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FEATURED ARTICLES

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‘Acetylcholinesterase Inhibitors’ — Janvie Naik

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Readers,

I hope you enjoy the eighth issue of the IYNA Journal! We greatly appreciate your continued (or new) readership.

From neurodegenerative disease to drug addiction, past editions of the IYNA Journal have explored disorders of the brain in great depth. In this issue, we turn to a somewhat brighter aspect of neuroscience: how we are fighting these diseases.

However, when it comes to treating neurological diseases, nothing can compare to pharmaceuticals. Undoubtedly, physical therapy, psychological counseling, and other techniques may help ameliorate symptoms; however, our focus in this issue of the IYNA journal is neuropharmacology.

Since drugs are used as treatment for disease, many of the articles in this edition fall under the disease section. Janvie Naik writes about acetylcholinesterase inhibitors (a treatment for Alzheimer’s), Robert Morgan examines the neuropharmacology of Alzheimer’s in more depth, Christian Gonzalez discusses pharmacological treatment Parkinson’s disease, and Tara Pattilachan explains neuropharmacology for psychosis.

How are these drugs developed in the first place? In the research section, Ronald Lao, Megumi Sano, Jacob Umans, and Meenu Johnkutty describe the Blood-Brain-Barrier; Jacob Umans, Megumi Sano, Lorrayne Isidoro, and Kyle Ryan discuss Pharmacology of Everyday Life; Meenu Johnkutty and Ethan Hiatt outline FDA approval.

As always, it is critical that we recognize all of our dedicated writers for helping us make this issue the success that it is. You can find all of their names and positions on our Contributors page.

If you have any questions, comments, or suggestions for us, please feel free to contact us at info@youthneuro.org. We hope you enjoy our eighth issue as much as we enjoyed writing it!

Best Regards,

William Ellsworth
Editor-in-Chief, IYNA Journal
Update from the Directors

IYNA Board of Directors

Readers,

We all hope you enjoy the eighth issue of the IYNA Journal! We are incredibly grateful for your continued readership, and we are excited to continue working on improving our journal and organization through the coming year.

Our Mission

In less than a year, we have grown from an idea to an international organization with members in almost 20 countries. We are incredibly grateful for the support of everyone within the IYNA and our supporters and collaborators outside of the IYNA, including the International Brain Bee, the Synapse Project, and Knowing Neurons. In the coming year, we as an organization will remain committed to creating an inclusive, global community of youths passionate about the brain. We believe that through the IYNA, we will be able to become and inspire the next generation of neurologists, neuroscientists, and neurosurgeons working together in an attempt to understand the inner workings of the brain and cure the devastating neurological diseases that take so many lives.

As always, if you are interested in contributing, check the “get involved” page on our website or email us at info@youthneuro.org. We are excited to see what awaits us in 2017, and hope that you can join us in furthering our mission.

Best Regards,

Jacob Umans and Nicholas Chrapliwy
Presidents

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Introduction
Our world is a green earth populated by living things, full of plants, animals, and various other living organisms. All of these life forms, however, could not exist without the chemical reactions that underlie every change in the universe. Chemical reactions are absolutely fundamental to life, not only in its abiogenesis and development, but also in the sustenance of its existence.

From a neurological standpoint, chemical reactions are equally fundamental, especially to the processes of communication between neurons on which all neural function is based. This communication occurs in the form of synaptic transmission, a process via which chemical agents called neurotransmitters pass a chemo-electrical message from one neuron to another.

Neuronal Communication

Neuropharmacology is an expansion on the study of intraneuronal and synaptic communication. A brief refresher of these topics will be provided; however, readers interested in a more detailed explanation of these processes should refer to the second and third Basics of Neuroscience articles which can be found in the second and third editions of our journal, respectively.

Neural communication is based on the propagation of an action potential, or impulse, along a network of neurons. Each neuron in the network receives a variety of signals at its branched dendrites, evaluating the compound of the received signals, taking into account location and timing, and, if the sum of the evaluated signals reaches a certain membrane voltage threshold, the neuron fires, further propagating the action potential along its axons. The axon terminals then relay the signal across a synaptic cleft to the next neuron.

Synaptic transmission is especially important to the field of neuropharmacology. This step in the relay of neuron communication serves not only as an intermediary between the presynaptic and postsynaptic neurons, but also as a chemical interlude between the electrical conductance in intraneuron communication. Upon reaching the axon terminal, the action potential triggers an opening of ligand-gated calcium ion channels, the cytoplasm of the axon terminal with calcium.
This in turn causes the exocytosis of a vesicle, expelling neurotransmitters into the synaptic cleft, which then bind to receptors on the plasma membrane of the postsynaptic neuron. Depending on the type of neurotransmitter, it will either cause an opening of ion channels or a cascade of reactions inside the neuron through substances called second messengers. The basis, therefore, for all synaptic communication is the transmission of a chemical message from one neuron to another.

Pharmacology

The study of neuropharmacology is devoted to the chemical reactions of the nervous system, particularly in regards to the effect of neuromodulating substances on the cellular function of the nervous system and the resulting effects on behavior. These two branches of neuropharmacology, being the direct cellular effect and the indirect behavioral effect, are known as molecular neuropharmacology and psychoneuropharmacology, respectively.

As mentioned in the previous section, neurons generally communicate through synaptic communication, during which a neurotransmitter binds to a receptor in order to produce a cellular effect. Chemical reactions are based on structure of the involved molecules: chemical bonds occur between regions of two distinct molecules, often a smaller molecule connecting to a larger protein. The activation of the receptor depends on a precise bond of the neurotransmitter to the active site of the protein. Therefore, only molecules with a very specific three-dimensional structure are able to bind to the protein successfully. This allows certain molecular substances, known as drugs, to function in a modulating way. Drugs can be defined as molecular substances that affect the cellular function of an organism; those that directly influence cellular processes can be categorized as either an agonist or antagonist depending on the nature of their function.

Agonists are similar in structure (in terms of the functional groups and three-dimensional structure) and thus are able to imitate a naturally occurring neurotransmitter, bind to a receptor, and either partially or fully replicate the effects of the neurotransmitter. Antagonists, on the other hand, block the function of the neuroreceptor. Antagonists generally work through either direct competition or allosteric regulation: competitive antagonists install themselves in the active site of the receptor without activating it while allosteric antagonists inhibit function by binding to a site other than the receptor and changing the shape of the active function, thus restricting the ability of naturally present neurotransmitters to bind to the receptor. The resulting chemical bonds force the receptor to change its shape.

In addition to acting at the synaptic connection, drugs can also interfere with function at presynaptic vesicular release and reuptake. As mentioned previously, release of neurotransmitters into the synaptic cleft is triggered by an influx of calcium ions. Consequently, a synapse can be inhibited or fully stopped if a drug interferes with calcium function, either by indirectly combining with the calcium to make it unable to bind or by inhibiting its receptor. Reuptake inhibition works in a similar way. Neurotransmitter reuptake is a process that allows reuse and recycling of neurotransmitters by recollecting them from the synaptic cleft and depositing them back inside the
neuron. Inhibition of proteins involved in this process is generally accomplished through use of either competitive or allosteric inhibitors. The ability to block this reuptake is utilized in drugs that attempt to treat some neurotransmitter imbalances through this given mechanism. Selective Serotonin Reuptake Inhibitors (SSRIs), for example, block the reuptake of Serotonin through allosteric regulation of the transport proteins involved. This allows serotonin neurotransmitters to stay in the synaptic cleft for longer and react more with receptors, and ergo places SSRIs among the preferred pharmacological treatments for clinical depression.
Caffeine

Nearly everyone understands that coffee can help people wake up in the mornings or stay awake during late nights, but far fewer understand exactly how it does this. One key pharmacological effect of caffeine is its competitive inhibition of the adenosine receptor. Adenosine, a dephosphorylated form of ATP, signals the shortage of energy in the brain and promotes sleeping. Adenosine is created over the course of the day, as a natural byproduct of using up our internal energy stores (it forms the core of adenosine triphosphate (ATP), the energy-storage molecule that powers most of the biochemical reactions inside cells). As a result, its accumulation means that the brain has used much of its available energy, meaning that sleep is necessary to restore energy [1][2].

