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Linking sleep and general anesthesia mechanisms : this is no walkover

V. Bonhomme (*, **, ***), P. Boveroux (**, ***), A. Vanhaudenhuyse (***), P. Hans (*, **), J. F. Brichant (**, ***), O. Jaquet (**, ***), M. Boly (***, ****) and S. Laureys (***, ****)

Abstract : This review aims at defining the link between physiological sleep and general anesthesia. Despite common behavioral and electrophysiological characteristics between both states, current literature suggests that the transition process between waking and sleep or anesthesia-induced alteration of consciousness is not driven by the same sequence of events. On the one hand, sleep originates in sub-cortical structures with subsequent repercussions on thalamo-cortical interactions and cortical activity. On the other hand, anesthesia seems to primarily affect the cortex with subsequent repercussions on the activity of sub-cortical networks. This discrepancy has yet to be confirmed by further functional brain imaging and electrophysiological experiments. The relationship between the observed functional modifications of brain activity during anesthesia and the known biochemical targets of hypnotic anesthetic agents also remains to be determined.

Key words : Sleep ; general anesthesia ; consciousness ; mechanisms.

Introduction

When referring to induction of general anesthesia, vernacular language often uses the expression of "putting someone to sleep". This is related to the behavioral characteristics commonly thought to be part of both states, including altered consciousness, reduced movements, and closing of the eyes (1). Besides behavioral similarities, sleep and anesthesia share common electroencephalographic modifications including slow wave activity (2). Hence, temptation of merging sleep and anesthesia mechanisms into a hodgepodge is high. In order to understand how hypnotic anesthetic agents produce an alteration of consciousness, three main types of experimental paradigms have been used. In vitro electrophysiological studies on neurons and brain tissues have allowed identifying their biochemical targets, mainly in terms of neurotransmitter systems, and ionic channels. Animal models, and the study of mutants, have confirmed the involvement of specific neurotransmitter systems, and shed light on the influence of hypnotic agents on sub-cortical arousal systems. Finally, electrophysiological and imaging studies in humans have evidenced their selectivity on specific functional regions and networks in the brain. The current challenge consists in making the link between all those mechanistic elements, compare them to the known mechanisms of sleep, synthesize the similarities and differences, and try to determine if the initiation of the cascade leading to the alteration of consciousness during sleep and anesthesia is located at the same place in the brain and involves the same brain mechanisms.

Vincent Bonhomme, M.D., Ph.D. ; Pierre Boveroux, M.D. ; Audrey Vanhaudenhuyse, Ph.D. ; Pol Hans, M.D., Ph.D. ; Jean François Brichant, M.D., Ph.D. ; Oceane Jaquet, Medical Student ; Melanie Boly, M.D., Ph.D. ; Steven Laureys, M.D., Ph.D.

(*) University Department of Anesthesia and ICM, CHR Citadelle, Liege, Belgium.

(**) Department of Anesthesia and ICM, CHU Liege, Liege, Belgium.

(***) Coma Science Group, Cyclotron Research Centre, University of Liege, Liege, Belgium.

(****) Department of Neurology, CHU Liege, Liege, Belgium.

Correspondence address : Vincent Bonhomme, University Department of Anesthesia and ICM, CHR Citadelle, Boulevard du 12eme de Ligne, 1, 4000 Liege, Belgium. Tel. : +32 4 2257117. Fax : +32 4 2257308. E-mail : vincent.bonhomme@chu.ulg.ac.be

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This will be the aim of the present review. After comparing the behavioral and electrophysiological characteristics of sleep and anesthesia, the systems sustaining arousal and the emergence of consciousness will be described. The known mechanisms of physiological sleep will then be summarized. This will allow placing hypnotic anesthetic agents within those systems and mechanisms by envisaging their multiple biochemical targets, their action on sleep and arousal pathways, and, finally, their functional effect on the brain.

