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Dopamine D3 receptor knockout mice exhibit increased hippocampal cAMP response element binding protein (CREB) following acquisition of passive avoidance memory

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The dopamine D3 (D_3R) receptor seems to be implicated in synaptic plasticity and memory-related processes as identified by several pharmacological and behavioral approaches (Laszy et al., 2005; Swant 2008). In a previous study we have shown that D_3Rs mediate an inhibitory effect on learning, since D_3R knockout ($D_3^{-/-}$) mice display enhanced cognitive performance in the single trial step-through passive avoidance task (PA) as compared to WTs (Micale et al., 2010; D'Amico et al., 2013). Formation of new memories is known to require *de novo* synthesis of proteins related to synaptic function, possibly through the activation of a number of signaling pathways including the mitogen-activated protein kinases (MAPKs), protein kinase B (namely Akt) and the activation of nuclear transcription factors such as the cAMP response element binding protein (CREB). However, no clear indications have yet been provided regarding the specific involvement of D_3Rs in the activation of these signaling cascades after acquisition of PA. Therefore, in the present study we assessed whether activity/phosphorylation levels of several MAPKs, Akt and CREB were differentially affected by PA in both wild-type (WT) and $D_3^{-/-}$ mice. Animals were divided into four groups: naive, unconditioned stimulus trained (USTA), conditioned stimulus trained (CSTA) and conditioned (CA) animals. Phosphorylation of MAPKs, including extracellular signal-regulated kinase 1/2 (ERK 1/2), c-Jun-N-terminal kinase (JNK) and p38, as well as of Akt and CREB were assessed by immunoblotting and immunohistochemical analyses. Results showed that acquisition of PA induced a significant increase in hippocampal pCREB levels both in WT and $D_3^{-/-}$ mice. However, the extent of PA-driven increase in pCREB levels was significantly higher in mice lacking D_3Rs. Similarly, hippocampal pERK 1/2 were further augmented in $D_3^{-/-}$ mice subjected to PA as compared to trained WTs. JNK and p38 phosphorylation was not affected neither by PA nor by genetic background. Finally, a significantly increased Akt activation was observed only when comparing naïve WT and $D_3^{-/-}$ mice, but not in response to PA acquisition. This result suggests that the Akt signaling cascade is influenced by the absence of the receptor, but only under basal conditions. In conclusion, the data here presented supports the notion that D_3Rs might modulate CREB phosphorylation after acquisition of PA, probably *via* activation of the ERK signaling pathway.