With prolonged wakefulness, increasing levels of adenosine are evident in the brain, initially in the basal forebrain (figure I) and then throughout the cortex. The increased levels of adenosine serve the purpose of slowing down cellular activity and diminishing arousal. Adenosine levels then decrease during sleep. As a result of this regular oscillation, adenosine concentration is linked to the circadian rhythm. Thus, by acting as an adenosine antagonist, caffeine prevents the processing of sleep-inducing signals to promote wakefulness [2].

Figure I: Localization of basal forebrain in the brain
Sugar

Almost everything we consume, from the late-night hot chocolate to that apple a day, contains sugar. This might sound daunting, but there is a good reason. Sugar is a general term used to describe carbohydrates, and glucose, a form of carbohydrate, is the primary energy source for our bodies, including the brain. In fact, even though the brain takes up only 2% of our body mass, it uses up more than 20% of our energy intake [3]. The brain depends on glucose to produce ATP, which is responsible for fueling a wide range of processes including the maintenance of sodium and potassium ion gradients by the Na+/K+ ATPase.

While other body tissues can shift to amino acids or fatty acids to produce energy, the brain has a strict dependence on glucose because neurons are not capable of storage and therefore must rely on the constant supply from the bloodstream. The transportation of glucose from the bloodstream is dependent on the blood-brain barrier (BBB) [4], a layer of endothelial cells separating blood vessels from the brain. Glucose transporters are embedded in both the inner surface of the layer, the luminal side, and the outer surface, the abluminal side. There are also auxiliary transporters floating inside the endothelial cells between the two membranes. The BBB can sense blood glucose levels and induce the creation of more glucose transporters or their migration from one membrane to another in response to low levels, and therefore is responsible for the regulation of glucose entering the brain.

Several neurotransmitters are also linked to glucose consumption [5]. For example, levels of serotonin rise in response to the presence of carbohydrates. This is because the neurotransmitter is derived from the amino acid tryptophan, whose levels vary depending on carbohydrate levels in the diet. Since serotonin secretion is also involved in functions such as mood regulation, blood pressure regulation, and sleep onset, there is a strong link between “sugar” and “mood.” Sugar also activates the reward system, or the mesolimbic pathway, from the ventral tegmental area to the nucleus accumbens (NAc). The NAc receives inputs from the amygdala, the prefrontal cortex, and the hippocampus, and serves as an interface of emotion, motivation, and action. Consumption of substances with high sugar content activates the mesolimbic pathway and dopaminergic transmission in the NAc, creating rewarding effects. Moreover, while the constant consumption of one type of substance will usually level out the activation of dopaminergic systems, sugar is one of the few substances that does not have this effect, which means its “rewarding effect” does not fade away with continued intake. Another popular belief about sugar and the brain is that sugar causes hyperactivity. While no studies have found significant results on this correlation, sucrose (disaccharide) and aspartame (artificial sweetener) have been shown to at least influence behavior. One’s blood sugar levels rise rapidly immediately after consumption, which induces increased production of insulin and reduces the levels of certain amino acids in the bloodstream such as tyrosine and phenylalanine, precursors of epinephrine and dopamine. Low levels of these neurotransmitters are linked to symptoms of attention deficit hyperactivity disorder (ADHD) [6].
Sugar is indispensable for the brain's normal functions, as the disruption of regular glucose metabolism can lead to severe conditions. For instance, only a brief period of glucose deprivation, a condition known as hypoglycemia, starves neurons and may result in dizziness, double vision, tremors, and excessive sweating. If these symptoms are prolonged, they may be followed by delirium, convulsions, and loss of consciousness.

Thanksgiving Turkey/Tryptophan

After a thanksgiving dinner, many people may begin to feel drowsy and decide to go to sleep early. This is often attributed to tryptophan; however, the idea that turkey induces sleep is actually no more than a myth. Turkey contains the same amount of tryptophan per unit of mass as chicken, and other sources of protein (even cheese) have more tryptophan per unit of mass. However, eating a large meal (as is customary on Thanksgiving) causes increased blood flow to the digestive system. This increase in blood flow to the digestive tract decreases blood-flow to the brain, causing sleepiness. 

Aspirin

Because of its widespread use, the drug Aspirin has become almost synonymous with any painkiller. But how exactly does this work? Aspirin, which has the active ingredient acetylsalicylic acid, is a Non-Steroidal Anti-Inflammatory Drug, which, as its name suggests, means that it is not a steroid (this use of the word steroid should not be confused with anabolic steroids that athletes may illegally use - formally a steroid is a compound that is related to cholesterol, like testosterone). In order to exert its painkilling effects, acetylsalicylic acid binds to a key amino acid of cyclooxygenase, an enzyme that produces prostaglandins. Because prostaglandins play a key role in producing inflammation and pain, inhibiting their production is an effective means to prevent pain.
One interesting property of cyclooxygenase (COX) is that it has two isoforms - in other words, the mRNAs that encodes the enzyme can be processed two different ways to produce two similar (but still distinct) proteins. COX2 is the isoform that plays a key role in the inflammatory response, but acetylsalicylic acid can also interact with COX1 because of its similar properties. However, COX1 does not contribute to the inflammatory response - it actually is a component of platelets. For this reason, Aspirin can also be used to prevent arterial thrombosis, a potentially deadly heart condition in which blood clots block an artery [9].

**Capsaicin**

No matter how cold a jalapeño pepper might feel, the minute we put one in our mouths and take a bite we are are overcome with an intense burning sensation. This experience can be explained when one considers a natural chemical contained in that jalapeño: capsaicin. Capsaicin is a compound found in many peppers that inflicts this sensation through indirect stimulation of our heat and pain receptors. It acts as an agonist on our TRPV1 channels to lower the threshold that the temperature needs to be to create the sensation of heat. Instead of the normal average threshold of 43 degrees Celsius, capsaicin shifts this to around room temperature. As a result, the capsaicin can often cause a painful and hot sensation in our mouths when we consume peppers or pepper derivatives, stimulating receptors that previously would have required intense heat or acidity to signal and produce the sensation of such burning. In addition to causing this painful sensation, capsaicin consumption can lead to decreased sensitivity and nociceptor function as well as decreased mitochondrial respiration for long periods of time after exposure. This increased exposure results in a temporary desensitizing effect on the receptors that it acts on [10]. Another interesting consequence of capsaicin is a temporarily increased metabolic rate. This comes as a result of an increase in the secretion of adrenaline due to the TRPV1 channels that capsaicin agonizes in the adrenal glands. Despite this temporary increase, Galgani et al. (2010) found there was no noticeable impact on metabolic rate when measured 2 hours after exposure suggesting that its effects are very minimal when it comes to metabolic rate and the secretion of adrenaline from TRPV1 receptors in the adrenal glands [11].

The amount of heat we feel when consuming chile peppers is directly correlated to the concentration of capsaicin in that pepper. This is measured in Scoville heat units. Scoville heat units, of which a jalapeño pepper has 10,000 and pure capsaicin, 16,000,000, are representative of the dilution in alcohol that would be required to remove the effect capsaicin has on TRPV1 channels. There are other compounds that are hotter than pure capsaicin, like resiniferatoxin, which has 16,000,000,000 heat units and can cause chemical burns if in contact with human skin [12].

Despite the intense burning and pain it can inflict on some, the irony of capsaicin is that it is known pharmacologically to have analgesic effects and is used to quell sensory peripheral nerve pain. In this context, though, it is topically applied. The benefit of its application is that it is a safer and more effective alternate to the typical treatment which uses opioids to treat neuropathic pain leading often to more side effects and the risk of addiction. But as well as these analgesic properties for peripheral nerve pain, there has been some studies that have implicated capsaicin in aiding and controlling cancer induced mucositis, which is an inflammation in the digestive tract [13]. Overall,
the wide array of effects of capsaicin and its prevalence in nature makes it useful in both basic and clinical contexts.

References


Figure 1: Memory loss and the brain. http://www.memorylossonline.com/glossary/basalforebrain.html
Acetylcholinesterase Inhibitors

Janvie Naik

Introduction

Acetylcholinesterase (AChE) inhibitors, which hinder the enzyme that breaks down acetylcholine, have a wide variety of uses and effects. Some types of AChE inhibitors are commonly used in disease treatments, and other types are used in insecticides and chemical warfare. People suffering from certain diseases, such as Alzheimer’s, benefit from the prevention of acetylcholine breakdown; however, certain types of AChE inhibitors have toxic effects and result in an excess of acetylcholine.