Behavioral and electroencephalographic characteristics of sleep and general anesthesia

The behavioral resemblance between sleep and general anesthesia does not outlive detailed analysis. According to Franks and Zecharia, sleep can be defined as "a naturally occurring, periodic state of rest during which consciousness of one's environment and responses to external stimuli are largely suspended" (1). However, resting attitude, altered environmental awareness, and suppression of responses to external stimuli are not the only behavioral elements that must be part of the description of sleep, and of other altered consciousness states. A more precise description should include the presence or absence of wakefulness, spontaneous or evoked purposeful movements, muscle tone, awareness of the environment, response to command, self perception, mental imagery, and reversibility upon external stimulation (Table 1).

Physiological sleep is not a unitary entity. One must discriminate the so called rapid-eye-movement (REM) sleep from the slow wave sleep (or non-REM sleep). During non-REM sleep, of course, wakefulness is absent, and the eyes are closed. Muscle tone is normal, and spontaneous movements occur. This state is associated with various degrees of consciousness alteration, whose reversibility by external stimulation depends on sleep depth. Awareness of the environment and ability to respond to command fall off. There is no awareness of self and mental imagery, despite possible occurrence of dream. REM sleep is more frequently associated with dreaming, and hence mental imagery, with virtual self perception. Due to muscle atonia, no movements occur, except for specific movements of the eyes. Awareness of the environment is altered, as well as response to command. REM sleep is easily reversed by external stimulation. Surface electroencephalographic

Table 1

Behavioral and surface electroencephalogram (EEG) characteristics of sleep and general anesthesia. n-REM = non-rapid-eye-movement ; REM = rapid-eye-movement ; Inhib. neurotrans. = agents that promote inhibitory neurotransmission such as barbiturates, propofol, benzodiazepines, etomidate, and halogenated vapors ; α_2 agonists = α_2-adrenergic agonists ; St.-dep. = stage-dependent ; Des. fast = desynchronized fast activity

		Sleep		General anesthesia			
		n-REM	REM	Inhib. neurotrans.	Ketamine	Xenon	α_2 agonists
Wakefulness		Absent	Absent	Absent	Present	Absent	Reduced
Movements	Spontaneous	Present	Absent	Absent	Present	Absent	Reduced
	Evoked	Present	Absent	Absent	Absent	Absent	Reduced
	Purposeful	Present	Absent	Absent	Absent	Absent	Reduced
Muscle tone		Normal	Atonia	Reduced	Normal	Few effects	Normal
Environment awareness		Absent	Absent	Absent	Absent	Absent	Reduced
Response to command		Absent	Absent	Absent	Absent	Absent	Altered
Self perception		Absent	Virtual	Absent	Absent/Virtual	Absent	Altered
Mental imagery		Dreaming possible	Present	Absent Dreaming during emergence	Present	?	Altered
Reversibility		St.-dep.	Yes	No	No	No	Yes
EEG features		Spindles K-complex Delta	Des. fast Theta	Beta activation Theta, Delta Burst suppression Isoeletricity Spindles	Reduced alpha Rhythmic theta Polymorphic delta Scattered beta	Similar to halogenated vapors	Spindles Delta and theta activity

(EEG) modifications during non-REM sleep include waxing and waning oscillations of 12-15 Hz frequency lasting for at least a half second (spindle oscillations) and K-complexes (high voltage negative peak immediately followed by a slower positive complex) at sleep onset, and widespread increased power in lower frequencies (delta waves or slow oscillations, 0.5-4 Hz) (2) at deeper stages. Slow oscillations originate in frontal regions and propagate to posterior regions of the cortex following a reproducible track (3). REM sleep displays EEG patterns that are close, but not identical, to those observed during the wake state, including low voltage desynchronized fast activity, and increased power in the theta range (4-10 Hz) (4, 5).

