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Cerebral mechanisms of general anesthesia☆,☆☆

Effets des agents d'anesthésie

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ABSTRACT

How does general anesthesia (GA) work? Anesthetics are pharmacological agents that target specific central nervous system receptors. Once they bind to their brain receptors, anesthetics modulate remote brain areas and end up interfering with global neuronal networks, leading to a controlled and reversible loss of consciousness. This remarkable manipulation of consciousness allows millions of people every year to undergo surgery safely most of the time. However, despite all the progress that has been made, we still lack a clear and comprehensive insight into the specific neurophysiological mechanisms of GA, from the molecular level to the global brain propagation. During the last decade, the exponential progress in neuroscience and neuro-imaging led to a significant step in the understanding of the neural correlates of consciousness, with direct consequences for clinical anesthesia. Far from shutting down all brain activity, anesthetics lead to a shift in the brain state to a distinct, highly specific and complex state, which is being increasingly characterized by modern neuro-imaging techniques. There are several clinical consequences and challenges that are arising from the current efforts to dissect GA mechanisms: the improvement of anesthetic depth monitoring, the characterization and avoidance of intra-operative awareness and post-anesthesia cognitive disorders, and the development of future generations of anesthetics.

Mots clés :
Anesthésie générale
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RÉSUMÉ

Comment marche l'anesthésie générale (AG)? Les agents anesthésiques sont des molécules pharmacologiques qui ciblent des récepteurs spécifiques du système nerveux central. Une fois liés à leurs récepteurs cérébraux, ils modulent des régions cérébrales diffuses interférant avec les réseaux neuronaux et conduisent à une perte de conscience contrôlée et réversible. Cette manipulation remarquable de la conscience permet chaque année à des millions de personnes d'avoir une intervention chirurgicale en toute sécurité la plupart du temps. Cependant, malgré tous les progrès accomplis, il nous manque encore une vision claire et exhaustive des mécanismes neurophysiologiques spécifiques de l'AG, du niveau moléculaire jusqu'au niveau global cérébral. Au cours de la dernière décennie, les progrès exponentiels en neurosciences et en neuro-imagerie ont conduit à une étape importante dans la compréhension des corrélats neuronaux de la conscience, avec des conséquences directe pour l'anesthésie clinique. Loin d'arrêter l'activité cérébrale complètement, les agents anesthésiques conduisent à un changement de l'état du cerveau, distinct, très spécifique et complexe, qui est de plus en plus caractérisé par des techniques de neuro-imagerie moderne. Il y a plusieurs conséquences cliniques et de nombreux défis qui se découlent des efforts actuels visant à disséquer les mécanismes de

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l'AG : l'amélioration de la surveillance de la profondeur de l'anesthésie, la caractérisation et l'évitement du phénomène de mémorisation et des troubles cognitifs post-anesthésie, le développement des futures générations d'agents anesthésiques.

1. Abbreviations

GA	general anesthesia
GABA	gamma-amino butyric acid
NMDA	N-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
CBF	cerebral blood flow
PET	positron emission tomography
fMRI	functional magnetic resonance imaging
EEG	electroencephalography
ESCoG	subcortical EEG
GNW	Global Neuronal Workspace

2. Introduction

Anesthetic agents are among the most widely used neurotropic drugs. In the central nervous system, anesthetics target specific receptors that are drug-dependent [1]. A reasonable understanding of the pharmacological effects of anesthetics exists today [2], but very little is known regarding the neural mechanisms by which this receptor binding results in sedation and loss of consciousness. General anesthesia (GA) could be defined as a reversible drug-induced state leading to unconsciousness, amnesia, analgesia and immobility along with physiological stability [3]. In the clinical practice, anesthesiologists define loss of consciousness as a loss of the ability for a patient to respond to a verbal request to move, or as failure of the patient to move to a rousing shake. This is a useful clinical definition for detecting a major change in the brain state, but it is limited for the understanding of the neurobiology of consciousness and to precisely monitor subtle changes of consciousness. Modern neuroscience techniques, such as neurophysiology and functional neuro-imaging, allow for the identification of specific brain network dynamics during conscious states, and during GA (see Fig. 1). These valuable tools are changing dramatically our view about the brain activity during GA. Conversely, the use of anesthetic agents gives an excellent opportunity to study consciousness [4], as already suggested in 1947 by Beecher. General anesthetics represent an experimental tool for generating and holding different controlled levels of consciousness with a stable and reproducible temporary manipulation of consciousness that is dose-dependent with slight variations from one subject to another. Thus, there is an increasingly tight, reciprocal and fruitful relationship between the anesthesia and the neuroscience fields. In this review, we describe the current state of the art knowledge about cerebral mechanisms of GA, stressing the fact that this is a very dynamic area of research that continues to yield new findings constantly.

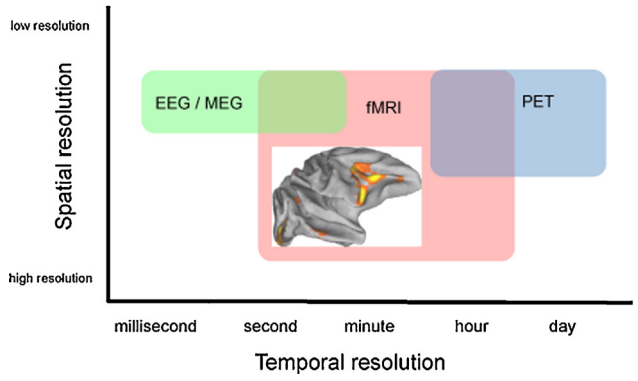

Fig. 1. Comparative diagram of temporal and spatial resolution of modern neuro-imaging techniques: electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET). These techniques allow the identification of specific brain network dynamics during conscious states and during general anesthesia. x-axis: temporal resolution; y-axis: spatial resolution.