What Does Acetylcholinesterase Do?

In order to understand AChE inhibitors, it is essential to first understand the functions of AChE and acetylcholine. Acetylcholine, the first neurotransmitter to be discovered, plays a wide variety of essential roles in the human body. It is involved in a variety of processes, such as learning and memory. Decreased levels of acetylcholine in the central nervous system are associated with Alzheimer’s disease. In addition, the neurotransmitter also has a role in movement; acetylcholine is released in neuromuscular synapses to contract muscles [1]. After acetylcholine has had an effect, AChE cleans it up from the synapse by breaking the neurotransmitter down into choline and acetic acid through hydrolysis, a process in which water is used for chemical breakdown [2]. Enzymes act by attaching a substrate to their uniquely shaped active sites; the AChE active site has two components: the anionic subsite and the esteratic subsite [2]. Acetylcholine binds to the AChE active site and undergoes hydrolysis [1].

![Diagram of AChE enzyme breaking down acetylcholine](image-url)

Figure 1: AChE enzyme breaks down acetylcholine [3].
By hindering catalytic activity, AChE inhibitors allow acetylcholine to remain in the synapse for a longer period of time, allowing the neurotransmitter to stimulate the receptors more. There are two types of AChE inhibitors: reversible and irreversible [2].

**Reversible AChE Inhibitors**

Reversible AChE inhibitors are used in treatments for Alzheimer’s disease. In Alzheimer’s pathology, synthesis of acetylcholine is inhibited, leading to abnormally low levels of the neurotransmitter [1]. Medications for Alzheimer’s target AChE in the brain, prolonging acetylcholine activity and therefore helping with symptoms relating to memory and cognition [3]. While these AChE inhibitors do not cure the disease, they lessen the severity of symptoms over the short-term. Rivastigmine, an AChE inhibitor used to treat Alzheimer’s, binds to the esteratic subsite of AChE, thereby preventing acetylcholine from binding to the active site for a certain period of time [2]. This medication has been shown to help with cognitive functioning; however, it may have gastrointestinal side effects which can be minimized by using a transdermal patch to take the medication. In contrast, galantamine, another medication for Alzheimer’s disease, blocks the anionic subsite of AChE, which also inhibits acetylcholine breakdown [3]. In addition to inhibiting AChE activity, galantamine interacts with the nicotinic receptors to make them more responsive to acetylcholine, further increasing the effect of the neurotransmitter. Due to this mechanism, galantamine can have an effect on other neurotransmitters such as GABA, glutamate, and monoamines, so it improves cognition and can also help with psychiatric illnesses. However, galantamine can also have gastrointestinal side effects [2].

**Irreversible AChE Inhibitors**

Irreversible AChE inhibitors most often have a toxic effect on the human body. Organophosphorus compounds, or OPs, are irreversible AChE inhibitors. They have a structure similar to acetylcholine, so they fit into the AChE active site and are split up by the enzyme. Through this process, the OPs phosphorylate AChE, thereby inactivating the enzyme. Once it is phosphorylated, AChE can no longer break down acetylcholine, so the released acetylcholine overstimulates the receptors. Severe OP poisonings can result in confusion, convulsions, and death, whereas less severe OP poisonings can lead to agitation and muscle weakness due to overstimulation. Due to their toxic nature, OP nerve agents are often used in chemical warfare. These nerve agents can be absorbed through the skin or through respiration, and they cause death by asphyxiation, or lack of oxygen. Since OPs inhibit AChE, the acetylcholine overstimulates muscarinic receptors, causing a loss of respiratory muscle control [2]. Although AChE inhibitors all have the common effect of slowing acetylcholine breakdown, they have a variety of uses, and can be either therapeutic or toxic.
References


Crossing the Blood-Brain Barrier
Ronald Lao, Megumi Sano, Jacob Umans, Meenu Johnkutty

Introduction
A prominent difference between physiology of mammals and other species is the presence of a cerebral vascular wall. The barrier, known as the Blood-Brain Barrier (BBB), is part of the brain’s natural defense. Although the BBB prevents harmful chemicals and viruses from entering the brain, it also prohibits many drugs from accessing the brain through vessels. As a result, doctors often need to inject drugs directly into the brain, which is an invasive approach that requires traumatic surgery on the skull. To circumvent this, scientists have developed a variety of ways to pass through the BBB in the recent years.

The Blood-Brain Barrier
The brain is protected by a layer of tightly joined endothelial cells that align on the blood vessels of the brain, which keeps harmful substances such as pathogens and toxins from entering the brain’s extracellular fluid. Although it allows passage of some compounds such as water, gases, hydrophobic molecules by passive diffusion, and glucose and amino acids by selective transport, it prevents the entry of a wide variety of microscopic objects, large or hydrophilic molecules, and certain toxins. Astrocytes are considered to be responsible for providing biochemical support to these endothelial cells and certain transmembrane proteins are responsible for stitching together the junctions between the cells. The main purpose of the BBB is to protect the brain from foreign substances as well as from hormones and neurotransmitters in the rest of the body, thereby maintaining a constant environment for the brain [1].

Targeted Delivery Via Microcapsules
The isolative function of the BBB often restricts flow of essential drugs to the brain. Therefore, to ensure that enough drugs have entered the problematic area of the brain, doctors often have to add a large quantity of drugs which consequently lead to different side-effects. Researchers recently found a more effective approach of delivering drugs via microcapsules. The microcapsules are made up of liquid crystal polymers (LCPs), which are a class of partially crystalline aromatic polyesters, substances known for their high mechanical strength, extreme chemical resistance, and inherent flame retardancy. These characteristics make LCPs suitable for making electrical and mechanical devices that require high strength and inertness. In this method, chemotherapy drugs are delivered using implantable microcapsules that are made of liquid crystal
polymers. By using 1.5-milliliter capsules, the drugs diffuse through small holes in the BBB. Through this method, doctors can accurately control the release rate of the drug over long periods of time.

Compared to intravenous injection of excessive amounts of drugs, this method is more controllable and reduces side-effects to its accuracy. Michael Lim, an associate professor of neurosurgery at Johns Hopkins, believes that this approach has a significant influence on patients who have their brain metastases surgically taken out to kill remaining tumor cells via the implantation of microcapsules [2].

**Nanoparticles and Ultrasound**

Since crossing the Blood-Brain Barrier is difficult, how about opening it? This was the initial idea behind the FUS-BBB opening technique. By using focused ultrasound (FUS) exposure in the presence of gas-filled microbubbles, scientists are able to open the BBB temporarily. First, patients are injected with the microbubbles which will travel through the bloodstream to all parts of the body, including the blood vessels that wrap around the brain. Then, they will wear a cap that contains transducers that direct ultrasound waves, which will be concentrated inside the body. The concentrated applied ultrasound causes the bubbles to vibrate, expanding and contracting at a rate of about 200,000 times a second, which loosens the tight junctions of the cells comprising the blood-brain barrier. As a result, high concentrations of chemotherapeutics and even relatively large molecules can enter targeted tissues. The BBB begins to close immediately after the ultrasound is turned off, which means that there are very few side effects and almost no long-term effects on ongoing brain activity. Most importantly, the treatment is painless and non-invasive and is one of the most promising techniques of overcoming the BBB [3].

In fact, this technique has already been tested on a human patient as part of a pilot study. Neurosurgeon Todd Mainprize, MD., physicist Kullervo Hynynen, PhD., and their team were able to deliver the chemotherapy agent doxorubicin to the brain of a patient with a malignant brain tumor. Although this was a pioneer trial in humans, Dr. Hynynen had been performing similar preclinical studies which had shown that the combination of ultrasound waves and microbubbles might not only allow for more effective drug delivery but also stimulate the brain’s natural responses to fight disease [4].

**Harmless Virus**

Since it’s so hard for large particles to pass through the BBB, why not try using nano-sized viruses as a vector instead? The idea of transplanting targeted DNA into viruses has always been a hot topic in research. However, their lack of gene mutation stability and damage to the human body has always been a major concern. Adeno-associated viruses (AAV) are non-pathogenic without the presence of adeno-viruses, therefore they always cause no symptoms in human body. In addition, AAV is a special virus that has the ability to stably integrate its genetic material into the host cell genome at a specific site (designated AAVSs) in the human chromosome 19. This factors indicate that AAV it is a very good media for transplanting DNA.