During general anesthesia, alteration of consciousness is achieved using anesthetic agents with hypnotic properties. All of them do not alter the above-cited behavioral elements in the same way. In that respect, different classes must be distinguished. Agents that mainly enhance inhibitory neurotransmission such as barbiturates, propofol, benzodiazepines, etomidate, and halogenated vapors suppress wakefulness, awareness of the environment and response to command, as well as self awareness. They also lessen muscle tone, and movements. When maintained at sufficiently high concentrations, reversibility by external stimulation is difficult. Hence, those agents produce a state that is rather close to deep non-REM sleep, with the exceptions of reduced muscle tone and movements, and less easy reversibility. However, dreaming has been reported during propofol and desflurane anesthesia (6), particularly during emergence from anesthesia. In case of dreaming, electroencephalographic activity is similar to that observed during REM sleep. Otherwise, surface EEG alterations achieved with those agents depend on the administered dose. When increasing doses, beta activation first occurs (low amplitude 13-30 Hz waves), followed by a progressive slowing towards delta activity, near burst suppression (bursts followed by periods of flat signal), and, eventually, isoelectricity (7). Spindles can be observed (6), and slow wave activity appears similar to slow waves of non-REM sleep with subtle differences (2).

Ketamine is certainly the most representative among the hypnotic agents that mainly act through an inhibition of excitatory neurotransmission. Nitrous oxide can also be considered as part of that class. These agents have long been qualified as "dissociative" (8), insofar as they produce unconsciousness while preserving wakefulness, a state close to the recently renamed vegetative state, or Unresponsive Wakefulness Syndrome (UWS) (9). During ketamine administration, spontaneous reptilian non purposeful movements are commonly present. Subjects loose awareness of their environment and response to command. Intense dreamlike experience often occurs, with inadequate self perception. Reversibility upon external stimulation is not obtainable at high doses. Regarding surface EEG, ketamine produces an increase in high amplitude rhythmic theta activity, reduced alpha activity (8-13 Hz), and polymorphic delta activity with scattered beta activity (10).

Alpha$_2$-adrenergic agonists and inert gases also have hypnotic properties but do not belong to the above-mentioned classes. The decreased alertness and the state of tranquility induced by α_2-adrenergic agonists such as dexmedetomidine or clonidine are easily reversed by external vocal or tactile stimulation. With increasing concentration of such agents, subjects long keep the ability to respond to verbal command, and several cognitive brain functions are preserved, although memory and motor skill impairment has been reported (11, 12). Hence, α_2-adrenergic agonists are remarkable in that they alter wakefulness while preserving several aspects of awareness. The associated EEG changes are characterized by an increased energy in the lower frequency band (delta and theta activity) and in the spindle frequency range (12-15 Hz) (1, 13). Therefore, α_2-adrenergic agonist sedation is behaviorally and electrophysiologically very close to non-REM sleep. Xenon is currently the only inert gas used in clinical practice. Although having different biochemical targets, its behavioral effects mimic those of halogenated vapors (14), as well as their effects on the electroencephalogram (10).

In light of the above descriptions, sleep and anesthesia-induced behavioral and electroencephalogram modifications are heterogeneous. Hence, it is necessary to describe the mechanisms known to sustain arousal and awareness, before deeply inventorying the mechanisms of each state and find the link between them.

Arousal pathways

Cortical arousal and wakefulness during normal waking is sustained by a complex network of interconnected nuclei, with reciprocal projections to the cortex. Those neural pathways can be divided into three categories, depending on the location of their nuclei of origin, namely the pons, the midbrain, and the hypothalamus-basal forebrain

Table 2

Schematic summary of arousal systems. + = arousal promoting effect ; – = inhibition ; LC = locus coeruleus

Location of nuclei	Neurotransmitter	Projections	
Pons	Acetylcholine	+ Prefrontal cortex	
		+ Arousal nuclei	Pons Thalamus MRF Basal forebrain
	Noradrenaline (LC)	+ Cortex	
		+ Arousal nuclei	Thalamus
		– Sleep promoting pathways	Basal forebrain Preoptic area
	Glutamate	+ Cortex	
	Serotonin	+ Cortex	
		+ Arousal nuclei	Thalamus Basal forebrain
Midbrain	Glutamate	+ Arousal nuclei	Pons Thalamus Basal forebrain LC
	Dopamine	+ Cortex	
		+ Arousal nuclei	Thalamus Basal forebrain
Hypothalamus	Orexin	+ Diffuse	Arousal nuclei Thalamus Cortex
	Histamin	+ Diffuse	Arousal nuclei Thalamus Cortex
Basal forebrain	Acetylcholine	+ Cortex	
		+ Limbic system	
		+ Thalamus	

(Table 2). A detailed description of each nucleus and its projections can be found in the excellent review by Franks (15).

