Global genetic deletion of $Ca_V3.3$ channels facilitates anaesthetic induction and enhances isoflurane-sparing effects of T-type calcium channel blockers

Simon Feseha[1], Tamara Timic Stamenić[1], Damon Wallace[1], Caesaré Tamag[1], Lingling Yang[4], Jen Q. Pan[4], Slobodan M. Todorovic[1,2,3]

1 Department of Anesthesiology, University of Colorado, Anschutz Medical Campus,
2 Neuroscience, University of Colorado, Anschutz Medical Campus
3 Pharmacology Graduate Programs, University of Colorado, Anschutz Medical Campus
4 Stanley Center of Psychiatric Research, Board Institute of Harvard and MIT

We previously documented that the $Ca_V3.3$ 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 $Ca_V3.3$ channels in anaesthetic-induced hypnosis and underlying neuronal oscillations. To address this issue, we used $Ca_V3.3$ knock-out (KO) mice and a panselective T-channel blocker 3,5-dichloro-N-[1-(2,2-dimethyltetrahydro-pyran-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 $Ca_V3.3$ 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 $Ca_V3.3$ 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.