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Meeting abstract

The non-opioid analgesic flupirtine is a modulator of $GABA_A$ receptors involved in pain sensation

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Background

Flupirtine is a centrally acting, non-opioid analgesic with muscle relaxant and neuroprotective properties. Although routinely used in the clinic, its mechanism of action remained poorly understood; it had been suggested to antagonize NMDA receptors and to activate G protein-coupled inward rectifier (GIRK) and KCNQ K^+ channels. Since spinal $GABA_A$ receptors are involved in pain sensation, we investigated the effects of flupirtine on this and other transmitter-gated ion channels.

Materials and methods

Perforated patch clamp recordings were obtained in primary cultures of rat hippocampal, sympathetic and dorsal root ganglion (DRG) neurons.

Results

Flupirtine (30 μM) enhanced currents evoked by GABA (10 μM) in all neurons investigated, but this effect was significantly larger in DRG than hippocampal or sympathetic neurons. In DRG neurons, flupirtine behaved as uncompetitive antagonist: it lowered EC_{50} values for GABA-induced currents 5.3-fold and depressed maximal amplitudes by 34%. In hippocampal neurons, EC_{50} values were reduced 3.1-fold; maxima remained unchanged. Flupirtine concentration-dependently enhanced currents evoked by 3 μM GABA up to 8-fold in DRG (EC_{50}: 21 μM) and 2-fold in hippocampal neurons (EC_{50}: 13 μM). In hippocampal, but not DRG, neurons, flupirtine (100 μM) alone elicited inward currents that were not additive to those evoked by pentobarbital, abolished by bicuculline, but not altered by flumazenil. Flupirtine (10 μM) failed to affect currents through NMDA, AMPA/kainate, glycine or nicotinic receptors in hippocampal and sympathetic neurons, respectively; it also failed to affect currents through GIRK1/2 channels, but concentration-dependently activated currents through KCNQ channels; this effect was more pronounced in sympathetic than DRG or hippocampal neurons.

Conclusion

These results reveal flupirtine as subtype-selecting allosteric modulator of $GABA_A$ receptors; its analgetic action may thus results from a combined action on $GABA_A$ receptors and KCNQ channels in pain pathways.

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