3. Consequences of general anesthesia on cerebral blood flow, metabolism and oxygenation

Nearly all anesthetic agents decrease in a dose-dependent manner the global cerebral metabolism, but have variable effects on global cerebral blood flow (CBF) [5]. There are two main classes of anesthetics:

- intravenous anesthetic agents, including the barbiturates (sodium thiopental, methohexital), the carboxylated imidazole derivative (etomidate, propofol), the benzodiazepines (midazolam), the dissociative agent ketamine, the alpha-2-adrenergic receptor agonists (clonidine, dexmedetomidine, medetomidine) and the opiate analgesics (fentanyl);
- volatile anesthetic agents, that are either gases at room temperature (nitrous oxide, xenon) or vapors of volatile liquids (isoflurane, sevoflurane, desflurane).

Intravenous anesthetics are known to reduce CBF, but volatile anesthetics have contradictory reports about their effects on CBF: minimal effects on CBF [6], increase of CBF [7] or even decrease of CBF for sevoflurane [8]. Brain blood oxygenation is reported to be higher under volatile anesthetics then under intravenous anesthetics [9]. Propofol decreases brain metabolism in every region of the brain by 30–70% at loss of consciousness [10]. Global metabolic suppression in each brain region during propofol anesthesia is correlated with the regional densities of the GABA-ergic receptors [11]: brain regions with a higher density of GABA receptors exhibit a higher decrease in regional glucose metabolism. The parietal cortical suppression is associated with a similar cortical suppression in parts of the frontal lobes [8,12]. Propofol decreases global CBF with a large regional decrease in the medial thalamus, the cuneus, the precuneus, the posterior cingulate and orbitofrontal cortex, which are brain regions implicating arousal and performance of associative functions [13]. CBF is more reduced than the cerebral metabolic rate of oxygen ($CMRO_2$), resulting in a decrease of the $CBF/CMRO_2$ ratio under propofol [14]. Midazolam reduces CBF via a decrease in the cerebral metabolic rate of oxygen [15]. Dexmedetomidine decreases CBF, due to direct α_2-receptor cerebral smooth muscle vasoconstriction or/and decrease in the cerebral metabolic rate [16]. Ketamine, a dissociative anesthetic agent, has a heterogeneous effect on cerebral metabolism with an increase in thalamic and limbic system metabolic activity [17] and decrease of glucose metabolism in the somatosensory and auditory

Table 1
Brain receptor targets of anesthetic agents.

Receptor	$GABA_A$	NMDA	Glycine	AMPA	Kainate
Intravenous anesthetics					
Barbiturates	++	/	+	--	--
Midazolam	++	/	++	-	-
Propofol	++	-	++	-	-
Etomidate	++	/	+	/	/
Ketamine	+	--	/	/	/
Volatile anesthetics					
Nitrous oxide	+	--	+	-	--
Isoflurane	++	-	++	--	++
Sevoflurane	++	--	++	--	++
Desflurane	++	--	--	/	--
Xenon	/	--	--	--	--

Adapted from Alkire and colleagues [37].
++: major potentiation; +: minor potentiation; --: major inhibition; -: minor inhibition; /: no effect. $GABA_A$: gamma-amino butyric acid, type A; NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

systems [18]. The mechanisms by which anesthetics cause alterations in cerebral blood flow, volume, metabolism and oxygenation are still poorly understood. Recently, ultra-high field MRI techniques showed promising tools to study cerebral hemodynamic under general anesthesia in vivo in animal models [9,19].

4. Cellular and molecular mechanisms of general anesthesia

Identifying molecular and pharmacological targets of general anesthetics in the central nervous system [1,20] has been crucial for establishing the existence of multiple mechanisms of anesthetic action. The first widely accepted theory of anesthesia was published in 1901 by Meyer and Overton, suggesting that most anesthetics are lipophilic and highly hydrophobic and that the lipid cell membrane of neurons may be an action site of anesthetic agents [21,22]. In 1984, Franks and Lieb showed that anesthetics might not work through a non-specific interaction with lipid membranes of neurons, but inhibit the function of a soluble protein, as a correlation of anesthetic power [23]. General anesthetics interact with specific binding sites within proteins [24] and might work by specific interactions with cellular protein channels, controlling synaptic transmission.

The two most important cerebral targets of anesthetics are gamma-amino butyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors, mainly those distributed in the cortex, thalamus, striatum and brainstem [20,25] (Table 1). These cerebral targets of general anesthetics include enhancement of inhibitory currents mediated by GABA and glycine protein channels, reductions of excitatory currents mediated by glutamate and acetylcholine protein channels, and enhancement of background potassium leak currents [26]. Barbiturates, etomidate, propofol, volatile anesthetics and benzodiazepines target $GABA_A$ receptors [1,27], the main inhibitory receptors in the brain, expressed in nearly one-third of all synapses [28]. Binding of GABA to the receptor causes a conformational change, inducing a channel opening with a flux of anions across the cell membrane, membrane hyperpolarization in neurons and a reduction in the success of an excitatory input in evoking an action potential. Reduction of excitatory neurotransmitter receptors by anesthetics contributes to inactivation of large regions of the brain, thus resulting in a neurodepressive effect of anesthetics [1,26] and unconsciousness [29].

