Impact of Kv3 Channel Modulator AUT3 on Auditory Temporal Resolution in Rats

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Background:
Voltage-gated K+ channels of the Kv3 subfamily enable fast firing of many central neurons and are strongly expressed in the central auditory system. However, they have been shown to decline with age (von Hehn et al., 2004), which could contribute to age-related auditory processing disorders including temporal auditory resolution deficits. In the present study, the effect of AUT3 (a novel drug positively modulating Kv3 channels) on auditory temporary resolution was examined in Fischer 344 (F344) rats. F344 rats are known to suffer an accelerated age-related decline in hearing performance (Syka, 2010). Evaluation of the temporary resolution was based on the measurement of ability to detect silent gaps in noise using a behavioral gap-prepulse inhibition paradigm.

Methods:
The effect of AUT3 was examined in aged (19-21-month-old) and young adult (3-4 month-old) F344 rats, using the acoustic startle response (ASR) recording. Amplitude of ASR and prepulse inhibition of ASR induced by gap (gap-PPI) were measured before and after AUT3 administration (30 or 60 mg/kg or vehicle, i.p.) using a cross-over design with at least 7 days between dosing sessions. 110 dB SPL broad-band noise bursts were used as startling stimuli; gaps from 5 to 50 ms, embedded in 65dB broad-band noise, served as prepulse stimuli. Hearing thresholds were assessed prior to the first drug administration and at the end of the study from auditory brainstem responses.

Results
In the control condition aged rats showed significantly smaller ASR amplitudes and weaker gap-PPI compared to the young-adult rats. The effect of AUT3 on the ASR depended on AUT3 dose. AUT3 at 60mg/kg significantly reduced ASR amplitude in both age groups while neither vehicle nor 30mg/kg dose of AUT3 affected ASR. The effect of AUT3 on gap-PPI was determined by age. Both tested doses of AUT3 significantly, but temporarily, increased the gap-PPI efficiency in aged rats, but did not alter gap-PPI in young rats. Hearing thresholds were unaffected by AUT3 administration.

Conclusions:
The deficit of gap-PPI indicates worsening of temporal resolution in aged F344 rats, similar to the deficits seen in aged humans. AUT3 significantly improved auditory temporal processing in the aged rats. These results suggest that AUT3, via positive modulation of Kv3 channels, has potential in the treatment of age-related hearing impairment.

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