Is General Anesthesia Modulated By The Viscosity and Volume of ISF?

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ABSTRACT

The cause of anesthesia is still unknown, despite the excessive usage and the perfection of its application. The multifactorial nature of the phenomenon and the failure of many theories thus far have consolidated the belief that there is no unifying hypothesis. We think otherwise. The physical aspects of anesthesia lead us to a single cause. We regard anesthesia as the cessation of the dynamic structural connectivity of the brain. This perspective reveals the viscosity and volume of ISF as the main factors that modulate anesthesia. We formulate our theory as a set of hypotheses that form a consistent basis. We try to back up each hypothesis with the available knowledge and we make some speculative extrapolations in order to create a complete framework. We clearly point out the open issues that need further observation and discuss the ways for verification. In the end, if viscosity and volume of ISF are the main factors modulating anesthesia, as we conjectured, its consequences will not be limited to the very concept of anesthesia but will reach to understanding of the mechanisms of memory formation, analgesia, and consciousness. Surprisingly, it can also shed light on a seemingly unrelated phenomenon: epilepsy, which can be considered a dual case of anesthesia.

Key Words: General anesthesia, ISF, viscosity of ISF, hydrophobic pockets, hyperbaric anesthesia, pressure reversal affect, critical volume hypothesis, cortical traveling waves.

INTRODUCTION

General anesthesia is the temporal suppression of the Central Nervous System (CNS) that results in the loss of sensation and awareness. The usage of anesthesia dates back to antiquity. In order to decrease the pain and suffering, opium and cannabis were utilized as well as physical methods like cold, nerve compression, and even infliction of a cerebral concussion [1].

The advance of modern chemistry yield a better understanding of chemical agents. The anesthetizing effect of nitrous oxide was first discovered by a dentist in the 19th century [1]. As a result of subsequent research and findings, anesthesia is now an indispensable part of modern medical practice.

There are now various anesthetics that are administered with precise procedures comprised of completely empirical observations. This is because, the mechanism of anesthesia is not known [1, 2]. Although the field is quite mature from the practical point of view, there is still no theory that can explain every aspect of the phenomenon. The complexity of the problem, failure of the proposed theories, and seemingly contradictory aspects lead to the widely accepted current belief that there is no unitary theory of anesthesia [1]:

> "Discovery of a single fundamental mechanism, which seeks to explain the whole of anesthesia ... , has become less and less likely in recent years. The state of anesthesia is more likely based on many different effects and on multiple molecular biological targets. These integrative thoughts sum up the multiple target hypothesis."

We think otherwise. We posit that anesthesia is a completely physical process. We base our perspective on well-established facts, a speculative mechanism that modulates the dynamical

connectivity of the brain [3], and some speculative extrapolations that require validation with future observations. In the end, we provide a simple unitary theory of anesthesia that is capable of explaining all of its aspects.

The knowledge of the correct mechanism of anesthesia will be helpful for the betterment of the medical practice. Even though marginal, there are still some shortcomings of anesthetic agents. For instance, early exposure to high amounts of anesthetics may cause bad results on the structure of the brain [4]. Therefore, the quest for better anesthetics is still an important issue. However, we believe that the knowledge of the correct mechanism will produce far more significant results in other fields where the mechanism of anesthesia is involved or correlated. These fields are short-time memory, sleep, consciousness, and epilepsy, which we view as a negatively correlated phenomenon to anesthesia.

GENERAL ANESTHESIA

General anesthesia suppresses CNS and results in analgesia, amnesia, immobility, and loss of consciousness. These effects are temporary. In general, there is no permanent residue. Transition to anesthesia during administration is gradual. Similarly, emergence from anesthesia is also gradual. Functions are lost and regained in a specific order [5]. The duration of anesthesia depends on the type of anesthetic and the administered dose [6].

Anesthesia causes such profound changes in the brain state that there are many target sites of action at different hierarchic levels: molecular, subcellular, cellular, local microcircuits in cortex, thalamus, hippocampus, cerebellum, and spinal cord [7]. Potential pharmacologic target sites of anesthetics are inhibitory GABA (ex: halothane is an GABA agonist) and

excitatory glutamate receptors (ex: ketamine is an NMDAr antagonist) [8], voltage-gated ion channels, glycine receptor, and serotonin receptor [9].

There are two types of anesthetics: intravenous and inhalational. Intravenous anesthetics include propofol, sodium thiopental, etomidate, methohexital, and ketamine. Inhalational anesthetics include desflurane, isoflurane, nitrous oxide, sevoflurante, and xenon. Each anesthetic produces different effects at different sites. Their molecular structures are very simple and so diverse that there seems no obvious structure and activity relationship.

