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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 :
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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.

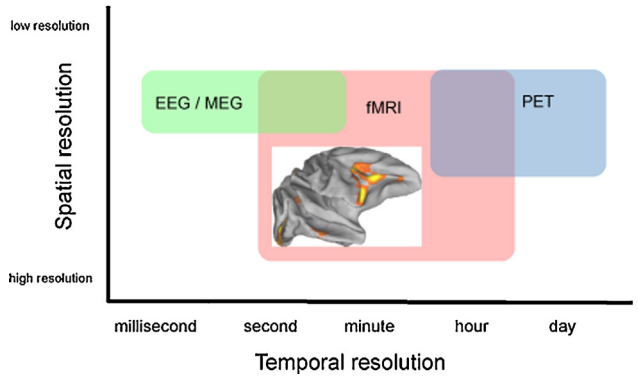

Fig. 1. Comparative diagram of temporal and spatial resolution of modern neuro-imaging techniques: electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET). These techniques allow the identification of specific brain 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