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OPINION ARTICLE

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Understanding of anesthesia – Why consciousness is essential for life and not based on genes

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ABSTRACT

Anesthesia and consciousness represent 2 mysteries not only for biology but also for physics and philosophy. Although anesthesia was introduced to medicine more than 160 y ago, our understanding of how it works still remains a mystery. The most prevalent view is that the human brain and its neurons are necessary to impose the effects of anesthetics. However, the fact is that all life can be anesthesized. Numerous theories have been generated trying to explain the major impact of anesthetics on our human-specific consciousness; switching it off so rapidly, but no single theory resolves this enduring mystery. The speed of anesthetic actions precludes any direct involvement of genes. Lipid bilayers, cellular membranes, and critical proteins emerge as the most probable primary targets of anesthetics. Recent findings suggest, rather surprisingly, that physical forces underlie both the anesthetic actions on living organisms as well as on consciousness in general.

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Introduction

The discovery of human anesthesia in 1846, by William T. Morton, especially its fast and reversible induction by ether; marks new era in our understanding of life.[1-3] This was a unique discovery which rapidly revolutionized medicine, but turned out to be difficult to explain.[1,2] Despite numerous theories proposed our understanding of anesthesia remains obscure.[2,3] Among the many theories trying to explain anesthesia, 3 stand-out as the most influential. Firstly, Claude Bernard and his theory colloidal-coagulation of protoplasm,[2,4] followed by Hans Horst Meyer and Charles Ernest Overton with their "Meyer-Overton rule," based on lipid solubility of anesthetics, have dominated the field since the late 1960s.[2] In the 1980s, the protein/receptor theory became dominant in explaining anesthesia via proteins acting as specific receptors for anesthetics.[5] However, inconsistencies with this theory called for a further updates.[3,6-10]

All life can be anesthesized

The father of experimental biology, Claude Bernard, performed numerous experimental studies which allowed him to conclude "that all life is defined by the susceptibility to anesthesia."[2,11,12] Claude Bernard's paradigm is still valid today as all organisms, even prokaryotic bacteria, are sensitive to anesthetics.[8,9,12,13-15] Subcellular organelles such as mitochondria and chloroplasts are sensitive to anesthetics as well,[16-21] which is in line with the prokaryotic sensitivity of both membranes and proteins recorded in bacteria.[14,22-24] Finally, several subcellular processes based on the cytoskeleton, such as cytoplasmic streaming and phagocytosis, are inhibited by exposure to diverse anesthetics.[6,25-30]

Early evolutionary origins of anesthesia: Endogenous anesthetics help to cope with stress

As discussed by James Sonner, the variability in response to anesthetics is extremely small in comparison to other drugs.[8,31] Moreover, the wide molecular diversity of compounds acting as anesthetics is very large, and additionally, the mystery of universal sensitivity of all living organisms to these compounds remains. All this suggests, in line with the Claude Bernard thesis, that the ability to respond to anesthetics is essential for life.[8] One possibility proposed recently by James Sonner and Robert Cantor is the existence of endogenous anesthetics which modulate organismal consciousness.[9] In fact, there are several metabolites that induce

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loss of consciousness if available in sufficiently large amounts. Sonner and Cantor discussed some, for example, ammonia,[32] acetone, β-hydroxybutyric acid,[33] and propionic acid.[34] Importantly, protective actions of endogenous anesthetics are active at the lipid bilayer of membranes,[8,9,35] which explains why even bacteria are sensitive to anesthetics. In addition, the protective actions of anesthetics include also cardioprotection,[36-38] protection from retinal damages,[39] and immunoprotection.[40] Finally, due to their actions also on bacteria, anesthetics also have antimicrobial effects.[23,41]

