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Molecular mechanisms of gastrointestinal disorders caused by general anesthesia

Nowadays it is impossible to imagine surgery procedures without general anesthesia. From the wide variety of general anaesthetics both intravenous (such as propofol, ketamine, fentanyl etc.) and inhalation anesthetics (such as isoflurane, sevoflurane, desflurane etc.) are some of the most commonly used in medicine. However, this class of drugs still presents many mysteries considering their molecular mechanisms of action, understanding of which is critically important for their safe and efficient use in surgery. Gastrointestinal (GI) tract motility is often demoted significantly after surgery operations at least in part due to anesthetic agents, but there is no in-depth explanation of the molecular mechanisms of such adverse effects. Postoperative paralytic ileus that disrupts the normal coordinated propulsive motility of the GI tract for 2 to 7 days develops in 10 to 30% of patients undergoing abdominal surgery, while there is no efficient and safe pharmacological treatment for this condition.

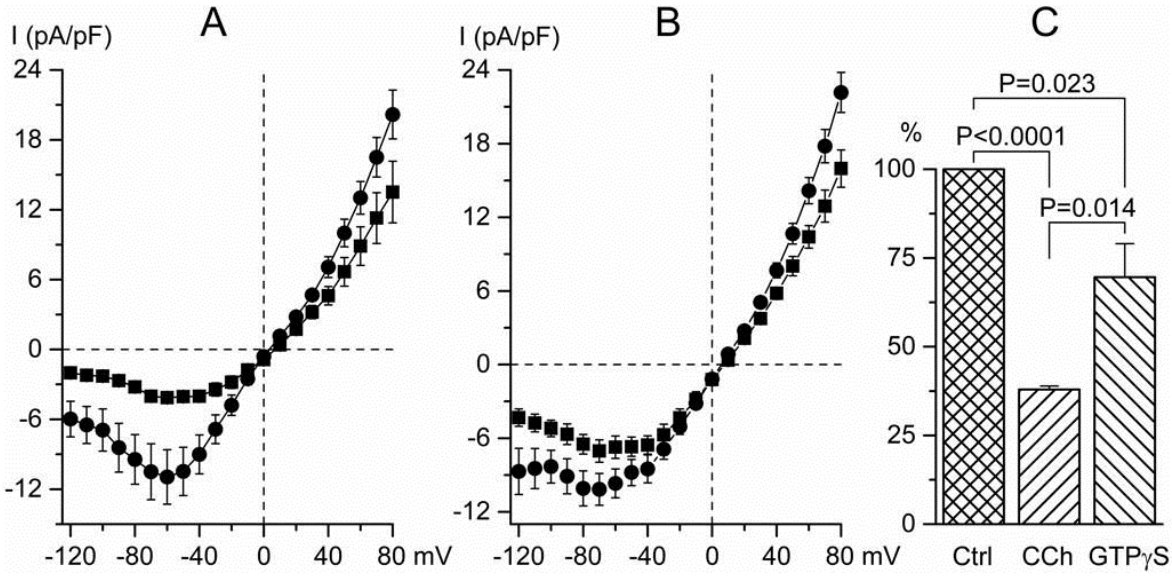

Fig. 1. Summary of the effects of isoflurane (0.5 mM) on muscarinic cation current evoked by 50 μM carbachol (n=8) (A) or by 200 μM GTPγS (n=5) (B). In each cell, steady-state I-V relationships were measured at peak response in control (circles) and at maximal inhibition by isoflurane (squares). Normalised current density at 60 mV showed statistically significant differences, as indicated (C).

The main purpose of general anesthetics is the inhibition of the central nervous system, which results in unconsciousness and a total loss of sensations. One of their molecular targets is represented by plasma membrane receptors and ion channels, both voltage-gated (e.g. two-pore-domain potassium channels, calcium and sodium channels) and ligand-gated (e.g. pentameric ligand-gated ion channels, such as the nicotinic acetylcholine receptors, serotonin receptors (5-HT_3), glycine receptors), as well as inhibitory anion channels ($GABA_A$).

