Max Planck Institute of Psychiatry

Identification of a significant role for the ventral hippocampus in neuropeptide S-elicited anxiolysis

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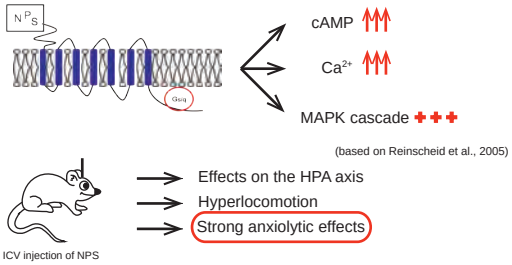
I. Background

1. NPS -- a potential novel therapy for anxiety disorders



(based on Reinscheid et al., 2005)

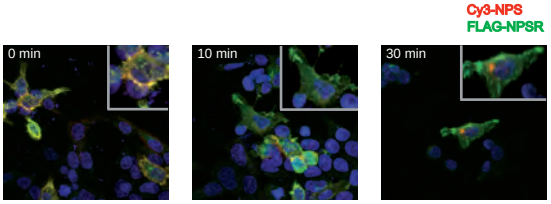
ICV injection of NPS

→ Effects on the HPA axis
→ Hyperlocomotion
→ Strong anxiolytic effects

(based on Xu et al., 2004 and Smith et al., 2006)

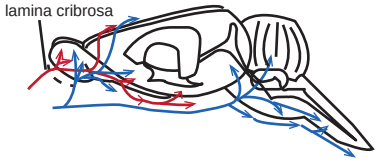
➡ NPS has high potential as an alternative anxiolytic therapy for anxiety disorders

2. Fluorophore-coupled NPS allows intracellular tracking



➡ Cy3-NPS stimulation of HEK cells transiently transfected with FLAG-NPSR shows that NPS specifically targets NPSR and that receptor-ligand complexes are subsequently internalized

3. Intranasal application bypasses the blood-brain-barrier and targets the CNS



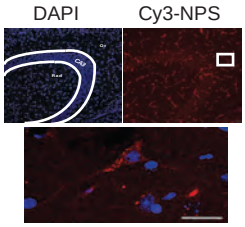
pathway along the olfactory nerves
pathway along the myelin sheaths of the trigeminal nerves

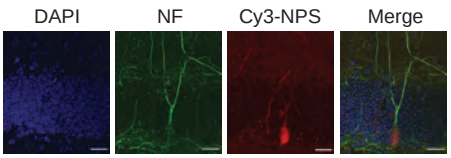
(adapted from Thorne et al., 2004)

➡ intranasal application represents a valid administration alternative to the intracerebral injection and can be readily implemented in patients

II. The hippocampus — a novel NPS target region

1. Intranasal Cy3-NPS application identifies the hippocampus as a novel NPS target region

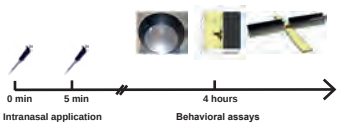


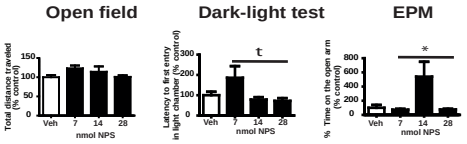


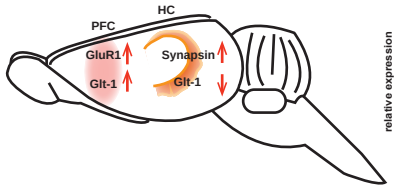
➡ intranasally applied Cy3-NPS is internalized exclusively into cells expressing the neuronal marker neurofilament (NF)

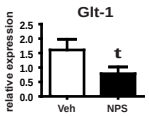
(Ionescu et al., 2012)

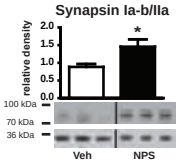
2. Intranasally applied NPS exerts anxiolytic effects in C57BL/6N mice and regulates protein and gene expression in the hippocampus (HC)





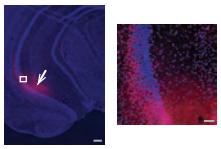


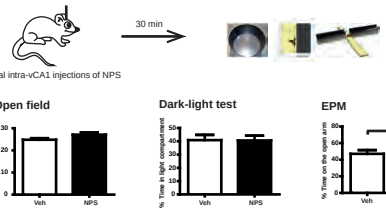




(Ionescu et al., 2012)

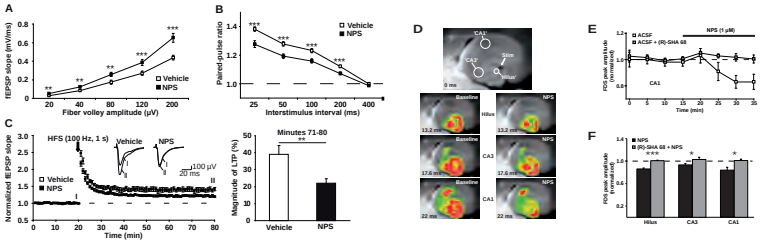
3. Local NPS injections into the ventral CA1 (vCA1) region lead to anxiolytic effects in C57BL/6N mice





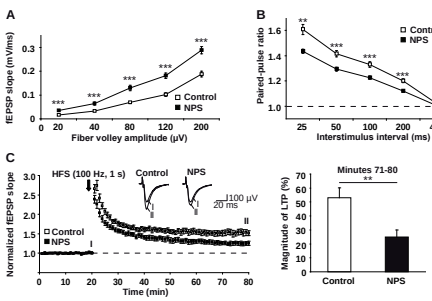
➡ NPS distribution remains locally restricted upon local injection into vCA1

4. Intranasally applied NPS impacts on basal glutamatergic neurotransmission and plasticity at CA3-CA1 synapses and weakens neuronal activity flow from DG to CA1



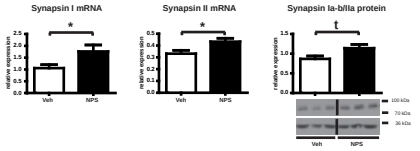
III. NPS in hippocampal pathology

1. Intranasally applied NPS affects glutamatergic neurotransmission and plasticity in high anxiety behavior (HAB) mice

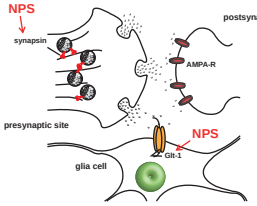


2. Intranasal NPS treatment counteracts pathological changes in hippocampal synapsin levels in a mouse model of PTSD

→ PTSD-like symptoms (Siegmund et al., 2007)
→ hippocampal shrinkage (Golub et al., 2011)
→ loss of hippocampal synapsin (Herrmann et al., 2012)



Overview



➡ in the hippocampus, NPS regulates expression of proteins involved in synaptic function at the presynaptic site (synapsin) and in glia cells (Glt-1)

➡ NPS actions in the ventral hippocampus may contribute to the anxiolytic effects of NPS treatment via modulation of amygdala activity

Conflict of interest: I.A. Ionescu, Y.-C. Yen, R. Landgraf, F. Holsboer and U. Schmidt declare a conflict of interest due to a patent application on intranasal NPS application pending since October 2012.

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