Transporters

Introduction

In lesson #1: *Plasma Membranes*, we discussed how plasma membranes are impermeable to mostly everything, and how large things could be brought into the cell in vesicles. In this lesson, we talk about how small things can be moved into or out of the cytoplasm through channels. A cell membrane is impermeable to almost everything. So, for a cell, it's about controlling permeability to substrates. We start with simple diffusion, then translate the diffusion equation into membrane permeability, the conductance of a membrane to a molecule.

Simple Diffusion

Small, nonpolar molecules such as CO_2 and O_2, and (even though polar) H_2O can diffuse through a cell membrane. They do so by following the law of diffusion.

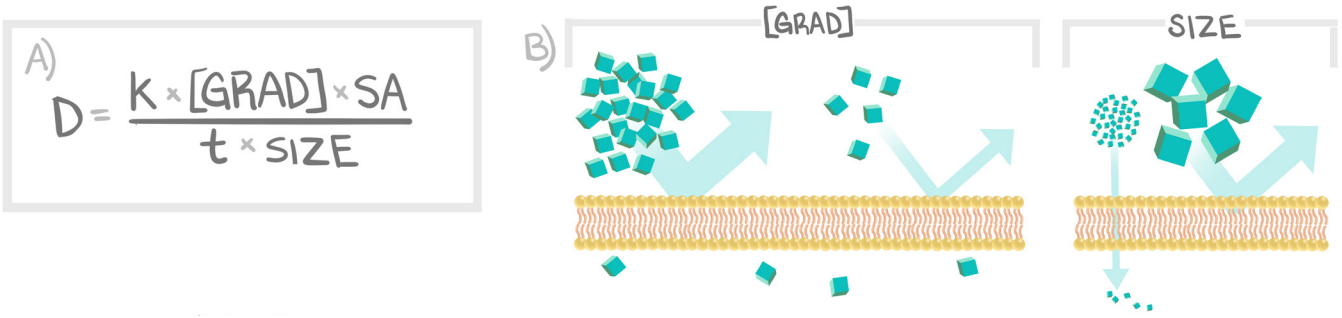

Figure 2.1: The Concentration Gradient Drives the Force
(a) Simple diffusion is based on the permeability, the concentration gradient, and the surface area of diffusion, and is inversely proportional to how far the molecule must travel and how large it is. (b) The cell membrane allows only very small molecules to diffuse through the membrane; this concentration gradient establishes a potential, a force, and the bigger the concentration gradient, the bigger the force.

The **concentration gradient** across a membrane is the driving force of diffusion, determining both direction and magnitude of movement of each substance across the membrane. All substances "want" to diffuse across the membrane **from high** concentration **to low** concentration, which defines the direction of diffusion. **The bigger the difference of concentration, the larger the driving force** (magnitude).

The **permeability** (*k*) of a molecule matters a lot. For cell membranes, **lipophilic molecules** can readily diffuse—there just aren't that many molecules like that. Those that are polar, ionized, or are otherwise hydrophilic have no trouble interacting with the polar head groups of phospholipids, but cannot penetrate the lipid bilayer. This is how cell membranes are effectively impermeable to all molecules except for small gases and lipophilic hormones.

The **more surface area** (SA) of a membrane there is, the **more readily a molecule can diffuse**. But the thickness of the membrane, **how far a molecule must travel** (t), limits diffusion.

Size matters in diffusion. **Large molecules don't diffuse** as readily as small molecules.

