ABSTRACT

Neuropharmacology is the study of how drugs affect cellular function in the nervous system. To better understand the basis behind drug development, one must first understand how neurons communicate with one another. Researchers are developing drugs to treat many different neurological disorders, including pain, neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, psychological disorders, addiction, and many others. To understand the potential advances in medicine that neuropharmacology can bring, it is important to understand how human behavior and thought processes are transferred from neuron to neuron and how medications can alter the chemical foundations of these processes. This article will focus on both behavioral and molecular neuropharmacology; the major receptors, ion channels, and neurotransmitters manipulated through drug action and how people with a neurological disorder benefit from this drug action.

KEYWORDS: different neurological disorders, including pain, neurodegenerative diseases.

INTRODUCTION

Neuropharmacology is a very broad region of science that encompasses many aspects of the nervous system from single neuron manipulation to entire areas of the brain, spinal cord, and peripheral nerves. To better understand the basis behind drug development, one must first understand how neurons communicate with one another. There are two main branches of neuropharmacology: behavioral and molecular. Behavioral neuropharmacology focuses on the study of how drugs affect human behavior (neuropsychopharmacology), including the study of how drug dependence and addiction affect the human brain (Everitt et al 2005).
To understand the potential advances in medicine that neuropharmacology can bring, it is important to understand how human behavior and thought processes are transferred from neuron to neuron and how medications can alter the chemical foundations of these processes. Once the neurotransmitter is released into the synapse, it can either bind to receptors on the post-synaptic cell, the pre-synaptic cell can re-uptake it and save it for later transmission, or it can be broken down by enzymes in the synapse specific to that certain neurotransmitter. These three different actions are major areas where drug action can affect communication between neurons (Wrobel, et al 2007).

Neurotransmitter/receptor interactions in the field of neuropharmacology are extremely important because many drugs that are developed today have to do with disrupting this binding process. With an increase in technology and our understanding of the nervous system, the development of drugs will continue to rise with an increase in drug sensitivity and specificity. Structure-activity relationship or SARs is a major area of research within neuropharmacology that tries to modify the effect or the potency (i.e., activity) of bioactive chemical compounds by modifying their chemical structure (Narahashi, T et al 2000).

**Behavioral Neuropharmacology**

One form of behavioral neuropharmacology focuses on the study of drug dependence and how drug addiction affects the human mind. Most research has shown that the major part of the brain that reinforces addiction through neurochemical reward is the nucleus accumbens. The image to the right shows how dopamine and serotonin are projected into this area. Drugs such as opium, alcohol, and certain plants have been used for millennia by humans to ease suffering or change awareness, but until the modern scientific era nobody knew how these substances worked. The first half of the 20th century saw psychology and psychiatry as largely phenomenological, in that behaviors or themes which were observed in patients could often be correlated to a limited variety of factors such as childhood experience, inherited tendencies, or injury to specific brain areas. Neuropsychopharmacology may be regarded to have begun in the earlier 1950s with the discovery of drugs such as MAO inhibitors, tricyclic antidepressants, thorazine and lithium which showed some clinical specificity for mental illnesses such as depression and schizophrenia (ECNP Newsletter, 2004).

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its actions on the brain. Intoxication is a short-term result of alcohol present in the brain that is attributed to changes in neuronal communication. This is also usually accompanied by an increase or decrease in the release of the neurotransmitter GABA causing many of the neurons in the brain to become hyper-excitible during withdrawal from alcohol. Since GABA, for the most part, is an inhibitory neurotransmitter, a decrease in its amount will result in a feeling of anxiety (Narahashi et al, 2000). Along with GABA, there have been many links to other neurotransmitters that are affected by long-term use of alcohol, including dopamine, serotonin, and glutamate (Narahashi et al, 2000).

The inception of many classes of drugs is in principle straightforward: any chemical that can enhance or diminish the action of a target protein could be investigated further for such use. The trick is to find such a chemical that is receptor-specific ("dirty drug") and safe to consume. The 2005 Physicians' Desk Reference lists twice the number of prescription drugs as the 1990 version. The FDA has approved drugs which selectively act on each of the major neurotransmitters such as NE reuptake inhibitor antidepressants, DA blocker antipsychotics, and GABA agonist tranquilizers (benzodiazepines).

**Molecular neuropharmacology**

Molecular neuropharmacology involves the study of neurons and their neurochemical interactions, and receptors on neurons, with the goal of developing new drugs that will treat neurological disorders such as pain, neurodegenerative diseases, and psychological disorders (also known in this case as neuropsychopharmacology). There are a few technical words that must be defined when relating neurotransmission to receptor action.

