

Mechanisms of Anesthesia: Towards Integrating Network, Cellular, and Molecular Level Modeling

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The mechanisms of anesthesia are surprisingly little understood. The present article summarizes current knowledge about the function of general anesthetics at different organization levels of the nervous system. It argues that a consensus view can be constructed, assuming that general anesthetics modulate the activity of ion channels, the main targets being GABA and NMDA channels and possibly voltage-gated and background channels, thereby hyperpolarizing neurons in thalamocortical loops, which lead to disruption of coherent oscillatory activity in the cortex. Two computational cases are used to illustrate the possible importance of molecular level effects on cellular level activity. Subtle differences in the mechanism of ion channel block can be shown to cause considerable differences in the modification of the oscillatory activity in a single neuron, and consequently in an associated network. Finally, the relation between the anesthesia problem and the classical consciousness problem is discussed, and some consequences of introducing the phenomenon of degeneracy into the picture are pointed out.

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INTRODUCTION

Although it was more than 150 years since Crawford Long first introduced surgical anesthesia (see Friedman and Friedland, 1998), we know surprisingly little about the neural mechanisms behind pharmacologically induced unconsciousness. This lack of knowledge pertains to all levels of brain organization. At the macroscopic level, we have knowledge about a number of brain structures that are affected by general anesthetics but we have little detailed knowledge as to which structures are critical for anesthesia. Similarly, at the mesoscopic level we know how anesthetics modulate cellular processes in a number of systems but not which modifications are critical. At the microscopic level we know much about how anesthetics affect cellular molecules but not which molecular structures are critically affected. And, consequently, we do not know how the effects on the different levels interact to produce anesthesia.

One key problem, complicating the determination of the anesthetic mechanisms at all levels, is the fact that anesthetics form a chemically very diverse group. General anesthetics comprise chemically unrelated compounds such

as the gases nitrous oxide, diethyl ether and halogenated hydrocarbons, and alcohols and barbiturates, as well as ketamine and propofol. Does this imply that anesthesia is caused by many different mechanisms? Is the traditional search for a common mechanism in vain? Solving this problem is closely connected with the notoriously difficult problem of solving the classical consciousness problem. Edelman and Gally (2001) have argued that one of the signatures of biological function is the phenomenon of degeneracy or functional redundancy, the phenomenon that completely different mechanisms lead to the same functional result. Edelman and Gally present an impressive array of examples, the noneffect of eliminating the albumine gene being one of the most convincing. Is the phenomenon of consciousness a case of degeneracy? Is anesthesia a case of degeneracy? As will be discussed below, these ideas lead to interesting consequences.

The main aim of the present article is to summarize briefly some aspects of current knowledge about the function of general anesthetics at different organizational levels. Such an attempt will necessarily also reflect current knowledge about the relation between neural and mental states, one of the great challenges for human rationality. Although there are several reviews of different aspects of anesthesia (Eckenhoff and Johansson, 1997; Franks and Lieb, 1994), surprisingly few attempts to cover multilevel questions have been made. This review attempts to identify some of the explanatory gaps in the present picture.

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MACROSCOPIC EFFECTS—MODIFICATION OF THALAMOCORTICAL LOOP ACTIVITY?

Which structures of the brain are critically affected by general anesthetics? The chemical diversity of anesthetic compounds suggests that a diversity of brain structures are affected. Recent attempts with fMRI, PET, and quantitative EEG studies on anesthesia in human brains support this suspicion, and allow us to construct tentatively a minimal model of what structures are critically involved in anesthesia (Alkire *et al*, 2000; Cariani, 2000; John, 2001). Figure 1 illustrates schematically this minimal model, mainly taken from Alkire *et al* (2000). The key components form a triangular network of corticothalamic, thalamocortical, and reticulothalamic neurons, comprising both positive and negative feedback loops. Anesthetics act—directly or indirectly—on numerous nodes in this network and through a variety of mechanisms. For the thalamocortical neurons the outcome is a switch from tonic to bursting firing, caused by a general hyperpolarization. At the cortical level, the anesthetic-induced modifications are associated with a switch from fast oscillatory field potentials, comprising gamma frequency oscillations (30–70 Hz), to slower delta (4–7 Hz) and theta (1–2 Hz) oscillations.