Pontine nuclei are cholinergic, noradrenergic, serotonergic, or glutamatergic. Cholinergic pontine nuclei project onto pontine, thalamic, mesencephalic reticular formation, and basal forebrain arousal nuclei, as well as onto regions of the prefrontal cortex. The locus coeruleus is the pontine source of noradrenergic neurons. It has a direct arousal effect on the cortex, and indirect effects through thalamic innervations and the inhibition of sleep-promoting pathways in the basal forebrain and preoptic areas. Pontine serotonergic neurons originate in the dorsal raphe and project onto the cortex, thalamus, and basal forebrain, while pontine glutamatergic neurons emerge from the oral pontine nucleus and project onto the thalamus and the cortex.

Arousal nuclei of the midbrain are glutamatergic and dopaminergic. Glutamatergic neurons project onto thalamic, basal forebrain, and pontine arousal nuclei, as well as onto the locus coeruleus. Dopaminergic neurons innervate the thalamus, the basal forebrain, and the cortex.

In the hypothalamus, orexinergic and histaminergic nuclei project diffusely to the cortex, thalamus, and other arousal nuclei. The cholinergic sources of the basal forebrain spread onto the cortex, the limbic system, and specific thalamic arousal nuclei.

From this schematic summary of the complex arousal network, it appears that acetylcholine, noradrenaline, serotonin, histamine, orexin, glutamate and dopamine are the main neurotransmitters of wakefulness, and that all of them can have direct arousal effects on the cortex. They endorse cortical

arousal, which is a prerequisite for the emergence of consciousness and its several components.

Emergence of consciousness

The conscious experience originates in the cerebral cortex. Two main theories are currently proposed to explain the emergence of mental content. The first one is the global workspace theory (16, 17). According to this theory, specialized functional brain networks made of hierarchically organized interconnected brain regions synchronize their activity to generate perceptual and mnemonic information. Interconnections between brain regions dynamically change according to circumstances. The generated information is pooled into a global workspace, and regulating systems allow one cognitive element or the other to separate from background information and emerge into the conscious field. The second theory is the information integration theory of consciousness (18), which has received more support from experimental evidence than the first one. In this theory, information would be generated by stereotypical patterns of brain responses, and integration of information would emerge from connectivity inside large scale cerebral networks. Some of those networks are qualified as resting state networks, or 'intrinsic connectivity networks' (19), because they elicit functional connectivity in a lying down individual with eyes closed, no external stimulation, and doing nothing else but thinking. Among the resting state networks, the medial frontoparietal default mode network (DMN) is involved in the awareness of self (20), and the dorsolateral frontoparietal executive control network (ECN) is involved in the awareness of the environment (21) (Fig. 1). Resting state auditory and visual networks have also been described (22). DMN and ECN have anti-correlated activities, that is alternate activation approximately every 20 seconds (21, 23). Conscious perception of external stimulation would only be possible during ECN activation. Peripheral sensory information would first reach the sensory networks through the thalamus and under the control of sub-cortical thalamo-regulatory systems involving the putamen (24). It would then pass through several hierarchically organized levels of integration, including cross-modal interaction. Other components of consciousness would be sustained by specific networks, such as the one for associative learning (25), emotions (26), or pain and its emotional components (27).

