MECHANISMS OF ANAESTHESIA – CLINICAL IMPLICATIONS

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How general anaesthetic drugs work was chosen as one of the 125 most important unanswered questions for Science's 125th anniversary issue (1). How these drugs work is basic and fundamental to how clinicians such as us administer general anaesthesia. I will try to summarise recent findings that inform our understanding of general anaesthesia (GA) and the clinical implications thereof.

General anaesthetic agents seem to be unique compared to other drugs. They seem not to have a simple mechanism of action characterised by a few actions on receptors or enzyme function. Disparate actions cause a unified clinical endpoint. Many receptors have been implicated in defining a mechanism of anaesthesia including GABA, glycine, NMDA, K^+ channel subtypes and Ca^{2+} channel subtypes. The GABA receptor has been central to our recent understanding however the GABA receptor is not necessary or probably sufficient to produce all the endpoints of anaesthesia (2,3,4,5). This makes it very difficult to believe in a unitary concept of general anaesthesia at receptor level.

In this talk I will review the effects of general anaesthesia at five different levels of structure, namely protein receptor, neuron, neuronal network, nuclei and whole nervous system structures.

One way of simplifying our understanding of the disparate molecular effects is to understand the electrophysiological effects at neuronal level. Most effects of GA increase or decrease the inhibitory or excitatory postsynaptic potential (IPSP or EPSP) respectively, effect the amplitude of the PSP or have a hyperpolarising effect on leak currents. There is often more than one pathway to the same electrophysiological effect with duplication and redundancy in neuronal circuits.

When we discuss clinical endpoints, it has become increasingly clear that different endpoints are mediated in anatomically distinct areas of the brain and spinal cord. Movement is predominantly a spinal cord reflex, hypnosis is probably mediated by the reticular activating system, hypothalamus, thalamus and neocortex and amnesia by the frontal lobe and hippocampus. This is most clearly demonstrated by the goat experiments performed by Joseph Anognini. By selectively anaesthetising brain alone or soma and spinal cord he was able to clearly demonstrate that the movement response is predominantly a spinal cord action (7).

If we look at brain nuclei involved in NREM sleep regulation, highly targeted intracerebral GABAnegic drug placement in rats completely mimics the hypnotic endpoint of anaesthesia (8). Knockin mice preparations for the ß2 GABA subunit are completely resistant to ablation of movement responses and partially resistant to hypnotic responses for etomidate and propofol (9). The clinical implications of these findings will be discussed during the talk.

In summary, general anaesthesia is a unique drug phenomena that can only be understood if we synthesise findings across many levels of brain and spinal cord organisation. I believe a better understanding of the phenomena and translating these basic science results makes us more able to make good clinical decisions.

References

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