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NEURAL NETWORK IN DRUG DISCOVERY - LEARNING THE STRUCTURE ACTIVITY RELATIONSHIP OF CHEMICAL MOLECULE MONOAMINE OXIDASE (MAO) INHIBITION

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Abstract: The biologically inspired Neural Networks are computer programs designed to simulate the way in which the human brain processes information. Neural network gather their knowledge by detecting the patterns and relationships in data and learn through experience. Neural network was not only used for classification of physiologically active substances but also for solving the quantitative structure activity relationship problem. An important part of drug design and discovery is to understand the structure-activity relationship of chemical molecules. Without this understanding, drug design and discovery becomes an intractable, blind search problem. The goal of drug discovery in this study was to learn structural pattern associated with Monoamine Oxidation both in high and low inhibition.

Keywords: Drug Design, Drug Discovery, Monoamine Oxidation, Neural Network, Pattern Recognition

I. INTRODUCTION

Drug discovery refers to the finding of a new drug which could be completely a new compound or a new derivative of existing compounds. So, drug discovery is the ultimate goal of drug design. Drug design is concerned with the design of a chemical compound that exhibits a desired pharmacological activity. Novel drug molecules can be invented by computer-based analysis and simulation [1]. Applications studies of chemical problems using pattern recognition techniques have been reported in a number of areas. The elucidation of chemical structure information from spectral data is a lone standing problem of chemistry. This is the area first studied and most intensively studied using pattern recognition [2]. Both structure and properties of drug molecules can be modeled before more rigorous analysis can apply. The procedure of drug design normally consists of the following steps:

a. Select a lead compound with a desired pharmacological property as the kernel for the drug to be designed.
b. Derive new drugs from the kernel under structure-activity principles and evaluate their properties.
c. Update the structure-activity principles from experimental observations on those drugs.
d. Go to step 1 or 2 and iterate unless some drugs have achieved satisfactory [1].

II. NEURAL NETWORK

The aim of Neural Network research represented the effort to understand and model how people think and how the human brain functions. A neuron is a nervous cell, which is the basic functional building element of nervous system. Only the human cortex consists of approximately 13 to 15 billion of neurons. Which are arranged into a hierarchical structure of six different layers and each neuron can be connected with about 5000 of other neurons. The human nervous system intermediates the relationship between the outward environment and the organism. This process proceeds by transmitting impulses from particular sensors called *receptors* which enable to receive mechanical, thermal, chemical and luminous stimuli to other nervous cells that process these signals and send them to corresponding executive organs called *effectors*.

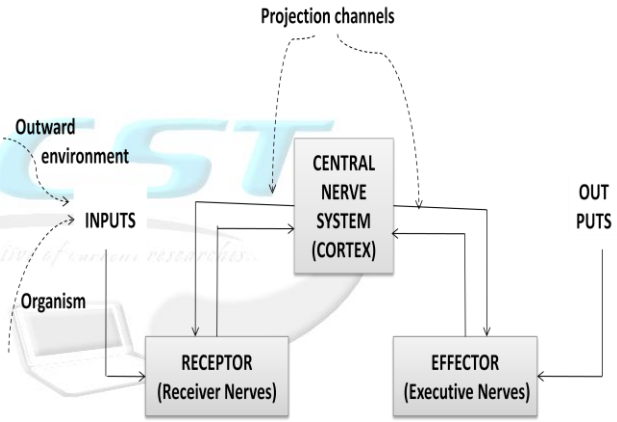

Figure 1: Block diagram of biological nerve system

These impulses passing through the projection channels where the information is preprocessed compressed and filtered for the first time possibly arrive at the cortex that is the top controlling center of the nervous system [3]. As show in figure 2 each cell consists of a cell body (soma) that contains the cell nucleus. Connected to the cell body are dendrites for incoming informations and a single long axon with dendrites for outgoing information that is passed to connected neurons. Informations are transported between neurons along the dendrites in the form of an electrical potential. If the potential reaches a certain threshold, the neuron is said to be activated and the information is delivered along the neurons axon to the dendrites, where it is passed on to the neurons [4].