Transient receptor potential (TRP) cation channels are a superfamily of polymodal cellular sensors that are involved in various physiological processes, ranging from transduction of sensory signals and to the regulation of $Ca^{2+}$and Mg^{2+} homoeostasis etc. are currently arising as yet another important class of ion channels sensitive to both intravenous and inhaled anesthetics at subclinical concentrations. They are activated by an enormous diversity of chemical and physical stimuli (such as pH,voltage, temperature, mechanical forces etc). Mammalian TRPC a subfamily of seven members (TRPC1-7)) have recently appeared as crucial players in the control of smooth muscle function (in various organs, such as the uterus, the airways and the gastrointestinal tract).

We showed that isoflurane inhibited muscarinic receptor cation current of the GI smooth muscles (mI_{CAT}) as the main side effect leading to intestinal paresis. mI_{CAT} normally causes smooth muscle membrane depolarisation following acetylcholine, the major parasympathetic excitatory neurotransmitter in the gut, release from motor enteric neurones, thus representing the main mechanism of the cholinergic excitation-contraction coupling in the GI tract. In brief, acetylcholine activates the M_2 and M_3 subtypes of muscarinic receptors, the main receptor subtypes present in various visceral smooth muscles. Cholinergic excitation leads to the opening of cation TRPC4 channels to generate mI_{CAT}, of which TRPC4 is the main contributor. In such a complicated system, disruption of muscarinic receptor signaling may develop at multiple levels, from muscarinic receptors, G-proteins, and ion channels, to Ca^{2+} metabolism and contractile apparatus. To shed light on the targeting points for isoflurane action within this complex system, we compared its effects on M_2 and M_3 muscarinic receptors and when muscarinic receptors were bypassed, on TRPC4 channels. The results of the experiments demonstrated significant inhibition of TRPC4 channels by isoflurane at clinically relevant concentrations, with some remarkable differences between current responses initiated with or without muscarinic receptor involvement, but the intricate molecular and single-channel mechanisms of this effect remain to be studied further.

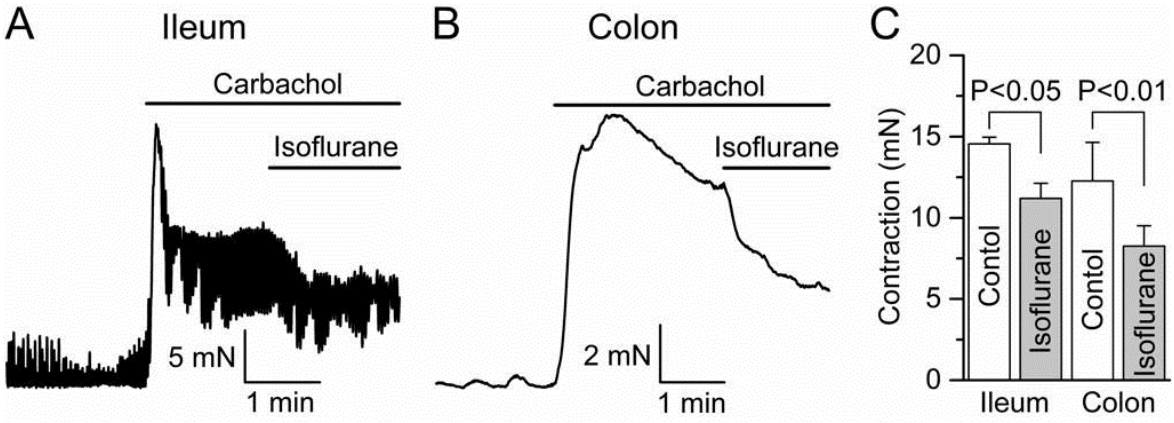

Fig. 2. Inhibitory effect of isoflurane on carbachol-induced intestine contraction. Representative traces illustrating isometric contractions of ileum (A) or colon (B) segments in response to carbachol (50 μM) followed by isoflurane application (3 mM) in the continuous presence of carbachol. (C) Summary of the measurements showing significant inhibition of carbachol-induced smooth muscle contraction by isoflurane. Maximal tension level was compared between carbachol and isoflurane (n=8).

An advanced understanding of ion channel mechanisms of anesthetics' side-effects will provide novel insights into how different channels are affected, as well as a better comprehension of how altered channel function influences GI tract motility. This will provide basis for the development of novel pharmacotherapeutic approaches to the correction of gastrointestinal disorders caused by general anesthesia.

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Publication

Inhalation anaesthetic isoflurane inhibits the muscarinic cation current and carbachol-induced gastrointestinal smooth muscle contractions.
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