

Role of BDNF in different neurodegenerative diseases

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Abstract

Neurodegeneration is the progressive loss of shape or characteristic of neurons, such as death of neurons. Many neurodegenerative diseases consisting of amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's occur due to neurodegenerative processes. Such sicknesses are incurable, resulting in progressive degeneration and loss of life of neuron cells. Neurodegeneration can be discovered in lots of different ranges of neuronal circuitry starting from molecular to systemic. Neurodegenerative ailment is an umbrella time period for a range of conditions which on the whole have an effect on the neurons in the human brain. Mind-derived neurotrophic element, additionally called BDNF, is a protein that, in people, is encoded by using the BDNF gene. BDNF is a member of the neurotrophin circle of relatives of increase elements that are associated with the canonical Nerve increase thing. Neurotrophic factors are determined inside the mind and the outer edge. BDNF acts on sure neurons of the valuable apprehensive system and the peripheral nervous machine, helping to support the survival of current neurons, and inspire the increase and differentiation of recent neurons and synapses. Inside the mind, it is energetic inside the hippocampus, cortex, and basal forebrain areas critical to learning, memory, and better wondering. It's also expressed within the retina, motor neurons, the kidneys, saliva, and the prostate. BDNF itself is critical for long-term memory. Even though the massive majority of neurons inside the mammalian mind are shaped prenatally, elements of the grownup mind maintain the potential to grow new neurons from neural stem cells in a procedure known as neurogenesis.

Keywords: neurodegeneration, brain-derived neurotrophic factor, nerve growth factor

Introduction

Brain derived neurotrophic factor (BDNF) is a neuro-defensive protein that regulates neuronal survival, growth and differentiation. The BDNF hypothesis of depression postulates that stress reduces BDNF concentrations in limbic device structures and this underpins the imperative pathogenic process in melancholy, even as antidepressants restore BDNF concentrations and through this alleviate depressive signs and symptoms. This idea has been derived from a wealthy literature and has drawn sizeable assist, so that it will be reviewed on this paper. Further this paper investigates the have an impact on of a not unusual unmarried nucleotide polymorphism (Val66Met) inside the gene encoding BDNF, which has a purposeful position in BDNF expression and can confer susceptibility to melancholy^[1].

Brain-derived neurotrophic issue, also known as BDNF, is a secreted protein secreted in humans, is encoded by using the BDNF. Its miles a member of the neutrophin own family of increase factors, NGF. BDNF acts on sure neurons of the vital fearful system and the peripheral fearful gadget, supporting to support the survival of current neurons, and encourage the increase and differentiation of new neurons and synapse. Neurodegeneration is the innovative lack of shape or feature of neurons, including demise of neurons. Many neurodegenerative sicknesses which includes amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's occur because of neurodegenerative methods. Such illnesses are incurable, ensuing in modern degeneration and demise of neuron cells. Neurodegeneration may be located in many distinctive tiers of neuronal circuitry ranging from molecular to systemic. Neurodegenerative disease is an umbrella term for a number

conditions which by and large affect the neurons inside the human mind. Neurodegenerative disease is an umbrella time period for various conditions which frequently have an effect on the neurons in the human mind. Mind-derived neurotrophic thing, additionally known as BDNF, is a protein that, in human beings, is encoded with the aid of the BDNF gene. BDNF is a member of the neurotrophin circle of relatives of increase factors, which can be related to the canonical Nerve boom factor. Neurotrophic factors are proteins, which play a crucial function in proliferation, differentiation, protection, plasticity, survival and function of neurons within the valuable and peripheral worried systems. These neuroprotective molecules exert sizable manage over the existence and demise pathways in cells. They participate in local responses to diverse types of neuronal stressors. In mammals, the neurotrophin brain-derived neurotrophic issue (BDNF) is a primary regulator of axonal growth and connectivity, neuronal differentiation, survival and synaptic plasticity. It is a key molecular goal in the development of medication in opposition to neurological problems. Several studies have proven the involvement of BDNF within the pathogenesis of neurodegenerative illnesses and psychiatric disorders, like depression and schizophrenia. The neurotrophic movements of BDNF had been installed with various neuronal populations. In the periphery system, BDNF has proven neurotrophic movements on small fiber sensory neurons concerned in sensory neuropathies

Brain Derived Neurotropic Factor (BDNF)

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family of growth factors, NGF. BDNF acts on positive neurons of the relevant worried system and the peripheral worried device, helping to assist the survival of existing neurons, and inspire the boom and differentiation of new neurons and synapse^[4].