Changes associated with sleep

Inhibitory nuclei that are active during sleep are mainly γ-amino-butyric acid(GABA)ergic and galaninergic. They are located in the preoptic area and basal forebrain. Their firing rate increases immediately prior to sleep. Among them, the ventro-lateral preoptic nucleus (VLPO) appears to play a key role (28). In the waking subject, the noradrenergic locus coeruleus tonically inhibits the VLPO. At sleep onset, this inhibition disappears, and the VLPO releases the inhibitory neurotransmitter GABA at several sites, including the histaminergic tuberomamillary nucleus (TMN), and all the noradrenergic, serotonergic, cholinergic, and orexinergic arousal nuclei described above. The widespread inhibition of arousal pathways switches tightly interconnected thalamic and cortical neurons from a tonic firing to a hyperpolarized and burst firing mode (1). As a consequence, thalamic oscillations occur, leading to the emergence of sleep spindles in the EEG. Diffuse synchronization of thalamic and cortical activity also occurs, resulting in the outbreak of slow delta waves. Functional brain imaging has revealed that global brain activity decreases during non-REM sleep, with marked relative decreases in selected brain regions including brainstem, thalamus, basal ganglia, and basal forebrain, as well as in the prefrontal cortex, anterior cingulate cortex, and precuneus (5). However, specific subcortical and cortical regions involved in the generation of spindles and slow waves increase their relative activity (5). Functional connectivity within the DMN is impaired during deep non-REM sleep (29), but not during light non-REM sleep (30). Perception and interpretation of external information, although still possible, is altered. It seems that, beside a possible guardian role of the prefrontal cortex in assessing saliency of incoming information and triggering an awakening response if necessary, there exists a sleep-induced deactivation of primary sensory areas (5).

The initiation of REM sleep depends on complex feed-back interactions between cholinergic REM sleep promoting neurons located in the tegmentum, and serotonergic, noradrenergic, and GABAergic REM sleep inhibiting neurons located in the dorsal raphe, locus coeruleus, and reticular formation (31). These interactions would lead to cyclic occurrences of REM sleep behavioral and EEG patterns, including muscle atonia, rapid-eye movements, and EEG disynchronization. Regarding global brain activity, no significant difference from wakefulness can be found, although

