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## Multiple D2 heteroreceptor complexes in the ventral striatum: Relevance for schizophrenia and cocaine use disorder and their treatments

**Statement of the Problem:** The discovery of allosteric receptor-receptor interactions in GPCR heteroreceptor complexes in the plasma membrane of nerve cells in the CNS gave a new dimension to brain integration, plasticity and neuropsychopharmacology. Aim of this study is to test the hypothesis that different types of D2 heteroreceptor complexes are new targets in the treatment of schizophrenia and cocaine use disorder. D2 receptors in the complexes can also interact with ion channel receptors, receptor tyrosine kinases and/or adapter proteins. Disturbances in the D2 complexes can contribute to schizophrenia development and cocaine use disorder through changes in the balance of the activity of diverse D2 homo- and heteroreceptor complexes of the ventral striatopallidal GABA anti-reward pathway regulating salience.

**Methodology & Theoretical Orientation:** Proximity ligation assays and biochemical binding techniques were used with behavioral correlates.

**Findings:** Agonist activation of A2A protomer in the A2A-D2 heteroreceptor complex inhibits D2 Gi/o mediated signaling but increases the D2  $\beta$ -arrestin2 mediated signaling. Through this allosteric receptor-receptor interaction, the A2A agonist becomes a biased inhibitory modulator of the Gi/o mediated D2 signaling, which may be the main mechanism for its atypical antipsychotic properties. The dopamine (DA) and glutamate hypotheses of schizophrenia come together in the signal integration in D2-NMDAR and A2A-D2-mGluR5 heteroreceptor complexes, especially in the ventral striatum. Cocaine self-administration differentially affected allosteric A2A-D2 receptor-receptor interactions in the ventral vs. the dorsal striatum.

**Conclusion & Significance:** Dysregulation of the meso-limbic DA neurons and their post junctional D2 heteroreceptor targets may be involved in producing the symptoms of schizophrenia. Potential differences in the composition and stoichiometry of the A2A-D2 heteroreceptor complexes, including differential recruitment of sigma 1 receptor, to the ventral vs. dorsal striatum may explain the selective antagonistic A2A-D2 receptor interactions observed after cocaine self-administration in nucleus accumbens explaining the anti-cocaine actions of A2A agonists.

### Biography

Kjell Fuxe has worked at Karolinska Institute, Sweden since 1960, became Prosektor in 1968 and Professor in 1979. He has been a Professor in the Department of Neuroscience since 2005. He published over 1589 papers. He is a member of Royal Swedish Academy of Sciences and foreign member of Mexican Academy of Sciences and was a member of the Nobel Assembly. He is mainly known for his work on central monoamine neurons, volume transmission and its different forms, receptor-receptor interactions in the CNS and neuropsychopharmacology.

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