Feature of BDNF

BDNF acts on positive neurons of the significant nervous system and the peripheral anxious gadget, supporting to aid the survival of present neurons, and encourage the growth and differentiation of latest neurons and synapses. Inside the mind, it's far active within the hippocampus, cortex, and basal forebrain—regions important to learning, memory, and higher questioning. It's also expressed inside the retina, motor neurons, the kidneys, saliva, and the prostate. BDNF itself is important for long-term reminiscence. Despite the fact that the significant majority of neurons within the mammalian mind are formed prenatally, components of the person mind keep the potential to develop new neurons from neural stem cells in a procedure called neurogenesis. Neurotrophins are proteins that assist to stimulate and control neurogenesis, the ability to make BDNF go through developmental defects inside the brain and sensory anxious system, and normally die quickly after delivery, suggesting

that BDNF plays an essential position in regular neural development.

Different vital neurotrophins structurally associated with BDNF include NT-3, NT-four, and NGF^[5, 6].

Synthesis and Release

BDNF is made within the endoplasmic reticulum and secreted from dense-core vesicles. It binds carboxypeptidase E (CPE), and the disruption of this binding has been proposed to reason the lack of sorting of BDNF into dense-core vesicles. Different trends consist of sensory neuron losses that affect coordination, balance, hearing, flavor, and respiration. Knockout mice additionally showcase cerebella abnormalities and a boom in the range of sympathetic neurons. sure varieties of physical exercising have been proven too markedly (threefold) boom BDNF synthesis inside the human brain, a phenomenon that's in part accountable for exercise-triggered neurogenesis and upgrades in cognitive function. Niacin seems to up modify BDNF and tropomyosin receptor kinase B (TrkB) expression as properly.

Parkinson's disease (PD)

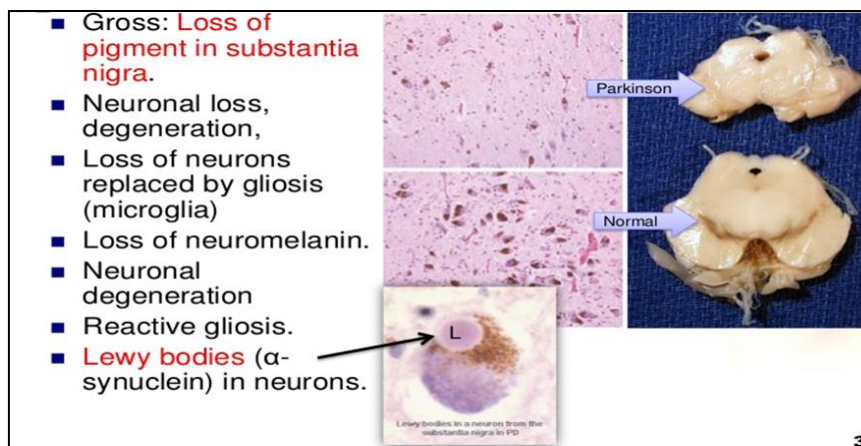


Fig 1: Pathology of Parkinson's diseases



Fig 2: Pathology of Parkinson's disease

Parkinson's disease is basically related to the slow lack of cells inside the substantia nigra of the brain. This region is accountable for the producing of dopamine. Dopamine is a chemical messenger that transmits signals between areas of the mind to coordinate hobby. As an instance, it connects

the substantia nigra and the corpus striatum to modify muscle pastime. If there is deficiency of dopamine inside the striatum the nerve cells on this place fire out of manipulate. This leaves the character not able to direct or control moves. This results in the preliminary signs of Parkinson's sickness.