Microbes, algae and plants release large amounts of volatile anesthetics

It is not generally appreciated that algae and plants release abundantly volatiles including well-known anesthetics such as chloroform, divinyl ether, ethylene, and methyl halides,[42-48] as well as n-alkanols which also have anesthetic actions.[49,50] Plant volatiles are released in such large amounts that they have a strong impact on the Earth's biosphere and atmosphere.[43,47] Importantly, algae and plants release these substances especially if under stress.[44,46,48] In addition, the anesthetic nitrous oxide is released into atmosphere in large amounts from soils and oceans.[1-53] Unfortunately, the authors of these papers fail to mention and discuss the fact that many of these stress-released algal, microbila and plant volatiles are also anesthetics. For example, nitrous oxide is almost exclusively regarded as a greenhouse gas, whereas divinyl ether is discussed typically as oxylipin[54,55] and ethylene as plant stress hormone.[56,57] However, the possibility that stressed organisms produce anesthetics to cope better with their stress should be considered. Besides classical anesthetics, stressed plant synthesize and produce many pain-relieving compounds,[58-62] including ethanol which is produced in plants via the synthetic activity of alcohol dehydrogenase, which acts in reverse in plants.[63,64] In stressed roots, for example, all 3 endogenous anesthetics (ethylene, divinyl ether, ethanol) are co-produced, which suggests delicate control of putative, still hypothetical, plant anesthesia. Relevant in this respect is the fact that all these 3 endogenous anesthetics are co-produced also in plant fruits, which flowering plants have evolved to be eaten alive by diverse animals. Moreover, ethylene, ethanol and other anesthetics also act to break the dormancy in plant seeds.[65]

Surprising status of ethylene: Ancient endogenous anesthetic essential for life?

Ethylene, a hydrocarbon and the simplest alkene, is a colourless flammable gas, which is widely used in the chemical industry. In biology, it is most famously known as a plant stress hormone. Less known is that ethylene is a very potent general anesthetic, which was used in human surgery as it has minimum side-effects and recovery from anesthesia is very rapid.[66-68] Ethylene has similar physical and lipid solubility properties to xenon,[66] and both these anesthetics have the least side effects. Importantly, not only plants, but also bacteria, fungi, algae and lichens are known to produce ethylene when under stress.[69-80] This suggests that ethylene is a molecule with fundamental relevance for life. On the basis of the anesthetic properties of ethylene and ether, Chauncey Leake synthesized divinyl ether, and showed that it had excellent anesthetic properties.[81,82] Divinyl ether maintains all the positive properties of ethylene, but is also more potent.[83] Intriguingly, stressed plants produce endogenously both ethylene and divinyl ether.[84-87] It is becoming obvious that plants, and their endogenous anesthetics, will turn out to be highly relevant for our understanding of the evolutionary origins of anesthesia. Very relevant in this respect are local anesthetics most of which are derived from the plant alkaloid cocaine.[88,89] Interestingly, there are also other plant alkaloids with properties of local anesthetics; such as atropine,[90] menthol,[91,92] and several other alkaloids.[93,94]

The relevance of endogenous controls over anesthesia for behavior and survival

A coherent and robust concept is emerging from the data discussed in this paper, which suggests that endogenous anesthetics are essential for the survival of plants, allowing them to cope with stress, to enter and break dormancy, as well as to generate tasteful fruits 'designed' to be eaten alive by animals and humans (for the sake of effective reproduction of flowering plants). Similarly, bacteria and fungi generate ethylene under stressful situations and there are several indications of endogenous anesthetics in animals and humans. In metabolic human diseases, several metabolites with anesthetic features accumulate in such amounts that they can impose temporary or permanent loss of consciousness (reviewed in ref. 9). Relevant in this respect is the well-known phenomena of transient loss of consciousness (sometimes referred as syncope, fainting, or blackout) which can be induced by diverse stress situations, serious wounding, as well as by powerful emotional stresses.[95-99] Transient loss of consciousness apparently has relevance to survival. It was proposed that this phenomenon has evolved in ancient times as an effective defense mechanism;[97,99] providing, in addition, protection against sensory overload. Moreover, it might also be the case that some of the numerous examples of so-called apparent death

