

Greenfield High School SMART Team

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Hungry Like PACAP Man – The Role of PACAP and PACAP6-38 in Eating Behaviors

PDBs: 1GEA ⁽¹⁾ and 2JOD ⁽²⁾

Primary Citations:

(1) Inooka, H., Ohtaki, T., Kitahara, O., Ikegami, T., Endo, S., Kitada, C., Ogi, K., Onda, H., Fujino, M., Shirakawa, M. (2001). Conformation of a peptide ligand bound to its G-protein coupled receptor. *Natural Structural Biology* 8: 161-165.

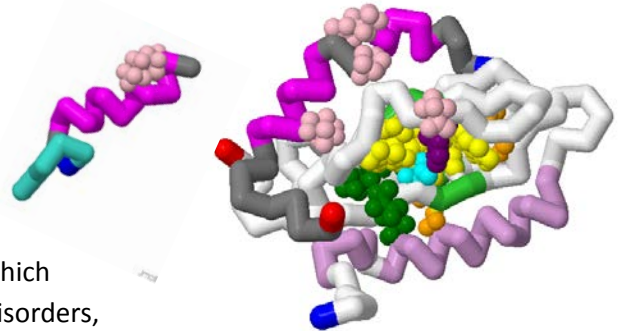
(2) Sun, C., Song, D., Davis-Taber, R.A., Barrett, L.W., Scott, V.E., Richardson, P.L., Pereda-Lopez, A., Uchic, M.E., Solomon, L.R., Lake, M.R., Walter, K.A., Hajduk, P.J., Olejniczak, E.T. (2007). Solution structure and mutational analysis of pituitary adenylate cyclase-activating polypeptide binding to the extracellular domain of PAC-1RS. *Proceedings of the National Academy of Sciences of the United States of America* 104: 7875-7880.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

According to the CDC, 34.9% of United States adults are obese, which is linked to premature death, heart disease, cancer, respiratory disorders, fertility problems, Type 2 diabetes, and stroke. Over- and under-eating are related to brain chemistry. A 38 amino acid peptide hormone in the hypothalamus, called pituitary adenylate cyclase-activating peptide (PACAP), may be linked to eating disorders. PACAP binds to PACAP type 1 receptor (PAC1R), a G-protein coupled receptor. Seven hydrophobic transmembrane (TM) domains hold PAC1R in hypothalamic cell membranes. PAC1R's extracellular domain (ECD) contains a ligand binding site. PAC1R's many negative residues attract PACAP's many positive ECD residues. PACAP's V19, K20, and L27 affect PACAP binding to PAC1R. K20 forms a possible salt bridge with PAC1R's G104, allowing PACAP to align parallel to PAC1R so PACAP's N-terminus interacts with PAC1R's TM domains. This activates PAC1R, sending a signal inside the cell. Too much PACAP may cause a person to stop eating and lead to eating disorders. PACAP6-38 is an antagonist formed when a protease removes the first five PACAP residues. When PACAP6-38 binds to PAC1R, eating increases, possibly leading to obesity. SuJean Choi, PhD wants to



determine how ratios of PACAP and PACA6-38 are regulated. The Greenfield SMART (Students Modeling A Research Topic) Team modeled PAC1R's ECD and its two ligands, PACAP and PACAP6-38, using 3D printing technology to investigate their relationships. Studying PACAP and PACAP6-38 regulation and brain chemistry involved in eating behaviors could improve people's lives and decrease obesity-related US medical costs. Program supported by a grant from NIH-CTSA.

Specific Model Information:

1GEA: PACAP (1-27)

- The alpha carbon backbone is colored gray.
- Amino acids 1-5 on PACAP are colored turquoise.
- Alpha helices on PACAP are colored magenta.
- Amino acids speculated to be important in binding PACAP to PAC1R (Val19 and Lys20 on PACAP) are colored pink.
- Where the N-terminus would be after residues 1-5 are removed by a protease to create PACAP6-38.

2JOD: PAC1R ECD & PACAP6-38

- The A chain alpha carbon backbone is colored white (PAC1R).
- Amino acids (Cys97-Cys54, Cys34-Cys63, and Cys113-Cys77) involved in disulfides bonds are colored orange.
- Disulfide bonds are colored yellow.
- Amino acids that stabilize and contribute to the hydrophobic nature of PAC1R's core (Trp64, Val93, Trp102, and Tyr109) are colored yellow.
- Amino acids that form a salt bridge within PAC1R to stabilize PAC1R (Asp59 is colored cyan and Arg95 is colored purple).
- Salt bridge between Asp59 and Arg98 on PAC1R is colored seagreen.
- Alpha helices on PAC1R are colored plum.
- Beta sheets on PAC1R are colored limegreen.
- The B chain alpha carbon backbone is colored gray (6-38PACAP).
- Amino acids speculated to be important in binding PACAP6-38 to PAC1R (Glu104 on PAC1R and Val19, Lys20, and Leu27 on 6-38PACAP) are colored pink.
- Alpha helices on PACAP6-38 are colored magenta.
- N-terminus of PAC1R and PACAP6-38 is colored blue.
- C-terminus of PAC1R and PACAP6-38 is colored red.
- Hydrogen bonds and structural supports are colored white.

<http://cbm.msoe.edu/smartTeams/>

The SMART Team Program is supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number 8UL1TR000055. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.