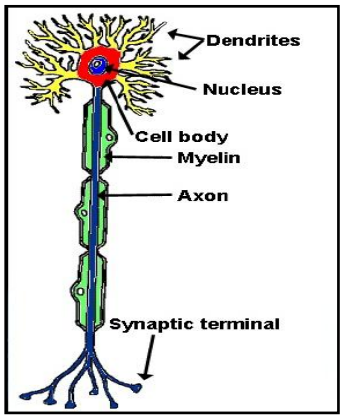

Figure 2: Biological structure of Neuron

2.1. Neural network computational model

The computational model of neural network has three layers an input layer, a hidden layer and an output layer. The size of the input layer depends on the number of inputs and the number of outputs being used to denote the states. Back propagation algorithm is used as the transfer function in the hidden layer. A serial adder and a sequential decoder are used for the implementation of the sequential machine [5].

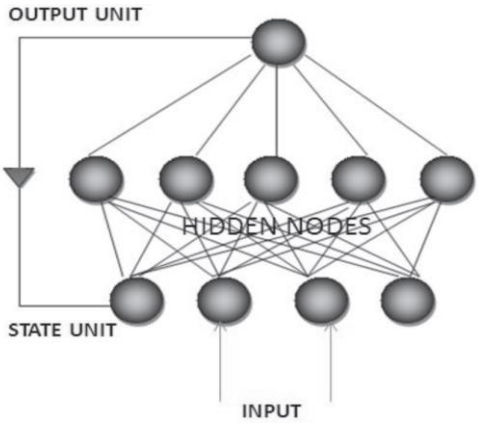

Figure 3: Neural Network Model

III. MACHINE LEARNING AND DRUG DESIGN

The history of applying machine learning techniques to chemistry can be examined from two related approaches: Pattern recognition and Expert systems. Pattern recognition was first applied to extract molecular structure from spectral data. Since then, the range of methods and the number of chemical applications have increased rapidly. Kowalski and Krischner present many interesting applications to drug design.

In the Expert system approach, DE|NTRAL and Meta-DENRAL programs were developed by Buchanan and Feigenbaum for chemical structure elucidation. DENTRAL infers the molecular structure of unknown compounds from mass spectral and nuclear magnetic resonance data. Meta-DENTRAL was developed to learn relevant knowledge that DENTRAL used. It learns fragmentation rules for given classes of molecules by heuristic search, generalization and specialization [1].

The discovery of drugs depends on a number of interdependent factors including insight, serendipity and persistence. A common characteristic of the successful program is a clearly delineated strategy based on quantitative pharmacological assays. The choice of drug design as the problem solving technique implies the selection of a rational approach that is based on detailed information concerning the structure of the target receptor or enzyme. An empirical strategy for drug discovery and is an iterative process of chemical modification emphasizing a stepwise improvement. Toward this end, it clear that medicinal chemistry along with molecular pharmacology and computer assisted design forms the new basis for drug discovery [6].

By starting the drug design process at the level of receptors and enzymes the variables of absorption, distribution, metabolism and excretion are set aside temporarily allowing the optimization of affinity or potency to become the key issue. The recent progress in molecular pharmacology to open new windows for discovery and although advances in design are being made, drug discovery today remains largely empirical, a mixture of intuition, experience and serendipity [6].

Drug design in its purest form detailed structural knowledge of the receptor or the active site of an enzyme. In certain cases, a thorough understanding of the reaction mechanism may serve as the basis on which to design specific inhibitors. The following figure illustrates the central role of lead discovery and optimization in the drug discovery process [6].

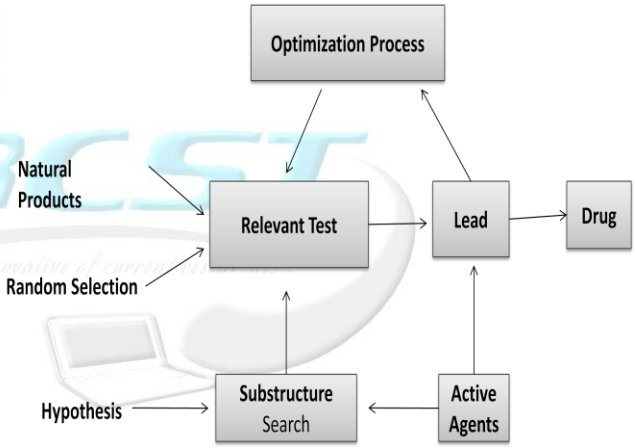

Figure 4: Neural Network Model

3.1. Quantitative Structure Activity Relationship (QSAR)

When direct information about the receptor is lacking or when the enzymatic mechanism is not fully understood more indirect approaches must be used to optimize the selected lead structure. Under these conditions lead development depends on building a meaningful structure-activity relationship. The two tools are available to search for such a relationship and when found to predict the biological response; they are Quantitative structure activity relationship and Pattern recognition.The first of these, QSAR has become known as the Hansch approach in recognition of the pioneering role of Corwin Hansch. This method is based on the biological response can be expressed in terms of a function of quantifiable physiochemical parameters, such as hydrophobic, electrostatic, steric and dispersion interactions [6]. Quantitative structure-activity studies were carried on a series of aminoindans and aminotetralines to monoamine oxidase (MAO) inhibition.