(*thanatopsis*) behavior in predator-threatened animals are not the result of deceptive/ mimicry behavior by the animal, (as typically interpreted) but rather due to the syncope-like transient loss of consciousness. Even at the cellular level, both stress and anesthetics can have similar paralyzing outcomes.[100-102]

Since ancient times, humans have been using natural anesthetics produced by plants and fungi to impose anesthesia, induce altered sensory states as well as psychedelic experiences.[60,61,63-106] In fact, human evolution is well known to be shaped by the consumption of alcohol.[107-109] This feature is shared not only with apes[110] but also with other animals such as wild treeshrews,[111] and even insects, which can also develop alcoholism under stress challenges.[112-114]

Furthermore, there are several similarities between the deep phases of sleep (REM sleep) and the state of anesthesia.[115-117] Although sleep and anesthesia are different phenomena, the underlying neuronal processes are common for both forms of the loss of consciouseness.[117-119] Although the precise roles of sleep and anesthesia are not fully understood yet, it is clear that sleep is essential for cognitive and survival reasons.[120-122] For example, REM sleep was proposed to generate a proto-conscious states relevant for the formation of the full-blown waking consciousness.[123] Similarly sleep and anesthesia are under endogenous control,[124] suggesting that the state of anesthesia has important, albeit still elusive, functions for organisms. Importantly, the sleep/ waking cycle controls sensitivity to anesthetics in Drosophila.[125] Relevant in this respect are also numerous examples where pain perceptions have been shown to be affected by expectations, cognition and meditation.[126-128] Moreover, pain responses in humans are mediated not only via conscious but also via unconscious processes.[129-131] Finally, there are close similarities between anesthesia and coma.[132]

Genes are not involved in switching off/on of consciousness via anesthetics

Anesthetics provided in the appropriate concentrations switch-off human-specific consciousness within a few seconds, precluding any role whatsoever for DNA and gene expression in those actions (Fig. 1). If anesthetics are maintained at their active levels, loss of consciousness is permanent as long as the anesthetics are present at critical levels. After their removal, the recovery of consciousness is often very rapid. Although some anesthetics have side effects, and can even be toxic (e.g. chloroform), the most effective ones – for example xenon, ethylene, and vinyl ether allow fast and smooth recovery. Again, the speed of regaining the consciousness precludes any active role for gene expression also in this process (Fig. 1). Of course, genes are relevant for the sensitivity of organisms to anesthetics and several mutants have been characterized which are less sensitive, or even not sensitive at all, to some of the anesthetics. But this is just due to the modifications or absence of critical proteins and membranes (Fig. 1) which induce the anesthetic action. The absence of gene involvement should not necessarily be surprising. Human erythrocytes, which have no nucleus and therefore no genes, still undergo the complex cellular process of circadian rhythm.[133] Genes may act to adjust circadian rhythm for variation in the regularity of the day/ night cycle, as, for example, incurred by traveling to other time zones, but they are not causal in circadian rhythm itself. This is clearly demonstrated by incubating 3 enzymes extracted from cyanobacteria with ATP: a relatively temperature independent 24 hour cycle of phosphorylation of one of the enzymes is observed.[134]

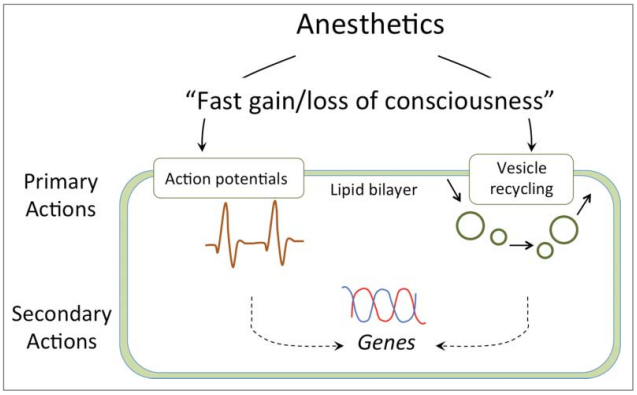

Figure 1. Fast loss and gain of consciousness after exposure and removal of anesthetics is based on primary processes linked to the plasma membrane (ion fluxes, electric activities, endocytic vesicle recycling), whereas changes in gene expression are playing only secondary roles.

