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New Theories on the Anesthetics' Mechanism of Action

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Abstract

Anesthetic techniques using different substances with anesthetic properties have been used since antiquity. However, even today, it is not known exactly how these anesthetics work, if there is a common site or if their action is multi-level. In this article we present the latest theories regarding the mechanism of anesthetics' action. Thus we will refer to the action of anesthetics on neural networks, we will discuss the fractal theory of consciousness as well as the soliton model and the theory of the action of anesthetics on the cellular cytoskeleton.

Keywords: *anesthetics, soliton, neural networks.*

Introduction

Anesthesia has begun to be used scientifically since the nineteenth century. However, despite the broad use of anesthetics, the mechanism of action is not fully understood. In the nineteenth century physiologist Claude Bernard stated that anesthesia occurs through a reversible coagulation of proteins. At the end of the same century, a theory has been accepted today that the potency of anesthetics increases with their lipid solubility (Meyer-Overton theory). Despite the evolution of the means of analyzing the functions of the human body, it was not possible to identify whether there is a common center of action for anesthetics or they act on several different levels or centers. Among the new sites of anesthetics discovered in the twentieth century are: two pore domain K^+ channel, GABA receptor, NMDA receptor and glycine receptor.

In recent years, new theories have emerged that attempt to explain anesthetics' mechanism of action, such as the soliton model, Hameroff's theory, action on neural networks or fractal theory of consciousness.

Material and Methods

Review or research papers indexed in the Pubmed database were used for obtaining the new perspectives regarding the anesthetics' mechanism of action.

Results

After analyzing the data from the scientific papers, some newer theories have attracted our attention. Thus, we shall present the theory of action on neuronal networks, on fluidity of cell membrane (soliton model) and on neuronal microtubules (Hameroff theory). Also, the fractal theory of consciousness can provide a new insight into the mechanism of anesthetics' action.

Neural Networks

Neural networks are made up from numerous highly interconnected neurons that work simultaneously to solve specific tasks [1, 2]. The first models on the functioning of neural networks were developed in the fifties and sixties of the twentieth century. They are based on mathematical algorithms that attempt to explain the way these networks work. The functionality of this network is based on a law that operates under the activation function. Using the EEG signal, an anesthesia depth monitoring algorithm was developed, based on the neural network model [3]. The neural network that the human brain is based on is called the **basal network** or **default network**. Anatomically, it is made from neurons in the medial temporal lobe, prefrontal medial cortex, posterior cingulate cortex, ventral precuneus and the medial, lateral and inferior parietal cortex. Connectivity modifications between

the neurons in these anatomical structures lead to pathological states, such as autism, schizophrenia and Alzheimer's disease [4, 5]. Recent studies suggest that a network named **salience network** is important as well in the functioning of the brain. It comprises the cingulate cortex and the frontal operculum and is also involved in the detection and orientation to "obvious" internal and external stimuli [6, 7, 8]. Anesthetics affect the activity of these neural networks [9, 6]. Another network that contributes to maintaining consciousness is based on the connection between the posterior cingulate cortex and the left parietal cortex, anterior cingulate cortex, intralaminar nuclei of the thalamus and the prefrontal medial cortex [10].

Effect of Anesthetics on Neural Networks

Sevoflurane at 1% concentration (0.5 MAC) reduces prefrontal connectivity in the medial and lateral areas, while posterior default mode network (DMN) connectivity remains unchanged. The connectivity of the somatosensory, visual and auditory cortices is not changed as well, while it decreases in the hippocampus and insula, explaining the amnestic and analgesic effect of low-concentration sevoflurane. A concentration of 2% (1 MAC) sevoflurane lowers global functional connectivity in the DMN [11]. Propofol decreased the integration of sensory information into high-order processing networks thus suppressing the cognition [12]. On the other hand, in a recent study on mice, the effect of propofol on histaminergic hub-like neurons in the tuberomammillary nucleus was analysed. These neurons have a significant role in maintaining consciousness. Analysing the data, the conclusion that histaminergic neurons from the tuberomammillary nucleus are not involved in propofol-induced anesthesia was reached [13].

