Chapter 1
Introduction

1.1 Ion Channel

The first ion channels to be discovered and characterized were the voltage-gated ion channels, found in nerve and muscle tissue. These ion channels open and close (gate) in response to changes in the membrane potential, or voltage. In order for neurons to conduct an electrical impulse, it is necessary for sodium, potassium, and calcium ion channels to open and close at the precisely the right times. When the so called action potential travels along the neuron's axon, the membrane potential (voltage), which is itself the actual signal, jumps quickly along it's length from a -70 mV inside the cell (compared to 0 mV outside of the cell) to +50 mV inside the cell and then back to a normal resting potential of -70 mV again.

Ion channels are usually found on the surfaces of cells and are therefore easily accessible to most small molecules such as toxins injected into the blood and lymphatic fluid by venomous creatures like some kinds of snakes, scorpions, bees, among many others.

The time-scale in which ion channels operate are very fast compared everyday human experiences. Many ion channels are capable of allowing ions thru at the rate of 100 million ions each second, and many of these channels stay open less than a millisecond at a time before closing again. This rapid rate of change which ion channels are capable of allows the cells, and consequently the organism

itself, a fine level of control over what goes in and out of a nerve or muscle cell, and how fast such exchange events occur. Speed is often a very important factor for survival in nature because the amount of time it takes to respond to danger in the environment can often mean the difference between survival or death. Since the proper functioning of nerve and muscle tissue is dependent on exchange of ions thru ion channels in the cell membranes, ion channel kinetics has evolved over millions of years to be very rapid indeed.

1.1.1 The ligand-gated ion channel

The ligand-gated ion channels are channels which bind to small molecules responsible for other types of regulation. These ion channels open or close depending on the presence of the type of ligand they bind to. For example, there are sodium ion channels which bind to the neurotransmitter ligand acetylcholine and open; while at the same time, other sodium ion channels may close upon binding the same type of ligand.

In this way, a single ligand can regulate ion channels differently depending on where they are found in the body. The nAChR ion channel is a sodium channel which gets its name because it binds to the ligand nicotine (n) as well as the ligand acetylcholine (ACh) and is therefore functions as a receptor (R) as well as an ion channel. There are also a host of ion channels which are gated by ligands found only in the insides of cells. These are therefore named intracellularly ligand-gated ion channels. G-protein coupled receptors(GPCRs) are capable of opening or closing certain ion channels indirectly by causing enzymatic cascades which result in ligand-formation to take place within the cell.

These various ligands are then able to change the function of the ion channel directly by either opening or closing the channel. Mechanical forces such

as those which initiate the sensations of touch and sound can be converted directly into electrical signals when ion channel are activated directly by these signals, whereas ion channels which gate in response to light (vision) and smell (olfaction) must be activated indirectly by way of GPCRs. It has been calculated that the ion channels in hair cells in the inner ear are capable of opening and closing in response sounds by movement of the hair cell's cilia hair by a distance equivalent to that of a single atom's diameter. The first and so far only mechanosensitive ion channel of this type that has been identified and cloned is from the fruit fly Drosophila's sensory brittle neuron.

ATP-synthase is the protein complex which lets hydrogen ions into the mitochondria and makes ATP in the process. No life is known to exist on this planet without the ATP manufactured by these protein/enzyme/ion channels.

Given the importance of maintaining a constant chemical environment within the cell, it is not too surprising that ion channels have been shown to be involved in host defenses. Defensins are small molecular peptide ion channels (peptides are very small proteins often less than 100 amino acids in length) modified to punch holes in cell membranes of bacteria and other pathogens and are found in extracellular fluids of mammals and other animals. Bacteria and even plants also produce them to attack microbes.

1.1.2 Lyotropic Liquid Crystals

Liquid crystals come in two basic classifications: thermotropic and lyotropic . The phase transitions of thermotropic liquid crystals depend on temperature, while those of lyotropic liquid crystals depend on both temperature and concentration. We will focus on lyotropic liquid crystals.

Lyotropic liquid crystals were actually discovered long before their thermotropic counterparts were known. However, the significance of liquid crystals was not understood, so most research has been done on thermotropics. Only fairly recently have lyotropic liquid crystals begun to catch up.

The molecules that make up lyotropic liquid crystals are surfactants consisting of two distinct parts: a polar, often ionic, head and a nonpolar, often hydrocarbon tail. Following the rule of like dissolves like, the head is attracted to water, or hydrophilic, and the tail is repelled by water, or hydrophobic. When dissolved in high enough concentrations, the molecules arrange themselves so that the polar heads are in contact with a polar solvent and/or the nonpolar tails are in contact with a nonpolar solvent.

Lyotropic liquid crystals are found in countless everyday situations. Soaps and detergents form lyotropic liquid crystals when they combine with water. In the kitchen, cake batters may harbor the liquid crystals as well. Most importantly, biological membranes display lyotropic liquid crystalline behavior.

1.2 Ligand Binding

Heme proteins are the best understand class of protein molecules. They are the most obvious candidate for trying to understand the effect of the overall protein on the local chemistry of small ligand binding. The kinetics of ligand binding to heme molecules has been studied over a large range of temperatures and solvent viscosities.

The binding of small ligands to heme proteins appears to be a simple reaction, described for the particular case of carbonmonoxide binding to myoglobin by the one step chemical reaction. Austin, Beeson, Eisenstein, Frauenfelder, and

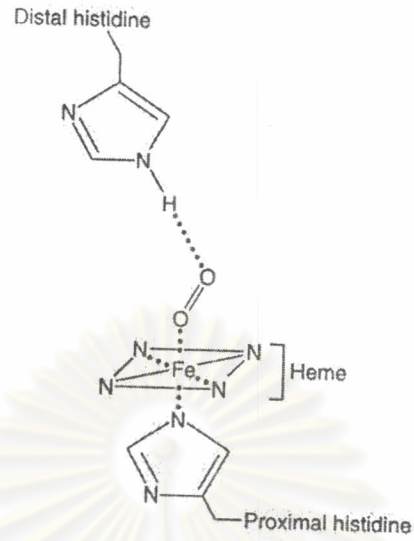

Figure 1.1: The ligand-binding site of heme created by a folded chain.

Gunsalus(1975) showed that data taken over wide ranges in time and temperature in which a CO molecule, coming from the solvent, encounters, not one, but three or four potential barriers.

Hemoglobin and myoglobin have closely related structures. Both contain the heme structure. In myoglobin the heme is bound to a polypeptide chain of 153 amino acids arranged in helical arrays. The polypeptide chain folds in a manner that creates a pocket in the protein for a heme group. Hemoglobin is made up of four polypeptide chains, each of which is similar in shape and structure to a myoglobin molecule.

Each heme unit in myoglobin and hemoglobin contains one Fe^{2+} ion bound to four nitrogen donor atoms in a square planar arrangement. This leaves the metal with two axial coordination sites to bind other ligands. One of these sites is bound to a histidine side chain that holds the heme in the pocket of the

protein. The other axial position is where reversible binding of molecular oxygen takes place.

Myoglobin plays an important role in the mammalian cell where it stores and transports oxygen and possibly also carries energy. An understanding of the reaction of myoglobin with ligands, particularly dioxygen and carbon monoxide, is desireble because it can serve as a prototype for more complex systems.

In this dissertation, we consider the ligan-gated ion channel currents in a nonstationary lyotropic model in chapter 2. The ligand-binding on protein hemoglobin is presented in chapter 3 and discussion is in chapter 4.

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