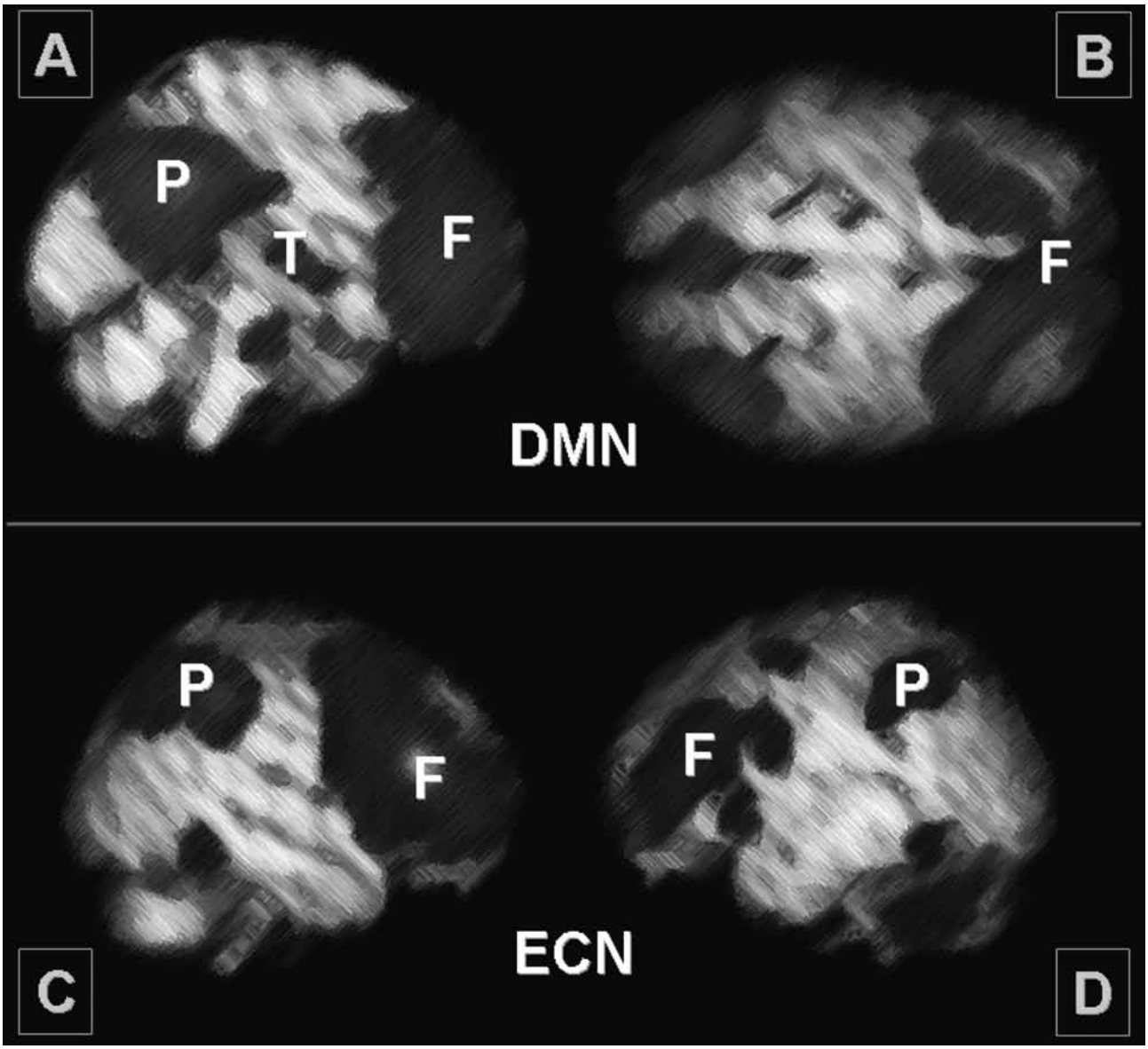

Fig. 1. — Artwork of some of the brain regions (dark) involved in two intrinsic connectivity networks sustaining consciousness. Upper part : sagittal (A) and cranial (B) view of the brain. The medial frontoparietal default mode network (DMN) sustains the awareness of self, and involves the mesiofrontal cortex (F), the posteromedial cortex (P, essentially the precuneus and the posterior cingulate cortex), and the thalamus (T). Lower part : right (C) and left (D) view of the brain. The dorsolateral frontoparietal executive control network (ECN) sustains the awareness of the environment and involves more lateral parts of the frontal and parietal cortex. Adapted from (66).

several brain regions increase their relative activity (e.g. tegmentum, thalamus, basal forebrain, amygdala, hippocampus, anterior cingulate cortex, and temporo-occipital areas), while others decrease it (dorsolateral prefrontal cortex, posterior cingulate, precuneus, and inferior parietal cortex) (5). In contrast to non-REM sleep, few are known about external information processing during REM sleep.

Biochemical targets of hypnotic anesthetic agents

Having summarized the physiology of waking and sleep, we can now discuss the possible targets of hypnotic anesthetic agents within those systems. The first level to be explored is the molecular level. In vitro electrophysiological recordings and the study of mutants have allowed identifying a large number of neurotransmitter receptors, ion channels, and other functional neuronal proteins that are sensitive to the action of hypnotic anesthetic agents. Among them, only a few have received enough experimental support to be linked to the clinical effect of anesthetic agents (15) (Table 3).

The first one is the type A GABA receptor, which can be synaptic or extra-synaptic, and is widely distributed across the brain. GABA is a major inhibitory neurotransmitter. Agents such as

Table 3

Principal biochemical targets of the hypnotic effect of anesthetic agents. Summarized from (15) and (14). + = activation ; – = inhibition ; 0 = no effect ; GABA = γ-amino-butyric acid ; $GABA_A$ R = GABA receptor type A ; NMDA = N-methyl-D-aspartate ; NMDA R = NMDA receptor ; 2P K channels = two-pore potassium channels ; n and m ACh R = neuronal nicotinic and muscarinic acetylcholine receptor ; Glycine R = glycine receptor ; HCN = hyperpolarization-activated cation channel ; Na channels = voltage-gated presynaptic sodium channels ; Vapors = halogenated vapors ; N_2O = nitrous oxide

