Original Research Paper

Volume-9 | Issue-5 | May-2019 | PRINT ISSN No 2249 - 555X

Pharma

RECENT APPROACHES FOR TARDITIVE DISKINESIA TREATMENT: AN OUTLOOK.

Manoj Kumar Katual*

University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab. *Corresponding Author

ABSTRACT The human brain is the most complex organs in the human body. It is made up of more than 100 billion nerves and communicates with other nerve cells through specialized nerve synapsis. Tardive dyskinesia (TD) is a delayed, involuntary lateral jaw and face movements, facial grimacing, lip wetting, muscle contractions like side-effects of antipsychotic medications. In 50% of the patients affected with psychosis has shown irreversible remission of TD. Dyskinesias can interfere with normal motor activity of the brain. Any type of imbalance in the functioning of the brain may give rise to neurodegenerative disorders. These diseases depend upon factors either genetic or environmental strongly associated with age and other devitalizing disorders of the nervous system.

KEYWORDS :

INTRODUCTION:

Approximately 30 million and more people gets affected by brain disorders worldwide. Neurodegenerative diseases are the ultimate consequence of mis-folding and perturbation of intracellular enzymes that affect the regulation pathway of protein trafficking. Besides that, mitochondrial dysfunction and/or oxidative stress have been implicated in causing neuro-degeneration. [1]

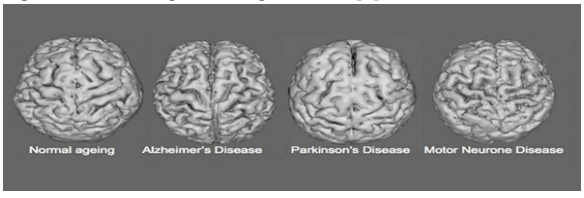

Fig 01: Anatomical view of Human brain during various Neuro-degenerative disorders. [2]

The above picture depicts how the neurons of the brain consistently differs from each other which results in progression of neuro-degeneration and eventually death.

Neuro-degeneration.

When the neuron of the brain and the spinal cord fails to function according to the signal received, the loss of nerve cells starts which refers to the neuro-degeneration. For instance brain receives the signal to eat but either the brain receives the signal too late or the neurons has lost the tendency to respond back to the signal, this situation arises only when the neurons are not functioning properly.

Etiology of neuro-degeneration.

- *Ageing*:

The major factor responsible for the depletion of neurotransmitters is ageing. Ageing is the main reason because the brain functioning is disrupted abruptly. The brain is unable to coordinate with body. **[3]**

Fig-02: Affected parts of human brain in Parkinson's Disease.[4]

- ***Altered Cellular metabolism*:**

The pathogenesis of disorders like Alzheimer's disease, Parkinson's, Multiple sclerosis, Friedreich's ataxia may involve the generation of free radicals along with dysfunctioning of mitochondrial genome. Though mitochondrial genome plays an important role in respiratory chain but in these disorders the genome performs complex activities which is associated with possible oxidant-antioxidant balance which underlies the defection in energy metabolism and induces cell death. Current concepts also involves the inhibition of complex I of the mitochondrial respiratory chain and alteration in the iron metabolism in lewy body disease also known as presymtomatic parkinsonism disease. Some studies also suggests that the fluctuation in the glutathione levels in the energy producing chain is a clue to the primary cause of parkinsonism disease.

- ***Free radical formation:***

Normally, when the aerobic cellular metabolism forms reactive oxygen species (free radicals), the oxidant/antioxidant balance acts as a defense system for our body by decisiving free radicals. However, this defense mechanism is malfunctioned due to incorporation or overproduction of reactive oxygen species which further lead to sensory loss of neuronal cells of the brain in neurodegenerative diseases. Despite the fact that oxygen is vital for living cells but if there is any impairment in the metabolism of cellular respiration, toxic and reactive molecules of oxygen are formed which end into origin of neural disorders. **[5]**

- ***Lewy body formation***

These are the abnormal inclusions formed during the endogenous mechanisms in the early stages of life by the aggregation of proteins in the substantia nigra region of the brain in tardive dyskinesia. These bodies are composed of structurally abnormal neuro filamentous assemblies. Recent studies have suggested that filamentous proteins are called α-synuclein which runs parallel with the normal filament axis in the brain.

- ***Neuro-inflammation:***

The central nervous system is composed of variety of cells- microglia cells are one of them which primarily participate in the immune response of the CNS. These cells are responsible for releasing pro-inflammatory mediators like IL-1, IL-6, and chemokines which contribute in the immunological processes of the brain. The triggering of microglials results in synergism between genes and P.D phenotypes (synuclein, parkin, Nurr1) promoting Neuro-degeneration of the brain cells.