Because the disease progresses, other regions of the mind and fearful device degenerate as properly causing a more profound motion disease.

A protein known as alpha synuclein seems to be worried in neuronal degeneration. Alpha synuclein is produced thru dopaminergic neurons and is damaged down by using manner of other proteins, which includes parkin and neurosin.

Defects in any of the proteins that smash down alpha synuclein can also result in its accumulation, ensuing in the formation of deposits known as Lewy bodies in the substantia nigra.

However, other mechanisms affecting the accumulation of alpha synuclein had been recognized, and it isn't clear whether or not Lewy bodies are a purpose of or arise as a result of the disorder. Other findings in humans stricken by Parkinson ailment consist of mitochondrial dysfunction, main to accelerated production of free radicals that motive considerable harm to mind cells, and heightened sensitivity of the immune device and neurons to molecules known as cytokines, which stimulate inflammation.

Symptoms

Tremor at relaxation is the characteristic function of PD that earned it the sooner call of the shaking palsy. Rest tremor occurs rarely in every other situation. The tremor is gradual and rhythmic. It normally starts in one hand and handiest later spreads to contain the opposite aspect of initial involvement. Pressure is a term meaning a tightness or boom in muscle tone at relaxation or during the complete variety of movement of a limb. It can be felt as stiffness within the limbs, the neck, or even the trunk. Bradykinsia is slowness in bobbing up or initiating motion, and reduce in high-quality motor coordination (manifested via the inability to button a blouse, cut meat, and so forth.). Gait (walking) lower inside the natural arm swing is visible first, and most effective later do issues with slow, small steps and shuffling (festinating) arise stability issues and impairment of posture usually occur late within the course of normal pd, and are actually the maximum disabling of all the signs.

Treatment

Following drugs used in treatment of Parkinson's disease ^[10, 11]

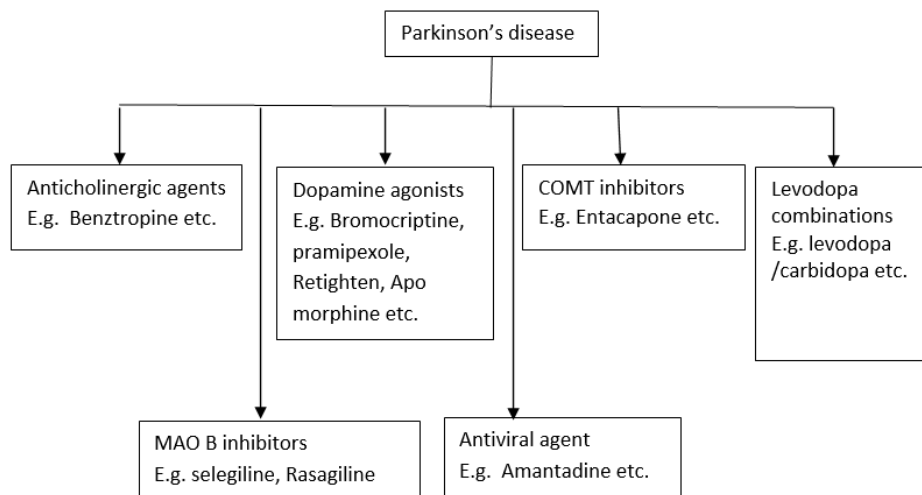


Fig 3: Parkinson's disease

Mechanism of action

Levodopa: Dopamine itself does not go the blood-brain barrier, but it's immediately precursor, levodopa, is with no trouble transported into the CNS and is transformed to dopamine within the brain. Big doses of levodopa are required, because a lot of the drug is decarboxylated to dopamine within the periphery, resulting in aspect outcomes that consist of nausea, vomiting, cardiac arrhythmias, and hypotension. **Carbidopa:** The outcomes of levodopa at the CNS can be substantially better through coadministering carbidopa, a dopa decarboxylase inhibitor that doesn't move the blood-brain barrier. Carbidopa diminishes the metabolism of levodopa inside the gastrointestinal (GI) tract and peripheral tissues; for that reason, it increases the provision of levodopa to the CNS. ^[10]