There are many theories that attempt to explain anesthesia. One of the earliest ones is Meyer-Overton theory, which states that the potency of an anesthetic is directly proportional to its lipid solubility [2]. This theory states that general anesthetics diffuse through the cell membrane and directly affect the lipid bilayer. However, lipid theory can not explain how general anesthetics can act so quickly, why different general anesthetics can have different potencies, and why general anesthetics are more potent in some cell types than others. For instance, xenon is a potent anesthetic gas but is very insoluble in lipids [10]. Furthermore, increasing the chain length of a hydrocarbon-based anesthetic beyond a certain size decreases its anesthetic potency (cut-off phenomenon) despite a further increase of its lipid solubility [11]. These drawbacks led to the development of protein-based theories of general anesthesia.

The main idea behind the protein-based theory is that the main sites of anesthetic action are the ion channels and neurotransmitter receptors on the neuronal cell membranes [2] and observations show that clinically relevant concentrations of many anesthetics modify the activity of ion channels and receptor proteins [11]. However, all anesthetics do not have the same effect at the same site. Additionally, chemically inert noble gases, which act as anesthetics, do not interact with proteins chemically. Furthermore, protein-based theories fall

short to explain the physical aspects of anesthesia (i.e. its relation to pressure, volume, and heat).

PHYSICAL ASPECTS OF ANESTHESIA

Anesthesia is not merely a biological phenomenon. In addition to chemicals, physical conditions affect it and in some special cases induce anesthesia alone.

Pressure

Anesthesia is tightly coupled to pressure. Under hyperbaric conditions (pressure levels higher than atmospheric pressure), nitrogen and noble gases such as argon, krypton, and xenon become anesthetics [2]. However, hydrogen, helium, and neon have no anesthetic effect at any pressure [12]. Helium and neon do not show anesthetic action before the convulsions that are followed by death [2]. Krypton shows anesthetic effects at higher pressures than Xe [2]. There seems a negative correlation between the atomic weight of the gas and the required pressure.

Even more intriguing is the pressure reversal effect. The effect of various anesthetics species can be reversed by application of high pressure conditions [2]. Hyperbaric pressure causes anesthetized animals to emerge from anesthesia [13]. This pressure reversal effect was discovered by Johnson and Flagler [14], who showed that anesthetized tadpoles regain normal activities at high pressures. Since then this observation has been confirmed with many other organisms and also with diverse anesthetics [15].

A related intriguing phenomenon is the analgesic effect of the sound. In a very recent work [16] neural circuitry behind sound induced analgesia is spotted in mice for the first time. This

is a significant sign that sound can alter the neural circuitry responsible for analgesia. Although the mechanism is not known, the pressure of the sound waves might have a role.

Volume

Changes in the volume are observed in anesthesia. Critical volume hypothesis [17] is one of the earliest hypotheses. The underlying idea is that anesthesia occurs when the volume of a hydrophobic region is expanded by a critical amount [17]. Observations support the correlation between volume expansion and anesthesia. Conversely, volume compression is accompanied by convulsion.

Critical volume hypothesis remains controversial since the observations can also be explained in terms of displacing the anesthetic from protein-binding sites [9].

Heat

The relation between heat and anesthesia is known even in antiquity. For instance, cold was applied for its analgesic effect [1]. A concomitant reduction in brain temperature is observed under anesthesia [18, 19].

Thermoregulation is a significant concern in operations. Inadvertent perioperative hypothermia is a common occurrence with both general and regional anesthesia [20]. Apart from environmental and body heat difference, intra-body heat distribution is altered differently under anesthesia. During craniotomy in cats, anesthesia can reduce brain temperature independently of core temperature [21]. A possible reason is that anesthesia reduces the metabolic rate and associated brain heat production [21]. In a very recent in vivo magnetic resonance thermometry observation, brain (white matter) temperature of canines is decreased more than threefold (4.8 ºC vs 1.4 ºC) than rectal temperature [22].

Heat is also effective in the recovery duration. In adult rats, applying pre-warming prevents peri-anesthetic hypothermia and also shortens the recovery duration [23]. There seems a linear relation between warming amount and recovery rate: recovery was significantly faster in the pre-warmed group, which is followed by the limited-warmed group and then the not-warmed group [23].

