Impact of Kv3 Channel Modulator AUT3 on *In Vivo* Auditory Processing in Mice

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Background:

Voltage-gated K^+ channels of the Kv3 subfamily have been shown to enable fast spiking in many central neurons. Kv3 channels activate at strongly depolarised membrane potentials to drive quick repolarisation after an action potential, and also rapidly de-activate to enable fast re-initiation of action potentials. Kv3 channels are strongly expressed in the central auditory system, at levels that can be modulated by auditory experience (such as exposure to noise). These channels are therefore potential targets for drug treatments aimed at ameliorating central auditory pathologies arising from noise exposure The aim of this study was to determine whether a novel modulator of Kv3 channel activity, AUT3, alters auditory brainstem responses (ABRs) in normal mice or in mice exposed to mild acoustic trauma.

Methods:

ABRs were recorded from anaesthetised naïve or noise-exposed CBA/Ca mice. Noise-exposed mice had been subjected to 105 dB SPL, 8-16kHz noise under anaesthesia, 1 day prior to ABR measurements. ABRs were recorded 30 minutes before and 2, 32, 62, 92 or 122 minutes after intraperitoneal administration of either AUT3 (60mg/ml) or vehicle solution. Auditory stimuli were presented in free-field, and included 50 μs 0-80 dB SPL clicks, as well as broadband noises followed by clicks. Analysis of ABRs involved calculation of thresholds, peak-to-trough wave amplitudes, wave peak latencies, inter-peak latencies and root-mean-square overall amplitudes.

Results:

There was a small, but significant increase ($p<0.02$) in the inter-peak-latency of ABR wave I to IV following AUT3, but not vehicle injections. This effect was observed in both naïve and noise-exposed mice; however, the latency of ABR wave I was not significantly affected. The latency shift in wave IV was evident in both absolute and inter-peak latency analysis. No significant effect of AUT3 injections (relative to vehicle injections) was observed for ABR thresholds, wave amplitudes, or overall root-mean-square amplitudes in either group of animals.

Conclusions:

AUT3, a Kv3 channel modulator, caused a small but significant increase in the latency of ABR wave IV in both noise-exposed and naïve mice, but no detectable change in either the latency of ABR wave I, ABR thresholds, peak-to-trough wave amplitudes, or overall root-mean-square amplitudes. These findings indicate that AUT3 causes no gross abnormalities in the ABR, but does have a subtle effect on the timing of late ABR waves, which may reflect an impact on auditory processing in higher central auditory structures such as the inferior colliculus.

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