Why are neurons exquisitely sensitive to anesthetics: clues from plants and chloroplasts?

There are several mysteries associated with anesthetics and anesthesia. One of them is the fact that neurons are more sensitive to anesthetics compared to other cells. Claude Bernard was the first to realize that depending upon concentration of an anesthetic, there are several stages of anesthesia. The first is loss of awareness and pain perception, but all vital biochemical processes are unaffected, the second is inhibition of respiration and other biochemical processes, the third is the loss of ability of all cells to react to stimuli and the cessation cilia movements and heart beating.[11,12] In humans, minimal alveolar concentrations (MAC) concept was introduced

to characterize the potency of inhalational anesthetics.[135] At 0.1- 0.3 MAC, most humans show sensory distortions, memory loss and sleepiness; at 0.3- 0.5 MAC, responses to verbal commands cease and loss of consciousness occurs; at about 1.0 MAC, insensitivity to noxious stimuli occurs.[68,135] This marked concentration dependency of anesthetic potency suggests that some cells, or cellular processes, are more sensitive than others due to perhaps a higher number of the critical binding sites for the anesthetics. In neuronal assemblies, there are large numbers of excitable cells organized, via synaptic cell-cell adhesions, into higher order cellular assemblies. These communicate via action potentials and accomplish synchronous and coherent oscillations dependent on sensory stimuli. It is perhaps important that the plasma membrane at synapses is actively engaged in the endocytic vesicle recycling, amplifying the critical area of membranes significantly and underlying the high excitability of neuronal membranes.[136-138] The high electrical activity of neurons is related to their active maintenance of the physical properties of the lipid bilayer and the internal physico-chemical properties in the fluctuating cellular environments. Anesthetics and action potentials are highly relevant in this respect.[8,136,139] Surprisingly, although plant cells are sometimes considered not to be excitable,[136,137] the opposite is true.[12,139-147] In plant cells, action potentials, vesicle recycling, and sensitivity to anesthetics seem to be related to the active protection of the plasma membrane against ionic and structural disturbances.[12,139,147-153] These issues are prominent especially in neurons and specialized root apex cells both of which are very active in both electrical activities and endocytic vesicle recycling.[143,147] For both neurons and specialized plant cells, the endocytic (synaptic) recycling apparatus enhances the sensitivity to anesthetics due to large area of plasma membrane and the associated recycling vesicles, which is supported by the dynamic cytoskeleton.[147,154-156] It is emerging that these unique properties of brain neurons and plant root apex cells makes them exquisitely sensitive to anesthetics (Fig. 2).

Claude Bernard was the first to note that chloroplasts and their photosynthetic pathways are more sensitive to anesthetics than mitochondria and their respiratory pathways.[12,25] One of the striking differences between chloroplasts and mitochondria is stacking of internal chloroplast membranes into synaptic-like assemblies known as thylakoid grana which are essential for the photosynthetic pathways.[157] Intriguingly, in this respect, synaptic-like MORN-domain proteins have been reported for the thylakoid proteome.[158] On the other hand, internal membranes of mitochondria are much simpler and never form such prominent membrane

