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Intrinsic activation/inactivation parameters of CaV2.1 calcium channels are shifted by Pregabalin, modulating neurotransmitter release

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Mechanisms by which Pregabalin (PGB) might act as an anticonvulsant are unknown. The α2-δ type 1 auxiliary subunit of voltage-gated calcium channels is the primary high-affinity binding site for PGB. Here we studied PGB effects on both postsynaptic excitatory transmitter responses of principal neurons from Medial Nucleus of the Trapezoid Body and presynaptic calcium currents (IpCa) present on the afferent called Calyx of Held in brainstem slices from mice, using whole cell patch clamp recordings.

We found that a dose-response relationship showed a maximum drug effect at 500 μM. At this concentration, PGB reduced the amplitude of EPSCs by a 30%. No differences were observed in the depression rate using high frequency trains. Faster rate of recovery from synaptic depression at 100 Hz was observed in the presence of PGB ($p=0.043$). We found no differences in the mean amplitude of miniature EPSCs while observing greater minis frequencies -PGB versus +PGB conditions (1.71±0.35 Hz and 0.49±0.06 Hz, respectively; $p=0.004$). On the other hand, multiple effects of PGB on the IpCa intrinsic properties were observed. PGB blocked CaV2.1 channels-mediated currents and decrease their facilitation during 100Hz train, without changing their voltage-dependence of activation. However, two-pulse inactivation protocol showed a larger rescue of the inactivation. Additionally, the inactivation curve observed with PGB showed a clear change on the kinetic but not on the half-activation voltage using a long conditioning pulse protocol. Supported by: UBACYT X-223; FONCYT (ANPCyT) PICT 2005-32113; 2006-199, Wellcome Trust (to ODU); FONCYT (ANPCyT) PICT 2007-01009 & PIDRI-PRH 2007 (to FU)