Function of BDNF in Parkinson's sickness

BDNF performs a position in the advertising of the survival and function of striatal dopaminergic neurons and in regulating synaptic connectivity. other research have shown that BDNF mind and peripheral tiers are decreased in PD patients in comparison to HC verified that remedy with anti

parkinsonian pills mayrise BDNF ranges. The position of physical interest in preventing PD onset or development has additionally been verified. BDNF maximum widely expressed and properly characterized member of the neurotropic family within the mammalian mind. It generated following cleavage of the precursor protein proBDNF and BDNF BDNFpro and the prodomuin are all biologically energetic functionally, BDNF has roles in various degree of neuronal in numerous of neuronal circuit development and additionally alter neural citrate shape and synaptic plasticity in person mind in molecular function BDNF in CNS and exceptionally lighting its therapeutic potential for situation which includes Parkinson's ailment stroke and spinal twine injury ^[12].

Alzheimer's disease (ad)

Alzheimer's disorder is a neurological ailment wherein the loss of life of brain cells reasons reminiscence loss and cognitive decline. A neurodegenerative kind of dementia, the disease starts offevolved moderate and receives gradually worse. ^[13, 14]

Pathology

The traditional neuropathological signs and symptoms of Alzheimer’s disease are amyloid plaques and neurofibrillary tangles. Plaques consist largely of the protein fragment beta-amyloid. This fragment is made from obvious molecule called amyloid precursor protein. Tangles consist of tau, a protein typically concerned in keeping the inner structure of the nerve cell. at the same time as tau is commonly changed by means of phosphorylation, or the attachment of phosphate molecules, excessive phosphorylation appears to

make contributions to tangle formation and stops the protein from sporting out its regular functions. Oxidative stress, or harm to mobile systems by using poisonous oxygen molecules known as free radicals, is also appeared as a pathology characteristic of Alzheimer’s. People with Alzheimer’s normally revel in brain inflammation. Many of the oldest sufferers with Alzheimer’s show symptoms of cerebrovascular disease further to traditional Alzheimer’s neuropathology