In the pharmacological application, structural features used for describing chemical molecules can be categorized as follows:

- Molecular weight
- Number of particular kinds of atoms, such as Oxygen's, Phosphorus sulfurs, carbons and halogens
- Number of particular kinds of bonds such as double bonds and triple bonds
- Number of particular kinds of bonds over number of particular kinds of atoms
- Number of particular kinds of groups
- Number of particular kinds of derivatives
- Longest chain of non-aromatic carbons
- Combination of the above features

The physical properties of molecules are also important because they are structure-dependent. Special molecular technology like infrared, mass spectrum, nuclear magnetic resonance and x-ray diffraction have created very useful features for structural analysis other than those mentioned above [1].

The learning object in the pharmacological application is the dependency of activity on structural features, which relationship can be used to guide drug design. To achieve this objective, the first step is to obtain a set of molecules which has been tested for a desired pharmacological activity. The next step is to select features to describe or represent the molecules. Then machine learning algorithms are applied to these data. There are three elements involved in this process: Data collection, Feature extraction and selection and Learning algorithm [1].

There are different types of ligand-based models, such as QSAR with 2D and 3D descriptors, 3D-CoMFA (Comparative Structure Activity Relationship), 3D-pharmacophores or ligand-network models. QSAR studies have become one of the most popular ligand-based approaches in modern chemistry. The main steps implicated in the development of a QSAR model are depicted below the figure [10].

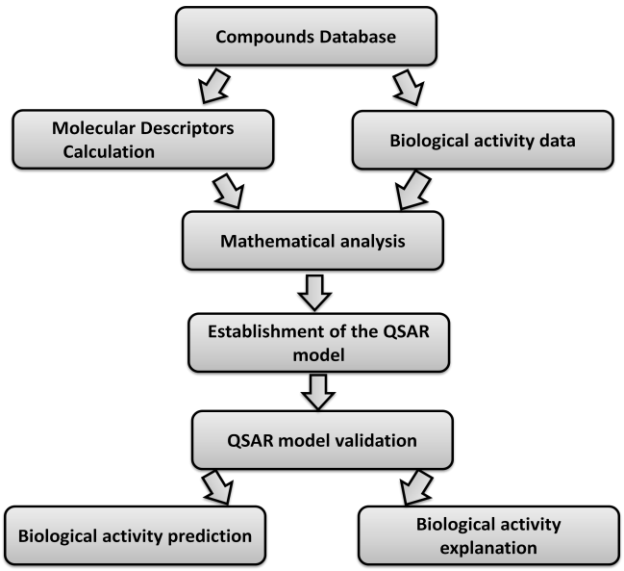

Figure 5: Flowchart showing the Main Steps involved in the Development of a QSAR Model

1. Collection of a database (molecular structures and biological activity values). The set of molecules used to develop the QSAR equation should be representative of the problem under investigation.

2. Calculation of molecular descriptors, depending on the nature of the molecular descriptors it is possible to distinguish between 2D and 3D QSAR. Topological or physicochemical descriptors, in which the 2D structure of the molecules is taken into account for their calculation, are used in the 2D QSAR. However, the development of QSAR with 3D descriptors, such as topographic or quantum-chemical descriptors implies the calculation of the most stable 3D conformation for the molecules as a previous step.

3. Data analysis to establish the model that relates the descriptors with the biological activity. Some techniques, such as Multiple Linear Regression (MLR), Linear Discriminant Analysis (LDA) or Partial Least Squares (PLS) regression have been widely applied. However, when no linear patterns can be found, the structure-activity relationship can be explained through non-linear methods, such as Artificial Neural Networks (ANN) or Support Vector Machine (SVM).

4. Model validation, here cross validation series (sub-sampling test), leave-one-out cross validation (jackknife test) or the evaluation of an independent external prediction series are useful procedures to validate the final model.

Once the QSAR model has been developed, biological activity prediction of new molecules and interpretation of the results focused on the molecular mechanism of action could be carried out [10].

