Anaesthesia Seminar by

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Volatile anaesthetic depression of hypoxic ventilatory responses: the role of TASK channels

Volatile anesthetics are widely used during surgery to maintain unconsciousness, but among undesirable side effects is the depression of breathing, especially postoperatively, contributing to increased morbidity and mortality, particularly in patients with pre-existing cardiorespiratory disease. This is exacerbated by simultaneous use of opioids and residual neuromuscular blockade. With c. 3 million general anesthetics in the UK alone, and an incidence of postoperative hypoxemia as high as 30%, even small risk reductions could yield large benefits.

This lecture reviews our group's work on carotid body oxygen sensing and the ventilatory hypoxic response (VHR). The degree to which different volatile anesthetics depress carotid body hypoxic response relates to their ability to activate TASK potassium channels. Most commonly, volatile anesthetic pairs act additively at their molecular targets. We examined whether this applied to carotid body TASK channels.
In humans, we have studied VHR using dynamic end-tidal forcing (DEF) and shown a specific order of potency for VHR depression across agents. In animals and cells, we have used the methods of glomus cell isolation, hypoxia-evoked rise in intracellular calcium ($Ca^{2+}i$, using the indicator Indo-1) and TASK single-channel activity (patch clamping) in native glomus cells and HEK293 cell line cells transiently expressing TASK-1.

We have confirmed the same order of potency at cell and TASK channel level, as seen in volunteers. In all three cell/molecular experimental models, the effects of isoflurane and halothane combinations were quantitatively consistent with the modelling of weak and strong agonists competing infr-additively at a common receptor on the TASK channel; specifically the TASK-1 subunit.

I will discuss the mechanistic implications of this for anesthetic action more widely; the implications for drug discovery and clinical application, and also the related work of our group on intravenous agents.

Date: 1 February 2024 (Thurs)
Time: 2:30pm
Venue: Lecture Theatre 1, 1/F,
3 Sassoon Road, Pok Fu Lam

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