Glutamate, the major excitatory neurotransmitter in the brain, activates two subclasses of receptors: the NMDA receptors and the non-NMDA receptors, split into α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors [30]. The activation of NMDA receptors necessitates binding of glutamate and either glycine or D-serine [31,32]. Depolarization of the membrane relieves the Mg^{2+} block and lets ions flow through the NMDA receptor. As for the $GABA_A$ receptors, the subunit composition of NMDA receptors determines their subcellular distribution, as well as their pharmacological and kinetic properties [30]. Volatile anesthetics, xenon and nitrous oxide act on the NMDA receptors by inhibiting their activity [33–35]: indeed, xenon has a minimal or no effect on the GABA ligand channels. Ketamine inhibits NMDA-mediated glutamatergic inputs with an excitatory activity in the cortex and limbic system, ultimately leading to unconsciousness [36]. In summary, anesthetics induce unconsciousness by changing neurotransmission, mainly of GABA and NMDA receptors, in the cerebral cortex, thalamus and brain stem [37].

5. Neurophysiological mechanisms of general anesthesia

5.1. Functional neuro-imaging to explore general anesthesia mechanisms

What is the cascade of events that follow the binding of an anesthetic agent to its molecular target, and leads ultimately to the remarkable phenomena of loss of consciousness? As shown in the previous paragraph (Table 1), anesthetics have different profiles of receptor affinity, but lead to the same state of loss of consciousness. This is probably due to common mechanisms that go beyond the initial cerebral site of fixation, to modulate remote brain areas, through global neuronal networks. This hypothesis is more and more addressed by neuro-imaging approaches. Neuro-imaging allows the exploration of the brain at the system level, thus allowing the investigation of brain network dynamics. There are different techniques with different temporal and spatial resolutions (Fig. 1):

- positron emission tomography (PET);
- functional magnetic resonance imaging (fMRI);
- magnetoencephalography (MEG);
- electroencephalography (EEG).

There are two fMRI modalities (Fig. 2):

- stimulus-driven fMRI, using stimulation paradigms such as sensory stimuli, behavioral tasks, pharmacological agents;
- resting-state fMRI (rsfMRI), where subjects are scanned without any stimulation to map spontaneous fluctuations of brain activity.

The latter modality is increasingly used in neuroscience to quantify the functional correlation (also termed as "functional connectivity") between distant brain regions. There are also two EEG modalities:

- raw EEG, with identification of classical waves (alpha, beta, gamma, theta, delta);
- event-related potentials (ERPs), where EEG is acquired during a stimulation paradigm (for example auditory stimulation), and repeated to extract specific electrical brain compounds.

5.2. How do anesthetics act on the cortex?

Positron emission tomography (PET) [10], functional magnetic resonance imaging (fMRI) [38], electroencephalography (EEG) [39] and subcortical EEG (ESCoG) recordings [40] give evidence of cortical mechanisms of GA induced unconsciousness.

Most general anesthetics decrease spontaneous neuronal firing in the cerebral cortex [41] and lead to a slowing of cortical oscillatory activity independently of subcortical structures [42]. This effect is for most anesthetic agents GABA-ergic and associated with slow EEG patterns, but ketamine-induced unconsciousness is associated with an active enhancement of high frequency

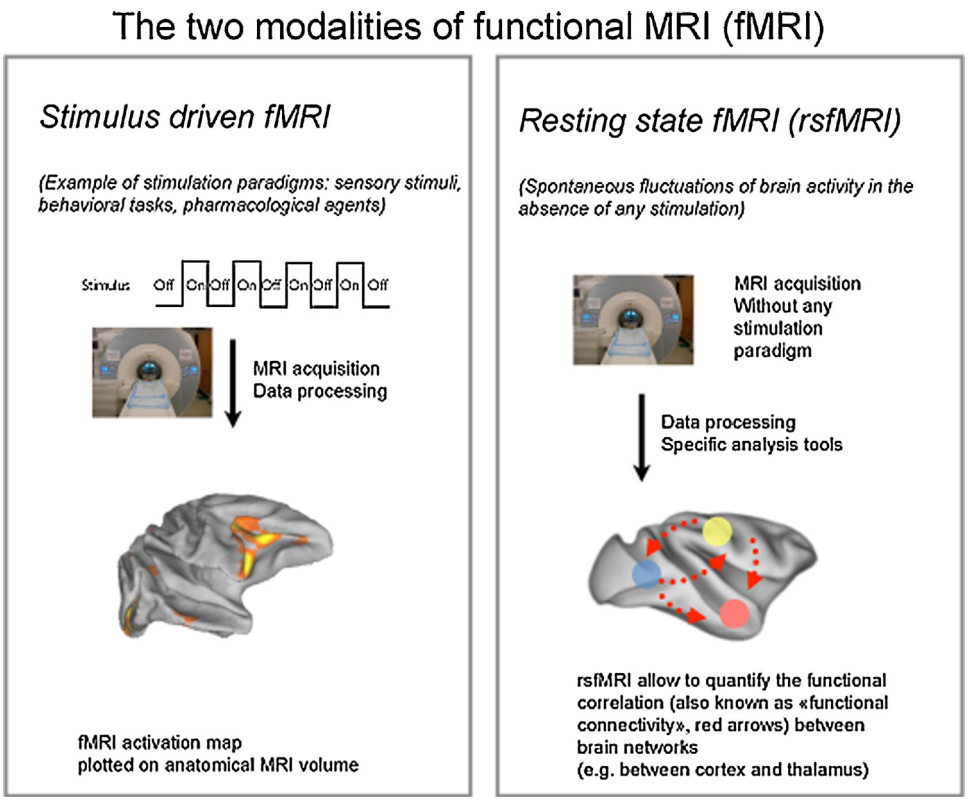

Fig. 2. Two modalities of functional magnetic resonance imaging that could investigate brain neural correlates of consciousness/unconsciousness or loss of consciousness. Stimulus-driven fMRI allows exploring the brain, either with active paradigms, which explore a response to a command, or passive paradigms (auditory, visual, ...). Resting-state fMRI allows exploring spontaneous fluctuations of the brain activity in the absence of any stimulation.

oscillations in EEG [43]. These studies support the idea that anesthetics operate primarily by having an interfering action on the cortex.