Application of heat increases neuron firing rates. For instance, increases in neuronal firing rates are reported in vivo with illumination-induced heating of 1 ºC [24]. Therefore, temperature reduction in anesthesia is compliant with the reduced excitability of neurons. However, it is not clear if the temperature reduction is a consequence of anesthesia or if it has a causal effect on anesthesia.

BRAIN INTERSTITIAL FLUID (ISF)

The physical aspects of anesthesia can not be understood without taking into account the environment of neurons, which is the brain interstitial fluid (ISF). Neurons and glial cells are surrounded by ISF and the extracellular matrix (EM) that forms the interstitial space (ISS). The brain ISS occupies approximately 15%-20% of the total brain volume [25]. It is an irregular, tortuous, and narrow space that can be as narrow as 20 nm at the synapses [26].

ISF is a water solvent that contains ions, gaseous molecules, neurotransmitters, proteins, and organic molecules [26]. There is a continuous and extensive transfer between cerebrospinal fluid (CSF) and ISF. CSF can also be considered as a reservoir responsible for the waste removal of ISF [27]. Approximately 20% of CSF originates from ISF [28, 29]. The main difference between CSF and ISF content is that ISF has about 2.5 times higher protein concentration [30]. The blood-brain-barrier (BBB) allows the passage of water, small

hydrophobic molecules (such as O_2, CO_2, hormones), and lipid-soluble molecules by diffusion, and selective transport of molecules such as glucose and amino acids by facilitated diffusion or active transport [31, 32].

The contents of ISF have a broad spectrum of physical and chemical properties, such as molecular size, water or lipid solubility, charge, and concentration [26]. The geometry of ISS sets the boundary conditions of the fluid flow in ISF [26, 33]. This geometry is very complex and can be characterized by many physical attributes: tortuosity, pressure, boundary area, boundary friction, surface elasticity, and boundary permeability [26].

The heterogeneous contents of ISF complicate the fluid flow further. The physical attributes of ISF contents that influence the fluid flow are: viscosity, osmolarity, mass density, electrical conductivity, thermal conductivity, and concentration [26]. The resultant flow velocity and diffusion rate of the fluid flow in ISF depend on all the previous attributes. We should also consider the temporal aspect of transport in ISF to have a better understanding of the complexity. Human cortical fast-spiking neurons can reach to instantaneous spiking rate of 453 Hz [34], which corresponds to a tremendously fast ion movement and that constitutes only a portion of the flow in ISF.

This highly complicated nature of ISF rightfully leads to the idea of the lack of a unitary mechanism of anesthesia if we focus on a single molecule or a biological subsystem. Because each component may involve in the process and sometimes in a contradictory way. If there is a unitary mechanism of anesthesia, then it should be of a more fundamental nature. To us, this nature can be nothing but physical. In the following section, we introduce such a physical understanding of anesthesia.

THEORY

The following set of hypotheses form the basis of the theory we propose:

Hypothesis 1: General anesthesia occurs as a result of the cessation of the dynamic structural connectivity of the brain.

Hypothesis 2: Dynamic connectivity depends on the physical aspects of the ISF.

Hypothesis 3: Environmental physical factors and administered chemicals change the physical aspects of the ISF.

Hypothesis 4: Administered chemicals that increase the viscosity of the ISF cause anesthesia.

Hypothesis 5: Induced anesthesia depends on the environmental pressure, the volume of the ISF, and heat.

Hypothesis 6: The rate and duration of the anesthesia depend on the amount, administration rate, and interaction of anesthetics with the molecular ingredients of the ISF.

Explanation and Supporting Evidence

Hypothesis 1 is the main base of our theory. We associate cognitive and perceptive functions of the brain (that are suppressed during anesthesia) with the dynamic connections in the brain. We envisage brain connectivity as being composed of two modes: stationary backbone and dynamic connections [3]. The stationary part has strong synaptic connections and can not be altered with immediate stimuli. On the other hand, dynamic connectivity is a function of the immediate stimuli and is responsible for the continuous adaptation to the environment. It is not unnatural to associate high-level cognitive and perceptive functions with dynamic connections since they are in continuous interaction with the external stimuli and the need for

immediate response eliminates the possibility of a learning procedure within a stationary network structure. How the external stimuli modulate this dynamic connectivity is not known but the electrokinesis hypothesis proposes a possible answer [3].

The association we make explains the temporary effect of anesthesia. Only dynamic connections are inhibited, which halts perception and cognition. On the other hand, the stationary backbone remains intact. After the effect of anesthesia is diminished, dynamic connection capability is regained and the brain continues to function from the previous state, which is encoded in the stationary backbone.