This June, a research paper published by neuroscientist Viviana Gradinaru and her colleagues at the California Institute of Technology showed that an AAV strain named AAV-PHP.B
most reliably crossed the BBB. The team then encoded green fluorescent proteins in the aforementioned strain in order to evaluate the success rate by tracking the green glowing growth in neurons. This experiment shows impressive results as the green glowing effect can last for a year. In the future this method has large potential to help treat patients having problems with gene mutations, peripheral nervous system etc [5].

**Liposomes**

Liposomes are artificially-synthesized membranes composed of one or more lipid bilayers. Because they can carry hydrophilic molecules within their membrane and hydrophobic molecules within the lipid bilayer, they are a powerful tool for drug delivery to the nervous system. With different molecules in the mixture used to synthesize lipids, the properties of the liposomes can be easily manipulated to ensure optimal uptake of its contents by the brain. The use of surface molecules that will be detected by BBB receptors (including transferrin and insulin) is essential to ensure that the BBB will take in the contents of the liposomes. Researchers have found that liposomes lead to a tenfold increase in the uptake of certain drugs, while liposomes designed to express transferrin on their surface lead to a seventeen-fold increase.

One emerging technique to promote the uptake of drugs involves the creation of immunoliposomes, which have antibodies attached to their surface to improve targeting to the BBB. Much like their counterparts without antibodies attached, immunoliposomes show considerable promise. A notable study used immunoliposomes containing an expression plasmid for Tyrosine Hydroxylase, which would reverse a mutation that prevents the production of normal dopamine, was able to target the striatum of mouse models of Parkinson’s Disease and restore normal enzymatic function [6].

**Shuttle Peptides**

One emerging technique to allow the entry of drugs into the brain is the use of shuttle peptides. While the FUS-BBB opening technique involves increasing the permeability of the BBB to all compounds, even for a short period of time, it carries the risk of allowing the entry of cytotoxic particles. Thus, researchers have more recently began to focus on allowing the particles to readily diffuse directly through the endothelial membrane.

In 2007, a key paper found that RVG29 was capable of selectively transporting molecular cargoes into the brain. Many shuttle peptides with high specificity interact directly with transporters, however, others can bind to gangliosides (lipids with multiple sugars attached to the head group) to mediate the transport of nanoparticles across the cell membrane. With such techniques available, medications can be more readily transported across the BBB and lead to improved treatment outcomes.

According to the Royal Society for Chemistry, “Peptides are more affordable, easier to characterize and to link to nanocarriers or proteins.” In preclinical testing within the laboratory, an increase in therapeutic effect was seen after shuttle peptides were used in various animal disease models, ranging from brain tumor, epilepsy, lysosomal diseases to neurodegenerative disorders.
Although these small biological delivery men have accomplished a great feat, more research still needs to be done in order to increase the efficiency and selectivity of these peptides [7].

The Significance of Crossing the BBB

Currently, an estimated 98 percent of potential drug treatments for brain disorders are unable to penetrate blood brain barrier. [i] Bypassing the BBB is crucial for these life-saving drugs to reach specific targets in the brain effectively and these non-invasive techniques are especially demanded because the constant delivery of a drug should not affect ongoing brain activity. For example, antibodies that could possibly wipe out the amyloid plaques in the brains of patients with Alzheimer’s diseases are not able to cross the BBB. A recent study at the Queensland Brain Institute in Australia showed that opening the BB with focused ultrasound reduced amyloid plaques and improved memory in a mouse model of Alzheimer’s, which may open doors for future clinical applications [8].

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Neuropharmacology of Alzheimer’s Disease
Robert Morgan

Introduction
In 1906, Dr. Alois Alzheimer diagnosed the first case of the disease that would come to be named after him, in a postmortem examination of the brain. Today, Alzheimer’s disease is the sixth most frequent cause of death in the United States, afflicting more than five million Americans. For early-onset Alzheimer’s disease, the cause of most cases has been identified as being genetic in nature, while for late-onset Alzheimer’s disease, the far more common form of the disease, a definite cause has not been determined. Treatment of both forms of Alzheimer’s disease is limited, as there is no known cure for either form of the disease, but there are several available pharmaceutical drugs which alleviate the cognitive and behavioral impairments associated with the disease by regulating neurotransmitters in the brain [1].

Diagnosis
As the presence of Alzheimer’s disease is not able to be discovered in the brain through brain scans such as CT, MRI, or PET and there are no other physically evident effects of the disease able to be discovered in a living subject, Alzheimer’s disease may only be definitively diagnosed after death. Before death, doctors must rely on more subjective methods of diagnosis (such as testing the memory of the patient) and ensure there is no other cause for the Alzheimer’s disease-like symptoms a patient may be experiencing. Additionally, a patient may have Alzheimer’s disease for ten or more years before exhibiting symptoms of the disease. Diagnosing severe Alzheimer’s disease after death is not nearly as difficult, as the disease results in a significant decrease in the size and mass of the brain, beginning first in the hippocampus and eventually spreading to other areas of the brain [1]. However, this may depend on age, as the brain of a sufferer of Alzheimer’s disease who is older than 65 years old may not be significantly different from the brain of someone of the same age who did not suffer from Alzheimer’s disease. Meanwhile, the brain of a subject with Alzheimer’s disease who is younger than 65 years old is likely to be notably different than the brain of someone of the same age who did not suffer from the disease. Brains which do not display significant atrophy relative to other brains of similar age require a molecular examination in order to definitively determine the presence of Alzheimer’s disease [2].
Neuropathology

The most well-known neuropathological change caused by Alzheimer’s disease (noted by Dr. Alzheimer himself) is the build-up of the proteins amyloid and tau in the brain, with amyloid being organized into clumps known as plaques and tau into tangles [1]. There are several different types of amyloid plaque, and the type most associated with Alzheimer’s disease is known as the neuritic plaque. In a neuritic plaque, $\beta A_4$, the form of amyloid found in amyloid plaques caused by Alzheimer’s disease is surrounded by neurites, malformed axons or dendrites. Diffuse plaques, located in the cortex of the cerebrum, are another type and are comprised solely of $\beta A_4$, although the $\beta A_4$ is less concentrated than in a neuritic plaque. End-stage plaques (or burned-out plaques), another type, are also comprised only of $\beta A_4$, but with similar concentration to that of $\beta A_4$ in a neuritic plaque, and thus are considered to be neuritic plaques which have lost their surrounding neurites. $\beta A_4$ may also be found in a brain afflicted by Alzheimer’s disease in the form of a congophilic angiopathy, which is when $\beta A_4$ builds up in blood vessels of the cerebral cortex. A congophilic angiopathy is one of the few ways in which Alzheimer’s disease may directly cause death. On the other hand, tau tangles tend to occur in a consistent form and distribution within brains suffering from Alzheimer’s disease. The tangles are comprised of fibers which wrap around each other, forming a helix, and are most commonly found in the entorhinal cortex, the hippocampus, the amygdala, and the neocortex. However, the presence of tau tangles does not confirm the presence of Alzheimer’s disease, since tau tangles are also found under several other neuropathological disorders. This, along with the frequency in which Alzheimer’s occurs in conjunction to other neuropathological disorders, complicates the diagnosis of Alzheimer’s disease [2].

Figure I: A side-by-side comparison of a healthy brain to a brain afflicted by severe Alzheimer’s disease [i].
Approved Pharmaceutical Treatments

Currently, there are five pharmaceuticals which have been approved by the United States Food and Drug Administration (FDA) for treatment of Alzheimer’s disease: Aricept (donepezil), Exelon (rivastigmine), Razadyne (galantamine), Namenda (memantine), and Namzaric (donepezil, memantine). Aricept, Exelon, and Razadyne all function as cholinesterase inhibitors, while Namenda targets the NMDA receptors. Namzaric functions as a cholinesterase inhibitor and targets NMDA receptors. Only Aricept has been improved for treatment of all severities of Alzheimer’s disease, while Exelon and Razadyne are approved for mild to moderate Alzheimer’s disease. Namenda and Namzaric are approved for moderate to severe Alzheimer’s disease. Furthermore, all of these drugs have several associated side effects [3]. With regard to how these drugs succeed in alleviating some of the cognitive difficulties associated with Alzheimer’s disease, the cholinesterase inhibitors inhibit the function of cholinesterases, specifically acetylcholinesterase. Acetylcholinesterase is an enzyme which breaks down acetylcholine, an important neurotransmitter in the brain. Low levels of acetylcholine have long been associated with Alzheimer’s disease (they were once even considered the cause). Therefore, by inhibiting acetylcholinesterase, these drugs increase levels of acetylcholine in the brain and thus the speed of neuronal communication in the brain [4]. Namenda, on the other hand, contains memantine, which functions by blocking the binding of $\beta A_4$ to NMDA receptors, glutamatergic receptors which are crucial to learning and memory. The disruption of these NMDA receptors by $\beta A_4$ significantly impairs the ability of affected neurons to function and may even cause their death. The memantine in Namenda succeeds in blocking $\beta A_4$ from binding to NMDA receptors while still permitting glutamate to interact with the receptors, thus successfully maintaining function of more neurons in the brain and thus cognitive abilities [5].