Which of these induced effects are critical for causing anesthesia? Do anesthetics act on a limited group of specific neurons or does anesthesia require simultaneous effects on several different nodes in this aggregate of structures? Or is anesthesia independent of *specific neuron effects* and depends mainly on modifications of *specific processes*?

These questions reflect closely related problems in the discussion on the neuronal correlate of consciousness. Also, here we can separate two families of theories. Either consciousness depends on activity in specific groups of neurons or it depends on specific processes in unspecified neurons in a larger population. Roughly speaking, the view of Crick and Koch (1990) can be classified as neuron specific. They search for specific ‘awareness neurons’, possibly characterized by a tendency to fire bursts synchronously, and possibly distributed in the cortex (the lower layers), thalamus, and the limbic system (Koch and Crick, 1994). Equally roughly speaking, we can classify the attempts by Tononi and Edelman (1998) as process specific. They look for a specific form of activity in cortical neurons that form a coherent but variable dynamic core as the correlate to consciousness. Similar ideas have been presented in terms of adaptive resonance (Grossberg, 1995), interneural synchrony (Singer, 1995), coherent oscillations (Llinas *et al*, 1998), and temporal coherence (John *et al*, 1997). Considering the different arguments used in the debate, we find the most likely solution to be a combination of the two main theories; consciousness depends on specific coherent activity in a specific population of cortical neurons. Similarly, we find the most likely explanation of anesthesia to be an anesthetic-induced modification of specific coherent activity in specific neurons; different neurons for different anesthetics. Note, however, that the neurons directly involved in consciousness need not necessarily be the neurons directly affected by general anesthetics.

