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Towards a better understanding of anesthesia emergence mechanisms: Research and clinical implications

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Abstract

Emergence from anesthesia (AE) is the ending stage of anesthesia featuring the transition from unconsciousness to complete wakefulness and recovery of consciousness (RoC). A wide range of undesirable complications, including coughing, respiratory/cardiovascular events, and mental status changes such as emergence delirium, and delayed RoC, may occur during this critical phase. In general anesthesia processes, induction and AE represent a neurobiological example of "hysteresis". Indeed, AE mechanisms should not be simply considered as reverse events of those occurring in the induction phase. Anesthesia-induced loss of consciousness (LoC) and AE until RoC are quite distinct phenomena with, in part, a distinct neurobiology. Although anaesthetics produce LoC mostly by affecting cortical connectivity, arousal processes at the end of anesthesia are triggered by structures deep in the brain, rather than being induced within the neocortex. This work aimed to provide an overview on AE processes research, in terms of mechanisms, and EEG findings. Because most of the research in this field concerns preclinical investigations, translational suggestions and research perspectives are proposed. However, little is known about the relationship between AE neurobiology, and potential complications occurring during the emergence, and after the RoC. Thus, another scope of this review is to underline why a better understanding of AE mechanisms could have significant clinical implications, such as improving the patients' quality of recovery, and avoiding early and late postoperative complications.

Key words: Delirium; Anesthesia; Isoflurane; Propofol; Consciousness; Awareness; Electroencephalography

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Core tip: Emergence from general anesthesia is not simply the reverse process of induction. The exhaustive knowledge of its complex neurobiological mechanisms is mandatory for avoiding or limiting a large number of anesthesia complications including altered mental status, and emergency awareness. Moreover, in a fascinating translational perspective, the study on this topic could provide new insights into the processes involved in cortical arousal, offering significant data to the research on brain arousal. On the other hand, research on the sleep-wake regulatory network, and on alterations in arousal processes could provide interesting suggestions for the general anesthesia research.

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INTRODUCTION

Emergence from anesthesia (AE) is the ending stage of anesthesia featuring the transition from unconsciousness to complete wakefulness and recovery of consciousness (RoC)^[1]. Although smooth and safe emergence is a primary target of anesthesia, during this critical phase a wide range of undesirable complications may occur. These AE complications include coughing, which may induce an increase in intracranial and intraocular pressures, respiratory events (e.g., laryngospasm) resulting in oxygenation problems, hypertension, and tachycardia as well as mental status changes such as emergence delirium (ED)^[2], and delayed RoC (i.e., hypoactive emergence)^[3].

From a neurobiological perspective, AE and RoC processes should not be simply considered as reverse events occurring in the induction of anesthesia. In mathematical terms, this non-linear system between induction and AE mechanisms represents a fascinating neurobiological example of "hysteresis"; thus, anesthesia can be ideally compared as a travel with a forward way (induction) which differs from that of the return (emergence). Recently, several research groups have demonstrated that the anesthetics-induced transition from wakeful state to loss of consciousness (LoC), and vice versa the RoC phase are subjected to the control of distinct neural circuits^[4,5].

The aim of this work is to provide a comprehensive review of the literature, for assessing the state of the art in research on AE processes. Because most of the research in the field concerns preclinical investigations, translational suggestions and research perspectives

are proposed. However, little is known about the relationship between AE neurobiology and AE potential complications. Thus, another scope of this review is to underline why a better understanding of AE mechanisms could have significant clinical implications, including an improvement of the patients' quality of recovery, and avoiding early and late postoperative complications.

NEUROBIOLOGY OF EMERGENCE

Mechanisms of emergence

Explanation of these mechanisms presupposes the knowledge of the action mechanisms of anesthetics, namely the neural correlates of anesthetics-induced unconsciousness. Although it does not represent the primary goal of this work, here we will try to underline the most recent pieces of evidence on the topic^[6-9]. This extremely complex matter can be simplified by assuming that anesthetics interfere with cortical and subcortical signals, inducing, in turn, changes in the functional/effective connectivity across brain regions. During general anesthesia, alterations in functional and effective connectivity from different brain regions (e.g., from frontal to parietal regions) have been widely demonstrated^[9]. For instance, inhalation anesthetic agents impair frontal-posterior interactions by interfering with the gamma (20-60 Hz) oscillations which have a key role in arousal and maintenance of consciousness^[10]. High-density electroencephalography (hd-EEG) demonstrated that propofol-induced LoC is characterized by an increase in frontal delta power as the result of cortical propagation of processes starting from subcortical regions (e.g., lateral sulci and cingulate gyrus)^[11]. In turn, these slow-delta oscillations propagate asynchronously across the cortex, inducing a functional disruption of the connectivity between distinct cortical areas. Moreover, by using a combination of positron emission tomography and functional magnetic resonance imaging (PET/MRI), Akeju *et al.*^[12] demonstrated that the main effect of dexmedetomidine-induced LoC was the impairment of the thalamo-cortical functional connectivity.