Developmental Pharmaceutical Treatments

A recently tested pharmaceutical which may be able to treat Alzheimer’s disease itself, rather than merely symptoms of the disease, is the antibody aducanumab. By targeting $\beta A_4$ found in high concentrations within the brain, the antibody succeeded in a clinical trial of 165 patients in breaking down amyloid plaques within the brain at a timely rate—amyloid plaques that accumulated over approximately 20 years were eliminated in 12 months. With the reduction in these amyloid plaques, participants in the study experienced improvement in their cognitive abilities. Despite the promising results of the study, the treatment is still far from being approved, as the study was done on a small-scale and there were some worrying side effects from the treatment, specifically amyloid-related imaging abnormalities (ARIA) likely caused by excess extracellular liquid in the brain. This excess in fluid could be the result of several different issues [6]. Although aducanumab and other promising potential treatments for Alzheimer’s disease provide hope for the future, currently available pharmacological treatments for Alzheimer’s disease are limited to treating the symptoms of the disease for finite periods of time, ultimately providing insufficient treatment to the millions suffering from the horrific effects of the disease.
References


Neuropharmacology of Parkinson’s Disease

Christian Gonzalez

Introduction

In 1817, six accounts of cases of a previously unclassified disease reported muscle paralysis, decreased strength, abnormal gaits and resting tremors in patients. Although these symptoms had been noticed centuries prior by accounts in Egypt and India, the observations described in “An Essay On Shaking Palsy” by the English surgeon James Parkinson were the first time that these symptoms were collectively classified as paralysis agitans [1]. About fifty years later, French neurologist Jean-Martin Charcot conducted further empirical studies investigating the symptoms observed by Dr. Parkinson. Through his investigations, he made advances in understanding the condition by distinguishing between signs including rigidity and bradykinesia. Following his publications, Charcot prompted the renaming of paralysis agitans to Parkinson’s disease, after the condition’s original observer [2].

Now, two hundred years later, Parkinson’s disease is one of the most common neurodegenerative disorders, affecting over ten million people worldwide [3].

Characterized by slowly progressing motor symptoms and accompanying neurological difficulty, Parkinson’s disease noticeably impacts the lives of patients. Consequently, anxiety and depression are quite common in Parkinson’s disease. There is currently no cure and no known cause, though research is continually being carried out to develop novel pharmacological treatments to treat the pathology of Parkinson’s disease.

Overview and Symptoms

Parkinson’s disease is a neurodegenerative disorder of the central nervous system that results in slowness of movement, muscle stiffness, resting tremors, and neurological difficulties specifically relating to memory and cognition. Typically, patients with Parkinson’s disease begin experiencing motor symptoms such as shaking and rigidity of movement before advancing to other physical symptoms such as difficulty thinking or behavioral issues. Collectively, the earliest prodromes of the condition are referred to as Parkinsonism [4]. This syndrome includes select motor symptoms such as bradykinesia and resting tremors, but excludes the other typical symptoms in Parkinson’s, specifically those later on in the pathology. The neurological symptoms that patients experience such as memory loss, and in some cases dementia, are rarer in Parkinson’s disease in comparison to motor signs, but are increasingly prevalent during the later, more advanced, stages of the disease. As
the disease progresses, other symptoms also become more prevalent, such as insomnia and depression [5].

**Causes**

Parkinson's disease is an idiopathic condition, meaning that there is currently no known cause of the disorder. The prevailing theory regarding the origins of Parkinson's disease is that there are several contributing factors that impact disease incidence. Genetics is thought to play a significant role in the onset of Parkinson's, as approximately 15% of all diagnosed patients have reported a family history of the disease [6]. Gene mutations are commonly observed in a large portion of Parkinson's patients; specifically, five genes have had a strong enough correlation made to establish them as causal genes with which to diagnose the disease: alpha-synuclein (SNCA), parkin (PARK2), PTEN-induced putative kinase 1 (PINK1), and Leucine-rich repeat kinase 2 (LRRK2). SNCA was the first causal gene to be identified, and duplications of the gene are a frequent hereditary indicator of the presence of idiopathic Parkinson's disease. Mutations in PARK2 have been associated with early-onset Parkinson's disease, in addition to a slower pathological progression of the disease. PINK1 is also linked to early-onset Parkinson's disease, and mutations in the gene have been verified to cause aggregations of abnormally folded proteins that result in cell apoptosis and mitochondrial dysfunction. In contrast to most of the other causal genes of Parkinson's disease, LRRK2 is the only one that has been shown to be clinically involved in the etiology of late-onset Parkinson's disease, rather than varieties that present themselves earlier on in the lives of patients. Besides genetics, environmental factors are being investigated for their role in the development of Parkinson's disease. As of right now, no environmental facets have been shown to directly cause the disorder, but high levels of lead and exposure to pesticides have been shown to increase the chances of developing Parkinson's disease [6].

**Pathophysiology**

The pathology of Parkinson's disease is considered to be caused by damage to an area in the cerebrum known as the **basal ganglia**. This cluster of cerebral nuclei deep within the brain functions normally by being intimately involved in control of voluntary motor movements, proper emotional management, and cognition. Specifically, dopaminergic neuronal cell death occurs in the portion of the basal ganglia known as **substantia nigra** (Latin for “Black substance”). During certain cases of the disease, upwards of 70% of neurons in the anterior portion of the substantia nigra can be affected. [7] Glial apoptosis in surrounding areas is also quite common, as is the presence of **Lewy bodies**. Lewy bodies are abnormal protein aggregations that gather in clusters inside the somata of neurons in the substantia nigra and the greater brainstem, often in places where neuronal death is most prevalent. This loss of dopamine-producing cells in the substantia nigra causes decreased brain activity and results in the symptoms of Parkinson's disease such as **hypokinesia** (decreased movement) and cognitive issues.
Diagnosis

There are currently no tests specifically designed to diagnose Parkinson's disease. Family histories of Parkinson’s disease and assessment of neurological health are the two most common diagnostic tools neurologists use when trying to reach an accurate diagnosis of the condition. Identifying whether or not a patient has mutations in causal genes of Parkinson’s is quite helpful during the diagnostic process, as is knowing if any relatives have been diagnosed with Parkinson’s disease. During a neurological examination, a neurologist will try to rule out the possibility of other diseases through evaluating the degree of motor and sensory impairment levels. It is also especially important to observe the gait of a patient to distinguish it from other movement disorders. To accomplish this, doctors sometimes conduct multidirectional walk tests to test the normality of their gait. *Positron Emission Tomography (PET)* may also be employed in diagnosis to identify decreased activity in the basal ganglia [9].

