

Global genetic deletion of Cav3.3 channels facilitates anaesthetic induction and enhances isoflurane-sparing effects of T-type calcium channel blockers

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We previously documented that the Cav3.3 isoform of T-type calcium channels (T-channels) is inhibited by clinically relevant concentrations of volatile anaesthetics, including isoflurane. However, little is understood about the functional role of Cav3.3 channels in anaesthetic-induced hypnosis and underlying neuronal oscillations. To address this issue, we used Cav3.3 knock-out (KO) mice and a panselective T-channel blocker 3,5-dichloro-N-[1-(2,2-dimethyltetrahydropyran-4-ylmethyl)-4-fluoropiperidin-4-ylmethyl]-benzamide (TTA-P2). We found that mutant mice injected with the vehicle showed faster induction of hypnosis than wild-type (WT) mice, while the percent isoflurane at which hypnosis and immobility occurred was not different between two genotypes. Furthermore, we found that TTA-P2 facilitated isoflurane induction of hypnosis in the Cav3.3 KO mice more robustly than in the WT mice. Isoflurane-induced hypnosis following injections of TTA-P2 was accompanied with more prominent delta and theta EEG oscillations in the mutant mice, and reached burst-suppression pattern earlier when compared to the WT mice. Our findings point to a relatively specific value of Cav3.3 channels in anaesthetic induced hypnosis. Furthermore, we propose that T-channel blockers may be further explored as a valuable adjunct to reducing the usage of potent volatile anaesthetics, thereby improving their safety.