Connectivity changes within distinct brain regions lead to different depths of anesthesia (DoA). Thus, loss of communication between the thalamus and the cortex is responsible for the beginning of LoC. Subsequently, changes in the cortico-cortical functional connectivity, and in the functioning of several brainstem nuclei (e.g., the ventrolateral preoptic nucleus) as well as in the connectivity between these structures and cerebral cortex are responsible for completing the induction process and, in turn, for maintaining the surgical anesthesia status. During the AE period, mechanisms responsible for LoC and anesthesia maintenance are gradually reversed, whereas other specific awakening mechanisms are activated. These mechanisms encompass several ascending arousal brain pathways

responsible for the activation and promotion of the emergence until the RoC. Among the arousal-promoting brain regions involved in the active AE processes, the thalamus has a key role^[13]. Alkire *et al.*^[14] proved in rats that midline intrathalamic microinfusion of nicotine reversed sevoflurane-induced loss of righting reflex (LORR), an indicative sign of unconsciousness in rodents. Other preclinical investigations, focusing on voltage-gated potassium channels, were performed to assess the role of thalamic central medial nucleus for AE induction^[15,16]. However, the thalamic systems are not the sole pathways involved in active AE. Investigations on the dopaminergic (DA) projections from the substantia nigra (SN) and ventral tegmental area (VTA) of the midbrain to the pedunculopontine, thalamus, dorsal raphe, locus ceruleus (LC), and laterodorsal tegmental areas, basal forebrain (BF), and lateral hypothalamus^[17,18] suggested the existence of a mesencephalic arousal pathway. It has been shown in animals that the intravenous administration of methylphenidate, or dextroamphetamine which increases the dopaminergic and adrenergic neurotransmission through the reuptake inhibition or the use of a D1 receptor agonist (chloro-APB) restores LORR and increases theta oscillations (decreasing delta- and alpha-power) during inhaled^[19,20] or endovenous anesthesia^[21]. Furthermore, Taylor *et al.*^[22] obtained the same results through a selective stimulation of the VTA dopaminergic neurons, whereas the administration of a D1 antagonist (SCH-23390) attenuated the arousal response. Thus, they called this active transition from the anesthetized state to the awake state "reanimation from general anesthesia"^[22].

The hypothalamus is another brain structure involved in the AE mechanisms. The orexinergic neurons are localized in a hypothalamic area around the fiber bundle of fornix. This orexin system (OS) plays a key role in induction of sleep-to-wake transitions, and maintenance of wakefulness^[23]. A series of studies proved that it facilitated AE in both intravenous^[24], and inhaled general anesthesia^[25]. More recently, Zhang *et al.*^[26] demonstrated in rats that isoflurane depressed the excitability of orexinergic neurons. Although both orexins (*i.e.*, orexin-A, OXA, and orexin-B, OXB) promoted emergence, OXA played a more significant role (through orexin receptor-1).

Functionally, the OS is related to the locus coeruleus norepinephrine system (LC NE), and the posterior hypothalamic histaminergic tuberomammillary nuclei (TMN HA)^[27] which are well-known wake-promoting cell groups of the sleep-wake regulatory network^[28], and implicated in the action mechanisms of inhaled anesthesia^[29]. In particular, LCNE is functionally connected to the posterior cingulate cortex (PCC), thalamus, and basal ganglia forming the LCNE arousal system, which has been suggested to have an important role in the AE^[30]. Orexinergic projections to the hippocampus, and basal ganglia have been also demonstrated^[31].

