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## Is anesthesia an epiphenomenon of cell life?

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**Abstract:** All living beings can be anesthetized and lose their sensitivity. When anesthetized organisms are left without protection, making it vulnerable to external stresses. Since it is difficult to see the advantage of such vulnerability, should we consider anesthesia as non-adaptive by-product of an intrinsic weakness of living cells?

Recently, the "New York Declaration on Animal Consciousness" of April 2024 proposed that there is a realistic possibility of conscious experience in most animals. As Konen and Zirlinger [1] point out in a recent special issue of *Neuron*, there has indeed been renewed interest in the neurobiological substrates of consciousness in recent decades, leading to many exciting research efforts in different areas of consciousness. Among these, recent advances in the neurobiology of consciousness have been made in the context of anesthesia [2]. Although, anesthesia essentially refers to medical practices and focus on the abolition of suffering induced by the administration of anesthetics during surgery (about 245 000 references on pubmed since 1849), if we go beyond the medical spectrum, anesthesia corresponds to the loss of aisthesis, the ability to perceive stimuli, and it has long been recognized that all living beings, from single cell organisms to plant and animals, can be anesthetized [2-6]. So, the question is, what potential does anesthesia offer living organisms, if we exclude its medical role which concerns only a tiny proportion of living organisms? Anesthesia is clearly different from other biological processes in which organisms are isolated from their environment. The latter required molecular, physiological and morphological changes to protect the organism during its isolation (e.g., seed or spore dormancy [7,8]). In anesthesia, on the other hand, the loss of sensitivity to environmental stimuli isolates the living organism without any further protection, making it vulnerable. What advantage could offset this situation?

If we start from what anesthesia represents at the cellular and molecular level: the cell, the basis of all living organisms, corresponds to a compartment which is not in equilibrium with its surrounding environment and which maintains the homeostasis necessary for the metabolic reactions inherent in life. As the surrounding environment changes, this cell is obliged to regulate its exchanges with this environment in order to maintain its homeostasis. Cells therefore need to be sensitive enough to perceive changes in the environment and have the mechanics to allow the exchanges that guarantee the maintenance of homeostasis. These exchanges are carried out by means of membrane transporters inserted into the membrane isolating the cell from its environment, and are highly regulated. These transporters are also often sensors of variations in the environment, and therefore players in sensitivity, as well as

being players in the regulations required for homeostasis. The ion channels are thus a prime target for altering cellular function and are therefore the main targets for anesthetics [5].

Sonner [9] proposed the hypothesis that the ability to anesthetize, deeply rooted in prokaryotic and eukaryotic lineages, has been conserved because it gives cells an adaptive advantage. In his hypothesis, in an ancestral environment, alteration of ion channel activities on a short time scale [seconds] by compounds plausibly present in the environment and that mimicked inhaled anesthetics, prevented the deleterious consequences of entry of positive charges into the cell. The definitive adaptation might be the membrane composition changes, on a longer time scale [minutes] that restored bilayer properties to normal, thereby increasing the fitness of the organism. Kelz and Mashour [10] highlighted the necessity of an evolution process as proposed by Sonner [9]. They explain that remarkable conservation across diverse living organisms has sparked the theory that natural selection may have led to an evolutionarily conserved anesthetic responsiveness dating back to a common unicellular ancestor. They further cite the observation of Alan Rechtschaffen who humorously stated that "if sleep does not serve some vital function, it is the biggest mistake evolution ever made". This is intended to reinforce the idea that there must be a "role" for anesthesia. On another side, if the necessity of sensitivity to environmental factors all of organisms from the simplest unicellular to the most complex pluricellular is largely described, it is obvious that the even brief isolation of an organism, that is to say without any capabilities of response to a changing environment, could be highly deleterious for the survival of this organism. Thus, why such a role for anesthesia would be maintained along evolution? As stated by Sonner himself [9] "such narratives have value only if they generate testable hypotheses leading to new observations beyond those used to develop the narrative. Second, processes that produce anesthesia in nature should be maladaptive [how does the anesthetized organism protect itself?...]...", but he remained on the idea that selection favors beneficial traits and that an evolutionary theory must identify these beneficial traits.

However, another hypothesis, could be that the ability to be anesthetized would correspond to another version of the "original sin" hypothesis proposed by Ameisen [11], according to which the power to self-destruct could have been, since the appearance of life, an inescapable consequence of the power of self-organization that characterizes life. As described in this hypothesis, living, building and reproducing means constantly using molecular "tools" that risk causing death at any moment. In the case of anesthesia, the same applies: living, building and reproducing means constantly using molecular "tools" that allow living beings to be anesthetized at any moment. Ion channels, which are involved in many of the processes necessary for life, have probably been present since its inception, and their inhibition can cause anesthesia. The existence of an ancestral pleiotropy of these ion channels [5] is a factor that easily explains the ubiquity of anesthesia observed in all living organisms. Anesthesia would thus be a structural and therefore ancestral consequence of cell life. In this way we should consider that anesthesia is not an adaptive process but an epiphenomenon of non-adaptive structures. In citing the famous adage of the evolutionary biologist Theodosius Dobzhansky, "Nothing in biology makes sense, except in the light of evolution," Sonner [9] overlooked the fact that natural selection is not the sole evolutionary force responsible for changes in allelic composition of populations. Adaptation does not account for all evolutionary phenomena; there are instances where useless traits are maintained during evolution [12].

In conclusion, adaptationism is perhaps an epistemological block on the question of the role of anesthesia in all living beings in our Western societies. Another limitation to this reflection could be due to the role of anesthetics as indispensable tools for the study of consciousness [2] since the ubiquity of anesthesia could lead us to question the possibility of a form of consciousness in all living beings. The debate has effectively emerged for some time. Some authors suggest that forms of sentience and consciousness having emerged in unicellular

organisms [13,14], facilitating behavior in all living organisms including plants [15], when other authors proposed that consciousness could only emerge from a brain with a significant level of structural and functional complexity [16,17], even though there is as yet no consensual theory of consciousness [18,19].

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