Reduction in functional connectivity under anesthesia is evident [35]. Brain activity in higher-order information processing regions is attenuated but not in the primary sensory areas [35]. That is, information transfer is not completely blocked. The connectivity of some regions is preserved. For instance, the connectivity of the posterior cingulate cortex, which is a major hub in the default mode network, is preserved under anesthesia [36]. Interestingly, unconsciousness processing of some stimuli is increased under anesthesia [35]:

> "Paradoxically, in some brain regions, scrambled words elicited greater activation than regular words during anesthesia, perhaps reflecting a greater effort to analyze word meaning. Both primary and association auditory cortices remained responsive to auditory stimuli, but the responses became nonspecific, suggesting a loss of higher level analysis."

These are functional connectivity observations. They do not guarantee physical connectivity changes as we imagine. For this purpose, we refer to cortical traveling waves. In a recent study [37], it is observed that propofol-induced anesthesia drastically alters cortical oscillations. The power (and hence range) and coherence of low-frequency cortical traveling

waves are increased. On the other hand, high-frequency waves are decreased and become more incoherent. A similar high-frequency activity attenuation is observed in rat brains [38]:

> "We found that isoflurane did not block the transmission of all electrical signals equally; the anesthetic had the strongest effect on higher frequency impulses that are required for functions such as cognition or movement, whilst it had minimal effect on low frequency impulses that control life-supporting functions, such as breathing.".

Although the reason is not known, we posit that dynamic physical connections can explain this phenomenon. The existence of dynamic connections increases the neuron spiking rate and as a result induces high-frequency oscillations, that also trigger the adjacent regions, in the cortex. When these dynamic connections are suppressed or decreased, the spiking rate is reduced and hence the frequency of the oscillations is decreased.

Hypothesis 2 states that the physical properties of ISF have an influence on the dynamic connectivity. Instantaneously changing physical connection likelihood of presynaptic boutons on axon terminals and dendritic spines depends on the physical environment the neurons reside in. The physical distance in between and the force exerted upon them to cause movement depend on the volume of ISF, applied pressure, and heat.

Hypothesis 3 is a straightforward consequence of Hypothesis 2. If dynamic connectivity is a function of the physical aspects of ISF, then one can alter dynamic connectivity by altering the physical aspects. This can be achieved by either changing volume, pressure, and temperature, or inserting chemicals that will change the viscosity of ISF.

Hypothesis 4 describes the mechanism that certain chemicals cause anesthesia. The chemicals that increase the viscosity of ISF reduce the contact likelihood of neurons by limiting the free

movement of axon terminals and dendrites. This, in turn, results in the cessation of the dynamic connectivity and anesthesia arises.

Big chemicals increase the viscosity of a fluid. This phenomenon was first noticed by Marshall and Mertzner [39] when they inserted long-chain polymers into oil, they observed that the fluid flow became much more viscous. Flow resistance generally emerges in a porous medium, rather than bulk solutions [40]. The geometry of ISF is such a porous medium. There exist local dead-space microdomains in ISF, that transiently delay the diffusion of substances [41]. Molecules that enter such a dead-space are constrained for a while before leaving [41]. This indicates that the viscosity of the ISF is heterogeneous and can be changed according to the contents. Hence, administration of external molecules into ISF may drastically alter its viscosity. The ones that increase the viscosity above a certain threshold have an anesthetic effect. Supporting evidence comes from a very recent in vivo diffusion MRI observation. Lindhardt et al. [42] observed significantly decreased diffusivity in the extracellular space of the anesthetized mouse brain with respect to the awake state.

Hypothesis 5 encapsulates the physical factors that influence anesthesia by means of their effect on dynamic connectivity.

Anesthetic state corresponds to high viscosity and enlarged volume of ISF. The effect of temperature is straightforward because viscosity strongly depends on the temperature. For liquids, viscosity decreases with increasing temperature in general.

Increasing the volume of ISF decreases the contact likelihood of neurons and hence the dynamic connectivity. An increase in the volume of extracellular space under anesthesia is evident. It forms the basis of the critical volume hypothesis [12] and is observed consistently [42].

The pressure issue is more complicated. Under constant temperature, the result of increasing the pressure is volume reduction. This corresponds to more excitability (i.e. the reverse of anesthesia) of neurons according to our theory. Pressure alone has a positively correlated influence on neural excitability [14]. To us, this is the underlying mechanism of the pressure reversal effect [13].

