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Enhanced expression of PACAP and of its high affinity receptor (PAC1) in the hippocampus and cerebral cortex of dopamine D3 knockout mice

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Dopamine (DA) D3 receptor (D3R) is a pre-synaptic autoreceptor whose main role is to modulate DA release through a negative feedback regulatory loop. Immunolocalization studies from our research group have previously described that these receptors, despite being relatively low expressed in the central nervous system (CNS), may still be detected in less discreet brain regions normally associated to memory function, including the hippocampus and the cerebral cortex (1). Consistent with these findings, genetic deletion of the D3R in mice (D3R-/-) has been shown to have profound repercussions on the formation of new memories, especially fear associative memories (2). While it is now well-accepted that such pro-cognitive effects in these mice are presumably due to the increased DA bioavailability caused by the lack of autoreceptor function, it still remains to be established if there are molecular determinants directly or indirectly involved in ameliorating this specific type of associative learning. Pituitary adenylate cyclase-activating polypeptide (PACAP) is an endogenous peptide which is gaining scientific relevance because of its prominent "cognitive enhancer" function and the recent developments suggesting its active participation in the acquisition and consolidation of fear memories (3, 4). Based on these evidences, we thought it could have been of scientific relevance to assess whether PACAP expression, as well as that of its binding receptors, are affected in knockout mice showing this peculiar behavioural phenotype. We found that PACAP immunoreactivity (IR) was present at low levels in CA1 hippocampal subfield while moderate staining was observed in CA2-CA3 fields and in the dentate gyrus (DG) of wild-type (WT) mice. In sharp contrast, PACAP-IR was remarkably increased in all CA subfields, and particularly in CA1, CA3 and the DG regions of D3R-/- mice. Regarding the cerebral cortex (CX), PACAP expression was restricted to the V cortical layer in WT mice, whereas in D3R-/- mice, stained neurons were apparent both in the IV, V and VI cortical layers, with an overall increased staining score. In line with these findings, the expression of the PACAP-preferring PAC1 receptor, which was detectable only at moderate levels in the CA2 subfield of WTs, was enhanced in both CA2 and CA3 of D3R-/- mice. Interestingly, PAC1-IR was already present at moderate levels in the II-III cortical layers of WT mice, but genetic deletion of the D3R caused a remarkable spread of PAC1-stained neurons throughout all cortical layers, with the exception of layer I. We conclude that the absence or blockade of functional D3Rs from the brain enhances both PACAP and PAC1 receptor expression levels in the hippocampus and cerebral cortex. Considering the ameliorative role mediated by PACAP-PAC1 signalling in cognition, we infer that enhanced PACAP peptide and receptor expression may relate to the specific behavioural phenotype of these mice.

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References

[1] D'Amico et al. (2013) Hippocampal neurofibromin and amyloid precursor protein expression in dopamine D3 receptor knock-out mice following passive avoidance conditioning.. Neurochem Res. 38:564-72; doi: 10.1007/s11064-012-0949-0.

[2] Castorina et al. (2013) Dopamine D3 receptor deletion increases tissue plasminogen activator (tPA) activity in prefrontal cortex and hippocampus. Neuroscience. 250:546-56. doi: 10.1016/j.neuroscience.2013.07.053.

[3] Taylor et al. (2014) Pituitary adenylate cyclase-activating polypeptide (PACAP) inhibits the slow afterhyperpolarizing current sIAHP in CA1 pyramidal neurons by activating multiple signaling pathways. Hippocampus. 24:32-43. doi: 10.1002/hipo.22201.

[4] Stevens et al. (2014) PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus. Proc Natl Acad Sci U S A. 111:3158-63. doi: 10.1073/pnas.1318954111.

Keywords

Dopamine D3 receptor; PACAP; PAC1; fear memories.