The role of neuropeptide Y in fear conditioning and extinction

The main function of fear and anxiety is to act as a signal of danger, threat or motivational conflict and to trigger appropriate adaptive responses. Emotional responses are predominantly mediated by limbic brain areas. Neuropeptides are highly expressed there and may have a significant impact on generation of fear and anxiety related behavior. Increasing evidence points towards an important role of neuropeptide Y (NPY) in the modulation of emotional behavior. NPY is a 36 amino acid peptide that is abundantly expressed in the central nervous system. NPY and its receptors (Y1, Y2, Y4, Y5) are involved in various physiological and pathophysiological processes including energy homeostasis, pain and epilepsy. Consistent findings across different rodent models demonstrated an anxiolytic effect of NPY. The presence of different NPY receptors in the amygdala and the effects of NPY on anxiety raise the question, weather NPY and its receptors may influence acquisition and extinction of conditioned fear. Therefore we investigated the effect of NPY deletion in *Pavlovian* fear conditioning, a simple form of associative learning. In this paradigm a conditioned stimulus (CS) usually a tone is paired with an unconditioned stimulus (US), typically a mild foot shock. After a few such pairings the CS alone comes to elicit a fear reaction. Repetitive presentation of the CS alone results in a reduction of the acquired fear response, a process called fear extinction.

In cued fear conditioning NPY knockout (NPY KO) mice show faster acquisition as well as increased expression and impaired extinction of conditioned fear. Adeno-associated viral vector (AAV-Vector) mediated re-expression of NPY in the basolateral amygdala (BLA) of NPY KO mice significantly reduced the increased acquisition of NPY KO mice during fear conditioning (Fig. 1A & B).

Long-term fear memory determined 24 h later, however, was still high. In addition there was a trend towards improved fear extinction, after re-expression of NPY in the BLA of NPY KO mice.

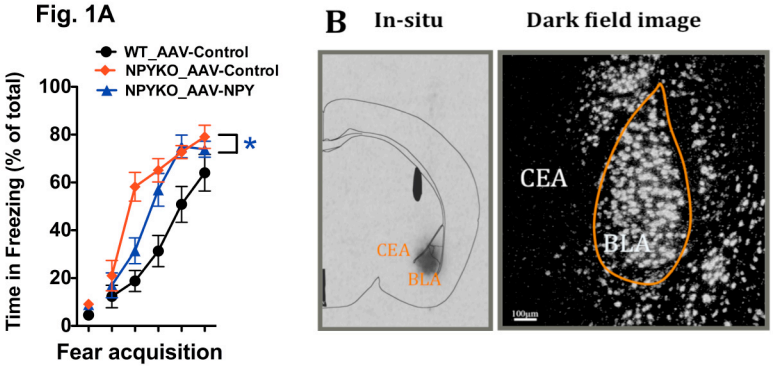

Fig. 1A&B – Fear acquisition after AAV-NPY infusion into the BLA of NPY KO mice (1A), localization of the injection site in the BLA by NPY *in-situ* hybridization, dark field image shows NPY vector mRNA positive cells in the BLA (1B).

Our findings using NPY KO mice indicate that NPY has a protective role in the acquisition of fear and facilitates extinction of conditioned fear. These effects seem to be mediated predominantly in the BLA, as shown by AAV-NPY vector injections.