IV.MONOAMINE OXIDASE (MAO)

Monoamine Oxidases are a family of enzyme that catalyzes the oxidation of monoamines. This enzyme was originally discovered by Mary Bernheim in the liver and was named 'Tyramine Oxidase' [9]. Monoamine Oxidases are a family of Flavin Adenine Dinucleotide (FAD) containing enzymes located in the mitochondrial outer membrane. MAO enzymes catalyze the oxidative deamination of endogenous and exogenous monoamines to the corresponding aldehyde, hydrogen peroxide and ammonia (from primary amines) or substituted amine (from secondary amines). The enzyme inhibition allows the monoamine neurotransmitters to remain active in the brain for longer periods. For this reason, MAO enzymes play a crucial role in the inactivation and regulation of intracellular levels of monoamine neurotransmitters [10].

Monoamines are neurotransmitters and neuromodulators that include serotonin, dopamine, norepinephrine and epinephrine. Many antidepressant drugs increase synaptic levels of the monoamine neurotransmitter; serotonin but they may also enhance the levels of two other neurotransmitters, norepinephrine and dopamime [7]. The description Monoamine was detailed below:

4.1. Monoamine definition and structure

Monoamines are a class of common and influential neurotransmitters. They have a similar structure and hence are largely influenced by the same types of drugs. They are largely produced in the brain stem where neurons have axons with many terminal buttons that reach deep into the brain. They modulate many functions, increasing or decreasing them as designed [16].

Mono

The prefix word 'Mono' standards for 'one, single, only or alone'. It can also be represented as containing one of the specified atom, molecule or group [13].

Amine

Amines are mostly easily thought of as close relatives to ammonia NH3. In fact, the word amine comes from the 'am' – of ammonia. In amines, the hydrogen atoms have been replaced one at a time by hydrocarbon groups [14]. Amines are organic compounds and functional groups that contain a basic nitrogen atom with a lone pair. Amines are derivative of ammonia, wherein one or more hydrogen atoms have been replaced by a substituent such as an alkyl or aryl group. These may respectively be called alkylamines and arylamines, amines in which both types of substituent are attached to one nitrogen atom may be called alkylarylamines[15].

4.1.1.Chemical structure of ammonia

The basic chemical structure is that f ammonia NH3, which the key atom being the central nitrogen atom. Try to remember that an amine is just like ammonia because ammonia is a simple molecule to recall. The basic ammonia structure is changed when the hydrogen atoms are replaced by alkyl groups to form amines. You can change one, two or all three of them and these are called primary, secondary and tertiary amines. You can see in the diagrams that the hydrogen atoms have been replaced by an 'R'. This R can represent any hydrocarbon side chain and is the generic term that organic chemist use. The naming of amines is pretty straight forward [14]:

(a) Primary amine

Primary amines arise when one of three hydrogen atoms in ammonia is replaced by an alkyl or aromatic, while primary aromatic amines include aniline [15]. Important primary amines include (CH3-NH2) and ethylamine (CH3-CH2-NH2). [14]

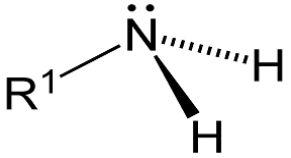

Figure 6: Primary amine with one hydrogen atom replaced with an R group

(b) Secondary amine

Secondary amines have two organic substituent's (alkyl, aryl or both) bound to 'N' together with one hydrogen or no hydrogen if one of the substituent bond is double [15]. Important representatives include Dimethylamine (CH3-NH-CH3) and methylethanolamine [15].

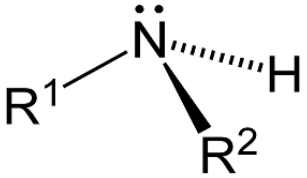

Figure 7: Secondary amine with two hydrogen atom replaced with an R group

(c) Tertiary amine

In tertiary amines, all three hydrogen atoms are replaced by organic substituents [14]. some examples are trimehtylamine CH3-N(C|H3)-CH3 [14].

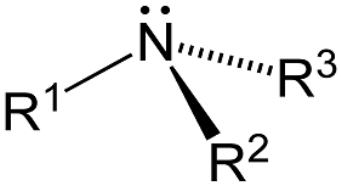

Figure 8: Tertiary amine with all three hydrogen atoms replaced with an R group

(d) Cyclic amine

Cyclic amines are either secondary or tertiary amines. Examples of cyclic amines include the 3-member ring aziridine and the six-membered ring piperidine. N-methylpeperidine and N-phenylpoperdine are examples of cyclic tertiary amines [15].