	Agonist/ Effect	Hypnotic anesthetic agents and their known effect							
		Propofol	Benzodiazepines	Barbiturates	Etomidate	Vapors	Xenon	N_2O	Ketamine
$GABA_A$ R	GABA/Inhibitory neurotransmission	+	+	+	+	+	0	0	
2P K channels	/Hyperpolarization – Inhibition – background modulation of neuronal excitability	0	0	0	0	+	+	+	+
NMDA R	Glutamate/slow components of excitatory neurotransmission					–	–	–	–
n and mACh R	Acetylcholine/cortical arousal	–		–		–	–	–	–
Glycine R	Glycine/neuronal inhibition					+			
HCN channels	/regulation of neuronal excitability and rhythmicity	–				–			
Na channels	/regulation of glutamatergic neurotransmission					–			

propofol, halogenated vapors, etomidate, benzodiazepines, and barbiturates have been demonstrated to promote GABAergic, and hence inhibitory neurotransmission (14).

Some types of potassium channels, the two-pore potassium channels (TREK, TASK, and TRESK channels), can be activated by hypnotic anesthetic agents, with a net result of hyperpolarization and neuronal inhibition. This is the case for halogenated vapors, nitrous oxide, ketamine and xenon (32). Those potassium channels are widely distributed across the brain, and are either presynaptic or postsynaptic. They are considered to be responsible for the background modulation of neuronal excitability.

Another major target of hypnotic anesthetic agents is the N-methyl-D-aspartate (NMDA) glutamate receptor subtype, whose inhibition causes extinction of the slow components of synaptic transmission (15). NMDA receptors are inhibited by halogenated vapors, nitrous oxide, xenon, and ketamine. This inhibition is mainly responsible for their anti-noxious effect at the level of the dorsal horn of the spinal cord, and can probably not account alone for their hypnotic effect. The other hypnotic agents, such as propofol, are not or only weak inhibitors of NMDA receptors (33).

Central cholinergic neurotransmission plays an important role in cortical arousal (34), and several hypnotic agents including propofol, barbiturates, halogenated vapors, xenon, nitrous oxide and ketamine have been shown to alter nicotinic and/or muscarinic transmission. The glycine receptor is another potential target, mainly for halogenated volatile anesthetics. It is frequently associated with $GABA_A$ receptors, and mediates neuronal inhibition (14, 15). Hyperpolarization-activated cation (HCN) channels are important regulators of neuronal excitability and rhythmicity (35), particularly in thalamocortical neurons where they contribute to modulate thalamocortical oscillations (15). Propofol, and, to a lesser extent, halogenated vapors inhibit those channels. Finally, presynaptic voltage-gated sodium channels are sensitive to the effect of halogenated volatile anesthetic agents, and their inhibition can delay glutamatergic neurotransmission (36).

Given the extraordinary multiplicity of biochemical targets, and their large distribution across the brain, there must be subtle agent- and dose-dependent differential tuning of the effect of hypnotic agents on each of them to end up with the pharmacodynamic consequences of anesthesia. Two options are available to understand this fine tuning, either look at the effect of hypnotic agents on specific sleep/arousal and consciousness networks using animal models, or examine the functioning brain using functional brain imaging or electrophysiological techniques.

Anesthetic agent targets within arousal and sleep systems

The behavioral and electrophysiological similarities between sleep and anesthesia have long prompted scientists to search for an anesthesia-operated consciousness switch within sleep/arousal networks (37). Indeed, there could be an enhancement of sleep promoting pathways activity, an inhibition of arousal systems, an alteration of thalamo-cortical interactions, or a combination of these mechanisms. Mutant rodents for specific receptors, stereotaxic lesions of selected nuclei, quantification of c-Fos protein (a marker of neuronal activity) expression, and brain slice or in vivo electrophysiological recordings in animals, in the presence of specific agonists or antagonists, have been used to evidence the effect of hypnotic agents on those systems. Most of these studies are indirect arguments of such effects, and translation to the in vivo human brain is not easy (37). In addition, the involved mechanisms could be different during induction of and emergence from anesthesia (38, 39). Among the arousal pathways, cholinergic, noradrenergic, serotonergic (15), orexinergic (40) and histaminergic (41, 42) systems have mostly been incriminated. The inhibition of arousal systems could be the result of a GABAergic neurotransmission enhancement within sleep pathways (28, 40). Regarding the cholinergic systems, the administration of centrally acting cholinesterase inhibitors can reverse propofol (34) and sevoflurane-induced (43) loss of consciousness in humans. In that case, a brain activity pattern similar to the wake state is restored (44). However, it could be that these effects only result from a sufficiently powerful activation of cholinergic arousal, independently from the basal mechanisms of anesthesia-induced alteration of consciousness (15). The strongest arguments for the involvement of sleep pathways during a pharmacologically-induced alteration of consciousness are probably those obtained for the α_2-adrenergic agonists clonidine and dexmedetomidine (13, 45) that inhibit the locus coeruleus.

