Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231-6345 (Online)
An Online International Journal Available at http://www.cibtech.org/jls.htm
2011 Vol. 1 (4) October- December, pp.137-144/Divya et al.
Research Article

MOLECULAR MODELING STUDIES OF PANCREATIC HORMONE RECEPTOR INTERACTION WITH β AMYLOID PROTEIN; IMPLICATIONS FOR ALZHEIMER'S DISEASE

Divya V, Kaysina Vazhudhi and *Manoj G Tyagi
Department of Pharmacology, Christian Medical College, Vellore 632002
**Author for Correspondence*

ABSTRACT
Pancreas secretes two hormones *i.e.* insulin and glucagon and these hormones act by stimulation of their specific receptors. In mammals, age is also associated with a decline in insulin like growth factor-1 (IGF-I) levels, a well known neuroprotective agent. Serum IGF-I increases adult neurogenesis, sustains neuronal health through a variety of fundamental homeostatic mechanisms, participates in brain angiogenesis, contributes to brain β-amyloid clearance and affects learning and memory. Overall, diminished trophic input resulting from decreasing serum IGF-I levels during aging likely contributes to brain senescence in mammals. A similar neuro-protective role for GLP-1 has been visualized. In this study the protein modeling and molecular docking was performed between the IGF-I, GLP-1 receptor and the β amyloid protein. The results suggest a reasonable interaction between IGF-I/GLP-1 receptor and β amyloid protein.

Key Words: *Insulin, Glucagon, Receptor, β Amyloid Protein, Alzheimer's Disease*

INTRODUCTION
Based on several lines of evidence, it was proposed that a neuroprotective network provides a tonic, pro-survival input to brain cells (Torres-Aleman, 2000). This network includes blood–borne insulin-like growth factor I (IGF-I). A first line of evidence in favor of this possibility is merely circumstantial. Serum levels of IGF-I decline with age and are altered in a remarkable variety of neurodegenerative conditions (Arvat *et al,* 2000; Busiguina *et al* , 2000). In addition, IGF-I is effective in protecting against all types of neuronal insults (Carson *et al,* 1993). Classical gene-targeting experiments showed that over-expression of IGF-I results in a larger brain size due to increased neuronal somas, increased numbers of specific brain cell populations and increased neuropil. On the other hand, mutant mice that survive with IGF-I deletions have reduced brain size (Beck et al, 1995). Therefore, neuronal size and number depends on IGF-I input. More specifically, and confirming this view, recent observations in serum IGF-I-deficient mice show reduced neuronal numbers. IGF-I is a known angiogenic promoter not only in the developing brain, but also in other tissues in the adults. Serum IGF-I also plays a role in how exercise affects the brain, and exercise stimulates brain angiogenesis (Bar *et al*, 1988; Black *et al*, 1990).

Glucagon like peptide 1 (GLP-1) is a 30–amino acid gut hormone secreted in a nutrient-dependent manner that stimulates insulin secretion and inhibits glucagon secretion and gastric emptying, thereby reducing postprandial glycemia. GLP-1 is derived from posttranslational proteolysis of preproglucagon, and its peptide sequence is identical in mouse, rat, and human((Ban *et al*, 2008). Active isoforms of GLP-1 include GLP-1(7-36) amide and glycine-extended GLP-1(7-37). After secretion from enteroendocrine L cells, GLP-1(7-36) amide is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) to its N-terminally truncated metabolite

