The Interaction of the Blood Brain Barrier and Drug Molecules.

What is the blood brain barrier, and why is essential for every human being on the planet? What drugs can make it through the blood brain barrier (BBB), and what effects do they have on the body? These are very important questions in the world of neuroscience and it turns out that there is a lot of chemistry behind the workings of one the human body’s most amazing defense systems. But this topic is not only interesting to neuroscientists; this topic is also interesting and meaningful to me, as I hope one day to become a pharmacist. The way that chemicals and drugs interact with and in the body and the chemistry behind all of it is a very relevant, exciting, and astounding field that always catches my attention.

So what is the blood brain barrier? The blood brain barrier is a semi-permeable barrier, acting first and foremost a defense system for the brain. This barrier allows the brain to block many substances that would be harmful, but in some cases even blocks molecules that could be life saving. A molecule is defined as the smallest particle of a substance that retains the chemical and physical properties of the substance. The blood brain barrier is made up of epithelial-like tight junctions, which are defined as an intercellular junction between cells that separate circulating blood in the brain from the brain's extracellular fluid. Within these capillaries, there are many specialized cells termed “endothelial cells.” These cells are what make the blood brain barrier work, and therefore, important. These cells make it possible for molecules to enter the brain in only two ways. The first way that
molecules can enter the brain is by free diffusion (no energy required), also known as lipid-mediated transport; the only other way that molecules can enter the brain is by catalyzed transport.¹ Catalyzed transport is identified as carrier mediated transport, which requires a lot more energy than the free diffusion allowed by some molecules through the blood brain barrier. A lipid is defined as a biological molecule that is soluble in non-polar solvents and not soluble in water. So what does this mean for the transportation of drug molecules across the blood brain barrier? Simply put, it means that lipid soluble drugs have no problem crossing the barrier (some good, some bad), and that larger molecules do not pass as easily, needing some type of carrier transport. Now that we have a general understanding of what the blood brain barrier is, let’s examine how certain drugs get through the BBB and what the their effects on the body.

The first drug that we will focus on is heroin. Heroin is mostly known as a recreational drug that reportedly gives the effects of an intense euphoria and deep relaxation. But to get these effects on the body, the drug has to somehow get into the brain, where the blood brain barrier comes into play. In a study done by the Oldendorfs, the couple, along with two other scientists, figured out how readily certain drugs enter the brain through the blood brain barrier. This was done by injecting the drug of choice into a lab rat and waiting fifteen seconds. After the fifteen seconds, the lab rat was decapitated to prevent any further diffusion of drugs into the brain. After the conclusion of the study, the Oldnedorfs found that sixty-eight percent of the heroin that had been injected made it into the brain.² Compare this sixty-eight percent to the base line of about two percent of sugar water diffused into the brain after fifteen seconds and you will notice that heroin diffuses into the brain quite

---

rapidly. But what properties make a certain molecule diffuse through the blood brain barrier more rapidly than another? Differing rates of diffusion of drug molecules can be explained by heroin’s lower affinity for bonding with general tissue than many of the other drugs. This low affinity for bonding with the tissue allows the drug molecule to “rocket” through the tissue of the blood brain barrier and not get hung up as easily. The cause of this low affinity for bonding with the tissue is the fact that the molecule is lipid soluble. Once inside the brain through, the blood brain barrier heroin breaks down into morphine (which we will examine next), which has a high affinity for bonding with the tissues of the brain. When the heroin is broken down into morphine, it bonds to opiate receptors in the brain creating the high. As with most drugs there is severe risk with the use of heroin. If too much heroin enters the brain and the blood system, the body will not be able to handle the amount of foreign substance, and the user will die of an overdose.

Morphine is another opiate that has many practical uses in the current medical world. It is considered the best substance for relieving pain in medical facilities around the world. But how rapidly does morphine diffuse into the brain, and what does the blood brain barrier have to do with it? The Oldnedorfs also ran trials with morphine and what they found was interesting. Through the same procedure of injection and decapitation, they found that morphine entered the brain, but not as readily as heroin. This makes sense, as heroin is one of the most lipid soluble opiates in existence, while morphine is one of the least lipid soluble. This limits the amount of morphine that can readily and quickly enter the brain because only lipid soluble molecules can enter through the blood brain barrier. So although morphine has a high

---

affinity to bond with the brain receptor cells, if it cannot get in the brain as easily, it will be a less effective opiate\textsuperscript{4}, which studies have shown and proven. Also, because morphine is less lipid soluble, it can undergo mediated transport to have its effects on the brain and body. Morphine, like the other opiates, is addictive and can cause overdoses and death in the most severe cases.