Pharmacotherapy

Treatment for Parkinson's disease involves a combination of therapy, drugs, and surgery. Occupational and physical therapy sessions can be effective in gait habilitation and improving how patients can perform tasks by teaching how to deal with symptoms. The most frequent surgery performed on patients with Parkinson's disease is **deep brain stimulation (DBS)**. During this procedure, areas of the basal ganglia such as the *globus pallidus, thalamus*, and *subthalamic nucleus* are targeted with electrical impulses generated by a neurostimulator in order to reversibly change brain activity in those regions to improve symptoms. Deep brain stimulation is only used if pharmacological treatments are ineffective in a patient. There are an array of medicines that can be prescribed to patients to manage their symptoms, but none are effective at altering the pathology or course of the disease. All of the pharmacotherapeutic drugs work differently, but the majority still work with the intent of modifying dopamine in some form. Doctors prescribe **levodopa (L-DOPA)** initially to treat a patient’s symptoms. This drug works by synthesizing dopamine to account for deficiencies in the neurotransmitter that occur in patients with Parkinson’s disease. **Carbidopa** is also sometimes used alongside L-DOPA to increase efficacy by enhancing L-DOPA and preventing
nausea that is often experienced as a result of taking L-DOPA alone. When combined into one commercial drug, they are collectively referred to as sinemet. **Dopamine agonists** are a class of drugs that also mimic the effects of dopamine, and are thus also used when treating Parkinson’s disease with pharmacotherapy. In addition, **MAO-B inhibitors** and **COMT inhibitors** are used to help patients by blocking monoamine oxidase enzymes and the activity of catechol-O-methyl transferase, respectively. **Amantadine** is another dopamine promoter integrated into Parkinsonian drug treatment, but it is not as effective as other treatments as it is a weak NMDA receptor antagonist. **Anticholinergics** are also frequently prescribed to treat Parkinson’s disease, but unlike most other pharmacological treatments, this drug class acts on the neurotransmitter acetylcholine rather than dopamine [10].

**Advocacy and Awareness**

If you would like to find out more information on how to get involved in helping patients with Parkinson’s disease, please contact the following organizations listed below.

- **National Parkinson Foundation**
  [http://www.parkinson.org/get-involved](http://www.parkinson.org/get-involved)

- **American Parkinson Disease Association**

![Image source: Wilkins Parkinson’s Foundation](http://www.wilkins-pf.org/pdtulip.php)

**Key Terms**

- **James Parkinson**- English surgeon who first described Parkinson’s disease
- **Jean-Martin Charcot**- French neurologist who coined the term “Parkinson’s disease”; widely regarded as the founder of modern neurology
- **Bradykinesia**- Slowness of movement observed in patients with Parkinson’s disease
- **Parkinsonism**- Neurological syndrome similar to Parkinson’s disease characterized by motor symptoms such as bradykinesia, rigidity, and resting tremors
- **Alpha-synuclein (SNCA)**- First causal gene to be associated with Parkinson’s disease
- **Parkin (PARK2)**- Causal gene associated with early-onset Parkinson’s disease

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PTEN-induced putative kinase 1 (PINK1)- Causal gene associated with early-onset Parkinson’s disease
Leucine-rich repeat kinase 2 (LRRK2)- Causal gene associated with late-onset Parkinson’s disease
Basal Ganglia- Cluster of nuclei deep within the brain involved in movement and motivation
Substantia Nigra- Midbrain structure that is important for movement and reward
Lewy Bodies- Protein aggregates that form in neurons of patients with Parkinson’s
Hypokinesia- Decreased movement observed in Parkinson’s disease
Positron Emission Tomography (PET)- Medical imaging technique used to study tissue functions with radioactive tracers
Deep brain stimulation (DBS)- Surgical procedure that provides therapeutic benefits to patients with movement diseases through transmitting electrical impulses to specific brain areas
Globus Pallidus- Subcortical nucleus in basal ganglia involved in voluntary movement control
Thalamus- Egg-shaped part of the brain involved in processing received sensory information
Subthalamic Nucleus- Subcortical nucleus in the basal ganglia whose function is unknown
Levodopa (L-DOPA)- Drug that can treat Parkinson’s through chemical synthesis of dopamine
Carbidopa- Drug that can treat Parkinson’s alongside Levodopa by synthesizing dopamine
Dopamine agonists- Drug class consisting of compounds that mimic the effects of dopamine
MAO-B inhibitors- Drug class consisting of chemicals that block monoamine oxidase enzymes
COMT inhibitors- Drug class consisting of medications that inhibit the activity of catechol-O-methyl transferase
Amantadine- Dopamine promoter drug that can treat Parkinson’s disease as well as the flu
Anticholinergics- Drug class that blocks the activity of the neurotransmitter acetylcholine

References
Neuropharmacology of Psychosis

Tara Pattilachan

Introduction
Psychosis is loosely defined as an abnormal condition of the mind that’s lost contact with reality. However, a broader definition encompasses mild, aberrant experiences to the complex, catatonic mental disorders such as schizophrenia. Throughout history, psychotic outbreaks were looked down upon and received heavy resentment. In the Middle Ages, patients with psychosis were imprisoned in dungeons alongside criminals or locked up in lunatic asylums [1]. Later, those who showed psychotic symptoms would be tried for the practice of witchcraft. The word “psychosis” was initially introduced in 1841, by Karl Friedrich Canstatt. It wasn’t until 1845 that Ernst von Feuchtersleben truly defined the term “psychosis” for its true worth—as an alternative to insanity and mania. It’s important to note that since the symptoms aren’t often physically noticeable, a diagnosis is reached using process of elimination. This method serves as evidence that psychosis is a field where scientific knowledge is deficient. In a subject so vast, there is only so much uncertainty. Therefore, it’s reasonable that scientists have tested with various classes of drugs to help control psychosis symptoms.

Origins of Psychosis and Distinction

When considering psychosis and potential drug treatments, it’s important to understand the causes of psychosis. Most cases stem from schizophrenia, a psychiatric disorder often characterized by hallucinations, delusions, catatonia, and the inability to draw a line between reality and delusions. There’s no clear cut answer to what causes it, but it has been proven that environmental factors, such as poor nutrition during pregnancy, and genetic factors that cause chemical imbalance in the brain are largely responsible for its occurrence. In diagnosis of psychiatric disorders, there are generally 2 types: organic, and functional. Organic disorders occur from a medical or physical disease, not from psychiatric illnesses. There is a clear cause. Functional disorders, on the other hand, are just the opposite. Those with functional disorders have no disease or noticeable damage that cause their symptoms. However, the DSM-5, the nationwide standard listing psychiatric illnesses, does not use this distinction.

The primary psychiatric causes of psychosis includes mood disorders such as severe depression and bipolar disorder, and delusional disorders. Psychotic symptoms are seen in patients with various personality disorders, post-traumatic stress disorder, dissociative disorders, and
sometimes in those with obsessive compulsive disorder. When medical conditions can cause psychosis, they become referred to as secondary psychosis. For example, neurodegenerative disorders such as Alzheimer’s, neurological diseases like multiple sclerosis, sleep disorders such as narcolepsy, and vitamin B₁₂ deficiency (hypocobalaminemia) can lead to secondary psychosis. Stress is also known to often trigger psychotic states, much like a history of traumatic events in one’s lifetime. However, it’s not uncommon to experience brief hallucinations without having any psychiatric disorders. In these cases, hypnagogic and hypnopompic hallucinations, alcohol intoxication, sleep deprivation, and bereavement can contribute to the sight of hallucinations. Hypnagogic hallucinations are vivid, often frightening, images and sounds one experiences just before sleep. Similarly, hypnopompic hallucinations are images and sounds one experiences when waking up. There are also subtypes of psychosis, which includes menstrual psychosis, monotheistic delusions, postpartum psychosis (after childbirth), myxedematous psychosis, occupational psychosis, among others. The most individualistic, however, must be cycloid psychosis, which is distinct from the more famous psychotic disorders such as schizophrenia and manic-depressive disorder. The unique features it has is that the onset is acute and usually reverse to a normal state, making it hard for difficult for diagnosis, but a literary theme favorite.

Interestingly, the mild form of schizophrenia known as schizotypy is associated with creativity. Research has shown “positive” traits may be unusual perceptual experiences and magical beliefs (associated with artists), and “negative” traits are usually physical and social anhedonia and introversion (associated with mathematical and scientific creativity) [2]. A familiar piece, The Starry Night by Vincent Van Gogh, 1889, is thought to represent the changes in color and light as it may appear in a psychotic state. Van Gogh himself, suffered from delusions and psychotic episodes [3].

Symptoms

The three main symptoms of psychosis are hallucinations, delusions, and catatonia. Hallucinations are defined as sensory perceptions in the absence of external stimuli, and are not to be confused with illusions (perceptual distortions). Hallucinations are seeing, hearing, or feeling things that don’t actually exist. Common manifestations include hearing voices, feeling sensations, and seeing nonexistent objects. The sensation of hearing voices are known as auditory hallucinations (paracusia). These voices may seem to interact with the patient, and may involve multiple personalities. Although auditory hallucinations are not specific to psychiatric disorders, it usually occurs in them, especially in schizophrenia. Auditory hallucinations are more anguishing when the voices are speaking in a derogatory or commanding manner.