- ***Tardive dyskinesia and psychosis*:**

Psychosis is a mental bipolar disability that is characterized by disorientation of thoughts, emotions, actions associated with delusions, hallucinations and disturbances in behavior, mood swinging, prolonged depression or extreme mania.

With the prolonged use of antipsychotic drugs, blockade of dopamine binding to the dopamine receptor present on the nigrostiatal pathway occurs which in turn leads to decreased amount of dopamine in substantia nigra thus causing extrapyrimidal effects. **[6]**

- ***Paranoid Delusion***: the person affected with psychosis starts assuming himself to be the suspect of the harmful activity.
- A false belief where the patient starts believing that he is held with special powers.
- The exact cause of psychosis is unknown but some other factors which may lead to psychosis:
- Genetic
- Hormonal imbalance

- Brain changes

In the cross sectional and longitudinal MRI studies, it was observed that comparative to patients who did not develop psychosis, the psychotic patients had less grey matter in the right medial temporal, lateral temporal, fusiform and orbitofrontal lobes of the brain.

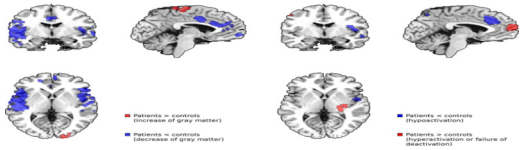

Fig-04: Grey matter and Cognitive brain response abnormalities [7]

There are different types of psychotic conditions which are interlinked with each other:

- Schizophrenia
- Bipolar disorder
- Psychotic depression

Schizophrenia is not a common disorder but it is a life threatening disorder. It is associated with the mental behavior of the person and it affects the normal functioning of thinking process. It involves mood swinging and this order starts between puberty and early 30s.

Bipolar disorder involves the elevation in the mood i.e the mood is either extremely up or depressed, stiff increase and decrease in the activity levels.

Various Treatments options available till date:

Antipsychotics
Antidepressants
Psychosocial treatments

- ***Antipsychotic drugs and tardive dyskinesia:***

The leading hypothesis shows that first generation antipsychotics produce dopamine receptor hypersensitivity, GABA insufficiency and modification in other structural units. This also suggests that newer atypical third generation antipsychotics develop less symptoms of tardive dyskinesia because of its specificity.

1. First generation antipsychotics (low potency)

Phenothiazines: Chlopromazine, Prochlorpromazine, Thioridazoine, Flufenazine

2. First generation antipsychotics (high potency)

Flufenazine, Butyrophenones: Haloperidol, Droperidol, Other: Pimozide, Thiothixene

3. Second generation antipsychotics

Olanzapine, Clozapine, Risperidone, Quetapine, Ziprasidone, Lurasidone

4. Third generation antipsychotics, **Aripirazole**

- ***Mechanism of action of Phenothiazines*:**

a) Dopaminergic neuron system:

In this pathway, the amino acid tyrosine is influxed through tyrosine channels into the presynaptic neuron and gets converted into inactive form of dopamine that is L-dopa. L-dopa gets converted into dopamine and these neurotransmitters are stored in neuro vesicles to prevent degradation. On the generation of action potential, the vesicles carrying the dopamine come near to the membrane thus releasing the dopamine into the synapsis. The dopamine binds to its Dopaminergic receptors and performs its specific function.

***b) Blockade of dopamine receptors by Phenothiazines and its derivatives*:**

Phenothiazines and metoclopramide are known to be the first generation antipsychotic agents. These drugs inhibit the binding of serotonin to 5HT receptors and dopamine to dopamine receptors. They not only bind competitively with these two receptors but also stimulate cholinergic receptors and decreases catecholamine transferases synthesis. Sometimes use to treat post effects like severe nausea and vomiting in migraine.

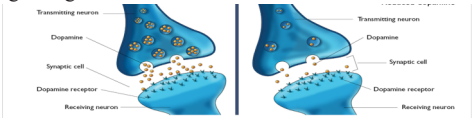

Fig-03: Level of dopamine in Normal cells v/s Parkinsonism [8]

***a) Phenothiazines toxicity*:**

Phenothiazines are used for treating mild anxiety or conditions like stress, primarily blocks dopamine D1 and D2 receptors but these drugs have shown the property to inhibit histaminic receptors and cholinergic muscarinic receptors leading to suppression of oral secretions and down regulation of body temperature, minimal respiratory depression along with occurrence of seizures.