The Fractal Theory of Consciousness

In the classical view of the world - linear and mechanistic - we consider that the whole is a manifestation of all its components that act independently and abide predefined rules. Non-linear systems are made up from codependent components, tightly interconnected. Thus, the smallest component malfunction will impact the whole system. According to this theory, the interconnections are more important than the components themselves. However, the most important attribute of non-linear systems is its ability to self-organize and to produce negative entropy. This emergence property of complex systems can only be understood by analysing system components individually. The whole is more than the sum of the components. An example of emergent phenomena are the positive and negative feed-back loops that physiological processes are based upon [14]. In 1975, the mathematician Benoit Mandelbrot introduces the idea of the fractal. In short, this theory states that each constituent represents the whole, or that the whole can be revealed at the level of each individual component [15, 16]. The geometry of fractals is based on the following formula:

$$D = \frac{\log(m)}{\log(\frac{1}{r})}$$

Where:

D = dimension of the fractal

m = number of components, branches and knots

r = size of the components

Thus, the size of the components is dependent on its location in the network.

Erhard Bieberich considers that conscious phenomena occur in a fractal-like structure that he calls *sentyon* - made up from molecules and atoms and that is a "particle" of a conscious moment. Opening calcium channels in this structure generates a calcium wave that is limited by the fractal geometry of the sentyon, which would be the final molecular basis of consciousness [17]. Thus the sentyon could be a target for anesthetics. On the other hand, analyzing the EEG signal fractality using dedicated functions such as DFA (detrended fluctuation analysis), we can determine the depth of anesthesia. In the figures below we can see the EcoG (electrocortigram) signal analysis results from isoflurane anesthesia in the rat at two different concentrations. The anesthetic depth was initially estimated using spectral analysis and we obtained a SEF (spectral edge frequency) = 22.56 Hz for light anesthesia and a SEF = 16.34 Hz for deep anesthesia. ECoG signals were acquired using BIOPAC MP 150 at a sample rate of 1 kHz.

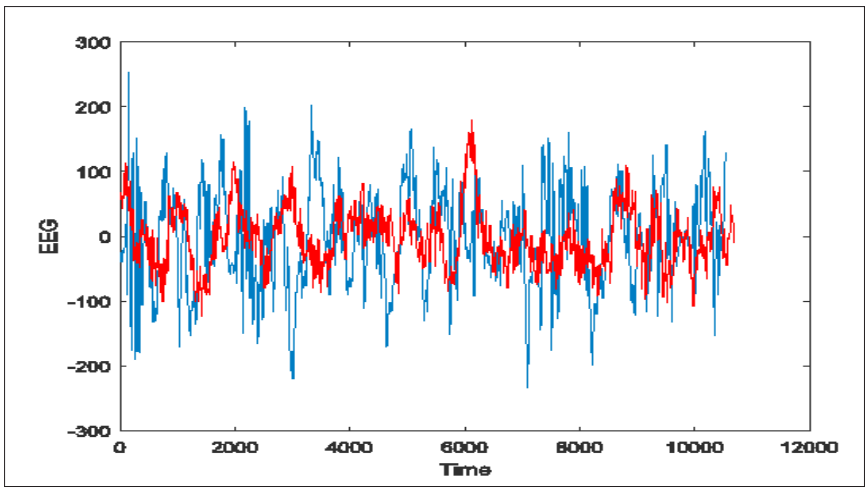

Fig 1. *Temporal comparison of the ECoG signal for light (in red) and deep (in blue) anesthesia depth.*

The Empirical Mode Decomposition (EMD) is a method to decompose a temporal signal into a set of elemental signals, the so-called Intrinsic Mode Functions (IMFs) and residuals. For both signals presented in the Fig. 1, the EMD technique was applied in order to analyze and find the differences between them. In Fig. 2 there are presented 4 out of 7 IMFs for the signal with high depth and in Fig. 3 for the one with low depth. As we can observed there are higher amplitudes of IMFs for the signal with high depth in comparison with the other one signal.