4.2. Naming Convention

Amines are named in several ways. Typically, the compound is given the prefix "amino" or the suffix "amine". The prefix 'N' shows substitution on the nitrogen atom. An organic compound with multiple amino grpups is called a diamine, triamine, tetraamine and so for. Systematic names for some common amines are illustrated below [15]:

Lower amines are named with the suffix 'amine'

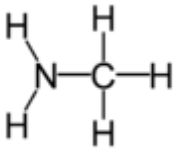

Figure 9: Methylamine

Higher amines have the prefix amino as a functional group. IUPAC however does not recommend this convention, but prefers the alkanamine form [15].

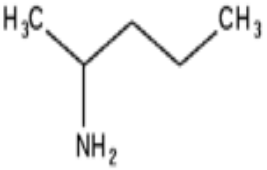

Figure 10: 2-aminopentane

4.3. Properties and Reactions

All amines have similar properties and reaction to ammonia, they are just modified by whatever is attached in the 'R' groups. Most of their behavior can be explained by the lone

pair of electrons in the nitrogen atom. This lone pair explains why amines are:

(a) Water soluble
The small amines of all types are very soluble in water. Larger amines are less soluble because they have long carbon chains that disrupt the hydrogen bonding in water [14].

(b) Hydrogen Bonded
All of the amines can form hydrogen bonds with water [14].

(c) Bases
The lone pair on the nitrogen can take part in coordinate covalent bonding and the amine can donate a pair of electrons to an H++. This means that amines are basic in nature [14].

4.4. Oxidase

An oxidase is any enzyme that catalyzes an oxidation-reduction reaction, especially one involving molecular oxygen (O_2) as the electron acceptor. In reactions involving donation of a hydrogen atom, oxygen is reduced to water (H_2O). Some oxidation reactions, such as those involving monoamine oxidase or xanthine oxidase, typically do not involve free molecular oxygen [17].

4.4.1. Monoamine Oxidase

A Family of enzymes involved in the metabolism of monoamines. Their role is to break down of monoamines has caused monoamine oxidase enzymes to be targeted in the treatment of disorders that are thought to involve low monoamine levels [18]. An enzyme in the tissue cells catalyzes the oxidative deamination of monoamines to Serotonin, Dopamine, Epinephrine, and Norepinephrine. MAO is responsible for the inactivation of neurotransmitters [19]. This inactivation was activated by monoamine oxidase inhibitors (MAOI) as described in the following section.

4.5. Neurotransmitter

Neurotransmitters are endogenous chemical that enable neurotransmission. They transmit signals across a chemical synapse, such as in neuromuscular junctions from one neuron to another neuron (target), muscle cell or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors in other synapses. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps to convert them. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown but more than 100 chemical messengers have been identified [8].

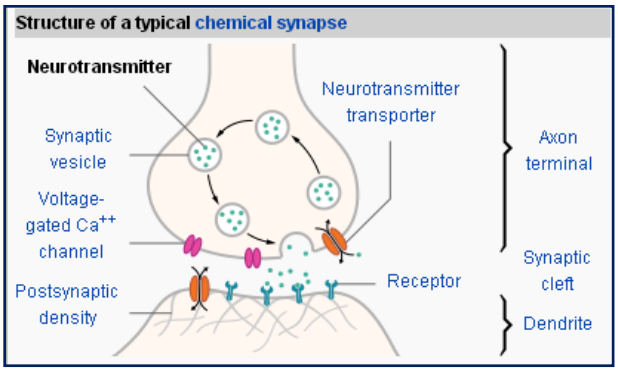

Figure 11: Structure of typical chemical synapse

The above figure describes the major elements in a prototypical synapse. Synapses are gaps between nerve cells. These cells convert their electrical impulses into bursts of chemical layers called neurotransmitters, which travel across the synapses to receptors on adjacent cells, triggering electrical impulses to travel down the latter cells [7].

