Different roles of T-type calcium channel isoforms in hypnosis induced by an endogenous neurosteroid epipregnanolone

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Background: Many neuroactive steroids induce sedation/hypnosis by potentiating gamma-aminobutyric acid ($GABA_A$) currents. However, we previously demonstrated that an endogenous neuroactive steroid epipregnanolone [(3β,5β)-3-hydroxypregnan-20-one] exerts potent peripheral analgesia and blocks T-type calcium channels (T-channels) while sparing $GABA_A$ currents in rat sensory neurons.

Methods: Here, we utilized electroencephalographic (EEG) recordings to characterize thalamocortical oscillations, as well as mouse genetics with wild-type (WT) and different knockout (KO) models of T-channel isoforms to investigate potential sedative/hypnotic and immobilizing properties of epipregnanolone.

Results: Consistent with increased oscillations in slower EEG frequencies, epipregnanolone induced an hypnotic state in WT mice when injected alone intra-peritoneally (i.p.) and effectively facilitated the hypnotic and immobilizing effects of a common volatile anesthetic isoflurane. The $Ca_V3.1$ (Cacna1g) KO mice demonstrated decreased sensitivity to epipregnanolone-induced hypnosis when compared to WT mice, whereas no significant difference was noted between $Ca_V3.2$ (Cacna1h) and WT mice. In contrast, epipregnanolone-induced hypnosis in $Ca_V3.3$ (Cacna1i) mice was substantially longer than in WT mice. Finally, when compared to WT mice, onset of epipregnanolone-induced hypnosis was delayed in $Ca_V3.2$ KO mice but not in $Ca_V3.1$ and $Ca_V3.3$ KO mice.

Conclusion: To our knowledge, this work is the first to report on the hypnotic properties of epipregnanolone in rodents. We speculate that distinct hypnotic effects of epipregnanolone across all three T-channel isoforms is due to their differential expression in thalamocortical circuitry. We posit that endogenous neuroactive steroids that target neuronal T-channels may have an important role as novel hypnotics and/or adjuvants to anesthetic agents.