COLOCALIZATION AND FUNCTIONAL INTERACTIONS BETWEEN PRESINAPTIC AMPA; NMDA AND GROUP I METABOTROPIC GLUTAMATE RECEPTORS

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Background and purpose: Electrophysiological studies described upregulation of NMDA receptor (NMDAR) function by metabotropic glutamate receptors (mGluRs) of group I occurring postsynaptically. Since release-enhancing NMDARs exist on noradrenergic terminals and group I mGluRs have been recently identified on these nerve endings, we have investigated if NMDAR-mGluR interactions also occurred at the presynaptic level.

Experimental approach: Rat hippocampus and human neocortex synaptosomes were labelled with $[^3H]$noradrenaline ($[^3H]$NA) and exposed to agonists and antagonists in superfusion. NMDA-evoked release was produced i) by removal of external Mg$^{2+}$ or, in alternative, ii) by contemporary application of NMDA and AMPA in Mg$^{2+}$-containing solutions.

Key results: 3,5-DHPG, inactive on its own, potentiated significantly both the release of $[^3H]$NA elicited by AMPA/NMDA/glycine and that evoked by NMDA/glycine following Mg$^{2+}$ removal. The effect of 3,5-DHPG on the AMPA/NMDA/glycine-induced release was insensitive to the mGluR1 antagonist CPCCOEt, but it was abolished by the mGluR5 antagonist MPEP; moreover, it was potentiated by the mGluR5 positive allosteric modulator DFB. When NMDARs were activated by Mg$^{2+}$ removal, both mGluR5 and mGluR1 contributed to the evoked release, the mGluR-mediated component of release being blocked only by a mixture of CPCCOEt and MPEP. Experiments with human neocortex synaptosomes show NMDAR-mGluR interactions qualitatively similar to those observed in rodents.

Conclusions and Implications: Group I mGluRs, both of the mGluR1 and mGluR5 subtypes, co-localize with NMDARs on noradrenergic terminals of rat hippocampus and human neocortex. Depending on the mode of activation, NMDARs exert differential permissive roles on the activation of presynaptic mGluR1 and mGluR5.