Functional effects of anesthesia

At this stage of our review, further understanding of the mechanisms of anesthesia-induced alteration of consciousness can only come from whole brain functional observations, using techniques that have enough spatial and temporal resolution. Among them, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), functional near infrared spectroscopy (fNIRS) and sophisticated electroencephalographic studies, combined with transcranial magnetic stimulation (TMS), have allowed substantial progress (46).

The first functional studies of the brain under anesthesia demonstrated that agents such as propofol (47, 48), halogenated vapors (49), barbiturates (50), benzodiazepines (51), xenon (52), and α_2-adrenergic agonists (13) dose-dependently reduce the activity of specific brain regions, including the thalamus, cuneus-precuneus, posterior cingulate cortex, and the fronto-parietal association cortices. The obtained images are similar to those observed during non-REM sleep, coma, generalized seizure, and UWS (53, 54). Most of these regions are part of the intrinsic connectivity networks DMN and ECN (23). Ketamine is an exception, as it offers a very different pattern of brain functional changes. Indeed, it produces activations in the anterior cingulate, thalamus, putamen, and frontal cortex (55, 56).

Considering these observations, anesthesia has obviously specific cortical effects. It could be proposed that, similarly to physiological sleep, anesthesia-induced modifications of cortical activity would be the result of its above-described subcortical effects. But the inverse is also possible, that is a primary effect on the cortex, with subsequent repercussions on cortico-sub-cortical interactions and activity in the sub-cortical structures. Accumulating evidence suggests that this second hypothesis is probably the right one.

Indeed, cortical effects of anesthetic agents occur at lower doses than sub-cortical effects (57-59), and higher order processing cortical areas are more sensitive than lower-order ones (60, 61). It seems that hypnotic agents, at least those promoting GABAergic neurotransmission, disrupt large-scale cortical connectivity and the ability of the brain to integrate information (62-64), while certain dynamic principles of the underlying networks are maintained (65). Connectivity and anticorrelation of DMN and ECN (66-68), and of other higher-order networks (69), is reduced by low concentrations of these agents. At those low concentrations, connectivity is preserved or even increased in lower-order sensory and motor networks (70), and thalamic activation by external stimuli still occurs (24). At concentrations producing loss of responsiveness, connectivity of DMN and ECN disappears, as well as their anticorrelation. In contrast, DMN and ECN become anticorrelated with thalamic activity (66), and connectivity in lower-order sensory networks is maintained with cross-modal interaction alterations.

Conclusions

Progress has recently been made in the understanding of the mechanisms of sleep and anesthesia-induced alteration of consciousness, and of consciousness itself. Anesthesia and sleep share common behavioral, EEG, and functional features. However, detailed analysis reveals that they probably originate from different backgrounds. Sleep is undoubtedly initiated in subcortical structures, while accumulating scientific data suggest an initial cortical origin for anesthesia, at least during the induction phase, with subsequent subcortical consequences. A simple reverse sequence of events during emergence from anesthesia is probably not what actually happens. These hypotheses remain to be confirmed, and verified for all classes of hypnotic anesthetic agents. The link with known biochemical targets also remains to be determined, as well as the exact sequential alterations of cortico-subcortical interactions. The currently available functional imaging and electrophysiological techniques have not yielded all their secrets yet, and further new elements can certainly be expected in the very near future.

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