The most convincing evidence that, to cause loss of consciousness, anesthetics first shut down the cortex, before affecting subcortical structures (thalamus), comes from a study by Velly et al. [40]. These authors used the unique situation of patients who had surgically implanted electrodes in subcortical nuclei (to treat Parkinson's disease) and who underwent general anesthesia to connect these electrodes into implanted neurostimulator, a procedure called deep brain stimulation. During induction of anesthesia (propofol or sevoflurane), the investigators recorded cortical EEG and ESCoG through the stimulator electrode (electrical contact points close to the thalamus). When loss of consciousness occurred, a clear change in the cortical EEG was observed first and then the thalamus EEG changed approximately 10 minutes later. This observation suggests that anesthetics first "turn off" the cortex before "turning off" the thalamus and localize the loss of consciousness with anesthesia in the cerebral cortex. The data also suggest that the thalamic activity decrease in the brain imaging studies of anesthesia occurs as a consequence of a decreased cortico-thalamic feedback to the thalamus. The effect of general anesthetics on the reactivity of cortical neurons to stimuli is more debated. Neuro-imaging allows exploring the brain, either with active paradigms (exploring a response to a command) or passive paradigms and isolate neural correlates of consciousness or loss of consciousness (Fig. 2). Most of these studies have been performed in animal models. Halothane (2.2%) reduces the sensitivity of striate cortex neurons to stimulus orientation, spatial frequency and contrast in the cat [44]. Cortical neuronal receptive fields are increased by light anesthesia and suppressed at deeper levels in the rat [45] and reliable neuron responses exists in the striate cortex in monkeys at isoflurane concentrations up to 0.9% [46]. Sustained response up to 300 ms in monkey striate cortex neurons are conserved under isoflurane and nitrous oxide anesthesia [46]. In the cat, late components (200–500 ms) of unit response to flash light in visual cortex are more sensitive to anesthesia than the primary response within 100 ms [47]. In rats, halothane (0.75%) reduces the long-latency (300 ms) firing of somatosensory neurons following cutaneous stimulation of the forepaw, while short-latency responses (within 50 ms) show only a small change [48]. Desflurane (2%–8%) keeps visual cortex neurons responsive to flash stimulation [49], but the long-latency (>150 ms) component of their response is attenuated. The early unit response was even amplified at the highest examined anesthetic concentrations (desflurane, 8%–10%) suggesting a neuronal hypersensitivity. The reason for the maintenance of the early cortical neuronal reactivity during anesthesia is unclear. Sensory specificity may increase with depth of anesthesia due to a reduction of associative inputs [50] and feedforward inhibition (GABA-mediated effects are suppressed) [51]. The cortical long-latency response is caused by a non-specific spino-reticulo-thalamic pathways [48]. In awake animals, this long-latency response is present in cells with large receptive fields and decreases with high stimulus frequencies (>2 Hz) and cryogenic blockade of the centromedian thalamic nuclei could abolish long-latency responses [52]. For that reason, the attenuation of the long-latency response of cortical neurons may have been due to a reduced non-specific input, while the specific inputs may have been augmented due to reduced feedforward inhibition.

One could think that general anesthetics work everywhere in the brain, but certain anesthetic agents have specific regional effects. Lateral frontal and parietal association cortices play an important role in conscious perception, attention, working memory and episodic retrieval [53,54] and these regions, together with the posterior cingulate and medial parietal cortex are of interest as potential neural correlates of a "global neuronal

workspace" underlying conscious processing [55,56]. In vegetative patients [57] and during propofol anesthesia [13], fronto-parietal regions are preferentially deactivated. Functional disconnection of the parietal cortex with frontal brain regions is associated with unconsciousness in the persistent vegetative state [58] and restoration of connectivity between parietal and frontal brain regions is associated with return of consciousness [59]. But the role of frontal cortical regions in consciousness remains uncertain [60] and frontal injuries may lead to an akinetic syndrome rather than a loss of consciousness [61]. This fronto-parietal system has an undeniable degree of homology with the "default network" of the brain [62] and the posterior cingulate and medial posterior parietal areas seem to be involved in the generation of the default brain functionality of the brain [63]. The "default network" of the brain is highly active in the unstimulated brain, but exhibits a decrease in activity during goal-directed behavior. Spontaneous activity is still present within the "default" system in states of general anesthesia-induced unconsciousness [64], during sedation [65] and in the vegetative state [66], even so it is reduced under propofol [67] and sevoflurane [68]. These findings suggest that baseline activity in these posterior brain regions is perhaps necessary, but probably not sufficient for conscious processing.

Resting-state activity is the spontaneous fluctuations of brain activity in the absence of any stimulation when the subject is conscious, lying down, with his eyes closed (Fig. 2). Among the most reproducible, resting-state networks figure the medial fronto-parietal default mode network, involved in awareness of self [69], the dorsolateral fronto-parietal executive control network, involved in awareness of the environment [70] and the auditory and visual networks [71]. The default mode network and the executive control network fluctuate with time in an anti-correlated manner [70]. Anesthetics act on these networks leading to a modification of cortico-subcortical interactions and subcortical structures activity. Connectivity in the default mode network and the executive control network is reduced under propofol and the anti-correlation between those networks disappears. Their activity becomes anti-correlated with the thalamic activity [72]. Connectivity in lower order auditory and visual networks is still preserved, including the thalamo-cortical connectivity. The subcortical thalamo-cortical-regularity systems, including the putamen, have an impaired functionality. It was suggested that this is the reason for an altered cortical integration of information [73].