Delusions are very separate from hallucinations; however, the two often get intermixed. Delusions are false beliefs that a person genuinely holds on to, without adequate evidence. The most common themes in hallucination are either grandiose (where the person believes they have certain powers or skills) or persecutory (the person believes others want to hurt them). Karl Jaspers, a German-Swiss psychiatrist of the 20th century, classified delusions into two types: primary and
secondary. Primary delusions are sudden and are not logically comprehensible, whereas secondary delusions are usually influenced by the person’s situations and background.

Catatonia is defined as a profoundly agitated state where the sense of reality is considered impaired. There are two manifestations of catatonic behavior; waxy flexibility means that if someone moves a part of their body, then the person will stay in that position no matter how odd and bizarre. A common example to describe this is raising someone’s hand and having their hand stay there. The other type is more outward and agitated, with high levels of mental preoccupation. Nonetheless, in both catatonias, there will be no reaction to what happens to them. Thought disorders are defined as an underlying disturbance to conscious thought, dependent on the effects on speech and writing. Those affected with have a disconnection between speech and writing, and their speech becomes incomprehensible. This phenomenon is well known as word salad.

Pathophysiology

The essential purpose of the brain is to collect information from the body and external environment, interpret, and produce a logical response. However, when there is impulsive activity in the primary sensory areas, hallucinations are perceived and are misinterpreted as real information from the real world. Studies involving psychosis show that there was less gray matter in the lateral temporal, right medial temporal, inferior frontal gyrus and the cingulate cortex in people with schizophrenia and those who suffer from psychotic outbreaks [4]. Research shows that untreated psychosis can lead to neurological damage [5]. In bipolar disorder, there may be increased activity in the left hemisphere, while in schizophrenia, there was more activity in the right. It appears that the 5-HT2A subtype of serotonin receptors are important for counterbalanced senses and staying in touch with reality, since psychedelic drugs that activate these receptors produce hallucinations [6].

The neurotransmitter dopamine is important to understanding psychosis. In particular, the dopamine hypothesis of psychosis states that psychosis is a result of overactivity of dopamine in the brain, especially in the mesolimbic pathway. This has been proven since the dopamine receptor D2 reduces the intensity of psychotic symptoms and substances increasing dopamine such as cocaine can trigger psychosis. New evidence leads to the possibility of the excitatory neurotransmitter glutamate and its dysfunction, along with the NMDA receptors playing a role in psychosis.
Diagnosis

There’s no test that can definitively diagnose psychosis. Psychosis is a diagnosis of exclusion. In these cases, the presence of the organic disease must be excluded from being a prerequisite for a proper diagnosis. The reason is, for some disorders, the psychosis must be present for a certain length of time. It is possible to attribute symptoms to simple errors in life such as lack of sleep and drugs. Another cause for not having a diagnosis of one particular disorder is that the professional may feel that the diagnosis might be offensive (albeit this is not modern thinking and reflects the societal stigmas attached to psychotic disorders) [7]. Many psychiatrists and clinicians do not perform this step accurately, often causing errors and misdiagnosis. Assessments, typically including history and a physical examination, can also be used to diagnose. Biological tests are usually for psychosis that are associated with medications, complications, toxins and substance use. The types of psychosis in these disorders can be established via the Brief Psychiatric Rating Scale (BPRS), measuring suspicion, hostility, grandiosity and hallucination. The Positive and Negative Symptom Scale (PANSS) can measure both the positive and negative symptoms of psychosis. The person may receive blood tests and brain imaging (such as MRI scans) to rule out physical illness or drug use like cocaine or LSD [8].

Pharmacotherapy and Medications

The treatment usually depends on the specific diagnosis, such as bipolar disorder or schizophrenia. The first and usual treatment for psychiatric treatment are antipsychotic medication (also known as neuroleptics), which can reduce the positive symptoms of psychosis within 2 weeks. As a result, neuropharmacology plays a big role in dealing with psychosis. Antipsychotics such as amisulpride, olanzapine, risperidone and clozapine are usually effective but may have more side effects. Olanzapine and amisulpride treat schizophrenia and bipolar disorder, among others. Risperidone can treat schizophrenia, bipolar disorder, and irritability caused by autism. Clozapine is
the most effective treatment for those who respond weakly to other drugs, but it has the serious side effect of causing agranulocytosis (lowered white blood cell count). Clozapine usually treats schizophrenia, but it can also lower the risk of suicidal behavior in patients as well. The most common side effects from taking antipsychotics are considerable weight gain, diabetes, as well as extrapyramidal symptoms (EPS).

EPS can include symptoms such as dystonia (continuous muscle contractions and spasms), parkinsonism (rigidity), akathisia (motor restlessness), tremors, tardive dyskinesia (jerky movements), and bradykinesia (slowness in movement) among others. The antipsychotics most associated with symptoms of EPS are fluphenazine and haloperidol. Fluphenazine can treat schizophrenia, while haloperidol treats certain types of mental disorders. There are two types of antipsychotics: typical (first generation) and atypical (second generation). Typical antipsychotics are the ones developed around the 1950s. The most common examples of these are Haldol (haloperidol), and Thorazine (chlorpromazine). They are useful, but they tend to have a high risk of side effects, some extremely severe. As you might presume, atypical antipsychotics were developed and approved for use later, around the 1990s. Clozapine (the first to be classified atypical), olanzapine, risperidone, and others are common example for these drugs. These drugs share the common characteristics of less side effects and extrapyramidal effects than in typical drugs. Antipsychotics should not be used with anti-anxiety drugs, antidepressants, levodopa, anticholinergic agents, alcohol, smoking, and many other substances. There may be gradual withdrawal symptoms associated with antipsychotics. Nausea, vomiting, hypertension and disturbances in sleep may occur as a result of sudden discontinuation. Other than drugs, therapies such as cognitive behavior therapy (CBT), psychoeducation, and family therapy may be helpful. A combination of both antipsychotics and therapies are the most effective in dealing with psychotic symptoms. [9]

If you are familiar with anyone facing these issues or want to support the fight against psychosis, contacting advocacy groups and organizations such as the National Alliance on Mental Illness (NAMI) and Schizophrenia and Related Disorders Alliance of America (SARDAA) may be helpful.

References


Perks of Being a Naked Mole-Rat
Megumi Sano

Introduction
The naked mole-rat (Heterocephalus glaber) is a burrowing rodent native to East Africa, famous for its large, protruding teeth, wrinkled naked skin, and many other peculiar physical characteristics. Moreover, naked mole-rats are eusocial mammals and, live in underground colonies. Thanks to natural selection, these animals have adapted their external and internal physiology to these harsh underground environments. Over the last decade, many of the strange physiological characteristics of this organism have been uncovered.

In 2014, scientists from University of Cambridge Department of Pharmacology established the Naked Mole-Rat Initiative (NMRI) which brings together experts to identify molecular explanations for the naked mole-rat’s unusual physiology.

Naked Mole-Rats and Their Habitat

The naked-mole rat is eusocial, cold-blooded, cancer-resistant [1], and can live for over 30 years [2]. An average of 75 to 80 individuals live together in complex underground systems in arid deserts of East Africa. These colonies can be three to five kilometers long [3]. Just like any other well-known example of eusocial species such as ants, bees, and wasps, each colony has a queen, one to three males responsible for reproduction, and sterile workers who are committed to foraging and maintaining the colony. They generally feed on large tubers found underground, which can provide the whole colony with a long-term food source. Their sharp front teeth allow them not only to eat these plant roots but also to dig through the dirt when foraging. In fact, about 25% of a naked mole-rat’s muscle mass is in its jaws. Moreover, these animals also consume their own feces, because eating the once digested food allows greater absorption of nutrients [4]. Just by looking at the basic characteristics of this species, one can see the effect of evolutionary pressure created by the harsh environment.

One of the distinct characteristics of the naked mole-rat’s habitat is low oxygen availability. The rodents exhale high levels of carbon dioxide which accumulate in the underground colonies due to poorly ventilated spaces. While the air humans normally inhale have carbon dioxide levels of less than 0.1%, naked mole-rats are able to live up to 10% carbon dioxide [5]. This extreme carbon-dioxide-rich environment is considered to be the reason for two of the most significant physiological characteristics of the naked mole-rat: acid insensitivity and hypoxia resistance.

