Título: ISOLATION OF VGF DERIVED NEUROPEPTIDE RECEPTOR

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Fecha de lectura: 29/06/2015

Programa de doctorado: Medcina Molecular

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> 201120_778966.pdf

Localización: BIBLIOTECA XERAL USC

Resumen: VGF (non-acronymic) is a ~68 kDa neurosecretory protein, belongs to the extended granin family of proteins, initially identified as a nerve growth factor (NGF) inducible gene product, is selectively synthesised mostly in neuronal and neuroendocrine cells. Due to the presence of paired basic amino acid residues (R ¿ Arginine, and K ¿ Lysine), the VGF sequence undergoes endoproteolytic cleavage to produce several smaller peptides, released upon stimulation via the regulated secretory pathway both in vitro and in vivo. There are data suggesting that the VGF-derived peptides are the biologically active, stored in dense core vesicles and secreted in order to play a role in inter cellular communication, and responsible for the diverse range of biological functions associated with VGF. Several of these VGF-derived peptides have been characterised and are involved in energy balance, reproductive behaviour, pain modulation and mood order.

Till now, the best characterized VGF derived peptide is designated as TLQP-21. As growing data is accumulating on the several significant biological effects of TLQP-21 like energy balance, pain modulation, gastric, reproduction, stress, diabetes; identification of its receptor(s) is of particular relevance. In light of this extensive array of effects, the very limited knowledge about its molecular mechanisms of TLQP-21 is remarkable. Recently, C3AR1 and gC1qR have been reported as receptors of murine TLQP-21. However,

human TLQP-21 whose sequence shows differences with respect to murine TLQP-21, exhibits at best very weak binding to these receptors, suggesting the existence of different receptors for human vs rodent TLQP-21.

Here using affinity chromatography and mass spectrometry-based protein identification, the heat shock cognate 71 kDa protein A8 (HSPA8) has been identified as a receptor of human TLQP-21. Binding of TLQP-21 to membrane associated HSPA8 in live SH-SY5Y cells was confirmed by cross-linking and FACS studies. Furthermore, molecular modeling studies show that TLQP-21 can be docked into the peptide binding pocket of HSPA8. The major task moving forward is to elucidate the signaling pathways of the ligand TLQP-21 and its receptor HSPA8. Identification of HSPA8 as a receptor of human TLQP-21 could open new approaches for diagnostics and therapeutics for a wide range of human diseases related with VGF, in particular those in which TLQP-21 has been shown to have an effect.