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Introduction

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G protein-coupled receptors (GPCRs) constitute the largest family of cell surface proteins involved in signal transduction. As such, they are the major targets for current and, most probably, future drug therapy. Among the many examples of available medicines interacting with GPCRs are the antihypertensive beta-blockers, opioid receptor agonists such as morphine, histamine H_1 and H_2 receptor antagonists as anti-allergic agents and antacids, respectively, and anti-depressants such as clozapine. The development of these and other drugs was the logical consequence of understanding receptor action. In traditional receptor theory, hormones and neurotransmitters are seen as the body's own receptor agonists that, after binding, turn on receptor activity that is otherwise silent. Any aberration in this process may be counteracted with either agonist or antagonist drugs.

Recent evidence, however, suggests that GPCRs have the potential to be 'active' even in the absence of an agonist. The first substantial report described this phenomenon for the δ-opioid receptor, which paved the ground for many further studies all pointing to the existence of so-called constitutive receptor activity. For instance, it turned out that some congenital diseases have their molecular origin in GPCRs bearing activating mutations. Retinitis pigmentosa and congenital night blindness are due to mutations in the visual pigment rhodopsin, which is a GPCR. The mutations cause this receptor to be spontaneously (or constitutively) active, leading to the disease.

Such exhibition of constitutive receptor activity led to a reclassification of drugs as well. It appeared that various ligands, previously considered antagonists without intrinsic activity, inhibit constitutive receptor activity. They act rather as 'inverse agonists', displaying 'negative intrinsic activity'. Other ligands, however, do not seem to influence the receptor's own activity; they are 'neutral antagonists'. It is obvious that this new subdivision impacts the course and nature of drug development programs in the pharmaceutical industry.

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Despite the tremendous research efforts over the past decade, there are a number of important open issues with regard to 'inverse agonism'. These include the following:

- What are the (patho)physiological consequences of 'inverse agonism'?
- What are the clinical observations for current drugs classified as inverse agonists?
- Is 'inverse agonism' linked to other novel receptor concepts such as oligomerization and allosteric modulation?
- Can structure-activity relationships be derived for inverse agonists, i.e. can inverse agonists be designed?

It is fortunate that the Esteve Foundation provided the means to organize their Xth symposium, held in S'Agaro, Spain (October 2–5, 2002) as a timely forum to address these issues. It turned out that constitutive receptor activity is indeed a feature of most GPCRs, with very few exceptions. Important proof-of-concept was provided in in vivo studies; this is particularly relevant since most studies in the past were done on rather artificial, engineered cell systems. The existence of putative endogenous inverse agonists was heavily debated. The cellular context of inverse agonism, i.e. the presence of helper and scaffold proteins, was presented, as were novel techniques to detect and quantify inverse agonism, also in a high-throughput mode. Interestingly, over the days of the conference, an integrated view emerged among the participants, which is, hopefully, reflected in the proceedings to this workshop. They hold the ensemble of individual contributions and the lively discussions that followed each presentation.