4.5.1. Types of Neurotransmitter

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides and monoamines is sufficient for some classification purposes. Here some major neurotransmitters are depicted below [8]:

a. *Amino acids*
Gultamates, Asparate, D-Serine, γ-aminobutyric acid (CABA), glycine

b. *Gasotransmitters*
Nitric Oxide (NO), carbon monoxide (CO), Hydrogen Sulfide (H_2S)

c. *Monoamines*
Dopamine (DA), Norepinephrine (noradrenaline, NE, NA), Epinephrine (adrenaline), Histamine, Serotonin (SER, 5-HT)

d. *Trace amines*
Phenethylamine, N-methylphenethylamine, Tyramine, 3-iodothyronamine, Octopamine, Tryptamine.

e. *Peptides*
Somatostatin, Substance P, Cocaine and amphetamine regulated transcript, opioid peptides.

f. *Purines*
Adenosine triphosphate (ATP), Adenosine.

g. *Others*
Acetylcholine, Anandamide

4.5.2. Identification of Neurotransmitter

There are four main criteria for identifying neurotransmitters [8]:

a. The chemical must be synthesized in the neuron or otherwise be present in it.
b. When the neuron is active the chemical must be released and produce a response in some target.
c. The same response must be obtained when the chemical is experimentally place on the target.
d. A mechanism must exist for removing the chemical from its site of activation after its work is done.

However, given advances in pharmacology, genetics and chemical neuroanatomy the term 'neurotransmitter' can be applied to chemicals that [8]:

- Carry messages between neurons via influence on the postsynaptic membrane

- Have little or no effect on membrane voltage, but have a common carrying function such as changing the structure of the synapse.

- Communicate by sending reverse-direction messages that have an impact on the release or reuptake of transmitters.

4.6. Types of MAO

In human there are two types of MAO, they are MAO-A and MAO-B. Both are found in neurons and astroglia. Outside the central nervous system: MAO-A is also found in the liver, pulmonary vascular endothelium gastrointestinal tract and placenta. MAO-B is mostly found in blood platelets [9]. Both isoenzymes have 70% identify/similarity in their primary amino acid sequence and they are coded by different genes with similar structure. They differ in cell and tissue distribution, inhibitor sensitivity and specificity in regards to the neurotransmitter types. Serotonin, epinephrine and norepinephrine are mostly denominated by MAO-A. Other neurotransmitters such as phenyl ethylamine are more specific to MOA-B [10].

4.6.1. Monoamine Oxidase-A (MAO-A)

The version of Monoamine Oxidase-A is also known as Warrior Gene or MAO-A, it is a human enzyme that is encoded by the MAO-A gene and also it is an isozyme of monoamine oxidase [11].

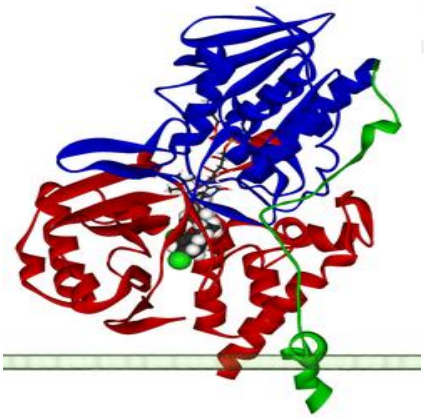

Figure 12: Ribbon diagram of an MAO-A monomer with FAD and clorgiline bound

In human there is a 30 base repeat sequence repeated in one of several different numbers of times in the promoter region of the gene coding for MAO-A. MAO-A levels in the brain as measured using position emission tomography are elevated by an average of 34% in patients with major depressive disorder [11]. MAO-A is of particular importance in the treatment of psychiatric disorders, such as depression and anxiety [10].

4.6.2. Monoamine Oxidase-B (MAO-B)

Monoamine Oxidase B also known as MAO-B is an human enzyme encoded by the Mao-B gene. The protein encoded by this gene belongs to the flavin monoamine oxidase family. It is an enzyme located in the outer mitochondrial membrane. It catalyzes the oxidative deamination of biogenic and xenobiotic amines and plays an important role in the catabolism of neuroactive and vasoactive amines in the central nervous and peripheral tissues. This protein preferentially degrades benzylamine and phenylethylamine. Like MAO-A it also degrades dopamine [12].

