in physiological learning and memory processes.[143] Anesthetics appear to "super-activate" the α5$GABA_A$ receptor and "highjack" the normal memory-regulating physiological functions, thereby causing profound inhibition and memory blockade (Fig. 4A).[111] Correlative *in vivo* behavioural studies showed that low clinically relevant doses of etomidate impaired hippocampal-dependent learning and memory performance in a manner dependent on the presence of α5 subunits (Fig. 4B).[111] Therefore, the activation of extrasynaptic $GABA_A$ receptors by etomidate is thought to inhibit LTP and thereby prevent memory formation (Fig. 5). Equally important, the anxiolysis, loss of righting reflex, and impairment of motor coordination produced by higher doses of etomidate were independent of the α5$GABA_A$ receptors.[126] Thus, the memory-blocking properties were mediated by etomidate modulation of α5$GABA_A$ receptors, but not sedation, anxiolysis, or immobility.

Interestingly, a study from the authors' laboratory showed that anesthetic actions on α5$GABA_A$ receptors might also contribute to persistent memory deficits in the early postanesthetic period.[144] Specifically, memory deficits for fear-conditioned learning were shown to last for up to 48 hr after mice were exposed to isoflurane (1.3%; 1 MAC) for one hour. These memory deficits could be prevented by pre-treating the mice (prior to the administration of isoflurane) with a drug that inhibits the function of α5$GABA_A$ receptors. Together, these findings suggest that activation of α5$GABA_A$ receptors during anesthesia may cause desirable memory blockade but also persistent undesirable memory deficits in the early postoperative period.[144] The role of other populations of extrasynaptic $GABA_A$ receptors in memory blockade, including those containing the α4 and δ subunits, is the topic of ongoing studies.[145-148]

Conclusions

In summary, anesthetics have many targets, and different concentrations and classes of anesthetics have different effects on the various types of memory. In turn, anesthetics are currently being used as powerful probes to gain fundamental insights into the biology and neuronal substrates of memory. Such insights may allow the development of strategies to prevent and treat memory disorders associated with anesthetic states, such as intraoperative awareness[149-151] and memory deficits in the postoperative period.[152-154]

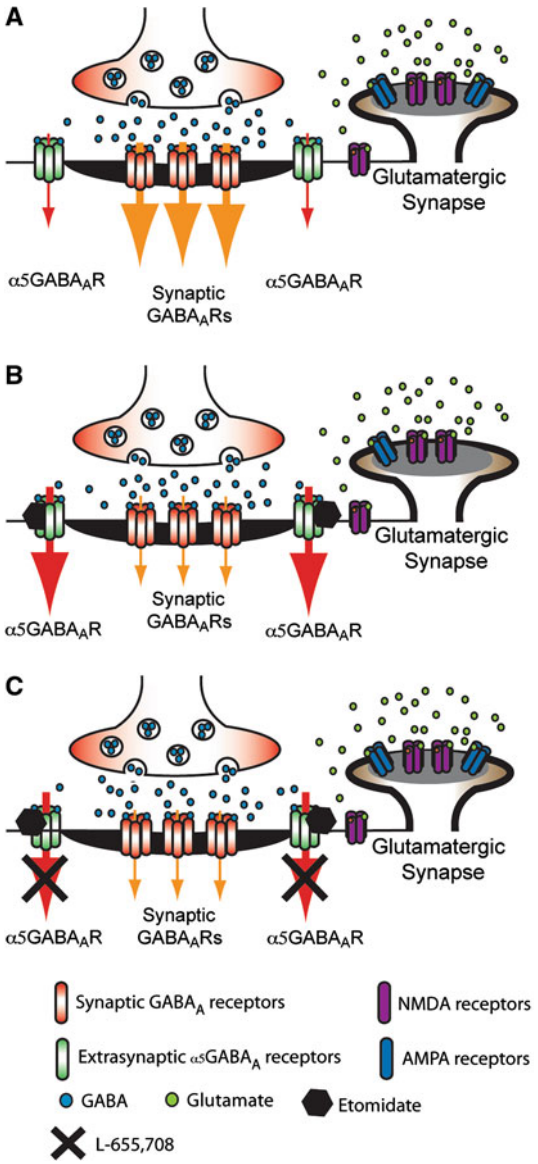

Fig. 5 A model showing that the activation of extrasynaptic α5 γ-aminobutyric acid $(GABA)_A$ receptors by etomidate inhibits long-term potentiation (LTP) and prevents memory formation. **A** Long-term potentiation can be induced after high-frequency stimulation because the excitatory glutamatergic synapses can be preferentially activated more strongly compared with the inhibitory GABAergic ones. **B** Etomidate activates α5$GABA_A$ receptors robustly and eliminates LTP induction due to dramatic increases in the α5$GABA_A$ receptor-associated shunting conductance. **C** L655,708 inhibits α5$GABA_A$ receptor activity and thereby reverses etomidate blockade of LTP. Reproduced with permission from *Martin LJ, Oh GH, Orser BA*. Etomidate targets α5 γ-aminobutyric acid subtype A receptors to regulate synaptic plasticity and memory blockade. Anesthesiology 2009, 111: 1025-35

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Conflicts of interest None declared.

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