Acid-Insensitivity
Because of their poor vision resulting from their small eyes, naked mole-rats must rely heavily on mechanical and thermal stimuli. However, they fail to perceive acid as a noxious stimulus. When Thomas Park, Ph.D and his colleagues at University of Illinois at Chicago injected the paws of unconscious naked mole-rats with acid and capsaicin, the rodents didn’t show any pain in either tests. To explore this unusual resistance further, the researchers then used a modified cold sore virus to insert genes for Substance P into the foot of these rodents. Interestingly, the genetically modified mole-rats pulled their foot back to lick it when capsaicin was injected, suggesting that the DNA was able to restore its ability to perceive the burning sensation. However, the mole-rats remained completely insensitive to acids, even with the genes for Substance P, which indicates a major difference in the molecular mechanisms between their response to capsaicin and to acids [6].

Recently, a study by Dr. Ewan St. John Smith from the University of Cambridge Naked Mole-Rat Initiative (NMRI) identified the molecular basis of this unusual acid-induced nocifensive behavior. In most vertebrates, nociceptors express several ion channels that are modulated by proton concentration to produce depolarization. When this depolarization reaches the activation threshold of voltage-gated sodium channels, an action potential is initiated. The study showed that in naked-mole rats, there is a gene variant in the voltage-gated sodium channel subunit NaV1.7. Although the protons in the acid activate certain ion channels, they simultaneously block NaV1.7 which prevents the generation of an action potential. In other words, the variant enables the inhibitory effect to outweigh the excitatory effect, therefore abolishing acid nociception [7].

**Hypoxia Resistance**

Due to the high-carbon dioxide, low-oxygen environments, the naked-mole rat’s metabolism has evolved to extreme hypoxia. In most mammals, even brief periods of oxygen deprivation can cause irreversible damage to the brain as it requires high levels of aerobic metabolism. This is because oxygen supply is indispensable for ATP production, which is necessary for the various neuronal functions including ion transport and neurotransmitter re-uptake. Without these functions, concentration gradients are significantly altered, leading to excitotoxic levels of neurotransmitters, which can trigger cell damage and death.

The neurons in a naked mole-rat’s brain can maintain synaptic transmission during both chronic and acute episodes of hypoxia. Researchers have studied the acute response of the mole-rat’s brain tissue using hippocampal slices in vitro, measuring oxygen sensitivity of synaptic transmission and using mice as the controls. Slices of the naked mole-rat and mice brains tolerated the replacement of half the oxygen in the provided atmosphere with nitrogen equally well. When the oxygen supply was further reduced, the mouse slice showed a much more rapid and severe decline in function than the mole-rat slice.

Furthermore, researchers decided to explore whether this hypoxia tolerance is resulting from the retention of juvenile characteristics into the adult period. They examined the expression of NMDA receptor subunits in the brains of neonatal and adult naked mole-rats and mice, as these
receptors play an important role in hypoxia-induced excitotoxicity. The finding was that the adult naked mole-rat brain retains a significantly higher proportion of GluN2D subunit (66% of neonate) than the adult mouse brain (13% of neonate), suggesting arrested development of hypoxia-tolerant characteristics [8].

What It Tells Us

Research on these bizarre-looking creatures may seem irrelevant to human applications. Nevertheless, some researchers argue that these findings are beneficial for developing new strategies and targets for a wide variety of conditions including chronic pain. By looking at an animal that naturally lacks the acid-sensing mechanism, researchers can begin identifying what exactly the mechanism is. The Cambridge NMRI is currently working to develop a new therapeutic for particular conditions associated with tissue acidosis, such as rheumatoid arthritis. Moreover, examining how nervous systems have adapted to acute and chronic hypoxia can shed light on therapy for conditions such as stroke and epilepsy [9].

References


The Food and Drug Administration (FDA): From the Lab to the Counter

Meenu Johnkutty and Ethan Hiatt

Introduction

In an age where reports of miracle drugs that can cure cancer are blazoned on evening broadcasts, many may wonder when these drugs can actually make it to the market. However, the road from the laboratory to your local pharmacy can often be a long one due to regulations by the FDA. Like many things in healthcare, the drug development process can be improved tremendously. By identifying the challenges present within the current drug development framework and implementing new integrative methods of conducting clinical trials, drugs can be approved quickly and in a more cost-efficient manner.

Background

The Food and Drug Administration, or the FDA, is an American government organization which evaluates new drugs before they are administered to the general public. The only way researchers can make their drugs available to the public is by getting them approved by the FDA in a process which can often take up to 10 years. Due to various stages of laboratory and animal testing, the approval process is quite lengthy. As the FDA contains various other sectors, the primary branch which evaluates promising new drugs is the Center for Drug Evaluation and Research (CDER). As its name suggests, the role of the CDER is to make sure the health benefits for a particular drug outweigh its negative side effects. If this is deemed to be so, the drug is placed on the market [1].

Drug Discovery

The process of drug discovery starts with identifying the target which the drug will act upon. In many cases, the target can be DNA, RNA, or a select protein. If modulating the target induces a therapeutic effect, the target is validated. Then, in a process known as assay development, compounds that interact with or modify the target are identified through a screening process. From these compounds, the most effective are selected through the use of animal models which test for the efficacy of the compounds. Once these compounds are further narrowed after animal testing,
they undergo an optimization process which enhances their selectivity and efficacy. Once this process is complete, the drugs are ready for clinical testing [3].

**Drug Development and Clinical Trials**

What happens once a drug reaches the FDA? The answer lies within the FDA’s Center for Drug Evaluation and Research. The CDER is primarily responsible for evaluating new drugs by making sure they work correctly. The CDER does not test drugs. Rather, it analyzes the data given to its sector by laboratories. Once promising data from a laboratory is obtained, researchers submit an Investigational New Drug application to the CDER. Thirty days are allotted for the FDA to evaluate the application. Once the application is in effect and the study has been approved, the drug sponsor begins their clinical trials [1].

A clinical trial is defined as an experiment where human subjects are used to test drug efficacy. Prior to human experimentation, several regulations and guidelines are followed in order to ensure the highest level of safety for human subjects. If a problem is encountered during the clinical trial, the FDA has the authority to delay or interrupt experimentation. Once the drug sponsor reviews the data and ensures that it meets FDA requirements for marketing approval, the sponsor submits a New Drug application with full information about manufacturing specifications and dosage forms for physicians and patients. By this stage, all of the major steps needed to launch the drug into the market have been completed. With additional forms and review, the FDA holds the final say as to whether a potential drug is safe for humans [1].

Aside from evaluating drugs before they reach the consumer, the FDA is also responsible for informing the public of health hazards. For example, in a recent press release issued by the FDA, researchers discovered that long exposure to anesthetics, especially for pregnant mothers, was linked to numerous negative neurological effects. Though doctors and scientists have not stated that temporary use of sedatives is harmful, it has been shown that the use of these medications in a span of over three hours can result in extreme neuronal loss. In a push to prevent these drastic incidents, the FDA proposed improved labeling that addresses the possible side effects more clearly. Doctors were also advised to discuss the possible side effects with patients before long procedures. Thus, this study shows the influence the FDA yields in the realm of research and public health [1].

**Drug Development Challenges**

The drug development process can be improved tremendously. However, the challenges that currently exist must be reconciled with. For one, the drug development process continues to be lengthy, costly, and muddled with uncertainty as to whether the drug will actually succeed. In the case of targeted therapies for neurological disorders, since the pathophysiology, or physiological processes associated with a disease or injury are often unknown, identifying targets for drug therapy is often challenging. Though animals models have given the scientific community tremendous insight into how a drug may react within the human body, the effects seen in an animal population can vary from what could possibly be seen in a sample human population. Since the human
population is quite heterogeneous, therapeutic effects seen in one human can also vary from those seen in another [3].

The Future of Drug Development

With the rising costs of conducting clinical trials, drug developers, regulatory groups, and patients have directly experienced the effects of declining productivity of the pharmaceutical industry. In an article published by *Nature*, researchers argue that the current sequential and distinct phases seen in the drug development process should and can be replaced with an integrated view that implements the Bayesian method, a statistical method which if implemented can lead to smaller and more informative trials [4]. Therefore, by rectifying the current costly and inefficient system of approving drugs with a more integrative approach, the FDA can make drugs available to the public in a more timely and cost-efficient manner.

References


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