Now that we have examined a couple of opiates, we will move on to something a little bit different. The next drug molecule that we will examine is that of cholesterol. Cholesterol is a steroid fat that is produced in two different parts of the body: the liver and the intestines. The working definition of steroid is any of a large class of organic compounds with a characteristic molecular structure containing four rings of carbon atoms, and the working definition of a fat is any natural oily or greasy substance occurring in animal bodies. The interactions of the blood brain barrier and the cholesterol are important because over twenty-five percent of the body's cholesterol is found in the brain\textsuperscript{5}! This molecule passes through the blood brain barrier, but when too much passes through, it has several severe health risk associated with it. Cholesterol's relation with the blood brain barrier is much different from the last two molecules we have examined. Because cholesterol is indeed a steroid fat, it is very lipid soluble, so it can enter the brain readily and without too many complications. Because of its high lipid solubility, the blood brain barrier is more responsible for maintaining a homeostasis of cholesterol in and out of the brain. An impressive system of apolipoprotein-dependent cells (cells in the BBB) is responsible for the recycling of cholesterol in and out of the brain. Another effect that cholesterol has on the blood brain


\textsuperscript{5}Meany, Steve. “Brain Cholesterol: Long Secret Life Behind a Barrier.” Division of Clinical Chemistry (1986). Pri
barrier is that it is believed to damage the barrier itself! It is believed that once too much cholesterol has passed through the blood brain barrier, it leaves open holes in the barrier, allowing for many harmful substances to enter and destroy the brain.\textsuperscript{6} The recycling of cholesterol in and around the brain is very important because once there is too much cholesterol inside, many serious health problems can arise. When there is too much cholesterol, the fatty nature of the molecule blocks the brain cells of essential vitamins (any of a group of organic compounds that are essential for normal growth), and nutrients (a substance that provides nourishment essential for growth and the maintenance of life that is needs to function correctly.) This can lead to a stroke, and then possibly paralization of the body.

Another ill effect of having too much cholesterol entering the brain is Alzheimer's disease, although not a lot is known about why cholesterol and Alzheimer's disease are related, in clinical trials the number of lab rats that developed Alzheimer's disease after injection of cholesterol reducing agent were significantly fewer than those who had not received the agent injection.\textsuperscript{7} As cholesterol has been identified to cause many illnesses in the body, specifically the brain, researchers have begun to look for a solution to lowering the brain cholesterol and they maybe have found it in the next molecule that we will examine: caffeine.

Caffeine is the best friend of any college student struggling to stay awake in the wee hours of the morning while studying for those huge final exams. So how does it enter the brain, and how does it interact with the blood brain barrier? Caffeine is a central nervous system stimulant in the human body that gives the user a feeling of alertness and


energy. Caffeine, like cholesterol, is a lipid soluble molecule, and thus, has a fairly easy time entering the brain. That is why someone who drinks a cup of coffee can feel the effect of the caffeine so quickly. Not only is the lipid solubility of caffeine good for alertness, it turns out that it may repair even the “holes” left in the blood brain barrier by cholesterol. Studies performed by John F. Wagener on rabbits have shown that rabbits on a cholesterol rich diet benefit from having a healthy dose of caffeine in their drinking water.\(^8\) But why is this so? The studies conducted by Wagener show that caffeine creates an increase in astrocytes, and an increase in microglia density. Astrocytes are part of the blood brain barrier, and are most importantly known for their regulation of ion flow through the brain. Microglia cells in the brain are also a part of the blood brain barrier, but their main responsibility is responding to inflammation in the brain, and taking down the inflammation. Because caffeine adds both of these cells back to the blood brain barrier, it is easy to see why it is considered a helpful agent to the brain, along with providing alertness and energy to those who need to stay awake.

At this point we have viewed molecules that have been for the most part lipid soluble, but what would happen if a non-lipid soluble molecule tried to cross the blood brain barrier? Glucose is the primary source for energy in many of the complex biological systems we know about today, allowing photosynthesis, to happen and life to go on. But how does glucose enter the blood brain barrier? As mentioned before, glucose is not lipid soluble so it cannot undergo free diffusion through the barrier it has to undergo the process of mediated transport. Although it is not lipid-soluble, it is still a very essential component needed to make the brain function properly. Because of glucose's high importance in brain function, it is necessary that it makes it into the brain somehow. This means that glucose has to bond to a

transporter to enter the brain. Glucose's primary transporter is known as the GLUT-1 protein.\textsuperscript{9} The transport molecule GLUT-1 can cross the blood brain barrier in many different locations spanning the whole BBB. The importance of glucose in the brain can be shown by PET scans which monitor the amount of glucose used in each area of the brain. Without the ability of glucose to bond to transporter molecules, we would not be able to use our brains on the high level that we do each and every day.

So what is the bottom-line? In the brain there is a protective barrier, known as the blood brain barrier. When highly lipid-soluble molecules come in contact with the barrier, they pass through rather readily (as shown by heroin and cholesterol), but some molecules, such as glucose, need help via active transport to enter the brain. There are also many complex relationships that come about when molecule cross the blood brain barrier, as shown with cholesterol's ability to leave “holes” in the blood brain barrier and caffeine’s ability to potentially patch up the “holes” left by the cholesterol. Molecules that enter through the blood brain barrier can be either helpful or harmful to the human body, and in high amounts, almost all molecules can have side effects. Sometimes, even molecules that would be life-saving cures are denied access into the brain by the blood brain barrier.

The study of the blood brain barrier is a very complex issue, and the understanding of it’s function has increased dramatically in the past two decades. There are still many properties that have yet to be explained about the blood brain barrier. In the future, one may hope that we will get a better grasp of the blood brain barrier, as a whole, and understand how and why all drug molecules affect the barrier and body the way that they do.

\textsuperscript{9}Farrell, C. L. "Blood-brain Barrier Glucose Transporter Is Asymmetrically Distributed on Brain Capillary Endothelial Lumenal and Ablumenal Membranes: an Electron Microscopic Immunogold Study." Department of Medicine University