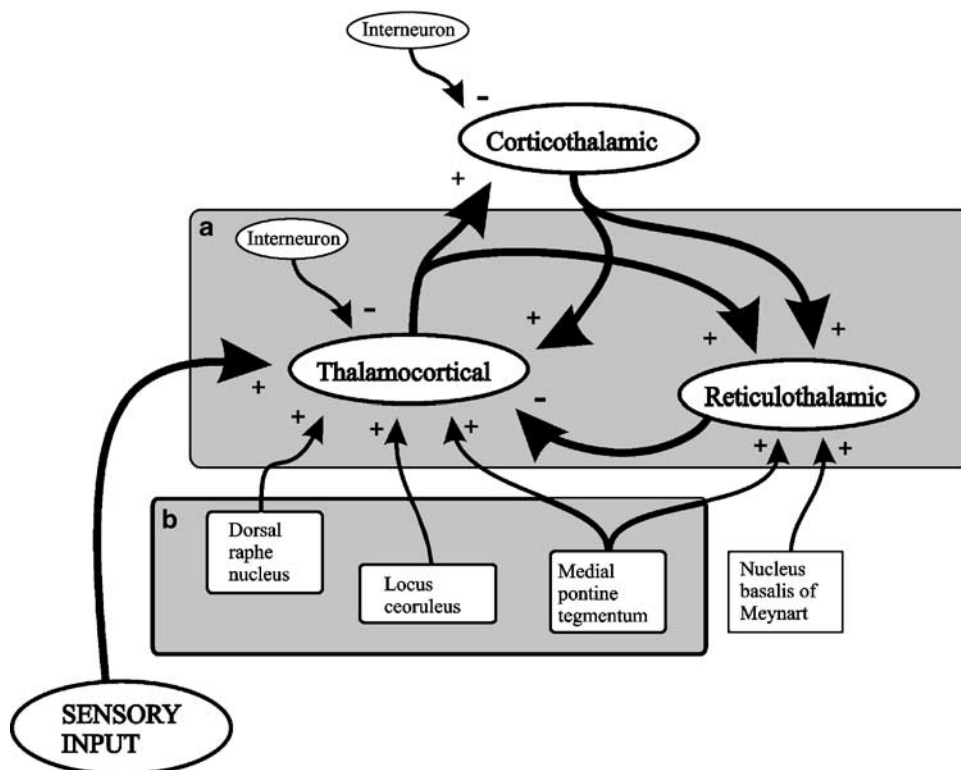


Figure 1 The basic triangular network of neurons involved in anesthesia. The depicted neurons and impulse pathways (marked by arrows) are assumed to be the main targets for general anesthetics. Thalamic and mesencephalic structures are indicated by (a) and (b), respectively, and excitatory and inhibitory synapses by + and – (after Alkire *et al*, 2000).

MESOSCOPIC EFFECTS—DISRUPTED COHERENCE?

Irrespective of whether specific neuron or specific process theories are closest to truth, which we do not know today, the question how the neuronal processes that give rise to consciousness are affected by general anesthetics remains.

Rhythmicity is a characteristic feature of neuronal processes, since long recognized in the classification of EEG patterns. Different forms of oscillatory activity are associated with different functional states; generally, and rather vaguely, high-frequency activity, in single neurons reflected as tonic firing, has been associated with conscious states, while low-frequency activity, and single neuron burst firing, have been said to characterize unconscious states (see Alkire *et al.*, 2000). How do general anesthetics induce the required shifts of activity? Again we can separate between two main groups of theories: (1) *suppression* theories, that assume that general anesthetics inhibit neuronal activity in critical brain structures and (2) *coherence* theories, which assume that general anesthetics disrupt coherent neuronal activity in critical brain structures (Cariani, 2000).

John (2001) summarizes the results from a long series of quantitative EEG studies of anesthetic effects in three points: general anesthetics induce (i) a general lowering of frequency over the whole cortex, (ii) a relative increase in

the activity of anterior cortical regions compared to posterior, and (iii) an increased coherence between low-frequency activity in frontal areas and an uncoupling between activity in anterior and posterior regions. From this we can conclude that neither a simple suppression nor a simple coherence theory does explain general anesthesia. Both increased and decreased activity as well as increased and decreased coherence characterize anesthetic-induced unconsciousness. Obviously, we have to search for more sophisticated theories to explain anesthesia.

The main determining factor of the frequency of brain rhythmicity has been searched for at network and at cellular levels. So far, experimental evidence favors intrinsic cellular oscillatory behavior as the determinant rather than the network connectivity *per se* (Hutcheon and Yarom, 2000). The intrinsic preference for a specific frequency of a neuron is reflected in its resonance behavior and is experimentally available. Furthermore, a theoretical dissection can couple the different features of the intrinsic oscillatory behavior to the activity different voltage-gated ion channels. However, there are relatively few examples of theoretical investigations of the oscillatory behavior of cortical neurons and even fewer of its modification by anesthetics.

Figure 2 shows model simulations based on recordings from a subpopulation of neurons in hippocampus (Johansson and Århem, 1992a). This type of neuron shows several

