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Review article

What is unconsciousness in a fly or a worm? A review of general anesthesia in different animal models

Oressia Zalucki, Bruno van Swinderen *

Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia

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ABSTRACT

All animals are rendered unresponsive by general anesthetics. In humans, this is observed as a succession of endpoints from memory loss to unconsciousness to immobility. Across animals, anesthesia endpoints such as loss of responsiveness or immobility appear to require significantly different drug concentrations. A closer examination in key model organisms such as the mouse, fly, or the worm, uncovers a trend: more complex behaviors, either requiring several sub-behaviors, or multiple neural circuits working together, are more sensitive to volatile general anesthetics. This trend is also evident when measuring neural correlates of general anesthesia. Here, we review this complexity hypothesis in humans and model organisms, and attempt to reconcile these findings with the more recent view that general anesthetics potentiate endogenous sleep pathways in most animals. Finally, we propose a presynaptic mechanism, and thus an explanation for how these drugs might compromise a succession of brain functions of increasing complexity.

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* Corresponding author.
E-mail address: b.vanswinderen@uq.edu.au (B. van Swinderen).

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1. Introduction

General anesthesia is a drug-induced, reversible state of decreased responsiveness, capable of being induced in all animals, no matter how simple their nervous system. In humans, there are several key components of general anesthesia, termed anesthetic endpoints, which encompass the changes in perception or behavior that are essential to general anesthesia: immobility, amnesia, analgesia and loss of consciousness (Antognini & Carstens, 2002). These endpoints, particularly the perception of pain and loss of consciousness, are typically only associated with humans or higher mammals, so how comparable are these endpoints across the animal kingdom? This question is particularly relevant for simpler invertebrate model organisms, such as the fruit fly (fly, *Drosophila melanogaster*), which has a tiny brain, or the nematode (worm, *Caenorhabditis elegans*), which does not even have a brain. What does 'unconsciousness' look like in a fly, or a worm?

Here, we outline human general anesthesia endpoints and compare these with endpoints in three model organisms, with the aim to identify the likely analogues for human loss of consciousness in these different animal models. Our purpose is not to outline a molecular characterisation of anesthetic endpoints, which has been extensively discussed elsewhere (e.g., (Chau, 2010; Franks, 2006, 2008; Rudolph & Antkowiak, 2004)). Rather, we offer a hypothesis to explain the progression of behaviors that are reversibly abolished by volatile general anesthetics that relates to behavioral complexity: with increasing anesthetic dose, more complex behaviors, requiring coordination among multiple neuronal pathways, are lost first, and more simple behaviors require a higher anesthetic concentration to be attenuated. We propose that this pattern reflects a common presynaptic target of general anesthetics, and that different anesthetic endpoints reflect successive categories of synaptic coordination required for different behaviors. Our hypothesis does not imply a unitary theory of action of anesthetics, but rather offers an explanation for how different brain functions are affected in succession through disruption of synaptic coordination by general anesthetics. Consciousness is but one of these functions in humans, so should not be central to defining general anesthesia.

What is general anesthesia?

General anesthesia encompasses various behavioral and physiological traits, termed endpoints. These endpoints are quantitative measures of arousal, ranging from behaviors to physiological signals, which are attenuated and potentially abolished (reversibly) by general anesthetics. As such, numerous endpoints could be studied under general anesthesia, from heartbeat, to haemoglobin function to pain, but which endpoints are relevant for surgery to proceed? Moreover, some endpoints are not single behaviors but rather can encompass a whole set of functionally related behaviors. For example, in considering the immobility endpoint of general anesthesia in animals, in response to a painful tail-clamp stimulus, many investigators consider a pawing motion or movement of the head towards the stimulus as a positive response to the stimulus, meaning it is gross, purposeful movement. In contrast, increased breathing, coughing, swallowing, chewing, the stiffening or simple withdrawal of the limb is considered a negative response. General anesthetics can also produce some undesired endpoints, such as cardiovascular and respiratory depression, nausea, and in extreme cases, death. Thus there is a need to accurately define general anesthetic endpoints, and the behaviors these entail, especially in animal models used to understand mechanisms of general anesthesia.

1.1. How is general anesthesia measured?

Since their introduction into medical practice in the mid-nineteenth century, there was a need for an accurate measure to compare anesthetic potencies to ensure accurate dosing. Indeed, some of first recorded anesthetic procedures performed with the inhalational anesthetics ether and chloroform resulted in patient deaths, which most likely stemmed from overdosing (Jacob, Kopp, Bacon, & Smith, 2013). Early measures assessed anesthetic depth based on reflexes, such as eye-blinking, and changes in breathing and muscle movement and tone (Guedel, 1937; Woodbridge, 1957). These measures proved to be unreliable between different inhalational compounds, limiting their clinical utility. In the early 1960s, Eger and colleagues in their research on both dogs and human patients introduced the concept of minimum alveolar concentration or MAC as a measure of general anesthesia depth (Merkel & Eger, 1963). MAC is defined as the minimum alveolar concentration of an inhalational anesthetic at which 50% of subjects do not respond to surgical incision. Importantly, Eger and colleagues showed that MAC was remarkably consistent, with anesthesia induced at a very similar dose in the dogs. Also, increasing the intensity of the stimulus did not change MAC. That is, administering two painful stimuli to the dogs, an electric shock and tail-clamp, did not increase anesthetic requirements. This suggests MAC is a reliable measure of general anesthetic potency.

Skin-incision remains the standard stimulus in humans for determining MAC, asking: "When this noxious stimulus is applied, is there any movement?" Movement is often defined as gross, purposeful movement, and thus simple reflexes are not considered. The definition of MAC closely ties this measure with immobility, a cardinal feature of general anesthesia. Since MAC represents the concentration at which 50% of subjects no longer respond to the surgical incision, MAC therefore reflects another common measure in anesthesia research: it is a general anesthetic 50% effective concentration, or EC_{50}.

How are these EC_{50}s calculated? In the case for human patients, MAC is measured with a quantal study design (Sonner, 2002). Patients are exposed to an anesthetic dose for a set-period of time, after which a skin incision is