5.3. How do anesthetics act on the thalamus?

A common effect of most agents involves the thalamic metabolism and blood flow and the thalamo-cortical–cortico-thalamic connectivity [74,75]. The thalamus is a relay for ascending and descending information to and from the cortex, transmits information among various regions of the cerebral cortex [76] and is also involved in the selection and modulation of distributed information processing across the cortex [77]. The thalamus is important for arousal regulation [78] and thalamic suppression by anesthetics led to the theory of the "thalamic consciousness switch" of anesthetic-induced unconsciousness [74]. This hypothesis suggests that the suppression of activity by anesthetics in the thalamo-cortical system (thalamo-cortical, thalamo-reticulo-cortical and cortico-thalamic network interactions) could happen through a multitude of anesthetic interactions at various brain sites, which all finally converge to hyperpolarize network neurons in the thalamo-cortical system. Electrophysiological work in animals shows that anesthetics have an ability to affect thalamo-cortical signaling [79].

Anesthesia is classically considered to induce unconsciousness by suppressing the activity of the ascending arousal system [80]. The ascending arousal system modifies the activity of the cerebral cortex via pathways starting in the brainstem and following dorsal and ventral ascending pathways [81]. The dorsal pathway spreads through the intralaminar nuclei (ILN) of the thalamus to the cortex. The ventral pathway, through the subthalamus and hypothalamus, targets the basal forebrain [82]. Intralaminar thalamic nuclei are fundamental to maintain cortical arousal [83]. The intralaminar nuclei of the thalamus project to the cerebral cortex (especially frontal medial and dorsolateral cortex) and the striatum [84]. The main projection of the central medial nucleus of the thalamus is to the medial and basal areas of the cortex. All intralaminar nuclei of the thalamus have input from the cortex.

Anesthetics compromise the firing pattern of the neurons of the thalamic network (i.e., thalamo-cortical, cortico-thalamic and reticulo-thalamic cells) at the cellular level, by hyperpolarizing their resting membrane potentials [85]. This diminishes the high-frequency rhythms characterizing the awake state and the synaptic transmission of sensory information through the thalamus [86]. Isoflurane (>0.8% concentration) suppresses the responsiveness of thalamo-cortical cells during high-frequency (30–100 Hz) somatosensory stimuli, suggesting that the effect of anesthetics on neuronal excitability depends on the stimulus presentation frequency [87]. With high-frequency somatosensory stimuli, the initial response to the onset of the stimulus was present, but the responses to following stimuli were quickly attenuated.

The cellular mechanism through which a thalamic consciousness switch might work is still unknown. Neuronal nicotinic acetylcholine receptors (nAChRs) are a plausible anesthetic target, because they are inhibited by many anesthetics [88]. This suggests that the localized decrease in regional thalamic activity during anesthesia in brain imaging studies might be due to a regionally antagonism of nAChRs and might really be a reflection of a localized direct action of anesthetics on the thalamus and not just a secondary reduction caused by decreased cortico-thalamic activity. Alkire et al., [89] examined the part of thalamic nicotinic mechanisms in unconsciousness induced by inhalational anesthesia (sevoflurane) in rats. Unconscious rats under sevoflurane received micro-infusion of nicotine in the central medial (CM) nucleus of the thalamus. The CM of the thalamus plays a role in arousal and seizure propagation [90] and micro-infusions of GABA agonists in the CM cause a loss of consciousness in rats. Nicotine micro-infusions in the CM led to an awakening of anesthetized rats from GA, even though they were in a chamber filled with sevoflurane at a constant level of MAC [89]. The theory for the thalamic consciousness switch seems to be supported by the nicotine reversal of unconsciousness by this experiment. Alkire et al., [78] also tried to induce unconsciousness with intrathalamic micro-infusions of a nicotinic antagonist (mecamylamine) to induce a loss of consciousness, but mecamylamine did not induce loss of consciousness. This suggests that the intralaminar thalamic nuclei, part of an elaborate network of the arousal system, may act more as a consciousness "on" switch, than as a consciousness "off" switch. The central medial thalamus seems to work in parallel with other arousal centers of the forebrain that control cortico-thalamic interaction and cortical function.

Anesthesia-induced unconsciousness cannot only be explained by cortical deafferentation or a lack of cortical responsiveness. Thalamo-cortical functional disconnection during general anesthesia is supported by human neuro-imaging data [75]. Liu and colleagues [91] showed recently that, at the awake state, thalamo-cortical connectivity is dominantly medial and bilateral frontal and temporal for the specific thalamo-cortical system and medial frontal and medial parietal for the non-specific system. In their study, deep sedation with propofol reduces functional connectivity by 43% in the specific thalamo-cortical system and by 79% in the non-specific thalamo-cortical system. There is

greater reduction of functional connectivity in the non-specific than in the specific thalamo-cortical system and the functional reduction is greater in the left hemisphere then in the right hemisphere. The authors suggest that the changes of functional connectivity in the non-specific thalamo-cortical system may correlate with the loss and return of consciousness.

The decrease in thalamic firing rates at high anesthetic doses is probably due to a decrease in excitatory cortico-thalamic feedback, mediated by glutamatergic and GABA-ergic receptors [92]. The effects of anesthesia on the thalamus may be indirect and determined by actions of the anesthetic agent on the cortex or even other brain areas that project to the thalamus [37,74,92]. This suggests that the switch in thalamic activity is mainly due to a reduction in afferent cortico-thalamic feedback and is not a direct effect of anesthesia on the thalamic neurons themselves.