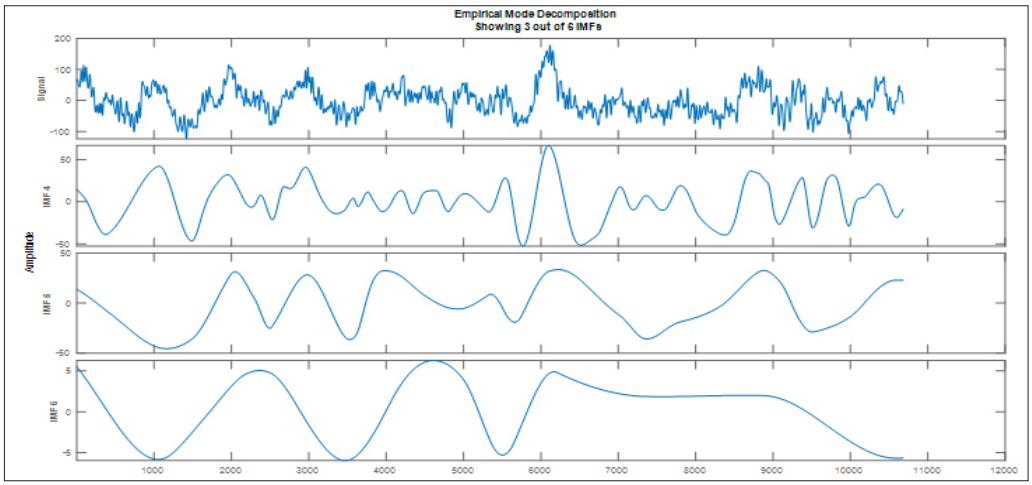

Fig 2. *Empirical Mode Decomposition of the ECoG signal for deep anesthesia.*

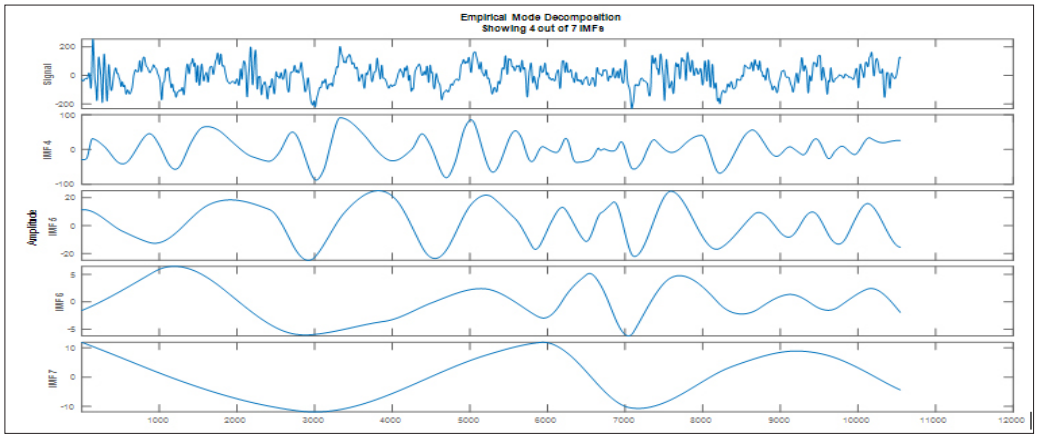

Fig 3. *Empirical Mode Decomposition of the ECoG signal for light anesthesia.*

The Soliton Model

This concept was introduced in 2005 by Thomas Heimburg and Andrew D. Jackson from the Niels Bohr Institute in Copenhagen, Denmark and it attempts to explain the neuronal impulse transmission [18]. All experimental observations cannot be explained by the classic model of Hodgkin and Huxley: theoretically, as a current passes through the cell membrane there is a heat dissipation, according to the resistor dissipation model. However, it was observed that during the membrane potential propagation, there is a release and a reuptake of heat as well. This likens the nervous impulse transmission to a sound wave (adiabatic). Furthermore, it is known that the transmission of an action potential is accompanied by a mechanical pulse, based on the cell membrane fluidity differences. Anesthetics can block nervous transmission by modifying membrane fluidity, through a change in its melting point [19].