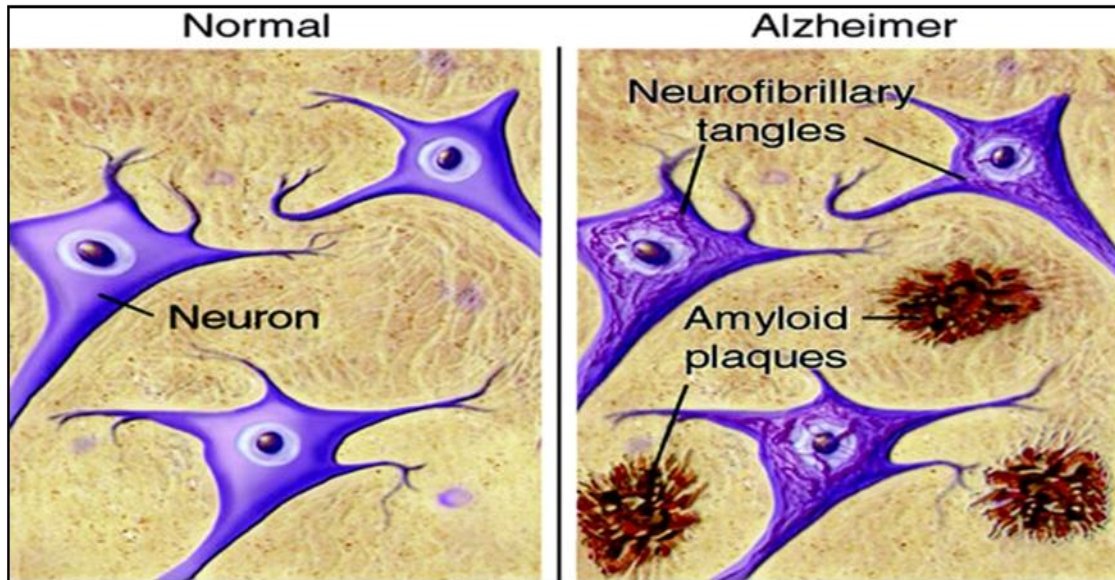


Fig 4: Pathogenesis of Alzheimer’s disease

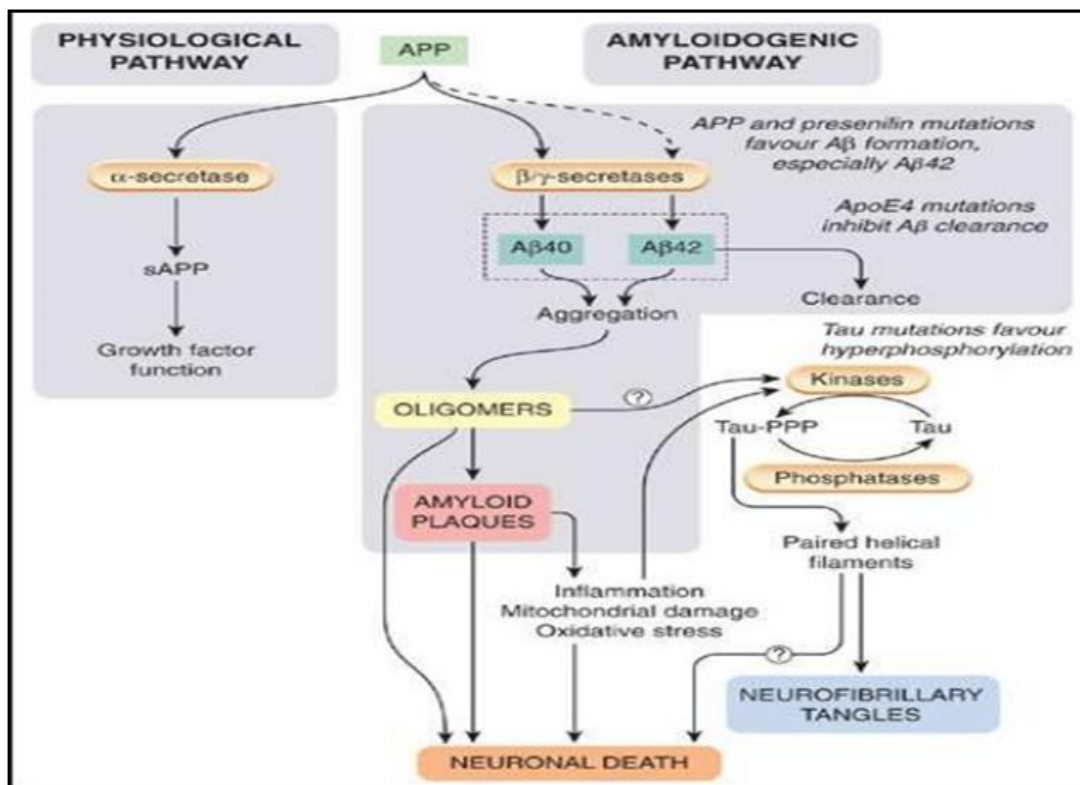


Fig 5: Pathogenesis of Alzheimer’s disease

Symptoms

Normal early signs and symptoms of Alzheimer's may also include: reminiscence: often forgetting recent activities, names and faces. Repetition: becoming increasingly more repetitive, e.g. repeating questions after a totally quick interval. Misplacing matters: frequently misplacing objects or setting them in peculiar places. Confusion: Uncertainty approximately the time of day. Disorientation: mainly faraway from everyday surroundings. Language problems: locating the right phrases. Temper and conduct: some human beings turn out to be disinterested in what's going on around them, turn out to be irritable, or lose confidence memory and wondering abilities: humans will discover that their capability to consider, suppose and make selections worsens. Conversation: communicate and language come to be tougher. Behavior: a person's conduct might also trade