GLP-1(9-36), which does not interact with the known GLP-1 receptor (Deacon *et al* 1995, Kieffer *et al*, 1995). Several studies suggest that genetic and biochemical data have coalesced to establish that β-amyloid peptide (Aβ) is a causative factor in neuron death and the consequent dimunition of cognitive abilities observed in Alzheimer's disease (Naslund *et al* 2000, Yan *et al* 1996). Plasma lipoproteins and their cell surface receptors influence sequestration and clearance of soluble Aβ, contributing to the etiology of the disease (Narita et al, 1997; Russo et al, 1998; Du *et al* 1998). Inflammatory responses and oxidative damage also appear to contribute to the loss of neurons in Alzheimer's disease (El-Khoury *et al*, 1996). Although the earliest cellular perturbations remain unclear, recent findings indicate that Aβ may act as an initiating factor in the death of neurons by inducing signaling pathways leading to apoptosis. However, the specific molecular target(s) transducing these Aβ effects has not been identified. The potential role of glucagon-like peptide -1 (GLP-1) treatment in AD. GLP-1 receptors are expressed in areas of the brain important to memory and learning, and GLP-1 has growth-factor-like properties similar to insulin. A key neuropathological feature of AD is the accumulation of amyloid-beta (Aβ). In preclinical studies, GLP-1 and longer lasting analogues have been shown to have both neuroprotective and neurotrophic effects, and to protect synaptic activity in the brain from Aβ toxicity.

A convincing amount of evidence has shown a beneficial effect of GLP-1 agonist treatment on cognitive function, memory and learning in experimental models of AD. GLP-1 analogues may therefore be the new therapeutic agent of choice for intervention in AD. This study was conducted to ascertain a direct protein-protein interaction of the pancreatic hormone receptors with β amyloid protein by using molecular modeling techniques.

MATERIALS AND METHODS

Molecular docking and protein modeling **:** Glucagon like peptide -1 receptor of glucagon was modeled using the 3D JIGSAW software since its structure was not available in the protein data bank (PDB). Docking is a modeling process in which the interactions between molecules are examined. The structure of Insulin like Growth Factor-I obtained from PDB was docked with β Amyloid protein using a Hex Software. In a similar way the modeled structure of Glucagon like Peptide -1 Receptor was docked with β Amyloid protein using Hex software. The structures of both the docked complexes were transferred to the GETAREA server for interface analysis.

RESULTS

The IGF -I receptor had a Swissprot ID (P08069) and PDB ID (HGR) while the GLP-1 receptor had a Swissprot ID (P43220). The Results of the molecular docking studies between IGF-I receptor, GLP-1 receptor and β Amyloid protein are shown in Table 1 and Figures 1 to 5.

DISCUSSION

The insulin receptor is distributed in a widespread, but selective, pattern in brain including olfactory bulb, cerebral cortex, hypothalalmus and cerebellum as reported in rodents. The IGF-I receptor, which can dimerize with insulin receptor affect its ligand affinity and specificity, as mentioned earlier, shows a similar distribution in the brain as the insulin receptor, and it also exhibits a distinct expression pattern compared to the insulin receptor when examined. Insulin receptor is expressed in various regions of the developing and adult brain, and its functions have become the focus of recent research. In this study we found that there was better interaction of

the IGF-I receptor with β amyloid protein as compared with GLP-1 receptor as depicted in the Table 1 and Figure 4. It would be pertinent to assume that there is a direct interaction of this AP molecule with the IGF-I receptor subsequent to tau phosphorylation. Thus this molecular docking study is unique and throws interesting light on the changes occurring in the brain of Alzheimer's patients.