In this complex scenario, there is a functional connection between OS, BF cholinergic structures (*i.e.*, medial septum, vertical limbs of the diagonal band of Broca, nucleus basalis of Meynert, and substantial innominate), and the brainstem ascending reticular arousal system (ARAS). Indeed, the BF has diffuse projections to all parts of the neocortex, basolateral amygdala, and hippocampus, whereas the ARAS has cholinergic cortical projections, and connection with the thalamus, hypothalamus, and the BF region, which in turn modulate the OS (feedback mechanism). The OS contributes to arousal processing by increasing cortical activity due to excitatory projections to wake-promoting cell groups in the posterior hypothalamus, BF, and brainstem. On the other hand, orexin neurons are controlled by positive and negative feedback mechanisms mainly mediated by the hypothalamus and other areas (*e.g.*, perifornical area)^[32] and more details on orexin pathways could be found in literature^[33]. Taken together, these data suggest that arousal processes at the end of anesthesia are triggered by structures deep in the brain, rather than being induced within the neocortex.

Electrical activity during recovery from anesthesia

The brain's response to anesthetics recorded with scalp electroencephalogram (EEG) represents the cortical synaptic activity of both excitatory and inhibitory post-synaptic potentials from cortical or thalamic neurons^[34]. Apart from this non-invasive EEG modality used in human studies, other approaches such as the electrocorticogram (ECoG, EEG measured directly from the cortical surface), stereoelectroencephalography (SEEG), an EEG performed via depth probes, are used in specific clinical settings (*e.g.*, SEEG in epilepsy) or for experimental investigations in animals. Moreover, neurophysiological changes in the brain under general anesthesia are often studied through a combination of EEG (including hd-EEG methods) with brain activity measures such as functional near-infrared spectroscopy (fNIRS)^[35], and neuroimaging modalities, (*e.g.*, functional magnetic resonance imaging, fMRI)^[36], or by combining EEG with electrodiagnostic methods, including electromyography and evoked potentials (EP)^[37].

Studies on EEG activity during anesthesia induced a significant impetus to research aimed at elucidating the dynamics of anesthesia. Again, technological advances, and mathematical approaches, allowed to apply several brain monitoring devices which are commonly used in clinical practice. However, explanation of features and clinical utility of DoA monitoring systems is not the scope of this review^[38].

Anesthesia-related electrical activity consists of a wide range of EEG patterns, mainly depending on the anesthesia phase (induction, maintenance and emergence), the DoA status, and the type of anesthetics used. Before induction, the awake subject with eyes closed shows a prominent alpha activity (10 Hz) which

is maximal over parieto-occipital scalp locations. After inducing anesthesia, EEG pattern shows an increase in beta activity (13-25 Hz) until the LoC^[39], whereas during the maintenance phase, different EEG patterns are observed, depending on the DoA level. During a light anesthesia, a decrease in EEG beta band (13-30 Hz) and an increase in both EEG alpha (8-12 Hz) and delta activities (0-4 Hz) may occur. As the DoA state becomes deeper, beta activity decreases, and there is an increase in delta and in alpha frequency band oscillations, with the latter being anteriorly located ("alpha anteriorization")^[40]. A further DoA status features an EEG pattern comprising flat periods interspersed with periods of alpha and beta activity. This characteristic EEG pattern, is known as *burst suppression*. It can be also recognized in deeper coma status due to various conditions including cerebral anoxia, cancers, drug intoxications, encephalopathies, or hypothermia^[41]. The anesthesia-induced burst suppression seems to be associated with a state of cortical hyperexcitability generated by decreased inhibition^[42].

As the anesthesia state deepens, EEG shows a progressive stretching between the alpha activities. The amplitudes of the alpha and beta activities progressively decrease, and in turn, the EEG assumes isoelectric form. In this context, the deepest DoA status has been reached^[43]. As to the correlation between EEG findings and different anesthetic agents, previous studies showed that this general scheme is particularly applicable for halogenated inhalational anesthetics, and propofol whereas, in contrast, opioids and ketamine usually induce less marked EEG changes. Furthermore, etomidate and barbiturates lead to a rapid shift toward the high voltage delta and theta frequencies^[44].

Classically, during emergence it is possible to observe a loss of delta activity, combined with a progressive decrease in frontal alpha power and increased higher frequencies^[45]. Moreover, ECoG studies showed that specific findings (*i.e.*, slow oscillation in large-scale functional networks) are maintained during the LoC and RoC phases^[46]. However, the canonical EEG sequence during AE can undergo changes. In a fascinating clinical study, Chander *et al.*^[47] described different AE patterns. At the beginning of AE, they recognized a pattern characterized by high power of alpha and beta bands (in 95% patients) and termed it as "Slow-Wave Anesthesia" (SWA). The minority of patients had an EEG with a very low spindle and delta power (called "Non Slow-Wave Anesthesia", NSWA). Interestingly, they also found that EEG patterns between start of emergence and RoC vary, and described four trajectories between the beginning of AE and the RoC. More recently, Liang *et al.*^[48] classified emergence EEG patterns in sevoflurane anesthesia. Using an integrated approach obtained by a multivariate statistical model, they identified four types of emergence EEG patterns. Interestingly, some of these emergence modalities were age-related and could be associated with postoperative mental changes.

