Dopamine D3 receptors control dysbindin-dependent executive functions alterations relevant to schizophrenia

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Dysbindin-1 is encoded by the dystrobrevin-binding protein 1 gene (DTNBP1) (Talbot et al., 2009). Several studies have associated DTNBP1 genetic variations with risk for schizophrenia (Morris et al., 2008) and reduced dysbindin gene function and protein expression have been reported in the hippocampus and prefrontal cortex of schizophrenic patients (Weickert et al., 2004, 2008). Reduced dysbindin levels have also been linked to increased D2-receptor (D2R) abundance on the neuronal surface (Papaleo et al., 2009) suggesting a pathophysiological link to positive, negative and cognitive symptoms of schizophrenia, which has long been thought to involve D2 mechanisms (Laruelle et al., 2003). However, whether this molecular interaction with dopamine receptors involves other dopamine D2-like receptors is unknown. Indeed, no studies have investigated the possible interaction between D3R and dysbindin-1 (Dys). Here, we tested the hypothesis that the functional interaction between D3R and Dys controls schizophrenia-associated behaviors and that Dys/D3R genetic modifications impact both neuronal excitability and extracellular dopamine levels in the mPFC. We generated and tested for the first time, double heterozygous D3R/dysbindin mutant mice (D3+/-*Dys+/-) and their controls littermates (D3+/+*Dys+/+, D3+/+*Dys+/-, D3+/-*Dys+/+) in a series of experiments to evaluate cognitive performances, electrophysiological and molecular implications of both Dys and D3R reduction. Dysbindin heterozygous mice (Dys+/-) showed working memory deficits ($p<0.05$, 4 and 30 seconds of choice-delays) in the discrete paired-trial variable-delay T-maze task. The partial genetic deletion of D3R completely rescued the dysbindin-1-dependent cognitive deficits ($p<0.05$, 4 and 60 seconds of choice-delays). In the layer V pyramidal neurons, a depolarization step of 1-s and 150 pA intensity showed a reduction of action potentials in current-clamp mode in heterozygous Dys mutant mice (D3+/+*Dys+/-) compared with their WT littermates (D3+/+*Dys+/+; **$P<0.01$), whereas there was no difference between WT and D3+/-*Dys+/- neurons in the spike frequency. Finally, in vivo microdialysis in the mPFC of freely-moving mice showed a restored WT-like dopamine levels in the mPFC of double heterozygous D3R/Dys mutant mice (D3+/-*Dys+/-) in comparison with D3+/+*Dys+/- mice (*$P<0.05$). These results demonstrate that the partial reduction of D3R is sufficient to rescue dysbindin-dependent cognitive alterations relevant to schizophrenia.

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