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Receptor–receptor interactions: A novel concept in brain integration

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ABSTRACT

A brief historical presentation of the hypothesis on receptor–receptor interactions as an important integrative mechanism taking place at plasma membrane level is given. Some concepts derived from this integrative mechanism especially the possible assemblage of receptors in receptor mosaics (high-order receptor oligomers) and their relevance for the molecular networks associated with the plasma membrane are discussed. In particular, the Rodbell's disaggregation theory for G-proteins is revisited in the frame of receptor mosaic model.

The paper also presents some new indirect evidence on A2A^D2 receptor interactions obtained by means of Atomic Force Microscopy on immunogold preparations of A2A and D2 receptors in CHO cells. These findings support previous data obtained by means of computer-assisted confocal laser microscopy.

The allosteric control of G-protein coupled receptors is examined in the light of the new views on allosterism and recent data on a homocysteine analogue capable of modulating D2 receptors are shown. Finally, the hypothesis is introduced on the existence of check-points along the amino acid pathways connecting allosteric and orthosteric binding sites of a receptor and their potential importance for drug development.

Contents

Abbreviations: AI, Aggregation Index; AFM, Atomic Force Microscopy; CPs, Check-Points; CHO, Chinese Hamster Ovary; DOR, Delta opioid receptors; DI, Disorder Index; DA, dopamine; GPCRs, G-protein coupled receptors; Hcy, homocysteine; KOR, kappa opioid receptors; LTD, long-term depression; LTF, long-term facilitation; LTP, long-term potentiation; MOR, mu opioid receptors; oGPCRs, orphan G-protein coupled receptors; PD, Parkinson's Disease; RM, receptor mosaic; RRI, receptor–receptor interactions; TM, transmembrane helix; UCP2, uncoupling protein 2; VT, Volume Transmission.

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[1] In the memory of my Professors, Paolo Crepax and Francesco Infantellina.

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1. Introduction

> . . . the benefits that molecular biology will bring to pharmacology, I believe, to be circumscribed by the state of physiological knowledge, models, and concepts.
> Sir James Black, Nobel Laureate 1988 (from: Boyd C.A.R., Noble D., *The Logic of Life: The Challenge of Integrative Physiology*, Oxford University Press, Oxford, 1993).

1.1. From a discussion on the membrane as an "informational connector" to the 'birth' of a model of a new integrative mechanism at membrane level

In the 1980 while discussing with Kjell Fuxe the current model of chemical transmission, which was basically based on the assumption that each transmitter binds to its receptor and the transmitter–receptor complex activates intra-cellular cascades and only after these steps the integration of several chemical pathways at cytoplasmic level could take place (see Fig. 1, upper panel), we put forward the working hypothesis that not only an integration of electrical, but also an important integration of chemical signals could already takes place at membrane level.

Thus, a new model (see Fig. 1, lower panel) was proposed pointing out that an integrative information handling is already occurring at membrane level especially via *Receptor–Receptor Interactions* (RRI). We pointed out that this intra-membrane control of the receptor signalling could have the important function of allowing the intra-cellular biochemical machinery to work on "conditioned" signals. Furthermore, it was underlined that RRI could be a part of intra-membrane and/or membrane-associated molecular networks likely involved in several high-order integrative functions. Actually, in the 1986 WGC Symposium we stated that:

> Very likely we will find out that some sophisticated elaborations of information are performed at the membrane level, via interactions within and among different classes of macromolecules (Fuxe and Agnati, 1987).

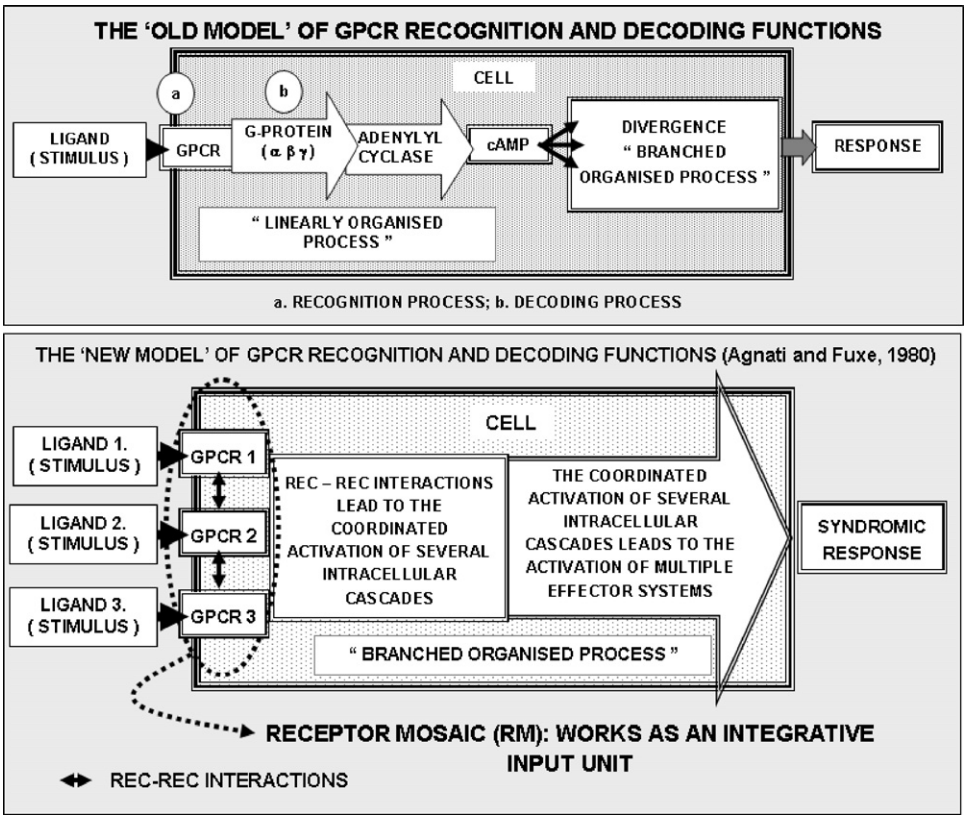

Fig. 1. The two model of recognition and decoding of signals performed by GPCRs are compared. The upper panel shows the classical model, while the lower panel presents the model suggested by our group.