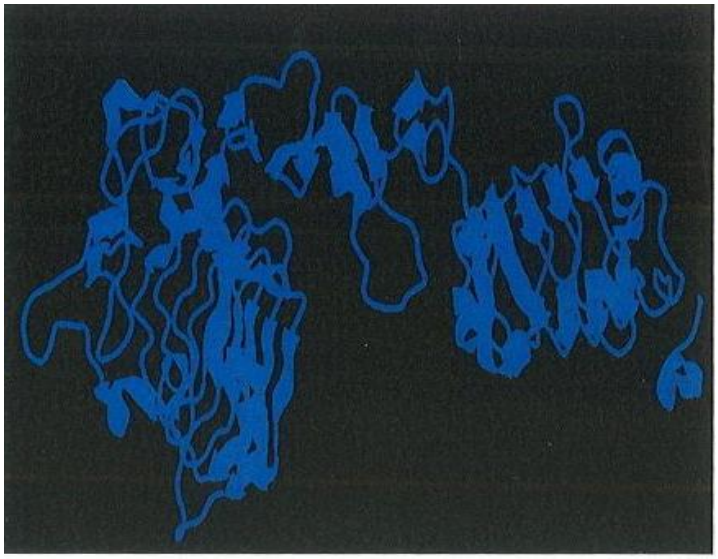

Figure 1: Structure of Insulin Like Growth Factor-1 receptor

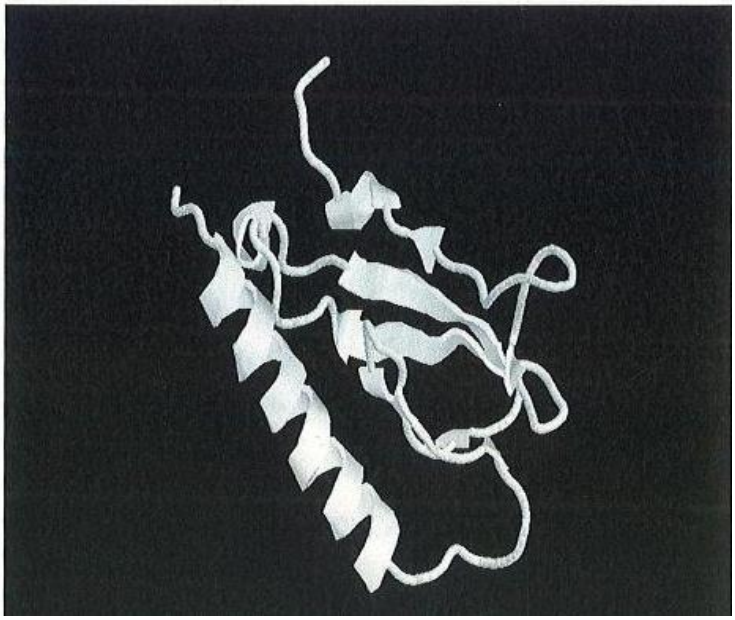

Figure 2: Modeled structure of Glucagon Like Peptide-1 receptor

