Allosteric modulation of GPCR signaling

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G protein coupled receptors (GPCRs) are the largest family of receptors for hormones and neurotransmitters and major targets for new therapeutics for a broad spectrum of diseases (1). Upon binding their ligand, GPCRs trigger diverse signals through a selectively coupling to multiple intracellular partners. This functional versatility is further allosterically modulated by the receptor cellular environment. However, the molecular mechanisms underlying the allosteric control of GPCR efficacy and functional selectivity are still obscure. We have developed an original molecular pharmacological strategy that relies on an *in vitro* system where a model GPCR, the ghrelin receptor GHSR, is reconstituted in a membrane mimicking environment, lipid nanodiscs. Getting this model allowed us to use a combination of computational, biochemical and biophysical methods to illuminate the molecular mechanisms underlying the allosteric modulation of GPCR signaling. I will present data demonstrating that a series of endogenous compounds – signaling proteins, ions, membrane lipids – specifically bind to GHSR. By doing so, they significantly affect the conformational dynamics of the receptor, and this in turns impacts on the functional outputs (2-5). All together, these data point at these cellular components as allosteric modulators of GHSR, making them an integral part of the ghrelin signaling machinery, following the "*on a souvent besoin d'un plus petit que soi*" rule.

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