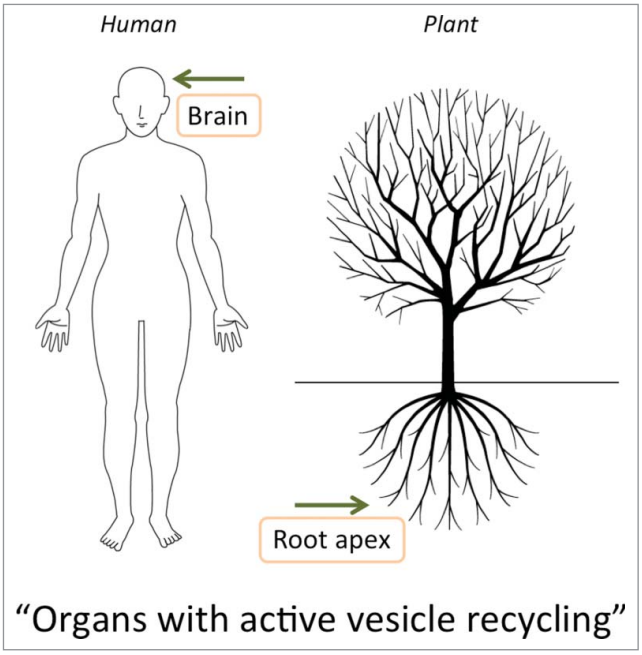

Figure 2. Both in animals and plants, organs with the highest activities of endocytic vesicle recycling and electric activities are implied in loss of consciousness (motility, sensitivity, and behavior).

stacks. Moreover, synaptic-like proteins including synaptotagmin-like E-SYT, yeast tricalbins and plant SYTs localize to membrane adhesions between intracellular organelles including plasma membranes, nuclei, mitochondria, chloroplasts, peroxisomes, ER membranes, and lipid bodies.[159-161] We are proposing that synaptic-like[157] stacking of thylakoid membranes into prominent chloroplast grana[162,163] is behind the higher sensitivity of the chloroplast photosynthesis to anesthetics[25] in comparison to the mitochondrial respiration (Fig. 3).

Physical nature of anesthesia and consciousness

The unique aspect of anesthesia and consciousness is that these deep mysteries challenge both biology and physics. In fact, there are many aspects of the actions of anesthetics on all life which implicate a profound physical basis for both anesthesia and consciousness. Action potentials have not only electrical, but also mechanical aspects, as they change significantly plasma membrane thickness and even the length of electrically active neurons.[164,167] Moreover, protein activity is also highly dependent on physical factors. For example, the tertiary structures of proteins are easily deformed and this affects their activity.

Interestingly, action potentials also generate heat in excited membranes[168-170] which then unfolds proteins and fluidizes lipid bilayers.[171] Also anesthetics unfold proteins and induce fluidization of lipid bilayers.[171-173]

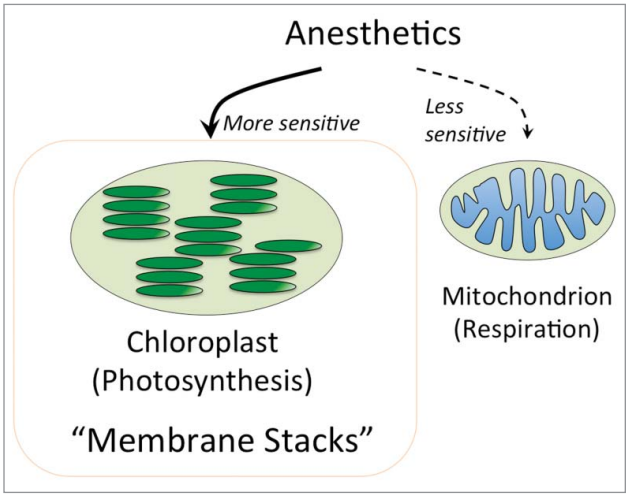

Figure 3. Claude Bernard discovered higher sensitivity of photosynthesis to anesthetics in comparison to respiration.[12,25] Chloroplast accomplish photosynthesis on stacked membranes know as thylakoid grana[162,163] which can be considered for inter-organellar synapses.[157] We propose that these stacked membranes are not only essential for photosynthesis but also makes this process more sensitive to anesthetics.