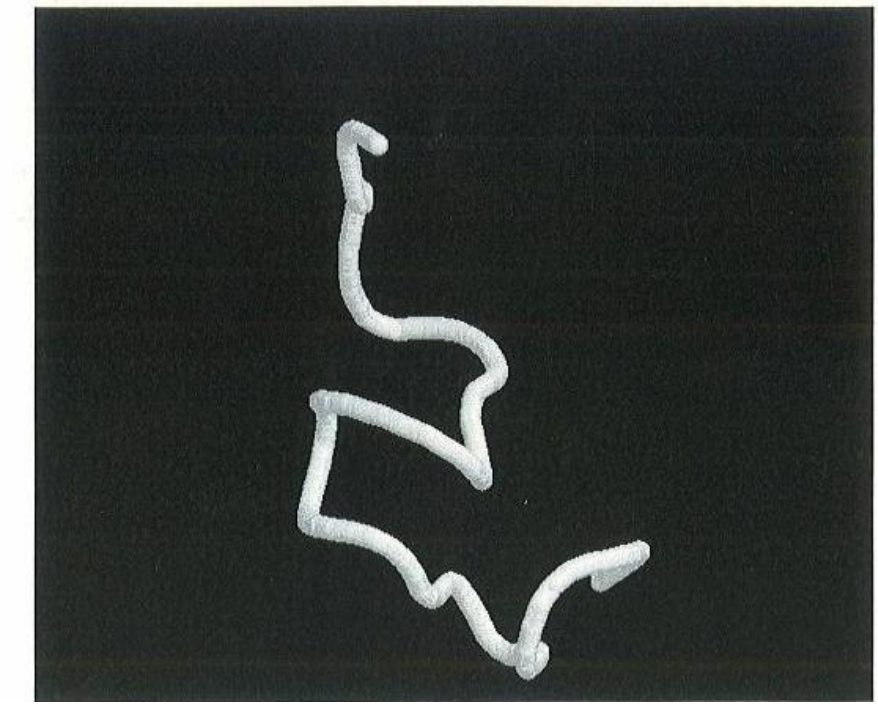

Figure 3: Structure of Beta Amyloid Protein

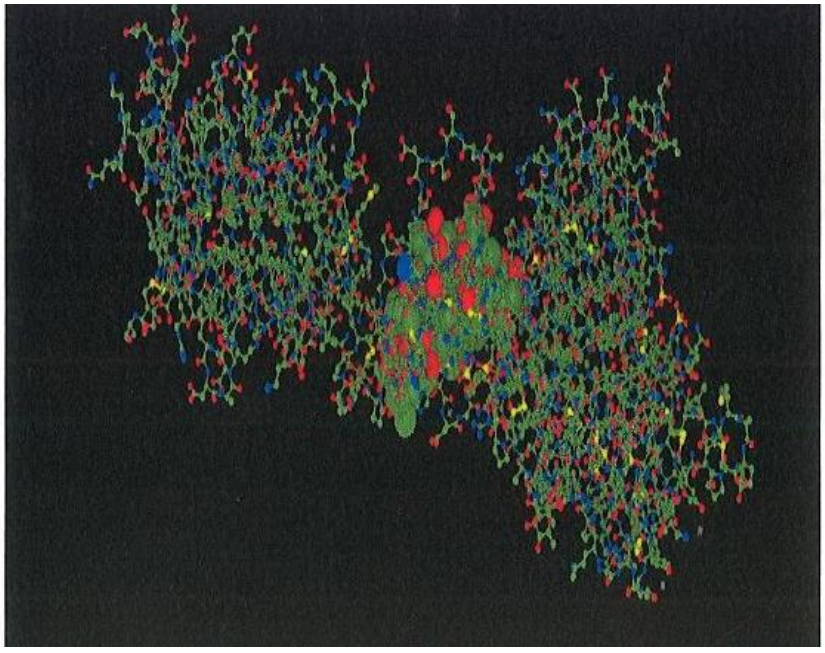

Figure 4: Docked structure of Insulin Like Growth Factor-1 receptor with Beta Amyloid protein

