ROLE OF IONOTROPIC GLUTAMATERGIC RECEPTORS IN THE REGULATION OF HIPPOCAMPAL NOREPINEPHRINE OUPUT IN VIVO

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Experimental evidences have indicated that, in vitro, hippocampal norepinephrine (NE) release is modulated by glutamatergic receptors. In this study, we evaluated the role of NMDA and AMPA glutamatergic receptors in the regulation of hippocampal NE release, by using horizontal microdialysis technique in freely moving rats. Samples of dialysate were analyzed by high-performance liquid chromatography with electrochemical detection.
Local administration of NMDA (10^{-6} M; 10^{-5} M; 10^{-4} M) through the dialysis probe induced a concentration-dependent decrease of hippocampal NE concentrations; on the contrary perfusion with the NMDA antagonist, MK801, at the same concentrations induced an increase of this neurotransmitter. Local perfusion with AMPA (10^{-6} M; 10^{-5} M; 10^{-4} M) showed a biphasic effect on extracellular NE concentrations, inducing a decrease of this neurotransmitter at low doses and an increase at high doses. Perfusion with the AMPA antagonist, DNQX, at the same concentrations failed to induce significant changes on hippocampal NE output. Moreover, local perfusion of the $GABA_A$ receptor antagonist, bicuculline (10^{-5} M), was able to completely antagonize the decrease of hippocampal NE output induced by NMDA and by the lowest concentration of AMPA, but not the increase of NE extracellular concentrations induced by the highest concentration of this drug.
Our data are consistent with experimental evidences suggesting the existence, in the hippocampus, of a inhibitory local circuit that regulates the activity of pyramidal neurons with a localization of NMDA receptors both on glutamatergic pyramidal cells and on GABAergic interneurons. Stimulation of NMDA receptors located on GABAergic neurons would increase their inhibitory tone on noradrenergic neurons thus inducing the observed decrease on NE output. The biphasic effect observed after local administration of AMPA might be due to the ability of AMPA to preferentially activate, at low doses, GABAergic interneurons, that in turn would increase their inhibitory tone on pyramidal cells. At higher concentrations of AMPA, stimulation of pyramidal cells might be sufficient to exceed the inhibition of GABAergic interneurons thus increasing the release of glutamate which in turn would increase NE output.
As the noradrenergic system has a crucial role in the modulation of emotionality, anxiety and in the stress response, a better understanding of the modulatory action of glutamatergic receptors on the activity of noradrenergic neurons might represent a step forward in the identification of new targets for drugs with a greater effectiveness in the treatment of stress and anxiety.