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Editorial

Implications of the Action Potential Pulse Concept in Understanding the Mode of Action of Anesthetics

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In recent publications [1,2] we introduced the concept of the action potential pulse (APPulse) which unifies our knowledge of the action potential based on the Hodgkin and Huxley [HH] model of the action potential [3] and the soliton pulse which accompanies it [4]. In earlier studies it was assumed that there were high enough concentrations of sodium channels in axon membranes to allow current to pass from one to another and to allow the action potential to pass smoothly along the membrane, but later work has shown that this is not the case [5]. Soliton pulses are now believed to mechanically distort sodium channels ahead of the action potential, allowing depolarization of the membrane and the smooth passage of the action potential once threshold has been achieved. Thus the APPulse is a combined electromechanical event where the speed of the soliton is determined by the membrane components and morphology. Furthermore, the soliton is capable of perturbation by external factors such as temperature or pressure [6]. Blockage to the APPulse can occur by blockage of the Na ion channels (as has been proposed for local anesthetics) and/or from blockage of the soliton.

According to Andersen., *et al*. [7], nerve membranes are an approximately equal mixture of lipids and proteins and two major theories of anesthesia have arisen. Initially the Meyer-Overton lipid hypothesis [8] seemed to indicate that lipids were the principal anesthetic target because of the correlation between anesthetic potency and their lipid/water partition coefficients. More recently it has been suggested that the principal effects of anesthetics are on ligand-gated channels [9]. This may in part be true, and we acknowledge that anesthetics have direct effects on ligand-gated channels. However, it ignores their likely effects on the voltage-gated channels that drive the action potential, which leads us to ask, what are the effects of anesthetic agents on voltage-gated Na channels in axons?

Heimburg [6] points out that biological membranes melt from a solid to a liquid state at physiological temperatures (although this phase transition must vary from species to species) which makes it possible for solitons to travel along nerve axons. He also indicates that both general and local anesthetics lower melting temperatures of membranes, making excitation more difficult. Wang [10] examined the effects of anesthetics on compound action potentials and action potentials from a single neuron and concluded that "Anesthetics move the chain melting transition temperature of membranes far away from the physiological temperature, which requires a higher free energy to induce the phase transition, resulting in a higher stimulation voltage to reach the maximum amplitude of the action potential". Furthermore, lipid channels displaying similar voltage clamp characteristics to sodium channels have been demonstrated in pure lipid membranes [11]. They are blocked by anesthetics and may add to the confusion over anesthetic effects on ion channels. We take the view that membrane lipids have a major role to play in our understanding of anesthetic mechanisms and would support the view that solubilization of general anesthetics in the lipid bilayer may cause a redistribution of the lateral pressures [12] that would normally cause opening of sodium channels during the action potential [2]. Others have suggested that clinical concentrations of general anesthetics do not have indirect effects on membrane protein function [13] and then assume that the effects on ion channels are direct, but they have not considered direct effects on the soliton itself. Since volatile anesthetics are applied to a cell in the clinical concentration range, i.e. at low

doses, their effects will not be "all or none". Thus, at low anesthetic doses the diffusion coefficient of Na will change the refractory periods of the action potentials making computation less stable. At higher doses solitons will be blocked preventing the APPulse.

In scientific research there are often conflicts between groups of scientists supporting opposing theories, but quite often the opposing theories, unify and a composite hypothesis emerges later. For example, in the 1950s it had just had become widely accepted that synaptic transmission was by chemical rather than electrical means when electrical transmission was conclusively demonstrated in the crayfish by Furshpan and Potter [14,15]. It is now known that gap junctions are the morphological structures underlying electrical synaptic transmission [16,17] and that they are ubiquitous in all multicellular animals [18,19]. Furthermore they exhibit plasticity and can be modulated by chemical synapses [20]. Given that electrical synapses may synchronize, or desynchronize the activities of groups of neurons, it is clear that although neurons have distinct structures, they do not necessarily act as single functional units. This in effect compromises the neuron doctrine [21] to some extent and partially supports the reticular theory [22] so that we now on the cusp of a new holistic unifying hypothesis for the function of nervous systems. Could the same now be true for our understanding of the mode(s) of action of anesthetics on the lipid/protein membranes of axons? If so, a better understanding of its various mechanisms yields the possibility of safer and more efficient forms of anesthesia.

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