and some people can grow to be unhappy or depressed. Anger and agitation become more not unusual and people may additionally develop anxieties or phobias. Hallucinations: humans can also revel in hallucinations, where they may see matters or human beings that aren't there. Restlessness: problems with dozing and restlessness at night often arise. Unsteadiness: humans may additionally turn out to be increasingly unsteady on their feet and fall more frequently. Each day activities: human beings steadily require extra help with daily sports like: dressing, toileting and consuming.

Treatment

Following drugs used in treatment of Alzheimer's disease [13, 15].

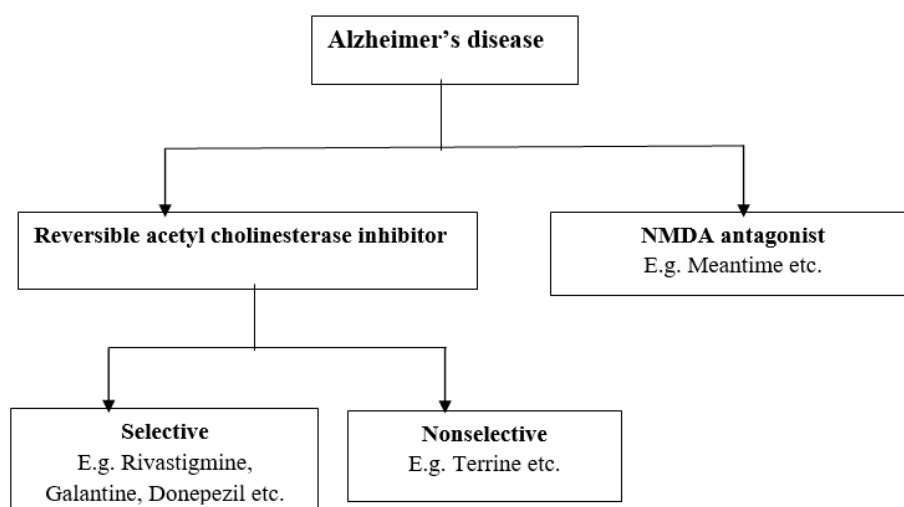


Fig 6: Alzheimer's disease

Mechanism of Action of Memantine

Memantine is the primary in a singular class of Alzheimer's disease medicinal drugs acting at the glutamatergic machine by way of blockading NMDA receptors. It turned into first synthesized by using Eli Lilly and agency in 1968 as a capability agent to treat diabetes; the NMDA interest become found inside the Nineteen Eighties. Memantine is marketed beneath the manufacturers Namenda / Auxura / Ebixa and memory amongst others. Memantine has been proven to have a modest effect in slight-to-extreme Alzheimer's ailment and in dementia with Lewy our bodies. Notwithstanding years of studies, there is little evidence of impact on mild Alzheimer's disease [17].

Role of BDNF in Alzheimer's disease:

It has been suggested that the early reminiscence dysfunction visible in Alzheimer's ailment may be related to the levels of BDNF in the hippocampus. Proof to guide this consists of appreciably decreased BDNF mRNA levels in Alzheimer's sickness hippocampus and parietal cortex and decreased protein levels of BDNF in entorhinal cortex, hippocampus, and temporal, frontal and parietal cortex. In contrast to mature NGF, mature BDNF protein can be visualized by way of western blotting, collectively with its seasoned-form. Both paperwork have now been proven to be decreased in Alzheimer's ailment, with a discount in mature BDNF of 23% reported in frontal cortex moreover a modern lower from everyday turned into visible in

proBDNF in MCI (21%), and compared with Alzheimer (30%) parietal cortex [18].