The Hameroff Theory

Stuart Hameroff, Anesthesiology Professor Emeritus from the University of Arizona and Sir Roger Penrose, Mathematics Professor Emeritus from the Oxford University, consider consciousness as the consequence of discrete physical phenomena, events that have always existed in the universe, are non-cognitive, proto-conscious and respect laws not fully understood [20]. Searching for the physical basis of consciousness in the human brain, he concludes that conscious phenomena are housed in the microtubules at the base of neural dendrites. He bases this conclusion on the observation that unicellular organisms like *Physarum* are capable of escaping a labyrinth and like *Paramecium* can swim, find food and reproduce. These simple life forms do not present synapses or neural networks that could integrate external stimuli. The microtubules' cytoskeleton is the only intracellular structure that could [21]. Microtubules are protein structures with a diameter of 25 nm and a length between hundreds of nanometers and meters, in the case of long axons. Hameroff affirms that the conformational modifications of microtubules are the basis of consciousness. His calculations lead him to the conclusion that microtubules are capable of 10^{16} operations per second per each neuron, a number equal to the number of operations per second the brain is capable of, in the classic view [22]. Thus, if conscious phenomena occur in the microtubules [23], it is obvious that anesthetics, that cancel the consciousness, should act upon them [24]. In the nineteenth century, before Meyer and Overton formulated their own theory on the anesthetics' mechanism of action, French physiologist Claude Bernard noticed that chloroform anesthesia in Amoeba leads to a modification in the viscosity of the cytoplasm. As it is known that the fluidity is maintained by protein polymerization, in this case, the cytoskeleton actin, we can conclude that chloroform acts on actin microtubules. Bernard even affirms that anesthesia is based on reversible coagulation of cell proteins [25]. In 1999, Kaech et al. demonstrated that volatile anesthetics act on the actin microtubules in neural dendrites [26]. It was noticed that halothane, sevoflurane, isoflurane and desflurane alter gene expression of tubulin (a component of microtubules) [27, 28, 29]. Furthermore, the cognitive dysfunction that follows sevoflurane anesthesia is concomitant with tau protein hyperphosphorylation and instability of the microtubules [30, 31]. While halothane is known to act on the alpha and beta monomers of tubulin, other volatile anesthetics are supposed to act either directly on the microtubules, either by modifying their adjacent environment [32]. As for gas anesthetics, there is no data on the microtubule interaction.

Conclusion

The mechanism of anesthetics' action is far from being elucidated. The new theories described in this article provide new insights into understanding the complexity of the anesthesia mechanism. We hope in the near future to have a final theory that explains the action of anesthetics.

References

[1] Agatonovic-Kustrin S, Beresford R. Basic concepts of artificial neural network (ANN) modelling and its application in pharmaceutical research. J Pharm Biomed Anal. 2000 Jun; 22(5): 717-27.

[2] Traeger M, Eberhart A, Geldner G, Morin AM, Putzke C, Wulf H, Eberhart LH. [Artificial neural networks. Theory and applications in anesthesia, intensive care and emergency medicine]. Anaesthesist. 2003 Nov;52(11):1055-61.

[3] Ortolani O, Conti A, Di Filippo A, Adembri C, Moraldi E, Evangelisti A, Maggini M, Roberts SJ. EEG signal

processing in anaesthesia. Use of a neural network technique for monitoring depth of anaesthesia. Br J Anaesth. 2002 May; 88 (5) : 644-8.

[4] Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008 Mar;1124:1-38.

[5] Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. NeurosciBiobehav Rev. 2009 Mar; 33(3) : 279-96.

[6] Guldenmund P, Demertzi A, Boveroux P, Boly M, Vanhaudenhuyse A, Bruno MA, Gosseries O, Noirhomme Q, Brichant JF, Bonhomme V,Laureys S, Soddu A. Thalamus, brainstem and salience network connectivity changes during propofol-induced sedation and unconsciousness. Brain Connect. 2013; 3(3): 273-85.

[7] Day GS, Farb NA, Tang-Wai DF, Masellis M, Black SE, Freedman M, Pollock BG, Chow TW. Salience network resting-state activity: prediction of frontotemporal dementia progression. JAMA Neurol. 2013 Oct;70(10):1249-53.

[8] Bonnelle V, Ham TE, Leech R, Kinnunen KM, Mehta MA, Greenwood RJ, Sharp DJ. Salience network integrity predicts default mode network function after traumatic brain injury. ProcNatlAcadSci U S A. 2012 Mar 20;109(12): 4690-5.

[9] Guldenmund P, Vanhaudenhuyse A, Boly M, Laureys S, Soddu A. A default mode of brain function in altered states of consciousness. Arch Ital Biol. 2012 Jun-Sep;150(2-3):107-21.

[10] Hudetz AG. General anesthesia and human brain connectivity. Brain Connect. 2012;2(6):291-302.

[11] Deshpande G, Kerssens C, Sebel PS, Hu X. Altered local coherence in the default mode network due to sevoflurane anesthesia. Brain Res. 2010 Mar 8;1318:110-21.