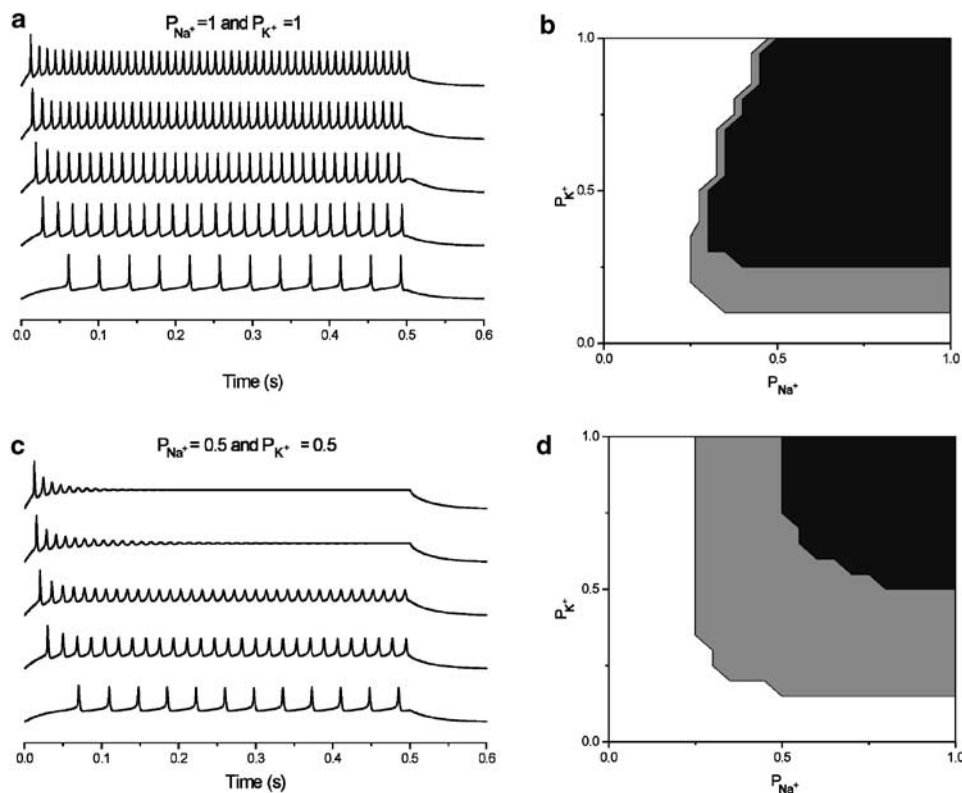


Figure 2 Anesthetic-induced modifications of the oscillatory behavior of a model neuron. (a and b) Computer simulations of the time evolution of oscillations under control conditions (a) and with 50% of the Na and K channels blocked (c). Stimulation level is 7, 11, 15, 19, and 23 pA. (b and c) The dependence of oscillatory behavior on Na- and K-channel density at high (b) and low (d) stimulation levels (23 and 7 pA). Values giving stable oscillations are marked by black and values giving damped oscillations by gray. Model based on voltage-clamp measurements of isolated small-sized interneurons from rat hippocampus (Johansson and Århem, 1992b). The equations used were modified Frankenhaeuser-Huxley equations and are described in Johansson and Århem (1992a), together with parameter values and calculation procedures. P_{Na^+} and P_{K^+} are Na and K permeability constants in relative units. The P_{Na^+} and P_{K^+} values experimentally determined, multiplied by 20, were assigned the value 1.0. These higher P_{Na^+} and P_{K^+} values were assumed to better represent the permeabilities of a typical rat hippocampal neuron than those of the relatively small subgroup of neurons studied by Johansson and Århem (1992b).

interesting features, such as graded action potentials (Johansson *et al*, 1992), spontaneous activity induced by single channel openings (Johansson and Århem, 1994), and the capability of functioning as a memory device (Johansson *et al*, 1995). The figure shows the activity of model neurons with different densities of Na and K channels, reflecting the effect of selectively blocking Na and K channels in a state-independent manner. Figures 2a and c show the time evolution of the oscillatory behavior at different stimulation intensities for a model neuron with normal Na- and K-channel densities (a) and with 50% blocked (c). As seen, the block forces the oscillatory activity into damped responses at high stimulation levels without eliminating the excitability *per se*. The frequency increases continuously with increased stimulation intensity till it reaches a saturation value of about 100 Hz. Figures 2c and d show the occurrence of damped and stable oscillations at different combinations of Na- and K-channel block for high (b) and low (d) stimulation currents (23 and 7 pA, respectively). As seen stable oscillations dominate at low stimulation levels, while damped oscillations play a bigger role at higher levels. The transition from stable to damped oscillations (ie a disruption of the oscillatory activity) is most easily obtained by equal block of Na and K channels at high stimulation levels, corresponding to high (pulsatile) activity of the surrounding network, but by selective block of Na channels at low levels, corresponding to low network activity. In short, the results suggest that an anesthetic, blocking Na and K channels state independently, can disrupt coherent oscillatory activity in a network of cortical neurons. They further suggest that the selectivity of the block plays a role. Selectively blocking Na channels is more efficient in an environment of low activity and unselective blocking in an environment of high activity. As already stressed, general anesthetics comprise compounds of great structural and functional diversity, including anesthetics blocking voltage-gated channels state independently and selectively (eg ketamine and alcohols). Thus, the discussed theoretical cases can be expected to be demonstrated experimentally. Furthermore, and as will be discussed below, the blocking mechanism *per se* (ie whether it is state dependent or independent) can be shown to be of importance for modifying the dynamic behavior of the cell.

