An Overview of the Biochemical Causes of Dementia Including Neurotransmitters and Hormones, with Potential Treatments Discussed

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Abstract

Dementia is a series of chronic, incurable neurodegenerative disorders which all commonly result in progressive psychological deterioration and eventually death. Presently, over 70 variations of dementia have been documented. This review paper covers the role of neurotransmitters (NTs) and hormones in the development/severity of the 5 most common variations of dementia: Alzheimer's Disease (AD), Lewy Body Dementia (LBD), Frontotemporal Dementia (FTD), Vascular Dementia (VD), and Parkinson's Disease (PD). NTs have proven to be crucial in maintaining neuroplasticity and basic cognitive functions. Hormones have shown their importance in long-term neurocognitive development and several biochemical regulation processes that maintain the brain's metabolism. There are several potential treatments for these variations of dementia, mainly based on NT and/or hormone level regulation therapy. A treatment strategy which combines and interchangeably utilizes NT and hormone level regulation therapy is also proposed. The goal of this review paper is to show that the main causes of dementia may be hiding in plain sight, and that with an optimistic mindset, a universal cure can be developed.

Introduction

Neurodegenerative disorders have existed for thousands of years. Dementia, in particular, is a disease that has been studied extensively for many years. Dementia constitutes impairment in memory and at least one domain of cognitive functioning (e.g. executive functioning, language, visuospatial skills, praxis, judgment, personality, abstract thinking) that represents a decrease from a previous level of functioning and results in impairment in daily activities. The variations of dementia come under two categories: Cortical and Subcortical Dementia. Cortical Dementia is usually progressive or degenerative, while tending to be associated with impaired language skills (aphasia), motor coordination (apraxia), perception (agnosia), reasoning or problem solving, learning, and recall. Subcortical Dementia may be progressive, static, or reversible and is often associated with cognitive slowing, emotionality (e.g. apathy, irritability, depression), and deficits in attention, arousal, and processing speed. Types of Cortical Dementia include: Alzheimer's Disease, Lewy Body Dementia, and Frontotemporal Dementia. Types of Subcortical Dementia include: Vascular Dementia and Dementia due to Parkinson's Disease. Below is a brief overview of each of the main variations of dementia in terms of statistics and key characteristics (Buffington et al, 2013).

Of the several different variations of dementia, the most common is Alzheimer's Disease (AD), as it accounts for roughly 50% of all cases. AD affects 11% of people aged 65 years or older and 32% of people aged 85 years or older in the United States. In 1907, Alois Alzheimer described the symptoms of his patient, a 51 year-old woman named Auguste Dieter, at the state asylum in Frankfurt, Germany: "Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything." Alzheimer used silver straining histological technique to microscopically examine Dieter's brain after her death. During this examination, he observed the hallmark signs of AD: Neuritic plaques (abnormal clusters of protein fragments), Neurofibrillary tangles (abnormal, insoluble twisted

fibers found inside neurons), and Amyloid angiopathy (abnormal buildup of amyloid proteins in the walls of blood vessels) (Buffington et al, 2013).

Lewy Body Dementia is the second most common form of cortical dementia, accounting for 20% of all dementia cases. It is estimated that prevalence rates could be as high as 5% among the entire US population and 31% among all patients with dementia. Onset of the disease typically occurs when patients are between ages 50 and 60 years and is slightly more common in men. Major signs include a cognitive profile marked by prominent impairment in attention, visuospatial functioning, and executive functioning, as well as sleep disturbance, extrapyramidal symptoms, visual hallucinations, and fluctuations in attention and alertness. However, as stated by Lewy Body Dementia Canada: “The exact progression of a person with Lewy Body Dementia will be unique. Let go of your expectations and preconceptions, pay attention to the reality of the changes, being as flexible as possible” (Buffington et al, 2013).

Frontotemporal Dementia (FTD) is the third most common of the cortical dementias. FTD is a group of heterogeneous disorders characterized by frontal cortical atrophy, temporal cortical atrophy, or both. Family histories of FTD are seen in 20% to 40% of patients with the disease. Onset of the disease can occur between ages 35 and 75 years but most commonly occurs between ages 50 and 60 years. The most striking feature which often brings patients to clinical attention is personality change. Czech-German psychiatrist Arnold Pick is credited with several important descriptions of dementia, including the first description of FTD. He states: “The clinical findings of senile dementia can be interpreted as a mosaic of circumscribed deficits of higher mental abilities (‘Herderscheinungen’); this fact may fail to be revealed when the process of atrophy occurs simultaneously at many places, thereby masking the appearance of the single symptoms” (Buffington et al, 2013).

Vascular dementia is the second most common type of dementia, as it accounts for 10% to 50% of all cases of dementia. The disease has a prevalence rate of nearly 3% among US adults aged 65 years or older. The term *vascular dementia* is most often thought to refer to cognitive impairment associated with large-vessel ischemic cerebrovascular disease (ie, stroke). However, cognitive impairment associated with ischemic white matter lesions in small vessels is far more common. This impairment can range in severity and type depending on the location and degree of tissue damage. Alois Alzheimer also made significant contributions to the foundational descriptions of vascular dementia, initially referring to the disease as “Arteriosclerotic atrophy of the brain” (Buffington et al, 2013).