Huntington's ailment

About Huntington sickness is a monogenetic hereditary neurodegenerative sickness caused by a defective gene on chromosome four. the HD gene is liable for generating a protein referred to as Huntington, a protein this is observed during the frame's tissue however this is most concentrated in the brain. [19].

Pathology

Huntington sickness additionally known as Huntington chorea, an exceedingly rare, and forever deadly, hereditary neurological ailment this is characterised through abnormal and involuntary movements of the muscular tissues and innovative loss of cognitive capability. The disorder became first described by the american medical doctor George Huntington in 1872. Signs and symptoms of Huntington ailment typically seem between the whole of 35 and 50 and get worse over time. They start with occasional jerking or writhing actions, called choreiform movements, or what seem like minor troubles with coordination; these actions, which might be absent all through sleep, get worse over the following couple of years and development to random, uncontrollable, and frequently violent twitchings and jerks. Symptoms of intellectual deterioration may also seem which includes apathy, fatigue, irritability, restlessness, or

moodiness; these symptoms may progress to memory loss, dementia, bipolar disease, or a toddler of a person with Huntington ailment has a 50 percentage chance of inheriting the genetic mutation related to the sickness, and all folks that inherit the mutation will eventually increase the ailment. The genetic mutation that reasons Huntington disorder happens in a gene known as HD (formally named Huntington [Huntington disease]). This gene, that's located on human chromosome 4, encodes a protein known as Huntington, which is shipped in certain areas of the mind, in addition to different tissues of the body. Mutated kinds of the HD gene include abnormally repeated segments of deoxyribonucleic acid (DNA) referred to as CAG

trinucleotide repeats. Those repeated segments bring about the synthesis of huntington proteins that incorporate lengthy stretches of molecules of the acid glutamine. While those odd huntington proteins are reduce into fragments for the duration of processing through cell enzymes, molecules of glutamine challenge out from the ends of the protein fragments, causing the fragments to stick to different proteins. The ensuing clumps of proteins have the ability to purpose neuron (nerve mobile) dysfunction. The formation of strange huntington proteins leads to the degeneration and eventual loss of life of neurons inside the basal ganglia, a couple of nerve clusters deep inside the brain that control motion.