MICROSCOPIC EFFECTS—MODULATING ACTIVITY OF CRITICAL ION CHANNELS?

What is the molecular mechanism of anesthesia? Of the different organization level approaches to the problem of anesthesia, the molecular level approach has probably been the most fertile so far. A number of investigations have successfully clarified the effects of general anesthetics in molecular detail (see Franks and Lieb, 1994). The problem, however, is not to determine molecular mechanisms in general, but to determine which molecular mechanism leads to anesthesia?

The first more detailed molecular theory was advanced by Charles Ernest Overton in his classical *Studien über die Narkose* 1901. In this classical work, he demonstrates the correlation between anesthetic effect and lipid solubility, measured as distribution coefficient in water–alcohol. Over the years, however, the Overton lipid theory lost ground to

theories assuming proteins as the critical target (but for modern lipid theories see Janoff *et al*, 1981; Ries and Puil, 1999a,b). Today, protein theories focus on ion channels (Franks and Lieb, 1994).

Which anesthetic-induced ion channel modifications are critical in causing anesthesia? On the basis of the rather fragmentary affinity measurements performed, we have to conclude that the main candidates are the ligand-activated GABA and NMDA channels. However, voltage-activated channels and background channels have also been suggested as the main targets. As repeatedly mentioned, the problem, however, is not to demonstrate that anesthetics affect channels, but to demonstrate which effects are critical in causing anesthesia.

At the center of the debate is the GABA channel. In the scenario discussed above (Figure 1), the anesthetics are assumed to activate GABA channels in thalamic neurons, which leads to hyperpolarization and to decreased activity in postsynaptic cortical cells. This is in accordance with the suppression theory. Mihic *et al* (1997) have by clever use of chimeric constructs localized the binding sites for volatile anesthetics on the GABA channel. But what about the generality of this mechanism? Does it also apply to other anesthetics? Besides some investigations on alcohol effects, we have little information.

A recent theory focuses on NMDA channels as critical targets for general anesthetics (Flohr, 1995). The NMDA channel has a unique position among channels in necessitating a dual action of both ligand (glutamate) and voltage to open. This means that they can function as coincidence detectors and act in associative networks. In accordance with this view, ketamin acts as a specific NMDA channel blocker (Flohr, 1995). But what about other general anesthetics? Do they block NMDA channels specifically? Under all circumstances, Flohr (1995) argues that ultimately all general anesthetics directly or indirectly inhibit NMDA currents and thereby certain neuronal activity, essential for consciousness.

Most general anesthetics have been shown also to block voltage-gated channels, but as a rule at higher concentrations (see Franks and Lieb, 1994). How general is this rule? Do all voltage-gated channel show lower affinity to general anesthetics than ligand-gated channels? Can we find specific ultrasensitive voltage-gated channels? A growing number of studies suggest that this may be the case. Most of these studies focus on K channels. That K channels are critically involved in anesthesia is already clear from the fact that Shaker channel is named after the *Drosophila* mutant, which under ether narcosis shows shaking movements (see Hille, 2001). The Shaker mutant was shown to lack the Shaker channel. The neural activity under ether narcosis evidently depends on the occurrence of K channels in neurons.