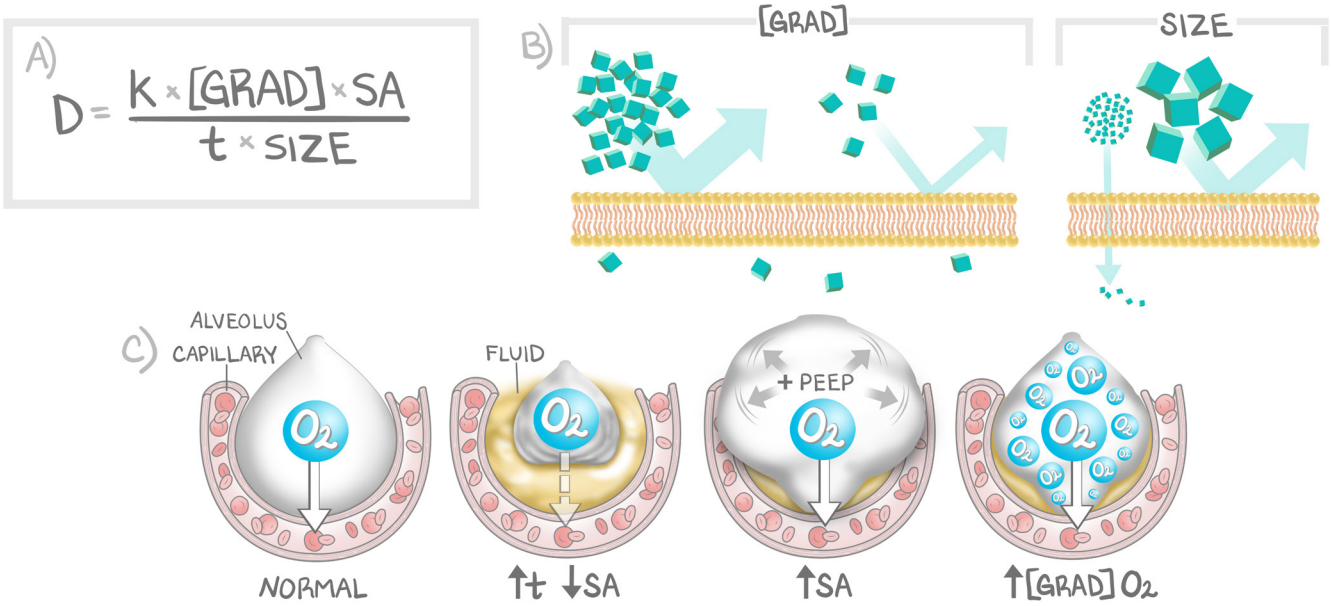

Figure 2.2: Surface Area Affects Diffusion
(a) In an alveolus, the barrier to diffusion is normally small. (b) In the setting of pulmonary edema, the surface area is decreased and the distance is increased, reducing the diffusion capacity of the collapsed alveoli. (c) Applying PEEP restores the surface area and decreases the distance to diffuse as alveoli expand. (d) Supplemental oxygen increases the concentration gradient.

The diffusion equation can be understood by considering the alveolar-capillary barrier for oxygen exchange. Oxygen diffuses into the capillaries from the lungs. If there is pulmonary edema, there is a collapse of the alveolus away from the capillary. This means that there is decreased surface area and a large distance for the oxygen to diffuse across. Thus, pulmonary edema results in low oxygen levels in the blood. By adding extra oxygen or applying positive end-expiratory pressure (PEEP), we can increase the concentration gradient (more oxygen in alveolus) and keep the alveolus from collapsing, maintaining the surface area.

This equation is good only for molecules that can diffuse across a membrane. Diffusion happens in chemistry. Selective diffusion happens in cell biology.

Translating the Diffusion Equation to Cell Membranes

The diffusion equation is great for understanding how molecules work in the chemistry lab and even on a larger scale within the body—but let's consider how to apply this equation to the actual impermeable cell membrane. Turns out, this application is a little bit easier to understand than the equation, with diffusion depending on three main factors: the **concentration gradient**, the **channel conductance**, and the **number of open channels**.