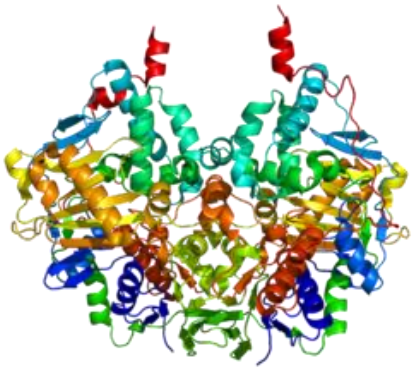

Figure 13: Ribbon diagram of an MAO-B

Monoamine oxidase-B has a hydrophobic bipartite elongated cavity that occupies a combined volume close to 700 A^3. hMAO-A has a single cavity that exhibits a rounder shape and is larger in volume than the 'substrate cavity' of hMAO-B. The first cavity of hMAO-B has been termed the entrance cavity (290 A^3) or active site cavity (390 A^3), between both an isoleucine 199 side chain serves as a gate. Depending on the substrate or bound inhibitor, it can exist in either an open or a closed form, which has been shown to be important in defining the inhibitor specificity of hMAO-B [12].

4.7. Function of MAO

As we know that Monoamine Oxidase is a mitochondrial enzyme that helps to maintain neuron firing rates by controlling the concentration of monoamines in the Central nervous system. The monoamines that are found in the central nervous system are the neurotransmitters: Serotonine, Dopamine, Adrenaline, Noradrenaline, Histimine and others. The monoamine oxidase enzyme, which is attached to the outer membrane of the mitochondria, oxidizes the neurotransmiters by taking of the nitrogen containing amine groups by a process called deamination is showed in the following figure[21].

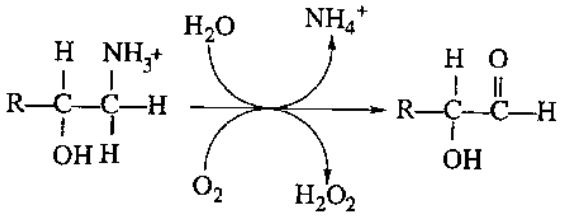

Figure 14: Deamination process

Monoamine oxidase is a flavin containing enzyme which exists in two forms, MAO-A and MAO-B. Since, there are two isomers of this enzyme there are two different mechanisms. Unfortunately, the mechanism of MAO-A is still unknown. The proposed mechanism of MAO-B on Dopamine is show. This illustration shows how MAO-B breaks down Dopamine to release ammonia and hydrogen peroxide. Then the hydrogen peroxide should be oxidized by Glutathione Peroxidase and turn into water. However, in the presence of Ferous ions which are associated with neuromelanin, transfer of a single electron

to the hydrogen peroxide will ultimate divide the hydrogen peroxide into two hydroxyl radicals [21].

V. DIFFERENCE BETWEEN MONOAMINE OXIDASE (MAO)

S.No.	Characteristics	MAO-A	MAO-B	References
1.	Metabolisms	MAO-A metabolizes neurotransmitters such as dopamine, norepinephrine and serotonin	MAO-B metabolizes nonchatechol-containing amines	[23]
2.	Inactivation and Inhibition	MAO-A is selectively inactivated in an irreversible fashion by low concentrations of the acetylenic inhibitor clorgyline	Mao-B is selectively inhibited in an irreversible manner by pargyline and selegiline.	[23]
3.	Regulation of MAO Gene Expression	The expression of MAO-A mRNA in various human tissues was as follows: Placenta>colon>prostate>heart>thyroid gland>salivary gland>other tissues.	The expression of MAO-A mRNA in various human tissues was as follows: Skeletal muscle>heart>spinal cord>liver>colon>kidney>uterus>other tissues.	[23]
4.	Treatment	MAO-A inhibitors have been typically used in the treatment of depression	MAO-B inhibitors are typically used treatment of Parkinson's disease	[12]
5.	Catalytic site	MAO-A is monopartite structure	MAO-B is a dipartite structure	[25]

Table 1: Difference between MAO-A and MAO-B

VI. MONOAMINE OXIDASE INHIBITOR (MAOI)

Monoamine Oxidase inhibitors (MAOI) are chemicals which inhibit the activity of the monoamine oxidase enzyme family. They have a long history of use as medications prescribed for the treatment of depression. MAOIs are also used in the treatment of Parkinson's disease and several other disorders. Monoamine oxidase inhibitors have historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs have failed. MAOI started off due to the unexpected discovery of that iproniazid was a weak MAO inhibitor. In 1952 originally intended for the treatment of tuberculosis. MAOIs became widely used as antidepressants in the early 1950s. When scientists discovered that there are two types of MAO enzymes (MAO-A and MAO-B), they developed selective compounds for MAO-B, reduce the side effects and serious interactions [20].

