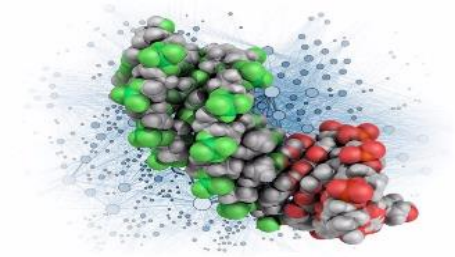

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Structural and dynamic understanding of the ghrelin receptor high constitutive activity

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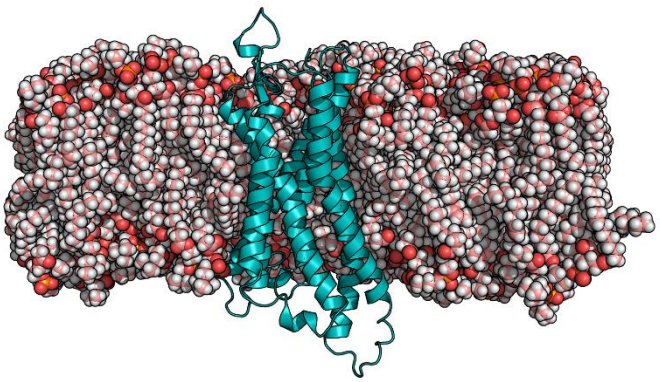
Graphical Abstract *(mandatory)*



Abstract. *(mandatory)*

Ghrelin is a peptide secreted in the gastric fundus and acts in hypophysis and hippocampus through a Class A G-protein Coupled Receptor (GPCR), the GHS-R1a. GPCRs are characterized by a seven transmembrane (TM) spanning α-helices, connected to three extracellular (ECL) and three intracellular loops (ICL). (1) Activation of this receptor is involved in a variety of functions from feeding and growth hormone release to promotion of learning and memory. Among GPCRs, GHS-R1a is characterized by an unusual high constitutive activity, in the absence of specific ligands. (2) Regarding this distinctive characteristic, a mutation, A204E, of this receptor leads to a reduction of its constitutive activity. (3)

To reveal more information about this distinctive receptor, 3D structure models of different stages of activation and of a particular mutation (A204E) of the GHS-R1a were created using homology modelling molecular docking

	and their differences analysed. Fully-atomistic molecular dynamics simulations are being performed initially with the pre-active model and the mutant, and will be followed by the remaining activation states. These simulations will give atomic detail to the necessary conformation rearrangements responsible for receptor activity. The structural and functional characterization of GHSR1a is an important step towards the design of specific drugs.

References *(mandatory)*

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