The following neurotransmitter/receptor interactions can be affected by synthetic compounds that act as one of the three above. Sodium/potassium ion channels can also be manipulated throughout a neuron to induce inhibitory effects of action potentials.

**GABA**

The GABA neurotransmitter mediates the fast synaptic inhibition in the central nervous system. When GABA is released from its pre-synaptic cell, it will bind to a receptor (most likely the GABA\textsubscript{A} receptor) that causes the post-synaptic cell to hyperpolarize (stay below its action potential threshold). This will counteract the effect of any excitatory manipulation from other neurotransmitter/receptor interactions.
This GABA\textsubscript{A} receptor contains many binding sites that allow conformational changes and are the primary target for drug development. The most common of these binding sites, benzodiazepine, allows for both agonist and antagonist effects on the receptor. A common drug, diazepam, acts as an allosteric enhancer at this binding site (Sigel \textit{et al.} 2002). Another receptor for GABA, known as GABA\textsubscript{B}, can be enhanced by a molecule called baclofen. This molecule acts as an agonist, therefore activating the receptor, and is known to help control and decrease spastic movement.

**Dopamine**

The dopamine neurotransmitter mediates synaptic transmission by binding to five specific GPCRs. These five receptor proteins are separated into two classes due to whether the response elicits an excitatory or inhibitory response on the post-synaptic cell. There are many types of drugs, legal and illegal, that effect dopamine and its interactions in the brain. With Parkinson's disease, a disease that decreases the amount of dopamine in the brain, the dopamine precursor Levodopa is given to the patient due to the fact that dopamine cannot cross the blood–brain barrier and L-dopa can. Some dopamine agonists are also given to Parkinson's patients that have a disorder known as restless leg syndrome or RLS. Some examples of these are ropinirole and pramipexole (Winkelman \textit{et al.} 2007).

Psychological disorders like that of attention deficit hyperactivity disorder (ADHD) can be treated with drugs like methylphenidate (also known as Ritalin), which block the re-uptake of dopamine by the pre-synaptic cell, thereby providing an increase of dopamine left in the synaptic gap. This increase in synaptic dopamine will increase binding to receptors of the post-synaptic cell. This same process is also used by other illegal stimulant drugs such as cocaine.

**Serotonin**

The serotonin neurotransmitter has the ability to mediate synaptic transmission through either GPCR's or LGIC receptors. Depending on what part of the brain region serotonin is being acted upon, will depend on whether the output is either increasing or decreasing post-synaptic responses. The most popular and widely used drugs in the regulation of serotonin during depression are known as SSRI's or selective serotonin reuptake inhibitors. These drugs inhibit the transport of serotonin back into the pre-synaptic neuron, leaving more serotonin in the synaptic gap to be used.
Before the discovery of SSRIs, there were also very many drugs that inhibited the enzyme that breaks down serotonin. MAOIs or monoamine oxidase inhibitors increased the amount of serotonin in the pre-synaptic cell, but had many side-effects including intense migraines and high blood pressure. This was eventually linked to the drug's interacting with a common chemical known as tyramine found in many types of food (López-Muñoz et al 2009).

**Parkinson's disease**

Parkinson's disease is a neurodegenerative disease described by the selective loss of dopaminergic neurons located in the substantia nigra. Today, the most commonly used drug to combat this disease is levodopa or L-DOPA. This precursor to dopamine can penetrate through the blood–brain barrier, whereas the neurotransmitter dopamine cannot. There has been extensive research to determine whether L-dopa is a better treatment for Parkinson's disease rather than other dopamine agonists. Some believe that the long-term use of L-dopa will compromise neuroprotection and, thus, eventually lead to dopaminergic cell death. Though there has been no proof, in-vivo or in-vitro, some still believe that the better long-term use of dopamine agonists be better for the patient (Shin, et al 2009).

**Alzheimer's disease**

While there are a variety of hypotheses that have been proposed for the cause of Alzheimer's disease, the knowledge of this disease is far from complete to explain, making it difficult to develop methods for treatment. In the brain of Alzheimer's patients, both neuronal nicotinic acetylcholine (nACh) receptors and NMDA receptors are known to be down-regulated. Thus, four anticholinesterases have been developed and approved by the U.S. Food and Drug Administration (FDA) for the treatment in the U.S.A. However, these are not ideal drugs, considering their side-effects and limited effectiveness. One promising drug, nefiracetam, is being developed for the treatment of Alzheimer's and other patients with dementia, and has unique actions in potentiating the activity of both nACh receptors and NMDA receptors (Narahashi et al 2003).

**REFERENCES**


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