Hyperbaric anesthesia of gaseous contradicts this explanation. We think this is due to the hydrophobicity phenomenon. Proteins have hydrophobic pockets (cavities) that determine their interaction with water. Gas molecules fill these hydrophobic pockets under hyperbaric pressures [2]. Hydrophobicity decreases viscosity [43]. Hydrophobic materials do not interact with water and hence the water flows more easily, appearing less viscous. Therefore, once the hydrophobic pockets of proteins are filled, their hydrophobicity decreases, and the viscosity increases, which decreases the dynamic connectivity and causes anesthesia.

There is an inverse relationship between the atomic number of the gas and the hyperbaric anesthesia. For instance, Kr shows anesthetic effects at higher pressures than Xe [2]. Interestingly, smaller atoms do not have an anesthetic effect at any pressure: “He and Ne do not show any anesthetic action before the onset of convulsions (followed by death)” [2]. This phenomenon can be explained as follows: Gas atoms start to enter into the hydrophobic pocket with increasing pressure. Larger ones are more likely to stay in the pocket at the same pressure. To keep the small atoms in the pocket, more pressure is needed. For the smallest ones, this high level of pressure can not be reached before death.

Hypothesis 6 describes the interaction of the anesthetics within ISF and its consequences on the rate and duration of anesthesia. The amount of the administered anesthetic is positively correlated with the viscosity increase. In the limiting case, lethal overdose occurs when too much anesthetic is given. This level corresponds to a severe viscosity increase that results in

the collapse of the autonomous systems. The rate of administration is also effective on the viscosity, which will result in anomalies [40]. Thirdly, the interaction of anesthetics (excluding the inert gaseous) with the ingredients of the ISF is also important. Their interaction with other molecules and involvement in metabolic processes will alter their influence on the viscosity change and duration of their effectiveness.

DISCUSSION

The proposed theory of anesthesia introduces a consistent and unified framework, unlike available theories that fail short to explain all aspects of the phenomenon, especially the physical ones. However, there remain two major open points that should be addressed. The first one is the a priori assumption, which is the association of dynamic connections to the high-level functions. The second one is the fact that not all molecules that pass the body-brain-barrier behave as anesthetics. In this section, we address these issues as well as our remarks on the verification of the proposed theory.

Attenuation in the activity of the higher-order function regions and functional connectivity under anesthesia is evident. However, functional connectivity is not equal to structural connectivity. Nevertheless, they are not completely unrelated: “although resting state functional connectivity is variable and is frequently present between regions without direct structural linkage, its strength, persistence, and spatial statistics are nevertheless constrained by the large-scale anatomical structure of the human cerebral cortex” [44]. To us, the large-scale anatomical structure that constrains functional connectivity is the stationary backbone. The dynamic physical connections are too rapid and short-lived that they are not observable

exactly. However, they are capable of exciting the neighboring neurons and establishing functional connectivity.

Anesthetics are not the only molecules that pass the body-brain-barrier. Every external material inserted into ISF should have an impact on the viscosity of ISF. This impact would be different for each material. Even, the amount of anesthetic required for complete anesthesia is not equal for every person [45]. The material, that increases viscosity above a threshold, is anesthetic. The decreased diffusivity in extracellular space under anesthesia is a promising indicator. However, in order to reach a strict conclusion, the effect of each anesthetic on the viscosity of ISF should be in vivo observed and compared to non-anesthetic materials.

Another verification experiment can be performed by means of temperature. Warming decreases the recovery duration in rats [23]. We expect a similar outcome in humans. The reverse should also be true. Cooling should elongate the recovery. Furthermore, if cooling can be applied solely to ISF, it should cause anesthesia-like consequences.

CONCLUSION

Contrary to the widely-acknowledged belief that general anesthesia does not a have unique mechanism, we think that its physical aspects point to a single mechanism. In this work, we propose such a unified theory of anesthesia. Although the speculative parts of the proposed theory require further observation for verification, it is capable of explaining all aspects of general anesthesia in a unified and consistent manner, unlike any other theory introduced hitherto.

If the proposed hypothesis is correct and the viscosity and volume of ISF are the major factors of the mechanism of anesthesia, its consequences will not be confined to anesthesia. Actually, its impact on other phenomena will be much more beneficial and profound. It will be helpful to understand the mechanisms of the short time memory, sleep, consciousness, and more importantly with regard to its benefits, epilepsy, which we consider as the dual case of anesthesia.

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FIGURES