Genetic-driven reduction of dopamine D3 receptor ameliorates dysbindin-dependent schizophrenia-relevant abnormalities

G.M. Leggio[1], S.A. Torrisi[1], F. Managò[2], S. Salomone[1], R. Mastrogiacomo[2], M. Mereu[2], F. Drago[1], F. Papaleo[2]

[1]Dept. of Biomedical and Biotechnological Sciences, Section of Pharmacology, School of Medicine, University of Catania, Catania, Italy
[2]Dept. of Neuroscience and Brain Technologies, The Italian Institute of Technology, Genova, Italy

Dysbindin-1 is encoded by the dystrobrevin-binding protein 1 gene (DTNBP1) and is located in synaptic sites throughout the human and mouse brain (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 *in vitro* (Iizuka et al., 2007; Ji et al., 2009), suggesting a potential pathophysiological link to psychosis, which has long been thought to involve D2 mechanisms (Laruelle et al., 2003). Dysbindin-1 directly interacts with G protein-coupled receptor-associating proteins (GASPs), which modulates lysosomal trafficking of various G protein-coupled receptors, including D2Rs (Whistler et al., 2002). Whether this molecular interaction with dopamine receptors involves others dopamine D2-like receptors is unknown. Indeed, as the D2R, the dopamine D3 receptor (D3R) also binds GASP-1 (Thompson et al., 2011). However, no studies have investigated the possible interaction between D3R and dysbindin-1. Aim of this study was to evaluate the possible *in vivo* interaction between D3R and dysbindin-1 in the manifestation of schizophrenia-relevant behaviors, by generating a novel double D3R/dysbindin-1 heterozygous mouse (D3R+/- Dys+/-). These double mutants, single D3R+/- and Dys+/- and their wild-type +/+ littermates were then tested in experimental behavioral paradigms such as the startle/prepulse inhibition (PPI) test and the working memory discrete paired-trial variable-delay T-maze task. Dysbindin heterozygous mice (Dys+/-) showed both an increased startle response to acustic stimuli ($p<0.001$) and working memory deficits ($p<0.05$, 4 and 30 seconds of choice-delays). The partial genetic deletion of D3R completely rescued the aberrant acoustic startle response of Dys+/-. Moreover, D3R+/- Dys+/- mice showed a significant increase of PPI response as compared to wild-type mice ($p<0.05$). Finally, in the discrete paired-trial variable-delay T-maze task, D3R+/- Dys+/- showed a better working memory performance as compared to D3R+/+ Dys+/+ ($p<0.05$, 4 and 60 seconds of choice-delays), again rescuing the dysbindin-1-dependent cognitive deficits. These results demonstrate for the first time that the partial reduction of D3R ameliorates dysbindin-dependent schizophrenia-relevant abnormalities. Importantly, these observation suggest a previously unexplored impact of dysbindin on D_3R trafficking and signaling.

Iizuka et al. (2007). *J Neurosci.* 27:12390-5.
Ji et al. (2009). *Proc Natl Acad Sci U S A.* 106:19593-8.
Laruelle et al. (2003). *Ann N Y Acad Sci.* 1003:138-58
Morris et al. (2008). *Biol Psychiatry.* 63:24-31.
Talbot et al. (2009). *Prog Brain Res*. 179:87-94.
Thompson et al. (2011). *J Biol Chem.* 286:1598-608.
Weickert et al. (2004). *Arch Gen Psychiatry.* 61:544-55.
Weickert et al. (2008). *Schizophr Res.* 98:105-10.
Whistler et al. (2002). *Science.* 297:615-20.