The conclusion that emerges for anesthetic effects on unconsciousness is a relative decrease in thalamic activity and changes in thalamo-cortical network interactions appear as important component of the neural correlate of unconsciousness. But, recent work show that also basal ganglia also play a significant role in the mechanisms of GA. Resting-state fMRI of the dynamic of cortico-subcortical networks under propofol-induced unresponsiveness is associated with functional disconnections from the striatum rather than the thalamus [73].

5.4. Do anesthetics act on other specific brain areas?

The procedure by which anesthetics cause unconsciousness and suppress arousal involves a complex network of the brain's arousal systems, including not only the cortex and thalamus. The hypothalamic systems may be important for interactions with anesthetic agents. The orexin system has been implicated in stabilizing the brain in either in a consciousness state or sleep state [93]. The tuberomammillary nucleus in the hypothalamus has been implicated in the sedative component of anesthesia mediated by $GABA_A$ receptors [94] and propofol, in part by $GABA_A$-mediated inhibition of release of histamine in the cortex from the tuberomammillary nucleus [94]. The limbic system participates in regulating the effects of anesthetics [95]. Micro-injections of barbiturates into the mesopontine tegmental anesthesia area in the midbrain cause rapid loss of consciousness [96] (again this effect could be due to a cortical effect, as this region containing nuclei that project broadly to the cortex). Because the spatial resolution of neuro-imaging is constantly improving, especially with the development of high- and ultra-high field MRI scanners, other important brain areas/networks for GA mechanisms may also be revealed in the future.

6. Current theories of general anesthesia

Progress in anesthesia research for a better understanding of the neurobiology of consciousness has generated a number of theories about anesthesia [74,97–99] and consciousness [100,101].

6.1. Global depression of the brain function by anesthetics

It was initially thought that the final common mechanism of anesthesia-induced loss of consciousness is due to a global depression of the brain function. This theory is based on the observations of reduced cerebral metabolism by most of the hypnotic anesthetic agents [10,102] and their depressing effect on EEG [103]. Most anesthetic agents induce first an activation (β waves) of the EEG, followed rapidly by a depression of EEG activity [104]. However, ketamine-induced anesthesia shows an increase in brain metabolism [105] associated with a concomitant increase in EEG activity. It therefore seems unlikely that a full characterization of the effects of anesthesia can be obtained by postulating only a regionally specific suppressive effect of anesthetics.

Using modern imaging methods (PET, fMRI, EEG) to study brain function under anesthesia changed conceptions, by showing that anesthetic agents act on different but specific brain regions. Propofol reduces activity in the thalamus, reticular formation, cuneus/precuneus, posterior cingulate cortex, prefrontal cortices and parietal associative cortices in a dose-dependent manner [13,106]. Similar brain regions have a reduced activity under volatile anesthetics [106], barbiturates [12], benzodiazepines [107] and α-2-adrenergic agonists [108]. In return, ketamine increases regional brain activity in the anterior cingulate cortex, the thalamus, the putamen and the frontal cortex [109].

6.2. A "consciousness switch" for anesthetics

One of the hypotheses for the mechanisms of loss of consciousness by anesthetics is the existence of a "consciousness switch". The first candidate for this "consciousness switch" is the thalamus with a change in the thalamo-cortical connectivity by anesthetics (Fig. 3B). Alkire et al. suggested that loss of consciousness induced by general anesthesia could be obtained by a thalamo-cortical hyperpolarization, due to a GABA neurotransmission enhancement and a glutamate and cholinergic neurotransmission inhibition at the stage of thalamo-cortical, cortico-thalamic and reticulo-thalamic loops [74]. A second candidate for the consciousness switch is the precuneus [110], known to pay a major role in conscious processes. But not all anesthetic drugs have the same activation/deactivation pattern in the brain, making the assumption of a single consciousness switch unlikely.

6.3. Anesthetics breaks "functional connectivity" between brain areas

Recently, a new hypothesis emerged: the theory that a change in cerebral connectivity underlies the anesthetic loss of consciousness (Fig. 3B). Task-induced visual [111], auditory [112–114], verbal [115], emotion [116], anticipation to pain [117] and memory [118–120] activation studies gave elements in favor of a network change during anesthesia. For anesthetics enhancing inhibitory neurotransmission, the first site of action seems to be cortical and within higher-level processing networks. They modify connectivity and anti-correlation of the default mode network and executive control network. Connectivity in other higher-order networks, including the emotional and memory networks [120] is also changed. Connectivity is preserved in lower order sensory networks, with an increase of the connectivity in sensory-motor networks. At sub-hypnotic concentrations, thalamo-cortical connectivity persists, but subcortical systems involving the putamen and controlling thalamic activity are decreased. The reticular formation is yet active, and the thalamus is activated by external stimuli. At a deeper stage of sedation, connectivity in higher-order networks is profoundly reduced. Anti-correlation between default mode network and executive control network vanishes. The activity into those networks is then anti-correlated with the activity in the thalamus. But even at a deep level of sedation, connectivity in lower order sensory networks is still existent, but cross-modal sensory interactions are changed.

