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MEETING ABSTRACT

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Neuropeptide Y and Y_2 receptors in hippocampus-dependent fear and spatial learning

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Background: Neuropeptide Y (NPY) is abundantly expressed throughout the central nervous system and especially enriched in limbic areas, such as the hippocampus and amygdala. NPY is well known to mediate anxiolytic and fear-suppressing effects, mainly through activation of Y_1 receptors. However, in particular in the hippocampus, presynaptic Y_2 receptors (Y_2R) are also highly expressed, but their role in fear learning is not clear yet. Our aim was to investigate the effect of NPY acting on Y_2Rs in the hippocampus in fear conditioning as well as spatial learning.
Methods: Y_2R knockout (KO) and wild-type mice were tested in hippocampus-dependent context fear conditioning. The time spent freezing was used as a measure of the fear response. To test whether Y_2Rs play a role also in non-emotional learning, animals were tested in the Barnes maze. Furthermore, we performed rescue experiments by re-expressing the Y_2Rs specifically in the hippocampus of Y_2R KO mice via microinjection of recombinant adeno-associated viral vectors (rAAVs), and repeated the same battery of behavioural tests. To determine the appropriate concentration of viral vectors and to confirm whether the vector-mediated Y_2Rs are functional, we employed classical receptor binding assays and functional GTPγS receptor binding, respectively.
Results: In context fear conditioning, Y_2R KO mice displayed increased freezing during fear recall and delayed fear extinction. Locally restricted re-expression of Y_2Rs specifically in the dorsal hippocampus did, however, reverse these behavioural deficits and restore extinction learning. On the other hand, Y_2R KO mice displayed improved spatial memory performance in the Barnes maze, which was reduced after re-expression of hippocampal Y_2Rs. Receptor binding suggested that 10^9 viral particles of rAAV6-Y_2R were sufficient to yield expression levels reminiscent of the wild-type hippocampus. In addition, GTPγS binding assays confirmed functional coupling of exogenously introduced Y_2Rs.
Discussion: Here, we demonstrated that Y_2Rs play a crucial role in contextual fear learning, since germline Y_2R deletion led to elevated fear expression and delayed fear extinction. Viral-vector-mediated re-expression of Y_2R in the hippocampus restored these deficits. In contrast, Y_2R re-expression impaired long-term spatial memory. Thus, Y_2R may inhibit fear conditioning by suppressing memory processes in the hippocampus.
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