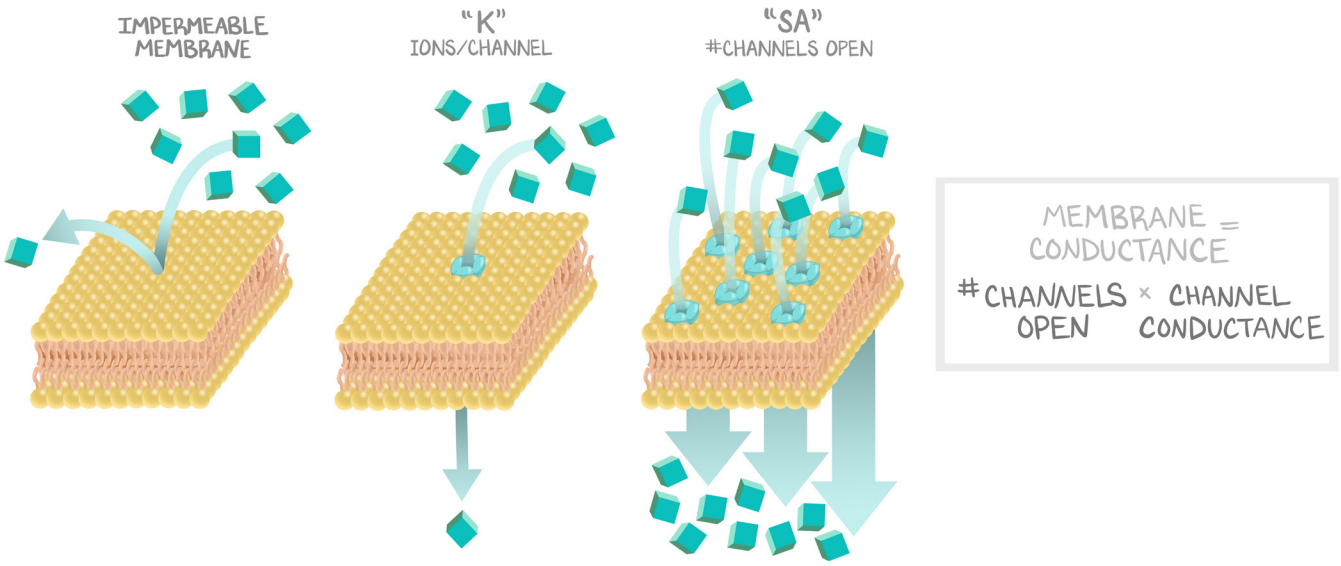

Figure 2.3: Membrane Conductance
An impermeable membrane generates a concentration gradient. A single channel has a certain permeability to a given ion. The channel conductance reflects "*k*" in the diffusion equation. How many channels are open reflects "surface area."

So we know that the **concentration gradient** is the driving force—direction and magnitude—for diffusion, when the membrane is permeable. But we also know that the cell membrane is impermeable to most molecules, so no matter how much a substrate "wants" to move down the gradient, it can't. But the cell can harness that desire to move (the energy of the gradient) by changing its permeability to certain molecules at certain times, using **transmembrane** proteins and **channels**.

Channels are conduits between the extracellular matrix and the cytoplasm. They can be **open** (substrate can flow) or **closed** (substrate can't flow). Channels are also **selective** for certain substrates. For example, a sodium-glucose channel will allow only sodium and glucose to pass through it. How well a channel allows diffusion of a specific substrate is called **channel conductance**, and it's determined by the size and shape of the molecule. Applying the channel conductance to the percentage of channels that are open provides the **membrane conductance**—how well a molecule can diffuse across a given membrane.

Now think back to that diffusion equation. The concentration gradient is still a driving force, but more indirectly by providing the energy to operate channels on the membrane. The number of channels open reflects the surface area—the more open channels, the faster a substrate can diffuse. The channel conductance is dictated by the permeability coefficient and the size of the molecule. And the thickness of the cell membrane is always the same.

"How many are open" is equivalent to the surface area of the diffusion equation. The more open channels, the faster a substrate can diffuse. *"Channel conductance"* accounts for the permeability coefficient and the size of the molecule (the size and shape of the molecule determine whether that channel will allow that molecule to diffuse). The thickness of the cell membrane is always the same. And the concentration gradient is determined by the concentration of the molecule on either side of the cell membrane.

