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*MEETING ABSTRACT*

## A1.30

### The anticonvulsant retigabine is a subtype selective modulator of $GABA_A$ receptors

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**Background:** Retigabine is a novel antiepileptic drug whose purported mechanism of action is the opening of $K_V7$ potassium channels. Nevertheless, at concentrations of 10 µM or above, this drug has also been reported to enhance currents through $GABA_A$ receptors. We sought to investigate this latter effect of retigabine in more detail.
**Methods:** For $GABA_A$ receptor current measurements, we used the perforated-patch method on cultured primary hippocampal neurons or tsA201 cells expressing various $GABA_A$ receptor subunit combinations. For $K_V7$ currents, $K_V7.2/7.3$ heteromers were expressed in tsA201 cells. Retigabine effects on seizure-like activity were investigated in hippocampal neurons in current-clamp mode under low $Mg^{2+}$ conditions and/or in presence of the $K_V7$ blocker XE 991.
**Results:** In primary cultures of hippocampal neurons, retigabine reduced seizure-like activity triggered by low $Mg^{2+}$ in a concentration-dependent manner with half-maximal inhibition at about 1 µM. This inhibitory effect was not altered when $K_V7$ channels were blocked with XE 991. Currents in hippocampal neurons evoked by increasing concentrations of GABA were not affected by 10 µM retigabine. However, when phasic GABAergic inhibition was prevented due to the presence of penicillin, retigabine did enhance GABA-induced currents. When tested in tsA201 cells expressing various combinations of $GABA_A$ receptor subunits, 10 µM retigabine enhanced currents through α1β2δ, α4β3δ, and α6β2δ receptors, but left currents through α1β2γ2S, α4β3γ2S, α6β2γ2S receptors unaltered. With αβ receptors, retigabine diminished currents through α1β2 and α4β3, but increased currents through α6β2 receptors. Modulation of α4β2δ and α4β3δ receptors by retigabine was the same. The enhancement of currents through α1β2δ receptors by retigabine was concentration-dependent and became significant at 1 µM.
**Discussion:** These results demonstrate that retigabine is a subtype-selective modulator of $GABA_A$ receptors with preference for extrasynaptic δ-containing receptors. This property apparently contributes to its antiepileptic efficacy.
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