

Inhibition by Neuropeptide S of the release of 5-HT and glycine from mouse amygdala and frontal/prefrontal cortex nerve terminals through activation of the Neuropeptide S receptor

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Neuropeptide S (NPS) is a neurotransmitter/neuromodulator that has been identified as the natural ligand of G protein-coupled receptors termed NPS receptors (NPSRs). The NPS-NPSR system is involved in the control of numerous centrally-mediated behaviours, including anxiety. As several classical transmitters play a role in fear/anxiety, we here investigated the regulation by NPS of the exocytotic release of 5-hydroxytryptamine (5-HT) and glycine in nerve terminals isolated from mouse frontal/prefrontal cortex and amygdala. Synaptosomes, prelabelled with the tritiated neurotransmitters, were depolarized in superfusion with 12-15 mM KCl and exposed to varying concentrations of NPS. The evoked release of [³H]5-HT in frontal/prefrontal cortex was potently inhibited by NPS (maximal effect about 25% at 0.1 nanomolar). Differently, the neuropeptide exhibited higher efficacy but much lower potency in amygdala (maximal effect about 40% at 1 micromolar). NPS was an extremely potent inhibitor of the K⁺-evoked release of [³H]glycine in frontal/prefrontal nerve endings (maximal effect about 25% at 1 picomolar). All the inhibitory effects observed were counteracted by the NPSR antagonist SHA 68, indicating that the neuropeptide acted at NPSRs. In conclusion, NPS can inhibit the exocytosis of 5-HT and of glycine through the activation of presynaptic NPSRs situated on serotonergic and glycinergic terminals in areas involved in fear/anxiety behaviours. The possibility exists that the NPSRs in frontal/prefrontal cortex are high-affinity receptors involved in non-synaptic transmission, whereas the NPSRs on amygdala serotonergic terminals are low-affinity receptors involved in axo-axonic synaptic communication.