1. Record Nr. UNINA9910137094503321

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| Titolo | Monitoring endogenous GPCRs: lessons for drug design |
| Pubbl/distr/stampa | Frontiers Media SA, 2015 |
| Descrizione fisica | 1 electronic resource (134 p.) |
| Collana | Frontiers Research Topics |
| Lingua di pubblicazione | Inglese |
| Formato | Materiale a stampa |
| Livello bibliografico | Monografia |

Sommario/riassunto

G protein-coupled receptors (GPCRs) are integral membrane proteins forming the fourth largest superfamily in the human genome. Many of these receptors play key physiological roles and several pathologies have been associated with receptor functional abnormalities. GPCRs therefore represent important goals for drug design in pharmaceutical companies since they constitute the target of about one third of the drugs currently on the market. However, endogenous GPCRs are most often difficult to study because of a lack of tools to target them specifically and single out their response to physiological or drug-elicited stimulations. Hence, studies mostly focused on recombinant receptors expressed in a variety of cellular models that do not always closely reflect the receptor natural environment and often deal with levels of expression exceeding by far physiological ranges. Recent technological developments combining for example genetically modified animals and advanced imaging approaches have improved our ability to visualize endogenous GPCRs. To date, trailing receptor activation, subsequent intracellular redistribution, changes in signaling cascade up to integrated response to a drug-elicited stimulation is at hand though the impact of a physiological challenge on receptor dynamics remains a major issue. Data however suggest that the receptor may embrace a different fate depending on the type of stimulation in particular if sustained or repeated. This suggests that current drugs may only partially mimic the genuine response of the

receptor and may explain, at least in part, their secondary effects. Commonalities and specificities between physiological and drug-induced activation can thus represent valuable guidelines for the design of future drugs.