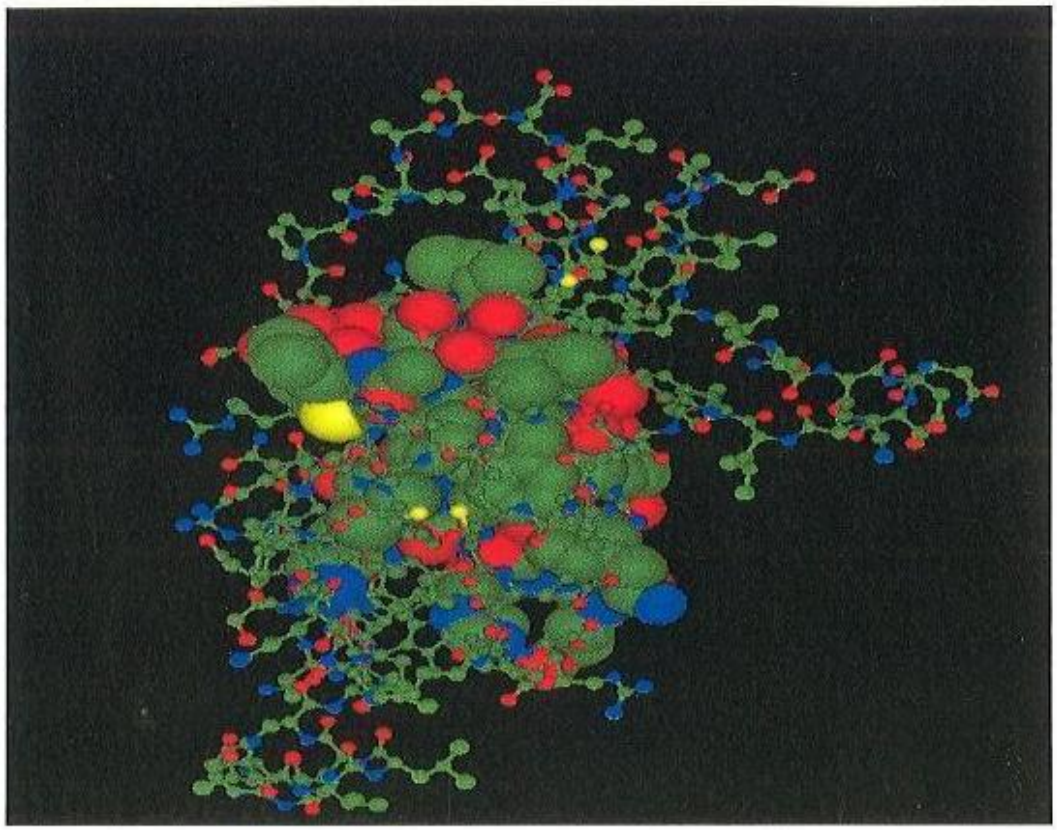

Figure 5: Docked complex of Glucagon Like peptide-1 receptor with Beta Amyloid protein.

Table 1: Data obtained from the GETAREA server

Docked Complex	**Total No. of Residues**	**No. of Residues present outside i.e. interface residues**	**No. of Residues present inside**	**Interface Residues: Residues present inside**
Insuin-β Amyloid protein	478	136	342	0.2: 0.7
Glucagon-β Amyloid protein	54	42	12	1.2 : 0.3

DISCUSSION

The insulin receptor is distributed in a widespread, but selective, pattern in brain including olfactory bulb, cerebral cortex, hypothalalmus and cerebellum as reported in rodents. The IGF-I receptor, which can dimerize with insulin receptor affect its ligand affinity and specificity, as mentioned earlier, shows a similar distribution in the brain as the insulin receptor, and it also exhibits a distinct expression pattern compared to the insulin receptor when examined. Insulin receptor is expressed in various regions of the developing and adult brain, and its functions have become the focus of recent research. In this study we found that there was better interaction of the IGF-I receptor with β amyloid protein as compared with GLP-1 receptor as depicted in the Table 1 and Figure 4. It would be pertinent to assume that there is a direct interaction of this AP molecule with the IGF-I receptor subsequent to tau phosphorylation. Thus this molecular docking study is unique and throws interesting light on the changes occurring in the brain of Alzheimer's patients.

On the other hand, it has been reported that GLP-1 can reduce the levels of amyloid- beta peptide in the brain *in vivo* and can reduce levels of amyloid precursor protein (APP) in cultured neuronal cells (During *et al*, 2003). It can modify APP processing and protect against oxidative injury. Hence glucagon is a novel therapeutic target for intervention in Alzheimer's disease. However we did not find a major interaction of the GLP-1 receptor with amyloid protein based on our molecular docking study as depicted in the Table 1 and Figure 5. Thus suggesting a different mechanism for its anti-amyloid activity.

However the IGF-I receptor (IGF-1R) shows more potential and is a transmembrane heterotetrameric protein complex that has 60% sequence homology to the insulin receptor (IR). IGF-IR also binds IGF-II and insulin with 2 to 15 and 1000 fold lower affinity, respectively (Khandwala *et al*, 2000). IRS-1/2 protein expression decreases with severity of neurodegeneration in AD brains, and the inhibiting phosphorylation of IRS-1 at Ser-312 and Ser-616 is increased, leading to impaired IR and IGF-IR signaling. Thus, IR/IGF-1R downstream signal transduction is impaired in AD brains, leading to the hypothesis that cerebral insulin/IGF-I resistance might be involved in the pathogenesis of AD (Zeslawski *et al*, 2001). However, it is still unclear whether these changes are cause or consequence of disease. This study can have implications for other associated neurological disorders.

ACKNOWLEDGEMENTS

The authors thank Mrs. Nidhi Tyagi, M.Sc for help in the preparation of this manuscript.