6.4. Anesthetics fragment neuronal networks at the onset of unconsciousness

How anesthetic agents induce loss of consciousness is still not completely explained today. Lewis et al. [121] investigated neuronal and circuit-level dynamics during propofol-induced loss

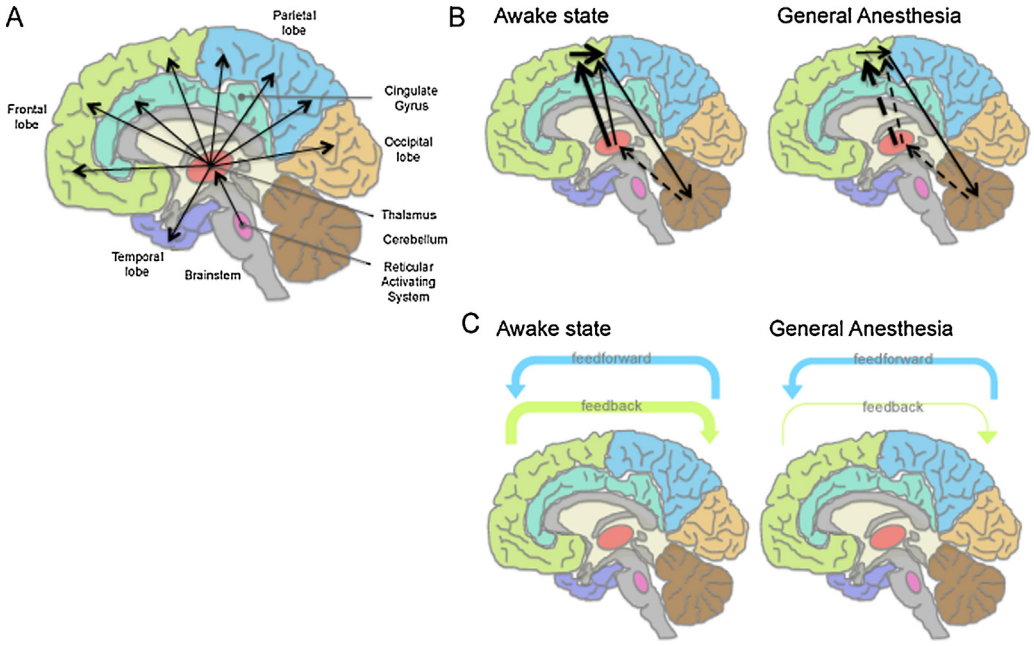

Fig. 3. A. Anatomy of the brain and projections of the reticular activating system and thalamus. B. The hypothesis of the thalamus as a "consciousness switch". Change in the thalamo-cortical and cortico-cortical connectivity between the wake state and GA [75]. C. The hypothesis that feedforward and feedback cortico-cortical projections are dissociated during anesthesia. Feedforward projections (blue) represent incoming sensory information and feedback projections (green) are essential for selection and interpretation of these information. In the awake state, feedback connectivity is dominant. During GA, feedback information exchange in the fronto-parietal (scheme), fronto-occipital, and parieto-occipital directions seems to be significantly reduced, while feedforward connectivity may largely persist.

of consciousness, by using simultaneous recordings of single units, local field potentials and intracranial electrocorticograms in epileptic patients. At the onset of propofol-induced unconsciousness, local and global neuronal network change simultaneously. Slow oscillations (0.1–1 Hz) suddenly appear asynchronously in the local field potential across the cortex, disrupting functional connectivity between cortical areas. These slow oscillations could be generated in the cortex [122], or be the consequence of an interaction between the cortex, thalamus, and thalamic reticular nucleus [123]. They seem to represent a fundamental component of propofol-induced loss of consciousness with fragmentation of neuronal networks and functional isolation of cortical regions [121]. However, significant functional connectivity is still preserved within local networks. Future work, especially in animal models, is needed to prove whether slow oscillations are sufficient to induce unconsciousness and if other anesthetic behave the same way, knowing that their molecular and neural circuit mechanisms could differ from those of propofol.

6.5. Anesthetics disrupt the balance between feedback and feedforward information exchange

Feedforward projections represent incoming sensory information and feedback projections are essential for selection and interpretation of these information. According to the hypothesis considered here, in the conscious state, feedback connectivity is dominant, but during GA, feedback information exchange between anterior and posterior cortical sites (transfer entropy) in the fronto-parietal, fronto-occipital, and parieto-occipital directions would be significantly reduced [124]. Anesthetic effects related with unconsciousness would therefore be due to the preferential reduction in feedback information transfer (Fig. 3C).

Directional connectivity from anterior to posterior brain regions (feedback connectivity) (from multichannel EEG measurements) is indeed diminished during GA with propofol [125], sevoflurane [125] and ketamine [125]. Feedback connectivity increases when patients start to respond to verbal commands. During propofol induction feedforward connectivity decreases, but during GA feedforward connectivity largely persists [126], suggesting that primary sensory systems are preserved under GA.

Propofol reduces fronto-temporal communication and suppresses frontal lobe activity before the temporal lobe activity during a language task when subjects became unresponsive [112].

The reason of the disturbance of cortical feedback by anesthetics is not clear. Depression of synaptic transmission by anesthetics may result in a loss of signaling, such that the more synapses involved, and the greater is overall suppression. Complex information processing, based on high synaptic connectivity, would be the most disturbed. It is also possible that general anesthetics block axonal conduction along unmyelinated fibers [127].

It is possible that the change in cortical information transfer for loss of consciousness happens in the local feedback loops of the posterior parietal cortex, including sensory and association regions, creating a generalized failure of information integration.

