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Multiple GPCR heteroreceptor complexes: New targets for treatment of Parkinson´s diseases

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The introduction of allosteric receptor–receptor interactions in GPCR heteroreceptor complexes of the CNS gave a new dimension to brain integration and neuropsychopharmacology. The molecular basis of learning and memory was proposed to be based on the reorganization of the homo- and heteroreceptor complexes in the post junctional membrane of synapses. Long-term memory may be created by the transformation of parts of the heteroreceptor complexes into unique transcription factors which can lead to the formation of specific adapter proteins. The observation of the GPCR heterodimer network (GPCR-HetNet) indicated that the allosteric receptor-receptor interactions dramatically increase GPCR diversity and biased recognition and signaling leading to enhanced specificity in signaling. Dysfunction of the GPCR heteroreceptor complexes can lead to brain disease. The findings of dopamine (D2R) and adenosine (A2AR) hetero and isoreceptor complexes in the brain over the last decade gave new targets for drug development in Parkinson´s diseases. We studied the possible reorganization of the A2A-A2A homoreceptor complex and the A2AR-D2R, A2AR-mGluR5 heteroreceptor complexes in the dorsal and ventral striatum in the hemiparkinson rat using the proximity ligation assay. The results were obtained in the dorsolateral striatum comparing the 6-OHDA lesioned side with the unlesioned side, 4 weeks after the lesion (6-OHDA microinjections into the medial forebrain bundle). The A2AR-D2R heteroreceptor complex was found to be significantly increased on the lesioned side ($p< 0.05$, Student's paired t-test , N= 4 rats), which was true also for the A2AR-mGluR5 heteroreceptor complex ($p< 0.05$, Student's paired t-test , N= 4 rats) . The A2AR-A2AR homoreceptor complex was not significantly altered on the lesioned side vs the unlesioned side. Thus, the loss of DA terminals and DA transmission in the dorsal striatum on the lesioned side leads to an altered balance of the hetero and homoreceptor complexes with significant increases of the A2AR-D2R and A2AR-mGluR5 heteroreceptor complexes on the lesioned side. In contrast, the A2AR-A2AR homoreceptor complexes were not altered on the lesiond side vs the unlesioned side. These results may be interpreted as indicating that in the untreated hemiparkinsonian rat the A2AR-D2R and A2AR-mGluR5 heteroreceptor complexes become more dominant favoring excitation of the dorsal striato-pallidal GABA neurons mediating motor inhibition. Hypokinesia becomes increased. The hypothesis is given that changes in the function of the dopamine and adenosine heteroreceptor complexes may especially help us understand the molecular mechanisms underlying the motor complications of long-term therapy in Parkinson's disease (PD) with levodopa and DA receptor agonists. In the indirect pathway the potential role of the A2AR-D2R, A2AR-D2R-mGluR5 and D2R-NMDAR heteroreceptor complexes in PD are covered.

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