Passive Membrane Transport

When a membrane transporter opens and that substrate is allowed to move **down its concentration gradient**, it's called **passive transport**. Passive transport is also called **facilitated diffusion**. It's passive because the only energy required to move that ion is the concentration gradient itself.

Pores are channels that are **always open**. But these are not powerful channels, and are often referred to as **leak channels** (such as the potassium leak channel that established the resting membrane potential of an excitable cell in #6: *Membrane Potential*). Pores are **always open**, but are generally **few in number** and have a **low channel conductance**.

Gated channels are pores with a cover. The presence of **gates** allows the membrane to regulate the pores, to decide when they are open or closed. When the gate is open, the substrate flows down its concentration gradient. When they are closed, a ligand, voltage change, or other process must act on these gateways for them to open. Gated channels often have a **high conductance** (when open, they readily let the substrate flow), such as the voltage-gated sodium channel of the action potential (General Physiology #8: *Action Potential*), and are **large in number**, but are **almost always closed**. So, usually, the membrane isn't permeable to a substrate (the membrane conductance is low), but suddenly, the cell membrane can become massively permeable to that substrate for a short amount of time.

Carriers are like an airlock. They are used to shuttle large molecules down their concentration gradient. But these channels require a **conformation change** to permit passage of the molecule. They bind their molecule and change shape, thereby moving the molecule down its concentration gradient. The channel then changes back to its original shape to move another molecule. Because they must undergo a conformation change, it's possible to **saturate** them, and therefore the **number of channels** is most important to determine the rate at which molecules of a given substance can move.