It can be assumed that the occurrence of different EEG patterns at the emergence reflects the different degrees of influence of brainstem activity on cortical re-connectivity, through the thalamus mediation^[13]. This evidence could prove that AE modulation can be mostly obtained by controlling brainstem activity (*e.g.*, by opioids). Although we adopted a general descriptive scheme (*i.e.*, anesthesia-induced EEG changes at the emergence), it is important to underline that because of the distinct mechanisms of action, different anesthetics may induce different types of EEG dynamics, also in the AE phase. Recent studies are increasingly characterizing these profiles^[49], especially with regard to dexmedetomidine^[50].

CLINICAL IMPLICATIONS

A better understanding of AE mechanisms has significant clinical implications, such as improving the quality of recovery of patients following surgery. It has been proved that the EEG modality at the emergence affected the residual level of sedation and post-operative pain^[47]. Thus, in a hypothetical scenario, it could be possible to modulate the path of emergence, choosing the one which correlates with the desired target. The possibility to increase the predictability of the time of emergence may help prevent delayed emergence - defined as the failure to regain consciousness 30-60 min after general anesthesia^[51] - and other more frequent AE complications, such as ED, and respiratory complications. This is a significant issue as delayed emergence was associated with a longer postoperative hospital stay^[52], whereas ED in children may lead to physical harm in the children and distress in patients, parents and staff. Moreover, although usually self-limiting, it can last up to 48 h, and children who manifested ED are more likely to suffer from new-onset postoperative maladaptive behavioral changes^[53]. Again, ED in adults can lead to serious complications, such as self-extubation, accidental removal of catheters and injury^[54].

Although about 20% of accidental awareness with recall during general anesthesia (AAWR) occur at the AE, and 90% of these cases are potentially preventable (*e.g.*, through the use of neuromuscular monitoring)^[55], in very rare AAWR cases there is no readily identifiable cause^[56]. A more precise AE management can help avoid these unexpected awakening events, which are often associated with severe psychological consequences, such as post-traumatic stress disorder (PTSD).

TRANSLATIONAL DATA AND RESEARCH PERSPECTIVES

Positive results from preclinical and clinical studies on this topic should encourage additional research (Table 1). For instance, clinical investigations should translate preclinical findings to evaluate possible interventions for inducing active AE, and in turn for

Table 1 Suggestions for additional research on emergence from anesthesia

Type of study	Topic(s)
Multicenter RCTs	Effects of drugs on AE time, features, and postoperative complications including mental status changes
Multicenter RCTs	Effects of antinociceptive interventions (<i>e.g.</i> , neuraxial anesthesia) on accelerating emergence and improving patient outcomes
Animal research (molecular/behavioral research)	Effects of AE modulation on molecular targets of neuroinflammation
Animal research (behavioral research)	Effects of AE modulation on early postoperative behavioral changes
Animal research (molecular/imaging/behavioral research)	Anesthetics mechanisms; Linkage between brain areas involved in cognitive functioning and AE features
Animal research/in humans	Neurophysiological changes under general anesthesia (<i>e.g.</i> , by combining EEG approaches with electrodiagnostic methods, including EMG and EPs, or with brain activity measures such as fNIRS, and neuroimaging modalities like fMRI)
<i>In vitro/In vivo</i> (<i>e.g.</i> , mutant analysis in <i>Drosophila</i>)	Anesthetic mechanisms (<i>e.g.</i> , genes encoding for second-messengers, memory formation substrates, ion channels, synaptic proteins)

RCT: Randomized controlled trial; AE: Anesthesia emergence; EMG: Electromyography; EPs: Evoked potentials; fNIRS: Functional near-infrared; fMRI: Functional magnetic resonance imaging.

