

45 Molecular modelling of the IgE receptor loops - lipid interaction

DIEGO ESPOSITO, MIRE ZLOH and WILLIAM A. GIBBONS

University-Industry Centre for Pharmaceutical Research, School of Pharmacy, University of London, 29-39 Brunswick Sq., London WC1N 1AX, U.K.

Integral membrane proteins contain hydrophobic transmembrane domains, that interact with the lipid bilayer, and extramembraneous domains that contact the aqueous phase and the polar surface of the membrane. This latter interaction could be important for the correct folding and packing of the transmembrane domains. For this purpose it has been intriguing to investigate the interaction of the loops which connect consecutive transmembrane helices with the polar heads of some of the most common phospholipid constituting membranes [1]. Previous conformational studies of the domains of the high affinity IgE receptor showed the evidence of the alpha helical structure in the two connecting loops in the organic solvents, indicating the conceivable 'TM-helix -Bend - Loop Helix - Bend - TM helix' motif [2]. Here we report molecular mechanics and dynamics studies of the interaction between peptides with sequences of the first extracellular loop (L1-2) and the second cytoplasmic loop (L2-3) of the β -subunit of the IgE receptor and the molecules glycerol-phosphatidylserine (GPS), glycerol-phosphatidylcholine (GPC), glycerol-phosphatidylethanolamine (GPE).

The interaction energies between 2 connecting loops of the β -subunit and the three different molecules has been calculated using the X-PLOR 3.1 program with the CHARMM 22x parameter set and dielectric constant of 80.0 to simulate the aqueous environment. The calculation were performed starting from alpha helical conformation of the peptide, and the backbone geometry was allowed to change during simulations. The peptide and interacting molecule have always been oriented with axis parallel to each other, in two orientations, and eight different positions were considered as described previously [3]. The two different protocols were employed: energy minimization protocol (4000 steps of the Powell minimisation) and modified simulated annealing protocol, (a 2 ps molecular dynamics heating stage at 600 K with a timestep of 1 fs, a 2 ps constant temperature molecular dynamics simulation at 300 K with timestep of 2 fs, and 2000 steps of conjugate gradient of minimisation stages). The interaction energies between the three molecules and the peptide were calculated relatively to those when the two molecules were far apart, and the interaction energies are averaged for two orientations for all positions.

A negative value for the interaction energy corresponds to a favourable conformation and indicates the stabilisation of the complex. All the calculated energies for all the conformation have resulted negative. Nevertheless, in all cases the energy differences between the lowest and the highest energy positions, were in the range of few kilocalorie per mole. Interaction energies between L1-2 and three molecules are shown in the Figure 1. Generally, GPC molecular interacts stronger with L1-2, than GPE and GPS. Lowest energy complex is formed when GPC molecule interacts with PHE 88, ASP89, VAL92 and LEU93 residues of the L1-2, and those residues are located on the opposite side of the highly charged side of the helix.

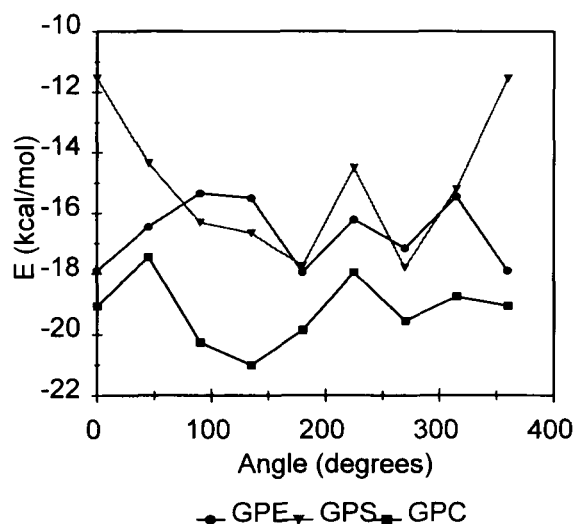


Figure 1. Interaction energies between connecting loop1-2 of the beta subunit of FcεRI (L1-2) and glycerol-phosphatidylserine (GPS), glycerol-phosphatidylcholine (GPC), glycerol-phosphatidylethanolamine (GPE).

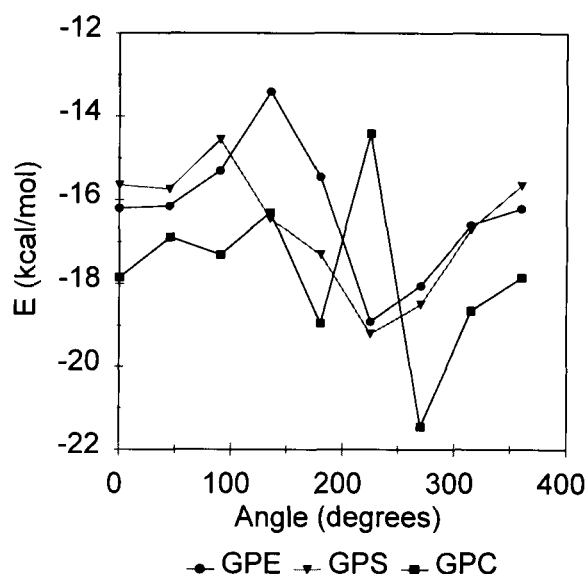


Figure 2. Interaction energies between connecting loop2-3 of the beta subunit of FcεRI (L2-3) and glycerol-phosphatidylserine (GPS), glycerol-phosphatidylcholine (GPC), glycerol-phosphatidylethanolamine (GPE).

The interaction energy curves for L2-3 peptide and three molecules are having similar pattern, but GPC forms slightly more favourable complexes with L12, than GPS and GPE (Figure 2.). There are lowest energy complexes for all three molecules, when they interact with THR143 and LEU144. Again, these residues are on the opposite side of the charged side of helix.

The alpha helix structure is one of the possible conformations that extracellular and cytoplasmic connecting loops could adopt in the final conformation of the receptor, and this assumption was supported by CD experiments, where the presence of the SDS micelles was inducing alpha helix structure in the L1-2 and L2-3 peptides[2].

The results of the molecular mechanics calculation are also supporting this assumption. It has been shown that GPC interacts stronger with extracellular loop L1-2 than GPE and GPS, and that was expected since the phosphatidylcholine lipids are major contributors to the outside layer of the membrane. For both loops, L1-2 and L2-3, there is a similar pattern in interaction energy curves for all three molecules, proving that there are sites for the more favourable interaction of the lipid head groups with connecting loops. These sites are on the opposite side of charged side of the helices, that are allowed to be in the aqueous phase.

Further studying of the conformational components of domain peptides within the high affinity IgE receptor, based upon energetics and structural interactions between receptor peptides and specific lipids, will improve understanding the mechanism of the allergy and other inflammating conditions.

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3. Zloh, M. and Gibbons, W.A. (1996) *Biochem. Soc. Trans. 24*, 305S