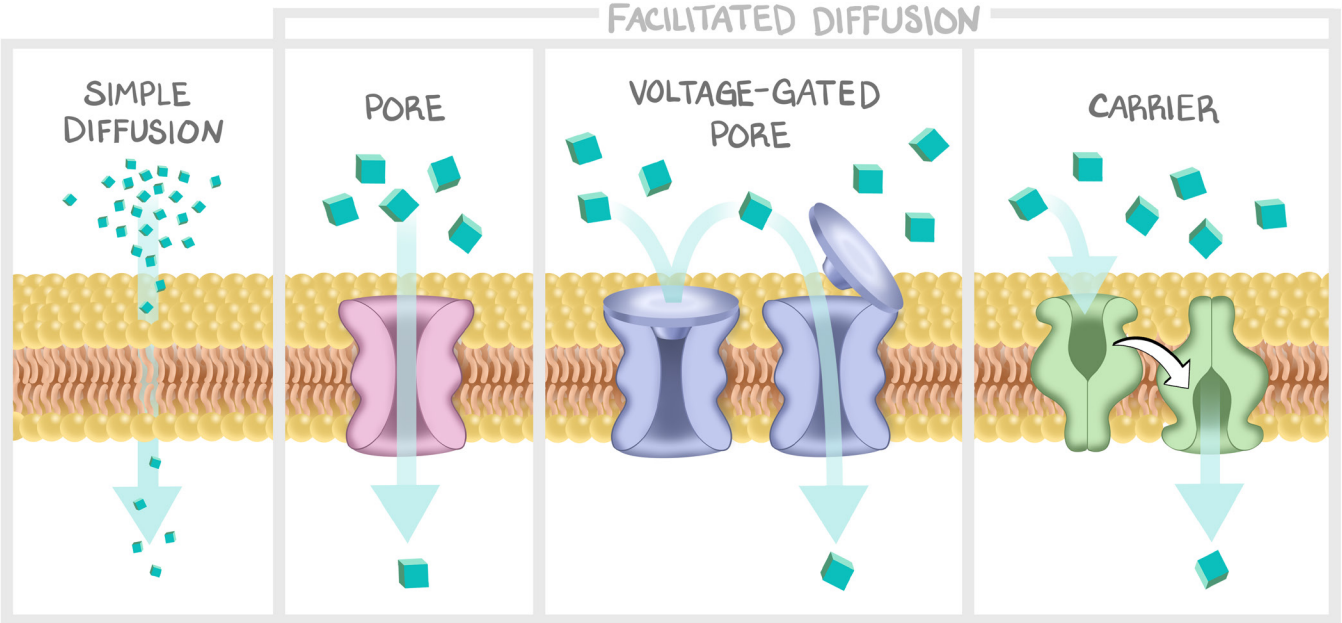

Figure 2.4: Passive Membrane Transport
Passive transport does not use energy because it carries the molecule down its concentration gradient. Simple diffusion needs no pore at all, but only very small molecules such as O_2, CO_2, and water can do this. Facilitated diffusion is diffusion down the concentration gradient, but only with some help. And there are many different kinds. Carriers saturate. The rest do not.

Active Transport

Active transport throws diffusion and conductance out the window. Because active transport moves a molecule **up its concentration gradient**, that is, **against the diffusion equation**, it cannot follow the rules of diffusion. This transporter does not harness the energy of the concentration gradient because it moves the molecule in the other direction of that energy.