preventing AE complications. For this purpose, thanks to its actions consisting of arousal promotion, and breathing enhancement, the dopamine uptake inhibitor methylphenidate was the first drug to be tested in humans. Researchers from the Ohio State University assessed, in adult patients, whether methylphenidate (given orally 20 mg, 2 h before induction) decreased the emergence time from isoflurane general anesthesia, and gave rise to a fast cognitive improvement with efficient pain control and post-operative nausea and vomiting (PONV) prevention (NCT02327195). To date, the recruitment status of this prospective, randomized, double-blind, placebo-controlled trial (RCT) is indicated as completed ($n = 54$) and we are waiting for the publication of the results. Probably, this RCT will encourage further research with a multicenter involvement and a greater sample. Another RCT in adult patients scheduled for pancreatic surgery is on-going at Massachusetts General Hospital (NCT02051452). Apart from the AE time effect, the investigators focused on safety and tolerability of methylphenidate in this clinical setting, and the impact on postoperative delirium (PD) and post-operative cognitive function (POCD). The study is expected to be completed in December 2018. We hope that results from this RCT will offer clinical data to better define the correlation between AE and postoperative mental status changes. Data from preclinical research suggested that other interesting molecules should be tested for evaluating their effects on emergence features and postoperative cognitive outcomes. Zhang *et al.*^[57] demonstrated that amantadine, a dopamine agonist used to treat Parkinson's disease and parkinsonism syndromes, attenuated post-operative learning and memory decline *via* inhibition of neuroinflammation in rodents. Interestingly, this study may suggest that interventions focusing on AE modulation may interfere with microglial activation and the cascade of neuroinflammation, implicated in POD/POCD pathogenesis^[58].

Clinical investigations should be carried out to better clarify results, and discrepancies of preclinical and clinical studies. Although OXA has been proved to be involved in arousal from general anesthesia in rodents^[24,26], and the Kushikata^[59]'s studies showed that plasma OXA significantly increased at AE from both propofol and sevoflurane anesthesia, Wang *et al.*^[60] proved that higher plasma OXA concentrations were not associated with a reduction in AE time in elderly patients. However, these patients showed a higher level of plasma OXA compared to young patients^[60], suggesting an age-dependent difference in the orexin-induced anesthesia arousal regulation. Probably, the lower density of orexin receptors in elderly can offer a potential explanation to the evidence that the elderly require a longer AE time^[61] despite a higher orexinergic activation.

In addition, we believe that further preclinical research may be necessary to evaluate correlations between AE mechanisms and postoperative cognitive complications. More detailed investigations in rodents should investigate the effect of AE modulation on early postoperative behavioral changes. In a translational perspective, indeed, a paramount aim should be to demonstrate whether any potential intervention on active AE processes can effectively induce an improvement in cognition, rather than just reducing the AE times.

Again, studies on the pathophysiology of PD, and POCD offer interesting prospects for further research. Alterations in the prefrontal cortex, and in the dopaminergic projection to the LC are implicated in the genesis of PD and POCD. Moreover, the orexinergic system is connected through the functional mediation of the TMN HA to the hippocampus, neostriatum, nucleus accumbens, and amygdala, which represent key regions involved in the pathogenesis of PD, and POCD^[62].

Further research is also warranted to better explain the mechanisms which induce AE activation.

Certainly, many aspects of the anesthetics are still to be elucidated. For instance, it has been demonstrated that the OS could be another possible target for isoflurane^[26], whereas the role of serotonergic neurones in dorsal raphe nucleus implicated in the mechanisms of general anesthesia^[63] on the orexinergic signal should be an interesting field of research for investigating the linkage between AE modalities and RoC features, such as pain and mood. Effects of specific antinociceptive interventions (e.g., neuraxial anesthesia) as potential mechanisms interfering with emergence processes and clinical consequences should be addressed in order to prove specific experimental findings such as the brainstem involvement in arousal dynamics. AE translational approaches could promote a feedback between different neuroscience fields of study. Thus, general anesthesia research could offer significant information to the research on mechanisms controlling arousal processes involved in physiological and pathological phenomena, such as sleep and coma^[43].

CONCLUSION

Neurobiologically, the ending stage of anesthesia is not simply the reverse process of induction. Recent findings demonstrated that induction and emergence are partly subjected to the control of different neural pathways. The exhaustive knowledge of these mechanisms may help prevent a large percentage of anesthesia complications, including altered mental status, and AAWR phenomena. Consequently, a better understanding of AE neurobiology could open a new era in anesthesia aiming to design new and safer anesthetic strategies. Moreover, in a fascinating translational perspective, the study on this topic could offer new insights into the complex mechanisms involved in cortical arousal, and provide significant data to the research on brain arousal processes and relative alterations. On the other hand, research on the sleep-wake regulatory network, and on alteration in arousal, and cognitive processes, could provide interesting suggestions for the general anesthesia research.

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