Importantly, the potency of anesthetics in inducing the loss of motility and consciousness decreases with the temperature increasing.[174-176]

Recent advances with xenon anesthesia strongly suggest that the currently favored proteins/ receptors model of anesthetics actions will require a serious update toward including the lipid bilayer as the primary target of xenon. This unique simple noble gas is chemically inert and acts on membranes only through its physical properties.[177,178] The physical nature of both anesthesia and consciousness is implicated also with the reversal of anesthetic induced loss of consciousness by high pressure. This pressure reversal was discovered by Johnson and Flagler who showed that anesthesized tadpoles regain activities at pressures of about 50 bar.[178] Since then this observation has been confirmed with many other organisms and also with diverse anesthetics. With respect to xenon, high pressure was shown to prevent free xenon diffusion within lipid bilayers and xenon was pushed out to accumulate in the middle of the lipid bilayer.[177] Furthermore, xenon was found to modulate the bilayer lateral pressure profile in a reversible fashion.[178] Xenon-induced changes to the critical proteins may be only the secondary consequences of these physical effects of xenon on lipid bilayers.[178,180] Alternatively, there might also be a genuine direct effect of xenon on proteins via their hydrophobic pockets. Intriguingly, xenon rapidly reverses electron spins and these electron spin effects were found to be different in Drosophila mutants which did not respond to the anesthetics.[10] The next perplexing finding is that both local and general anesthetics show similar physical effects on membranes by lowering their melting temperatures and this anesthetic effect is reversed by high pressure.[167,181,182] There are further issues suggesting that physical phenomena are related to both anesthesia and consciousness based on quantum aspects of physical reality.[7] In conclusion, solving of theses mysteries will be based on both, biology and physics, and relevant to both. This fundamental advance in our knowledge will help to understand the basic question of biology posed by the famous physicist Erwin Schrödinger: 'what is life?'.[183]

The implications of a lack of a role for genes in consciousness

As noted above, the rapidity of the switching on and off of consciousness by anesthetics precludes a role for the necessarily slower action of gene expression. It can be argued that genes are in fact only necessary to 2 quite small, but nevertheless important, aspects of the life process, namely reproduction and the storage of necessary data (base sequence) to transcribe the peptides essential for the cell to function.[184] On this model, organisms as we know them today, were preceded by metabolizing proto-cells based on proteins; which regulated themselves in order to realize a proto-phenotype with the ability to engage in purposeful behavior. Such cells could not replicate themselves, but divided due to stresses on the cell membrane. The crucial step to true life as we know it was to recruit nucleobases to encode peptide sequences in DNA, thus allowing true replication and evolution to more complex organisms to commence. It has long been known that even the most primitive of organisms are capable of *purposeful* behavior[185-187] and that this can only be due to cellular proteins processing environmental information detected at the cell membrane.[188] Enucleated cells commutate with nucleated cells, obtaining small molecules to correct the deficient cells,[189] but are also able to survive up to several months[190,191] and organize their circadian clocks without any DNA and gene expression.[133] These considerations lend weight to the proposal that anesthetics act by disrupting the activity of proteins as enzymes,[5] specifically the (mostly not understood) processes in protein information processing, perhaps with those associated with membranes.

Outlook

Although it is not clearly stated by most of the authors discussing consciousness, and some even claim that consciousness is an epiphenomenon, it is very obvious that consciousness is essential for survival and life in general.[192,193] Anyone of us losing consciousness would not

be able to survive a few days without the devoted assistance and help from our fellows. Similarly, life is not possible without recognizing danger via pain[194] and other kinds of negative experiences safeguarding survival,[195-197] all based on consciousness. It is obvious that consciousness is essential for any organism to have online access to their sensory information about their environments.[193,198] Importantly, consciousness gives all organisms ability to act as agents of their own interest[199,200] which is essential for their survival. This is essential for organisms to navigate successfully in complex environments that challenge their survival.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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