It is a class of medications used to treat depression. They were first introduced in the 1950s as the first class of drugs designed for depression. It works as chemicals in out brain, neurotransmitters that allow brain cells to communicate with each other. Depression is thought to be caused by low levels of the neurotransmitters deopamine, serotonin and norepinephrine which collectively are called monoamines. A chemical found naturally in the body, monoamine oxidase removes these neurotransmitters in the body. By inhibiting the monoamine oxidase, MAOIs allow more of the neurotransmitters to remain in the brain, thus elevating mood through improved brain cell communication [22].

VII.RESULTS

In this study, Kowalski and Krishcner's data are used. The data were originally used by Martin and co-workers to determine the structure-activity relationship in a series of aminoindans and aminotetralines to monoamine oxidase (MAO) inhibition. Each compound is desired by four structural descriptors (symbolic features), four physical properties (numerical features), and the biological activity of MAO inhibition both in vitro and in vivo. Notice that the physical properties also reflect structural characteristic. The goal of drug discovery program in this study was to learn structural patterns associated with MAO inhibition. The compounds were arranged into two classes: low activity (inactive or slightly active) and high activity (moderately active and most active). The drug discovery program built for this task is how in following figure 15 and 16, the patterns obtained is shown in figure 17 and 18. The design of new compounds based on these patterns was not conducted because of practical constraints [1].

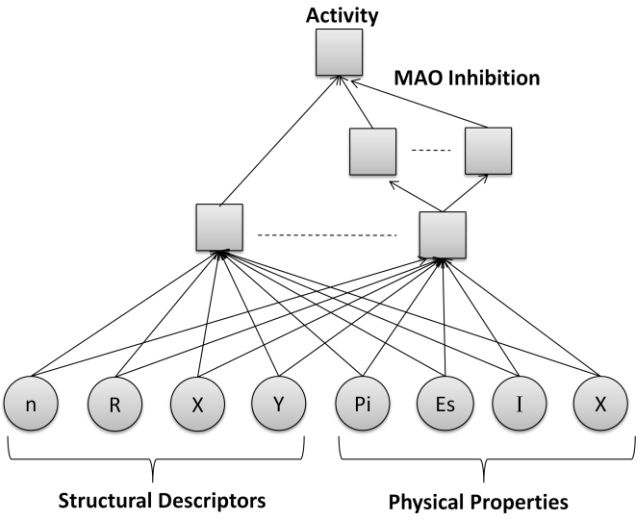

Figure 15: The neural network for learning the structure activity relationship of molecules

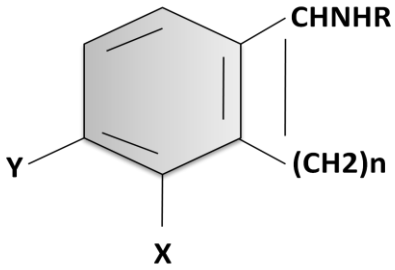

Figure 16: The structural pattern of a molecule

The chemical structural patterns associated with monoamine oxidase inhibition was figured below

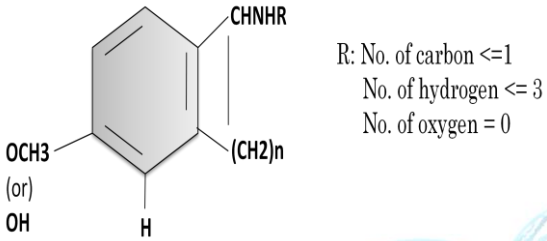

Figure 17: The structural pattern for high MAO inhibition activity

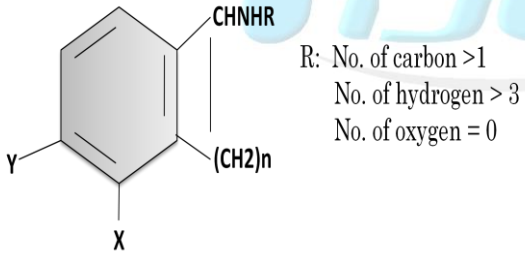

Figure 18: The structural pattern for low MAO inhibition activity

VIII.CONCLUSION

Drug design is a very complicated problem. The identification of the structure activity relationship is the central part of drug design. Only when this relationship is clearly understood can better drugs be designed. However it is difficult to acquire such knowledge since it requires the synthesis and testing of a sufficient number of chemical compounds in the first place. Pattern recognition techniques have been applied to drug design. Most of them represent molecules numerically and attempt to quantify structure activity relationships. The main problem with this kind of approach is that some structural information can only be represented symbolically and the notion of distance simply fails to apply.

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