6.6. Anesthetics preclude the integration of information

If sensory stimuli are still capable of activating corresponding cortical areas under GA, what makes a difference of data processing between GA and the awake state? Conscious cognition depends on information integration through large regions of the cortex. Tononi and Edelman [128] affirmed that: "Activation and deactivation of distributed neural populations in the thalamo-cortical system are not sufficient bases for conscious experience unless the activity of the neuronal groups involved is integrated rapidly and effectively". Consciousness depends on integration of information within the thalamo-cortical system [129]. PET imaging and fMRI studies show that anesthetics block functional connectivity [75,124]. One hypothesis for anesthesia-induced unconsciousness is that it is due to the failure of the brain to interpret and integrate the sensory information it receives and that anesthetics could cause unconsciousness by preventing the

integration of information in the thalamo-cortical system [37,74,98]. However, this hypothesis requires an additional understanding of how anesthetics affect functional integration across neural systems [130].

Cortical integration requires the cooperation of multiple specific brain regions. Cortico-cortical connectivity is important for integration and may allow elaboration of the cortical representations, essential for giving rise to conscious contents. The brain can be in one of a numerous configurational states at any moment. The recognition of a specific state signifies a decrease of prior uncertainty. For Tononi, consciousness requires a "large repertoire of brain states" (information) and their "availability to the system as a whole" (integration). Consciousness may be suppressed in two main ways: by reducing the repertoire of available brain states (decreasing the amount of information) or by interrupting the communication among the system components (decreasing integration). Either or both of these can occur with anesthetic agents [37]. Anesthesia-induced unconsciousness, as a disconnection of thalamo-cortical connectivity, is supported by a change in effective thalamo-cortical and cortico-cortical connectivity. The thalamus and cortex no longer effectively interact with one another at the point of anesthetic-induced unresponsiveness [75]. Cortical ability for neural information integration, measured by approximations of Tononi's measure (Phi), is significantly reduced by propofol (in the EEG gamma band) [112,131]. Recently a new theory-driven EEG index of the level of consciousness called the perturbational complexity index (PCI) was proposed [132]. This measure is based on a theoretical framework assuming that consciousness requires the integration of information across multiple brain regions. Importantly, PCI is independent of the subject's sensory processing and behavior, since it is calculated after perturbing the cortex with transcranial magnetic stimulation (TMS). PCI could reliably discriminate, in single individuals, wakefulness, sleep, and anesthesia, thus paving the way for its use to monitor anesthesia depth. However, one of the challenges will be to apply TMS in clinical anesthesia routine.

The connectivity analysis also leads attention towards the lateral cerebello-thalamo-cortical system, whose supposed role is in motor control. The cerebellar inputs to the cortex through the thalamus are assumed to represent excitatory influences on motor output regions (M1) after selecting incoming sensory and motor information [133]. Disruption of the cerebello-thalamo-cortical signaling during anesthesia is an interesting discovery that may match with Cotterill's idea that consciousness is a controller of motor output [134].

6.7. Anesthetics act on the Global Neuronal Workspace

The Global Neuronal Workspace (GNW) consists of "a distributed set of cortical neurons characterized by their ability to receive from and send back to homologous neurons in other cortical areas horizontal projections through long-range axons mostly originating from the pyramidal cells of layer 2 and 3" [55]. The global neuronal workspace (GNW) model states that perceptions (e.g. sensory stimuli) become conscious when the information they carry becomes available to multiple brain networks that are made of cortico-cortical long-range axons in prefronto-parieto-temporo-cingulate cortex. Recent data show that bottom-up connections depend on AMPA receptors and feed forward-driven activity is strongly reduced by AMPA receptor antagonists [135]. The top-down connections, which are slower, more numerous and diffuse, primarily involve NDMA receptors. Inputs in higher areas compete with each other via GABA-ergic inhibitory interneurons. The winning representation is transmitted to other cortical regions using additional long-distance connections. There is increasing experimental evidence that the neuronal activity in areas dense in GNW neurons with long-distance connectivity is highly altered by anesthetics [136] and on-going work is exploring the causal relationship between GNW modulation and loss of consciousness during GA [137]. The Velly et al. [40] study could be interpreted that during GA induction, the loss of consciousness is paralleled by a widespread cortical activity disruption, while the delay for thalamic activity disruption is related to the indirect consequences of cortical feedback on the thalamus [37].

7. Conclusion remarks and perspectives

The view of general anesthesia as a "whole brain shutdown" is not supported by experimental findings. Instead, new concepts are emerging to explain the loss of consciousness during GA. They are based on the neuroscience of consciousness and are driven from clinical research, experimental findings and neuroscience modeling. We now have reached a critical point in the neuroscience of consciousness. Theoretical models and neuro-imaging findings have now led to a new theory of consciousness based on objective measurements of brain activity during different states and levels of consciousness. When an anesthetic molecule is delivered to a patient, it binds to its specific cellular membrane receptor and causes dramatic alterations in brain physiology. Anesthetics differ in their specific molecular receptors, in their targeted brain regions, and in their consequences on brain hemodynamic and metabolism. However they all lead to the same striking phenomena, the loss of consciousness. Thus, the dissection of GA mechanisms may seem elusive. However, advanced functional neuro-imaging techniques are beginning to elucidate the striking perturbations of "cross-talks" between distant brain areas caused by anesthetics. All anesthetics seem to ultimately interrupt the integration of information in a broad set of higher-order cortical regions, even though sensory stimuli are still able to activate their corresponding primary brain areas. This opens a complete new field for neuro-anesthesia research. Because it is challenging to perform these advanced functional imaging techniques in the clinical framework [138], the development of these techniques in animal models, especially non-human primate models, is of great importance for the field [137]. Finally, there are several clinical consequences and challenges that arise from the current efforts to dissect GA mechanisms: the improvement of anesthetic depth monitoring, the characterization and avoidance of intra-operative "awareness" and post-anesthesia cognitive disorders, and the development of future generations of anesthetics.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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