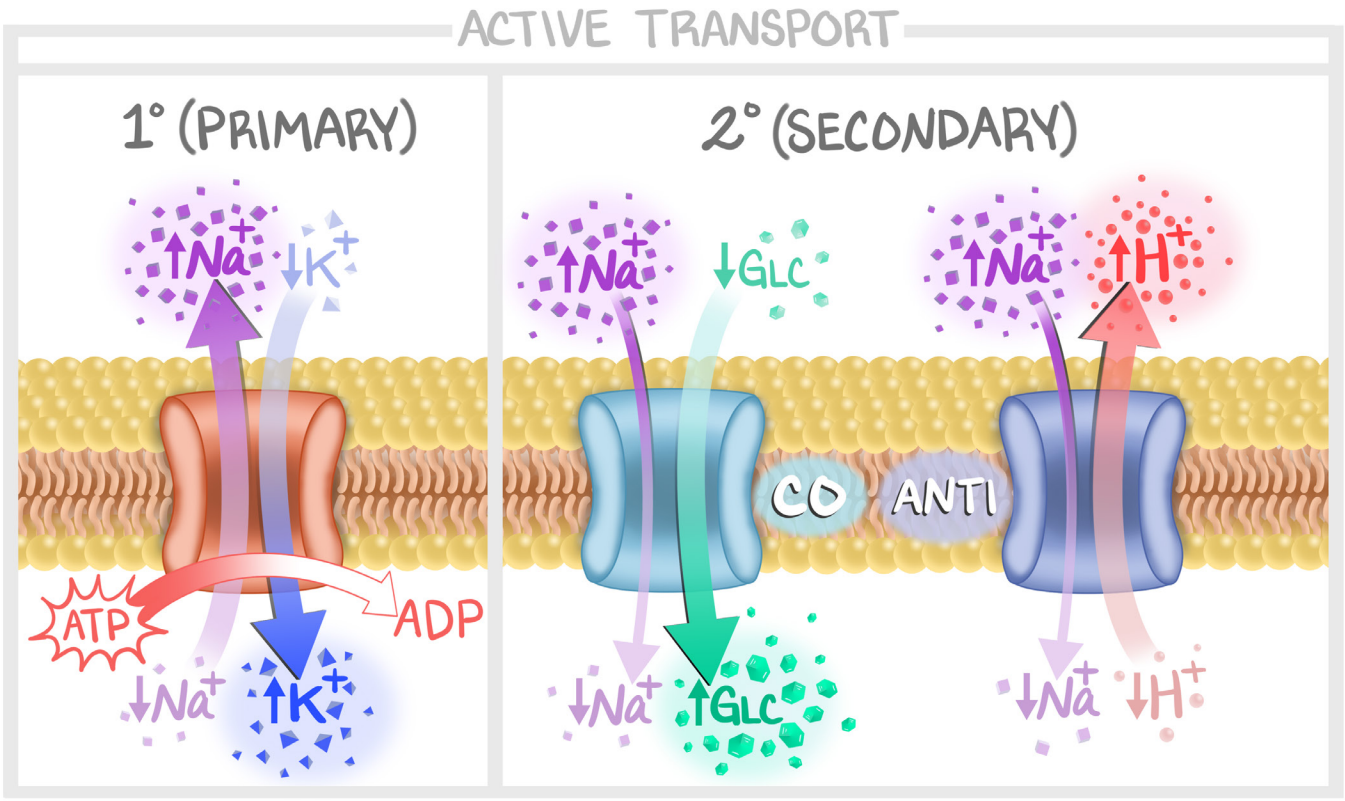

Figure 2.5: Active Transport
Active transport occurs in one of two forms. Primary active transport harnesses the hydrolysis of high-energy compounds like ATP to move ions against their concentration gradient. Secondary active transport moves one molecule down its concentration gradient and uses that energy to move another against its concentration gradient. Cotransport shows both molecules moving in the same direction relative to the cytoplasm. Antiporters move molecules in opposite directions.

Therefore, for active transport to happen, **energy must be added** to the system. Energy can be obtained in a number of ways. **Primary active** transport is active transport that gets its energy from **hydrolyzing ATP**, whereas **secondary active** transport is active transport that gets its energy in **any other way**. The transporters that don't use ATP will often harness the energy of another substrate's concentration gradient. The energy gained by allowing one substrate to move down its concentration gradient (what that substrate "*wants to do*") allows the transporter to move another substrate against its concentration.

Primary active transport utilizes ATP to move solutes up their concentration gradient. The famous **Na^+/K^+-ATPase** uses ATP, hydrolyzes it to ADP, and harnesses the energy contained within that bond to move both Na^+ and K^+ against their concentration gradients: 3 Na^+ leave the cell, 2 K^+ enter the cell. This establishes the high concentration of sodium outside the cell and the energy concentration of potassium inside the cell that is so crucial to other transporters, action potentials, and life.

In **secondary active transport**, the energy comes NOT from ATP, but from the downhill movement of one or more other solutes that move either in the same direction as the actively transported solute (**cotransporters/uniporters**) or in the opposite direction (**antiporters/exchangers**). These transport proteins DO NOT USE ATP for their energy source—they utilize the energy gained from one of the molecules being transported down its concentration gradient.

Cotransport and antiport can confuse learners. Be careful about which feature determines the vocabulary. A cotransporter is **active** because one substrate is going up its concentration gradient. It's **secondary active** because it doesn't use ATP. It's **cotransport** because the **substrates travel together** (either both into the cell or both out of the cell). An antiporter is **active** because one substrate is going up its concentration gradient. It's **secondary active** because it doesn't use ATP. It's **antiport** because the **substrates pass each other** (one enters while the other leaves the cell). It's the relationship **to the cell** that determines cotransporter vs. antiporter.

Cotransport is when one solute moves down its concentration gradient, generating energy, while at the same time the other molecule goes up its concentration gradient, traveling in the same direction with respect to the cell. The **Na^+-glucose cotransporter** (SGLT 1) harnesses sodium's energy into the cell, down its concentration gradient, to bring glucose into the cell—both Na^+ and glucose travel in the same direction, into the cell. **Na^+-K^+-2Cl^-** (renal tubules) is responsible for regulating ions, and uses the Na^+ going down its concentration gradient to bring K^+ and 2Cl^- against their concentration gradient with it into the cell.

Antiport is when one solute moves down its concentration gradient, generating energy. At the same time, the other molecule goes up its concentration gradient, traveling in the opposite direction. The **Na^+-Ca^{2+} antiporter** utilizes the energy of sodium coming down its concentration gradient (3 Na^+ in), harnesses that energy, and uses it to push calcium up its concentration gradient (1 Ca^{2+} out). The **Na^+-H^+** antiporter uses the same effect: one sodium in, down its gradient (1 Na^+), and one hydrogen out, up its gradient (1 H^+).