

Thesis Intro

1 What are pLGICs

1.1 What is an ion channel

1.1.1 Conducts ions across membrane

1.1.2 Transmembrane proteins

1.1.3 Essential for various cellular functions (EXPLAIN)

1.2 What are the general structural features of pLGICs

1.2.1 Ion channels made of 5 subunits

1.2.2 EGD beta sheets with binding pockets-Gated by various ligands

1.2.3 TMD 5 bundles of 4 alpha helices-interacts with membrane

1.3 What is the physiological significance of pLGICs, ie: what do they do

1.3.1 Eucariot: Mediate neuronal function

1.3.1.1 nAChR and 5-HT3R-cationic receptors activate action potential

1.3.1.2 GABAaR glycine receptors-anionic receptors inhibit action potential

1.3.2 Procarotic ELIC-GLIC-We don't know

1.4 Where are pLGICS found in Mammals

1.4.1 Central and periferal nervous system

1.4.2 Post-synaptic junction in brain and muscle

1.5 Health related issues of pLGICs

1.5.1 See most recent paper

2 Lipids and membranes

2.1 Model Membranes

2.1.1 What is a lipid

2.1.2 What is a membrane

2.1.3 What causes domain formation

2.1.4 What effect does Chol have on a membrane

Merge Lipids and Membranes; sub group native and model

2.1.5 What effect do PUFAs have on a membrane

2.2 Native Membranes

2.2.1 How does membrane compositions vary across cell types

2.2.2 What are medical issues of too few n-3 PUFAs

3 Protein modulation by lipids

3.1 Which lipids have been most studied

3.1.1 Cholesterol, saturated, mono-unsaturated, sphingo-Anionic, Neutral

3.2 How do Lipids affect function

3.2.1 Modulate function

3.3 What are known functional effects of chol

3.3.1 Required for function, ~20-30% of membrane composition

3.4 What conditions have anionic lipids promoted function

3.4.1 I do not know...

4 Sequence/Structure and lipid binding

4.1 What role might structure of the protein play in lipid occ

4.1.1 M4 as a lipid sensor

4.1.2 M4 cone/star resulting shape effect minimized by PUFAs; and stabilized by GHQL

4.1.3 Inter-subunit "cone" stabilized by chol; occupied by saturated

4.2 How might sequence play a role in lipid- protein binding

4.2.1 Charge repells anionic lipids

4.3 How/why can proteins deform membranes

4.3.1 M4 provides cone/star shape; unfavorable to membrane

4.3.2 Size of TMD my cause hydrophobic mismatch

5 pLGIC boundary lipids

5.1 Are boundary lipids conserved across pLGICS sequences

5.1.1 No; anionic lipid occupation changes based on location of cationic amiono-acids

5.2 What are possible mechanisms by which lipids could affect protein function

5.2.1 Prevent protein from "colapsing"

5.2.2 Minimize deformation energetics

5.3 How would the membrane composition affect boundary lipids

5.3.1 Different membranes; different lipids: How much of lipid x can you get and does lipid y act as a reasonable replacement?

5.4 Why might the distribution of lipids matter

5.4.1 function

5.4.2 Deformation energy minimization

5.4.3 Some lipids may exacerbate poor function if bound to specific locations

6 Methods

6.1 Where are pLGICs experimented in

6.1.1 Model membranes : boundary lipid studies

6.1.2 Oocytes : functional studies

6.1.3 Model "rings" structural studies

6.2 What are the experimental approaches that have been used to identify boundary lipids for membrane proteins

6.2.1 Florences quenching

6.2.2 Mass Spec

6.2.3 Spin Label

6.2.4 Cryo-EM or x-ray Chrystalography (lesser extent)

6.3 How can we determine whether a lipid affects function via domain formation vs direct ligand-like interactions

6.3.1 Electrophysiology

6.3.2 Florences quenching

6.3.3 NMR?

6.4 Why do MD simulations

6.4.1 Computational Microscope

6.4.2 Rooted in physics

6.4.3 Acts as predictor, or supporter for experimental studies

6.5 What computational tech have been used to predict pLGIC-boundary lipids?

6.5.1 Atomistic simulations

6.5.2 Docking

6.5.3 Coarse-Grained Simulations

6.6 Why is docking not ideal

6.6.1 I DO NOT REMEMBER

7 Point of this thesis

7.1 What is the knowledge gap- ie What general question does this particular thesis hope to answer

7.2 What was the trajectory of the thesis? ie how do the different chapters fit together and build on eachother?