Allosteric receptor-receptor interactions in heteroreceptor complexes give a new dimension to molecular neuroscience

The biological principle of formation of homo and heteroreceptor complexes with allosteric receptor-receptor interactions including GPCR-GPCR, GPCR-Ion Channel Receptor and GPCR-RTK heteroreceptor complexes appears to be accepted. This takes place through direct physical interactions through homomerization or heteromerization involving also sets of plasma membrane-associated adapter proteins and can include e.g., ion channels and transmitter transporters. The heteromerization alters receptor protomer recognition, signaling and trafficking and thus their pharmacology and function. One emerging new concept in molecular neuropharmacology is that a dysfunction or disruption of allosteric receptor-receptor interactions with formation of novel heteroreceptor complexes contributes to disease progression in the CNS including addiction. They form major integrative centers of signaling in the CNS and play an important part in learning and memory and are proposed to form molecular engrams crucial for long-term memory. The heteroreceptor complexes are new targets for neurotherapeutics in the CNS giving us a new field in molecular neuroscience. The demonstration of multiple D2 heteroreceptor complexes in ventral and dorsal striatum including A2A-D2, NTS1-D2, 5-HT2A-D2 and oxytocinR-D2 heteroreceptor complexes opened up a promised land for drug development in Parkinson's disease, schizophrenia and drug addiction. Understanding these D2 heterocomplexes and their dysfunction in these diseases leads to new strategies for their treatment, avoiding side-effects and optimizing combined treatments. This development includes heterobivalent drugs to selectively target each heterodimer. Also, the discovery of many 5-HT1A heteroreceptor complexes, like the FGFR1-5-HT1A heterocomplex, of high dynamics opens up new understanding of the molecular basis of neuroplasticity and its relevance for depression.

Biography

Kjell Fuxe has worked at the Karolinska Institutet since 1960, became Prosector in 1968 and Professor in 1979. Since 2005, he is a Professor Emeritus at the Department of Neuroscience. He published over 1589 papers (1224 papers are found in PubMed). He is a member Royal Swedish Academy of Sciences and foreign member of the Mexican Academy of Sciences and was a member of the Nobel Assembly at the Karolinska Institutet for many years. He is mainly known for his work on central monoamine neurons, volume transmission and its different forms, receptor-receptor interactions in heteroreceptor complexes in the CNS and neuropsychopharmacology.

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