

MEETING ABSTRACT

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Antiepileptic activity and subtype-selective action of flupirtine at GABA_A receptors

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Background

Flupirtine is used as analgesic drug with muscle-relaxant properties. In addition, it has been suggested to possess antiepileptic properties. Recently, flupirtine has been revealed to simultaneously act at K_v7 channels and GABA_A receptors. Here, antiepileptic activity and underlying mechanisms of action of flupirtine were investigated.

Methods

We used the patch clamp technique and primary cultures of hippocampal neurons or transfected tsA cells to investigate effects of flupirtine.

Results

In hippocampal neurons, flupirtine reduced seizure-like activity with no effect at 1 to 3 μM, and maximal effects at 10 to 30 μM; it enhanced currents through K_v7 channels with EC₅₀ values at 6 μM. Flupirtine (30 μM) modulated GABA-induced currents in hippocampal neurons by reducing EC₅₀ values for GABA threefold and maximal current amplitudes by 15%. Hence, flupirtine acted as an uncompetitive antagonist. Flupirtine did not alter rise time, decay time, or amplitudes of miniature inhibitory postsynaptic currents (mIPSCs), but enhanced the bicuculline-sensitive tonic current. When phasic GABAergic inhibition was blocked by penicillin G (5 mM), flupirtine enhanced maximal amplitudes of GABA-evoked currents by 43%, but hardly affected EC₅₀ values. As these results suggested that flupirtine was able to differentiate between different GABA_A receptor subtypes, its effects on recombinant GABA_A receptors were

investigated in tsA cells. With α1β2γ2 receptors, flupirtine reduced EC₅₀ values for GABA threefold and maximal current amplitudes by 25%; with α1β2 receptors, it reduced EC₅₀ values for GABA twofold, but reduced maximal current amplitudes by 35%.

Conclusions

These results indicate that flupirtine (i) exerts antiepileptic activity, (ii) modulates tonic, but not phasic, GABAergic inhibition and blocks K_v7 channels in hippocampal neurons, and (iii) affects GABA_A receptors in a subunit-dependent manner.

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