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**Heterodimerization between dopamine D2 receptor and M1 muscarinic acetylcholine receptor**

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About 30–50% of all drugs target G protein-coupled receptors (GPCRs), which is the largest receptor family and is involved in many physiological processes. Since the last two decades, various studies have led to the acceptance that GPCRs do not primarily reside in the plasma membrane as a monomer, but are capable to form homodimers, heterodimers or multimers. Interestingly, various interacting protomers with the dopamine D2 receptor (D2R) have been described and a change in G-protein coupling with the D2R has been observed upon heterodimer formation. However, most studies cannot unambiguously conclude a direct interaction between GPCRs in native tissue.

The cholinergic system plays an important role in neurological processes, a network involved in arousal, cognitive processes (e.g., learning and memory) and attention. In pharmacological animal models of epilepsy and Alzheimer’s disease (AD) the cholinergic GPCRs are targeted with pilocarpine (agonist) and (methyl-)scopolamine (antagonist), respectively. The administration of a high dose of pilocarpine causes status epilepticus (SE), which progresses into spontaneous seizures, resembling temporal lobe epilepsy (TLE) in humans. The administration of scopolamine induces memory impairment, which relates to the intellectual dysfunction in AD patients. Till now, literature only mentions the formation of M1 muscarinic acetylcholine receptor (mACHR) homodimers and heterodimers with M2 and M3 mACHRs. A novel interaction with the D2R could modulate the function of this GPCR: both receptors are co-distributed in several brain regions and both are located at post-synaptic membranes. The M1 mACHR is coupled to the Gαq/11 and D2R to the Gαi/o protein. The cholinergic system is able to modulate the ligand affinity of the D2R, which could be due to GPCR heterodimerization. On the other hand this suggests that the dopaminergic system could tune the cholinergic system, thereby ascribing a more prominent role for dopamine in diseases which are less related to dopamine.

In our studies, we have identified heterodimerization between D2R and M1 mACHR by co-immunoprecipitation (coIP), bioluminescence resonance energy transfer (BRET) and complementation (NanoBiT) assays in transfected HEK 293 cells. The next steps will be the validation of the heterodimer in native tissue. The D2R–M1 mACHR interaction will be tested by coIP, proximity ligation assay (PLA) and time-resolved fluorescent resonance energy transfer (TR-FRET).

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