A presynaptic mechanism of general anaesthesia

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Intravenous general anaesthetics such as propofol and etomidate are understood to exert their sedative effects by acting on postsynaptic GABA(A) receptors in the brain, to presumably potentiate a sleep-promoting pathway [1]. We have recently discovered that clinically-relevant concentrations of general anaesthetics also have a clear presynaptic effect [2, 3]. Using super-resolution microscopy, we found that application of 3μM of propofol to mammalian and insect neuronal preparations impaired the mobility of a key protein required for neurotransmission, syntaxin1A. Imaging experiments as well as electrophysiology showed that propofol decreased synaptic release events, suggesting that impaired neurotransmission is a direct consequence of the effects on presynaptic syntaxin1A mobility. Further genetic and biochemical analyses suggest that propofol acts on an emergent protein target involving SNAP-25 as well as munc-18, before the formation of release-ready SNARE complexes. Therefore, one hypothesis we are pursuing is that propofol impairs the recruitment of SNARE proteins (specifically syntaxin1A and SNAP-25) from reserve pools to release sites, rather than affecting the synaptic release events resulting from already formed complexes. This view of general anaesthesia might provide a level of explanation for why recovery from anaesthesia can often be problematic, especially in more vulnerable patient populations. To establish a link between local effects on syntaxin1A at every synapse in the brain and consequent changes in whole brain dynamics and behaviour, we are using a *Drosophila melanogaster* model that allows us to image whole-brain activity in behaving animals under general anaesthesia. In this way, we will be able to better disambiguate the presynaptic effects of general anaesthetics such as propofol and isoflurane from post-synaptic effects on sleep-promoting pathways in the brain. We will conclude by presenting an overview of our current 2-step hypothesis for general anaesthesia [4], considering how the combined pre-and postsynaptic mechanisms of these drugs might lead to the behavioural condition observed as general anaesthesia.

References

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