REFERENCES

Arvat E, Broglio F and Ghigo E (2000). Insulin-like growth factor I: implications in aging. *Drugs Aging* **16**, 29–40

Bar RS, Boes M, Dake BL, Booth BA, Henley SA and Sandra A (1988). Insulin, insulin-like growth factors, and vascular endothelium, *American Journal of Medicine* **85**, 59–70

Beck KD, Powell-Braxton L, Widmer HR, Valverde J and Hefti F (1995). IGF-I gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. *Neuron* **14**, 717–730

Black JE, Isaacs KR, Anderson BR, Alcantara AA and Greenough WT (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats.*Proceedings of the Naional Academay of Science USA* **87**, 5568–5572

Ban K, Hossein Noyan-Ashraf M, Hoefer J, Sebastian Bolz S, Drucker DJ and Mansoor H (2008). Cardioprotective and Vasodilatory Actions of Glucagon-Like Peptide 1 Receptor Are Mediated Through Both Glucagon-Like Peptide 1 Receptor–Dependent and –Independent Pathways.*Circulation.***117**:2340-2350

Busiguina S, Fernandez AM, Barrios V, Clark R, Tolbert DL, Berciano J and Torres-Aleman I (2000) Neurodegeneration is associated to changes in serum insulin-like growth factors.*Neurobiology of Disease*. **7**, 657–665

Carson MJ, Behringer RR, Brinster RL and McMorris FA (1993) Insulin-like growth factor I increases brain growth and central nervous system myelination in transgenic mice, *Neuron* **10**, 729–740.

Deacon CF, Johnsen AH and Holst JJ (1995). Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite *in vivo*. *J Clinical Endocrinology and Metabolism*. **80**:952–957.

Du Y, Bales K, Dodel R, Liu X, Glinn M, Horn J, Little S, and Paul S (1998) α-2 macroglobulin attenuates β-amyloid peptide 1-40 fibril formation and associated neurotoxicity of cultured fetal rat cortical neurons. *Journal of Neurochemistry*. **70**, 1182-1188

During M J, Cao L, Zurga D S, Francis J S, Fitzsimons H L, Jiao X, Bland RJ, Klugman M, Banks WA, Drucker DJ and Haile CN (2003) Glucagon-Like peptide-1 receptor is involved in learning and neuroprotection. *Nature Medicine* **9** (9): 1173-9

El Khoury J, Hickman S, Thomas C, Cao L, Silverstein S, and Loike J (1996). Scavenger receptor mediated adhesion of nicroglia to β amyloid fibrils. *Nature* **382**, 716-719

Khandwala H M, McCutcheon IE, Flyvbjerg A and Friend KE (2000). The effects of insulin like growth factors on tumorigenesis and neoplastic growth. *Endocrinology Reviews*, **21**,215-244

Kieffer TJ, McIntosh CH and Pederson RA (1995). Degradation of glucose dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 *in vitro* and *in vivo* by dipeptidyl peptidase IV. *Endocrinology*, **136**:3585–3596.

Naslund J, Haroutunian V, Mohs R, Davis K, Davies P, Greengard P, and Buxbaum J. (2000), Corelation between elevated levels of β amyloid peptide in brain and cognitive decline. *Journal of American Medical Association* **283**, 1571-1577

Narita M, Holtzman D, Schwartz A, and Bu G (1997). α-2 macroglobulin complexes with and mediates the endocytosis of β –amyloid peptide via cell surface low density lipoprotein receptor-related protein.*Journal of Neurochemistry* **69**, 1904-1911

Russo C, Angelini G, Dapino D, Piccini A, Piombo G, Schettini G, Chen S, Teller J, Zaccheo D, Gambetti P, and Tabaton M (1998). Opposite roles of apolipoprotein E in normal brains and in Alzheimer's disease. *Proceedings of National Academy of Sciences U S A.* **95**, 15598-15602

Torres-Aleman I (2000). Serum growth factors and neuroprotective surveillance. *Molecular Neurobiology*, **21**, 153–160

Yan S, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, Migheli A, Nawroth P, Stern D, and Schmidt A (1996). RAGE and amyloid β peptide neurotoxicity in Alzheimer's disease. *Nature* **382**, 685-691

Zeslawski W, Beisel H G, Kamionka M, Kalus W, Engh R A, Huber R. Lang K and Holak T A (2001). The interaction of insulin-like growth factor-1 with the N-terminal domain of IGFBP-5. *The EMBO Journal.* **20**,14, 3638-3644