[12] Liu X, Lauer KK, Ward BD, Rao SM, Li SJ, Hudetz AG. Propofol disrupts functional interactions between sensory and high-order processing of auditoryverbal memory. Hum Brain Mapp. 2012 Oct; 33(10): 2487-98.

[13] Zecharia AY, Yu X, Götz T, Ye Z, Carr DR, Wulff P, Bettler B, Vyssotski AL, Brickley SG, Franks NP, Wisden W. GABAergic inhibition of histaminergic neurons regulates active waking but not the sleep-wake switch or propofol-induced loss of consciousness. J Neurosci. 2012 Sep 19; 32(38) : 13062-75.

[14] Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit Care Med. 2000 Jul;28(7): 2193-200.

[15] Mandelbrot B. How long is the coast of britain? Statistical self-similarity and fractional dimension. Science. 1967 May 5; 156(3775):636-8.

[16] Mandelbrot BB. Stochastic models for the Earth's relief, the shape and the fractal dimension of the coastlines, and the number-area rule for islands. ProcNatlAcadSci U S A. 1975 Oct;72(10):3825-8.

[17] Bieberich E. Introduction to the fractality principle of consciousness and the sentyon postulate. CognitComput. 2012 Mar; 4(1):13-28.

[18] Heimburg T, Jackson AD. On soliton propagation in biomembranes and nerves. ProcNatlAcadSci U S A. 2005 Jul 12;102(28):9790-5.

[19] Heimburg T, Jackson AD. The thermodynamics of general anesthesia. Biophys J. 2007 May 1; 92 (9) : 3159-65.

[20] Hameroff S, Penrose R. Consciousness in the universe: a review of the 'Orch OR' theory. Phys Life Rev. 2014 Mar;11(1):39-78.

[21] Penrose R. Shadows of the mind: an approach to the missing science of onsciousness. Oxford, Oxford University Press 1994

[22] Hameroff SR. The brain is both neurocomputer and quantum computer. Cogn Sci. 2007 Nov 12; 31(6):1035-45.

[23] Hameroff SR, Watt RC. Information processing in microtubules. J Theor Biol. 1982 Oct 21; 98(4): 549-61.

[24] Hameroff SR. The entwined mysteries of anesthesia and consciousness: is there a common underlying mechanism? Anesthesiology. 2006 Aug;105(2): 400-12.

[25] Leake CD. Claude Bernard and anesthesia. Anesthesiology. 1971 Aug; 35(2):112-3.

[26] Kaech S, Brinkhaus H, Matus A. Volatile anesthetics block actin-based motility in dendritic spines. ProcNatlAcadSci U S A. 1999 Aug 31;96(18):10433-7.

[27] Fütterer CD, Maurer MH, Schmitt A, Feldmann RE Jr, Kuschinsky W, Waschke KF. Alterations in rat brain proteins after desflurane anesthesia. Anesthesiology. 2004 Feb;100(2):302-8.

[28] Kalenka A, Hinkelbein J, Feldmann RE Jr, Kuschinsky W, Waschke KF, Maurer MH. The effects of sevoflurane anesthesia on rat brain proteins: a proteomic time-course analysis. AnesthAnalg. 2007 May;104(5):1129-35, tables of contents.

[29] Kalenka A, Hinkelbein J, Feldmann RE Jr, Kuschinsky W, Waschke KF, Maurer MH. The effects of sevoflurane anesthesia on rat brain proteins: a proteomic time-course analysis. AnesthAnalg. 2007 May;104(5):1129-35.

[30] Le Freche H, Brouillette J, Fernandez-Gomez FJ, Patin P, Caillierez R, Zommer N, Sergeant N, Buée-Scherrer V, Lebuffe G, Blum D, Buée L. Tau phosphorylation and sevoflurane anesthesia: an association to postoperative cognitive impairment. Anesthesiology. 2012 Apr; 116(4): 779-87.

[31] Eckenhoff RG, Planel E. Postoperative cognitive decline: where art tau? Anesthesiology. 2012 Apr; 116(4): 751-2.

[32] Livingston A, Vergara GA. Effects of halothane on microtubules in the sciatic nerve of the rat. Cell Tissue Res. 1979 Apr 30; 198(1): 137-44.

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