Covarrubias and Rubin (1993) also argue for a K-channel theory of anesthesia, focusing on a specific channel type. Their results suggest that Shaw channels are more sensitive to volatile anesthetics than are other channels. Consequently, they regard Shaw channels as the critical targets for anesthetic action. We have in preliminary experiments shown that Shaw channels are more sensitive to ketamine and propofol than other Kv channels (K_d values for Kv2.1 are about 10 times lower than for Kv1.2; Nilsson *et al*, 2003). Nicoll and Madison (1982) also demonstrate specific effects

Table 1 Sensitivity of Ion Channels to General Anesthetics

Channel	Anesthetic	Type of effect	Reference
<i>I. Ligand-gated channels</i>			
GABA _A	Volatile	Agonist	Zuo <i>et al</i> (1996)
	Volatile	Agonist	Mihic <i>et al</i> (1997)
	Volatile	Agonist	Franks and Lieb (1994)
	Barbiturates	Agonist	Franks and Lieb (1994)
	Ketamine	Antagonist	Zuo <i>et al</i> (1996)
NMDA	Volatile	Antagonist	Franks and Lieb (1998)
	Volatile	Agonist	Flohr (1995)
	Ketamine	Antagonist	Flohr (1995)
nACh	Volatile	Agonist	Scheller <i>et al</i> (1997)
	Volatile	Antagonist	Lin <i>et al</i> (1995)
	Barbiturates	Antagonist	Andoh <i>et al</i> (1997)
	Barbiturates	Antagonist	Franks and Lieb (1997)
<i>II. Voltage-gated channels</i>			
Kv	Volatile	Antagonist	Kulkarni <i>et al</i> (1996)
	Volatile	Antagonist	Harris <i>et al</i> (2000)
	Ketamine	Antagonist	Kulkarni <i>et al</i> (1996)
BK	Volatile	Antagonist	Denson <i>et al</i> (1996)
<i>III. Background channels</i>			
TREK	Volatile	Agonist/antagonist	Patel <i>et al</i> (1999)
K _{An}	Volatile	Agonist	Franks and Lieb (1988)
S	Volatile	Agonist	Winegar <i>et al</i> (1996)

Effects of general anesthetics on ion channels, suggested to have a causal role in anesthesia. Volatile anesthetics include halothane, isoflurane, chloroform, and diethyl ether.

of general anesthetics on K channels, but in this case activating effects. We have similarly described a barbiturate-induced increase in K-channel currents, although only at high potentials (Århem and Kristbjarnarson, 1985). It is not unreasonable to expect an increased interest in K-channel theories of anesthesia in the near future.

Recently, background channels also have come into focus as critical targets for anesthetic action. Both enhancement and block of TREK, TRAAK, and TASK channel currents have been reported at low concentrations of volatile anesthetics (Patel *et al*, 1999). Perhaps most remarkable is the enhancement of currents through a background channel in specific neurons of the snail *Lymnaea stagnalis*, induced by volatile anesthetics (Franks and Lieb, 1988). Another case of anesthetic-induced effects on a background channel is the block of flicker channels in myelinated axons at low concentrations of local anesthetics (LAs) (Bräun *et al*, 1995). However, the picture is still fragmentary. Table 1 summarizes some reported effects of general anesthetics on ion channels, assumed to have a causal role in anesthesia.

THE MOLECULAR MECHANISM OF LOCAL ANESTHETICS: A MODEL FOR GENERAL ANESTHETICS?

How do general anesthetics affect ion channels? Above, we showed simulations of blocking a model neuron by a

state-independent mechanism (Figure 2). However, the effects induced by general anesthetics most likely are more complex. One group of anesthetic compounds studied in molecular detail is the LAs. To study the mechanisms of general anesthesia, it is therefore rewarding to consider LAs as model compounds.

The critical feature of local anesthesia is a block of the nervous impulse and is assumed to be caused mainly by a direct block of Na channels. The block has been shown to be state dependent (the modulated receptor hypothesis; Hille, 1977; Hondeghem and Katzung, 1977). Since the early 1970s the location of the binding site has been assumed to be in a postulated internal vestibule. Many of these early predictions have been confirmed in a later work, highlighted by the structural determination of a K channel (Doyle *et al*, 1998). This structural determination of the channel naturally specifies and constrains the hypotheses of anesthetic-blocking mechanisms. Figure 3a shows schematically how a LA is assumed to block voltage-gated channels, displaying the interaction with the gate at the internal surface. As a comparison Figure 3b shows, equally schematically, a state-independent mechanism. This type of mechanism has been best analyzed for certain natural toxins, the most well-known being tetrodotoxin (TTX).