- ***Pharmacokinetics of Phenothiazines:***

An oral preparation is available (10 mg and 25 mg tablets); however, oral bioavailability is low and somewhat variable (20–55%). Higher doses are necessary if this route is used and the effect is difficult to predict. A dose that is ineffective in one patient may cause profound and prolonged sedation in another. Acepromazine is very lipophilic and is widely distributed throughout the body. The degree of protein binding is high. Phenothiazines, including acepromazine, are metabolized by hepatic microsomal enzymes.

- ***Mechanism of action of high potency antipsychotics:***

a) Metoclopramide is commonly used to prevent nausea and vomiting like symptoms and treat other gastrointestinal dysfunctioning. It is used as an antiemetic drug by interfering in the dopamine circuit present in the mesolimbic region of the brain. [**9]**

b) Blocking dopamine d2 and other serotonin receptors: At higher doses of metoclopramide produces hypersensitivity of dopamine in the post synaptic neurons which causes elevation in the level of dopamine and serotonin in the brain thus the patient is experiences delusions and sensations of hallucinations. Dopamine is an excitatory neurotransmitter, usually when dopamine is released into the synapsis it binds to either d1 or d2 receptors on the post synaptic neuron which further stimulates the conversion of inostidylyl tri phosphate into calcium.**[10]**

c***) Pharmacokinetics of haloperidol***: Large doses of haloperidol can safely be given intravenously and intramuscularly for rapid neuroleptisation; the bioavailability of this agent administered orally ranges from 60 to 65%. This range may vary from individual to individual. Although not conclusive from different clinical studies, it appears that a plasma haloperidol concentration range of 4 µg/L to an upper limit of 20 to 25 µg/L produces therapeutic response**.[11]**

CONCLUSION:

Numerous pharmacologic agents have been investigated for the treatment of TD. A comprehensive review of evidence-based recommendations for the management of tardive syndromes has recently been focused. However, highlighted a few of these anti-dyskinesia agents in an effort to quickly educate the reader regarding the available options for treating TD has lime lighted in this article.

ACKNOWLEDGEMENT:

The author is highly thankful to Dr.Gurfateh Singh, University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, India & Dr.S.L.Harikumar,Central University, Jharkhand for their constant encouragement and support for preparing this article. The author hereby declares no conflict of Interest.

REFERENCES:

1. Saba Sheikh, Safia, Ejazul Haque, and Snober S. Mir, Neurodegenerative Diseases: Multifactorial Conformational Diseases and Their Therapeutic Interventions, Journal of Neurodegenerative Diseases. 2013.Vol 3 (2), P.p:1-8.
2. J Neural Transm Suppl. Jellinger KA, Neurodegenerative disorders with extrapyramidal features: a neuropathological overview, 1995;46: P.p33-57.
3. Raffaele Lodi. Oxidative stress, mitochondrial dysfunction and cellular stress response in Friedreich's ataxia, the journal of neurological disorders, 2005.Vol 233, Issue 1-2, P.p 145–162.
4. Bayani Uttara, Ajay V. Singh, Paolo Zamboni, and R.T Mahajan , Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options,bentham science publishers limited, , Vol.7 (1),P.p: 65-74.
5. W.R Gbb, A.J Lees, The relevance of lewy body to the pathogenesis of idiopathic Parkinson's disease, Journal of Neurology, Neurosurgery and Psychiatry, Volume 51, Issue 6.Marcin Wojtera, Beata Sikorska , Tomasz Sobow, Microglial cells in Neuro-degenrative disorders, trimedia folia neuropathol , eISSN no. 1509-572, volume 42 (4), P.p: 311-321.
7. Jae kyung Lee, Thi Tran, Malu G. Tansey, Neuroinflammation in Parkinson's Disease, Journal of Neuroimmune Pharmacology, December 2009,Volume 4, Issue 4, P.p: 419-429.
8. Jungjin Kim, Eric MacMaster, Thomas L. Schwartz, Tardive dyskinesia in patients treated with atypical antipsychotics: case series and brief review of etiologic and treatment considerations, the journal of interventions in clinical practices, 2014, P.p no: 1-9.
9. Gary J. Tucker, Psychosis Psychology, Encyclopedia Britannica.
10. J Neural Transm Suppl., Neurodegenerative disorders with extrapyramidal features: a neuropathological overview, Current Pharmacology, 1995; 46 pages 33-57.
11. Marcus Mcgill, Timothy J. Legg, O'Donovan MC, Craddock NJ, Owen MJ. Psychosis: Causes, Symptoms and Treatments, Medical News Today Genetics of psychosis; insights from views across the genome. Human Genetics. 2009, 126(1):3-12.