Neuropeptide S (NPS) and its cognate G protein-coupled receptor were recently reported to have anxiolytic-like and arousal effects. NPS receptors are predominantly expressed in the brain, especially in limbic structures, such as amygdala, olfactory nucleus, subiculum and retrosplenial cortex (RSA). It has been suggested that a dysfunction in glutamatergic neurotransmission via NMDA receptors is involved in the pathophysiology of schizophrenia. Histologically, when administered to animals, NMDA receptor antagonists including dizocilpine have been known to produce cytoplasmic vacuoles in rat retrosplenial cortex neurons. Since NPS receptors are prominently expressed in RSA we studied the effect of NPS on dizocilpine-induced neurotoxicity in RSA neurons.

Pretreatment with NPS (0.01, 0.1, or 1 nmole, i.c.v.) attenuated the dizocilpine-induced neuropathological changes in rat RSA in a dose dependent manner. NPS also suppressed the increase of extracellular ACh levels in RSA produced by administration of dizocilpine (0.5 mg/kg). In the prepulse inhibition (PPI) test, animals pretreated with NPS significantly recovered from dizocilpine-induced disruption of PPI.

Both the neuropathological changes and the disruption of PPI induced by dizocilpine can be attenuated by pre-administration of only atypical antipsychotics such as clozapine or olanzapine but not by acute administration of typical antipsychotics like haloperidol. Our study suggests that NPS has protective effects against psychotic and neurotoxic symptoms produced by NMDA receptor antagonists. Thus the NPS receptor might be an interesting target for development of novel antipsychotic drugs.