Concerning the LA block of Na channels, Catterall and colleagues (Ragsdale *et al*, 1994) have suggested that the

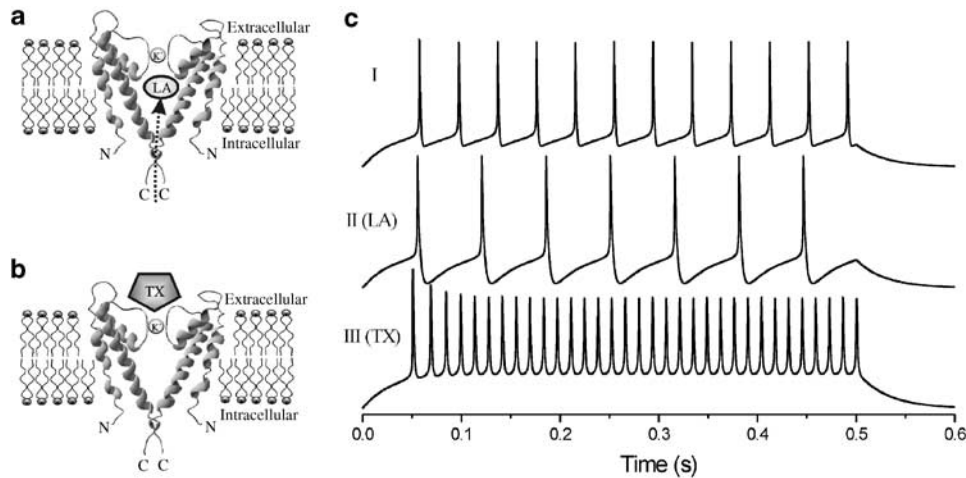
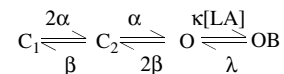


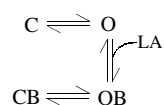
Figure 3 Modifying the blocking mechanisms modifies the oscillatory behavior. (a and b) Schematic diagrams of two ways of blocking a K channel. The channel structure shown is two subunits of KcsA, prepared using Swiss-PdbViewer (a) An open-state dependent block by a LA. LA can only reach its binding site when the channel gate is open. (b) A state-independent block by a toxin (TX). (c) Computer simulations of blocking the K channels in the model neuron of Figure 2 by an open-state (middle panel) and a state-independent (lower panel) mechanism. Upper panel shows the control case. The control and the state-independent block cases were computed as in Figure 2. In the state-dependent block case the computation of the K-channel activation parameter n (see Johansson and Århem, 1992a) was based on equations describing the state diagram:



where C_1 and C_2 denote closed states. The rate constants α and β are defined in Johansson and Århem (1992a). The blocking transition rate constants κ and λ were assumed to be 5 m/s/mM and 1 m/s, respectively, and the anesthetic concentration to be 1 mM.

binding site in Na channels is a hydrophobic pocket formed by two aromatic residues in the internal vestibule. Possibly, π bonds play a role in this interaction. But how do LAs interact with K channels that do not have aromatic residues in the internal vestibule?

We have studied this and related questions by analyzing the effects of LAs on a series of voltage-gated K channels (Nilsson *et al*, 2001). The results show that the mechanism of block can be summarized by the following simple state diagram:



where C and O denote closed and open channel states. OB and CB denote the corresponding states but with the LA bound to the channel. The scheme means that the LA binds to the channel in open state (O) and transfer the channel to a nonconducting open-bound state (OB). At depolarization, the channel either pass into a closed but unbound state (C) or into a closed and bound state (CB), depending on the channel type. The probability to pass into a CB state is larger for Kv2.1 than for any other Kv channel (Nilsson *et al*, 2001). This simple scheme explains most of the experimental data reported and thus replaces several other models in the literature. A simple extension of the model also explains most of the effects on inactivating channels. Thus, it explains recent results contradicting the traditional view that channels in inactivated state bind LAs better than in other states (in accordance with Vedanham and Cannon, 1999). It explains the phenomenon of use dependence without the traditional assumption of two pathways or sites of action (Hille, 2001). It

