Kettle Moraine High School SMART Team

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Leptin and PACAP: Possible Co-op?

PDB: 1AX8

Primary Citation:

Zhang, F., Basinski, M.B., Beals, J.M., Briggs, S.L., Churgay, L.M., Clawson, D.K., DiMarchi, R.D., Furman, T.C., Hale, J.E., Hsiung, H.M., Schoner, B.E., Smith, D.P., Zhang, X.Y., Wery, J.P., Schevitz, R.W. (1997) Crystal structure of the obese protein leptin-E100. Nature 387: 206-209

Format: Alpha-carbon backbone

RP: Zcorp with plaster

Abstract: More than one-third of American adults are obese, and obesity-related conditions including diabetes, hypertension, and stroke are among the leading causes of preventable deaths. Leptin is a hypophagic hormone secreted by fat cells, thought to regulate satiety. The Ile14 residue in leptin is crucial for the interaction between leptin and its receptor. Leptin helices A and C interact with the CRH2 domain of the leptin receptor. Mutations to Ile14 disrupt the docking conformation in a manner that prevents helices A and C on leptin to position parallel with CRH2 thereby, affecting the binding efficiency. Mutation to the Ile14 residue results in excessive feeding and weight gain. The neuropeptide pituitary adenylate cyclase activating polypeptide (PACAP) produces identical hypophagia via the hypothalamic ventromedial nuclei (VMN) to that of leptin. The proximity of leptin and PACAP receptors combined with their functional similarity suggest they could collaborate to induce hypophagia through a shared intracellular signaling cascade. By identifying critical molecular sites necessary for leptin action, we may better understand how PACAP and leptin receptor signaling are linked, whether changes to the residue also alters PACAP signaling and the degree to which it contributes to obesity or eating disorders. The Kettle Moraine High School SMART (Students Modeling A Research Topic) Team has modeled leptin using 3D printing technology to investigate structure function relationships. Inquiry into leptin and PACAP interactions may reveal the nature of

interdependency between neural and peripheral energy-regulating systems in the VMN, new applications of hypophagic drugs, and the biological cause of obesity.