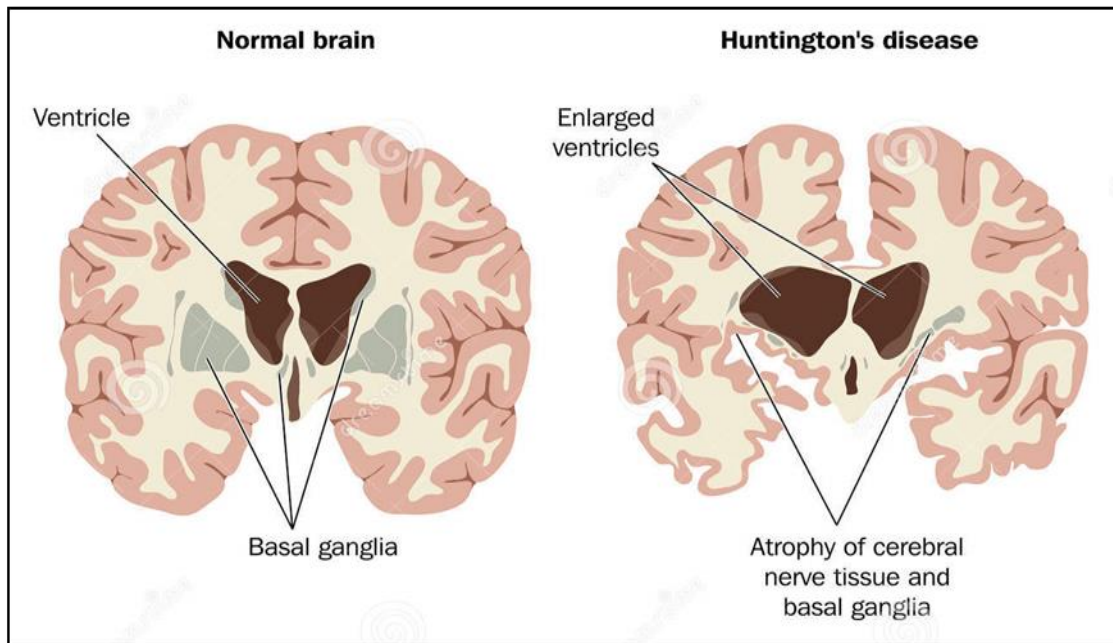


Fig 7: Pathogenesis of Huntington`s Disease

Symptoms

Signs and symptoms can appear at any age, but maximum commonly do so between the 35 and fifty five years. Below is a list of signs which can be relevant in a few instances. it is crucial to do not forget these may also vary depending at the character: moderate uncontrollable actions, Clumsiness, Stumbling, some moderate symptoms of lack of emotion,

lack of recognition, moderate attention troubles, Lapses in brief-term memory, melancholy, mood modifications - this can encompass antisocial conduct and aggression ^[19].

Treatment

Following drugs used in treatment of Huntington Disease

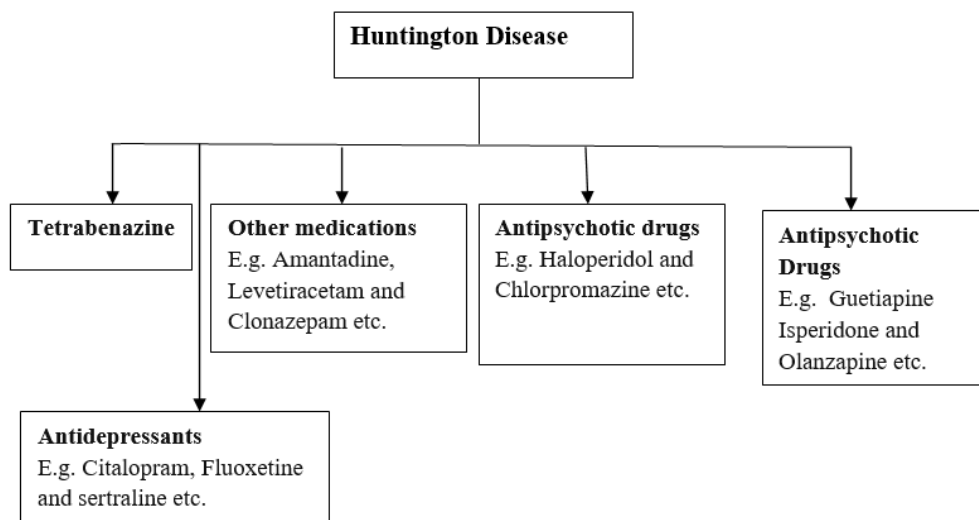


Fig 8: Huntington`s disease

The Mechanism of Action

Citalopram

The antidepressant, antiobsessive-compulsive, and antitremulous movements of citalopram are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Citalopram blocks the reuptake of serotonin on the serotonin reuptake pump of the neuronal membrane, improving the moves of serotonin on 5HT1A autoreceptors. SSRIs bind with considerably less affinity to histamine, acetylcholine, and norepinephrine receptors than tricyclic antidepressant pills [20].

Role of BDNF in Huntington's disease

BDNF performs a function in the mechanism of antidepressant drug motion. The antidepressants known to affect BDNF ranges are selective serotonin reuptake inhibitors (SSRIs) and lithium moreover, memantine, riluzole, (a non-competitive inhibitor of ionotropic glutamate NMDA receptor) cystamine and cysteamine, have lately been proven to growth BDNF levels and their results on HD had been Serotonin might also have defensive consequences on striatal and cortical neurons by using activating cyclic AMP and CREB signals, which additionally cause BDNF expression; different target genes of cyclic AMP-CREB signalling that may play a role within the neuroprotective effect of SSRIs include Bcl-2 and NFkB.

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