explains the lack of use dependence for some LAs by assuming a faster block rather than the traditional assumption of no binding. In short, it explains much of the data explained in the literature by much more complex models. In addition, it is more reasonable in the light of present day view on the molecular structure of ion channels. The LA is presumably bound to K channels by hydrophobic bonds. For a more detailed information about this issue we have to await 3D structure determinations. Meanwhile, we have to rely on results from mutation experiments and molecular dynamic calculations that are under way.

In a previous section we described how the oscillatory dynamics of hippocampal neurons are modified by a state-independent block (Figure 2). How does a state-dependent block of Scheme 1 type affect the dynamics? Figure 3c shows the results of such a comparison. It shows simulations of the same model hippocampal neuron as in Figure 2, modified by a state-dependent (middle panel) and a state-independent (lower panel) selective block of K channels. In both cases, a steady-state block of 50% was assumed. As seen, the two ways of blocking the channels show drastically different results. The state-independent block increases and the state-dependent block decreases the frequency of the oscillations. The reason for the differential result is that the state-independent block shortens the recovery time and poises the membrane at a level close to threshold while the state-dependent block induces a longer recovery time because of a 'foot-in-the-door' effect. The two types of mechanism thus theoretically disrupt oscillatory activity in different ways.

As repeatedly pointed out, general anesthetics act through a variety of mechanisms, including different forms of state-independent (ketamine, alcohols) and state-dependent

(LAs) block. Considering the accumulating evidence for an essential role of voltage-gated channels in anesthesia (see the discussion of selective sensitive K channels above), the simulation data presented here may explain some aspects of the varying profiles of the anesthesia induced by the anesthetics mentioned above.

CONCLUSIONS

In summary, we have to conclude that surprisingly little is known about the detailed mechanisms of anesthesia. Nevertheless, the fragmentary data presented above allow us to construct a minimal consensus view. Presented bottom-up wise, it assumes that general anesthetics modulate the activity of ion channels, the main targets being GABA_A and NMDA channels and possibly voltage-gated and background channels, thereby directly or indirectly hyperpolarizing neurons in thalamocortical loops, and thereby disrupting coherent oscillatory activity in the cortex. In our view, it does not seem unreasonable that the ultimate target is NMDA channels.

However, the explanatory gaps in this minimal scheme are obvious. At all organizational levels, the importance of an integrated approach is forced upon us. The two computational cases presented above are illustrative; subtle changes at the ion channel level cause drastic differences in the activity at the cellular level (Figures 2 and 3c).

As repeatedly stated, the problem to understand the mechanisms of anesthesia is closely related to the problem of determining the neural correlate of consciousness. Possibly, consciousness is a case of degeneracy, as discussed by Edelman and Gally (2001). Possibly, consciousness is caused by many interacting mechanisms, each in itself or in interaction with other mechanisms sufficient to create consciousness. Is it the degeneracy character of the neural mechanisms causing consciousness the reason for the difficulties to define its neuronal correlate? However attractive this idea may look, it seems contradicted by the remarkable fact that so structurally different compounds cause anesthesia, that is, the view that consciousness is such a vital function that it displays degeneracy. This rather suggests that anesthesia is a case of degeneracy (ie there are many interconnected ways for anesthetics to cause unconsciousness). This would suggest that unconsciousness, possibly like sleep, is an adaptive phenomenon. Populations of animals with brains that easily can switch from conscious to unconscious states have survival advantages compared to populations with more robust brains that resist unconsciousness. Such a view opens up new approaches to the problem. How it could be harmonized with the view that consciousness is degenerate is a theoretical challenge, reminding us of the close connection between the problem of anesthesia and the classical problem of consciousness.

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