Individuals who have Parkinson’s Disease can develop slowly progressing dementia, typically later in the disease process (on average 10 years from the onset of Parkinson’s Disease). The overall prevalence of dementia in patients with Parkinson disease is approximately 30%. This prevalence increases to 48% after 15 years from initial diagnosis. For this disease, the incidence of dementia increases with greater physical impairment. The cognitive profile is notable for predominant executive dysfunction, as well as impairments in attention, visuospatial functioning, and memory. PD was named after English surgeon James Parkinson who described the progression of the disease by stating: “As the disease proceeds, the hand fails to answer with exactness to the dictates of the will.” Now that we have discussed what each variation of dementia entails, let us move on to a series of substances with very important roles in these diseases (Buffington et al, 2013).

A key factor within the biochemical roots of AD and other neurodegenerative diseases would be neurotransmitters. Neurotransmitters (NTs) can be defined as: molecules that amplify, transmit, and convert signals in cells, having an essential role in information transmission

throughout the nervous system. NTs are crucial for communicating sensory, motor, and integrative neuronal messages, affecting many functions, such as emotions, thoughts, memories, movements, and sleep patterns. Over 200 NTs have been identified since 1921, but the exact number of NTs is unknown. Canonical NTs are commonly divided into amino acids, amines, and other molecules. Amino acids represent a very important class of chemical messengers, having significant roles in the CNS.(e.g. GABA). Monoamines are a representative group of NTs with clinical significance in motor functions, emotional responses, motivations, and behavioral functions(e.g. Dopamine). Some other examples of NTs are: Acetylcholine, Adenosine Triphosphate (ATP), and Carbon Monoxide (CO). NTs are directly involved in dementia mainly through their roles in neuroplasticity and basic cognitive functions (Teleanu et al, 2022).

Another important biochemical root of AD and other neurodegenerative disorders would be hormones. Hormones can be defined as: biological compounds used by multicellular organisms to organize, coordinate, and control the functions of their cells and tissues. However, it is difficult to delineate between hormones and other factors that carry information in an organism, whether cytokines, growth factors, or autacoid factors. All three of these factors have typical hormone-like function, making them increasingly difficult to differentiate. No clear boundaries exist between hormones and other types of signaling molecules. This is because some cytokines, growth factors and autacoid factors act like typical hormones in certain situations. Some examples are: erythropoietin, fibroblast growth factor FGF23, asprosin and lipocalin-2. The role of hormones in physical and neurological growth/development and behavioral regulation makes them essential in the analysis of the biochemical causes of dementia (Stárka, Dušková, 2020).

It is important to mention that these diseases unfortunately do not currently have a cure and symptoms can only be mitigated. The treatment methods for these diseases utilize the vital roles of several neurotransmitters and hormones and their connection to dementia. Specifically, they are used to lessen the severity of and possibly begin the reversal of major symptoms across all variations of dementia. This review paper aims to exhibit the crucial role of neurotransmitters and hormones in causing neurodegenerative diseases, specifically the many variations of dementia, while also showcasing potential treatment methods that could bring humanity closer to a cure. The primary goal of this paper is to provide a potential answer to the question: “Do the causes of dementia expand beyond hereditary contraction, and if so, can they eventually be treated?”

Key Words: Dementia, Alzheimer’s Disease, Lewy Body Dementia, Frontotemporal Dementia, Vascular Dementia, Parkinson’s Disease, Neurotransmitter, Neuroreceptor, Hormone.

Methods

The NIH database Pubmed was used to acquire the studies included in this review. The terms used to search for these studies include: “Neurotransmitters and dementia”, “Hormones and dementia, and “Variations of dementia.” The studies included were all published within the last 20 years, making them fairly recent. These 12 studies thoroughly cover the roles of neurotransmitters/receptors and hormones in several variations of dementia. Demographics for these studies mostly consist of elderly patients with dementia and control groups of healthy elderly people.

Results

Alzheimer's Disease (AD)

NTs/Receptors and AD

Glutamate is one of the most abundant neurotransmitters (NTs) in the mammalian Central Nervous System (CNS). Glutamate is measured at concentrations of 5–15μmol/g in wet tissue. The vast majority of the excitatory neurotransmission in the mammalian CNS is mediated by glutamate and its receptors, mainly iGluRs, ligand-gated ionotropic (a group of transmembrane ion-channel proteins which open to allow ions to pass through the membrane) glutamate receptors. iGluRs also play fundamental roles in synaptic plasticity, the underlying molecular mechanism behind learning and memory. The disruption of the normal signaling via iGluRs is implicated in a wide range of neuropathological disorders and diseases such as epilepsy and brain damage, Parkinson's Disease (PD), AD, Huntington's, Multiple Sclerosis (MS), thereby making iGluRs important drug targets for therapeutic purposes. One particular subgroup of iGluRs is selectively gated by specific agonists N-methyl-d-aspartate (NMDA), thus named as NMDA receptor (NMDAR) (Figure 1.). Insufficient synaptic NMDAR signaling greatly compromises neuronal cell survival (Wang, Reddy, 2018).

However, excessive stimulation of glutamatergic signaling results in excitotoxicity, the pathological process where nerve cells are damaged and killed or neurological trauma such as stroke occurs due to excessive stimulation from neurotransmitters, primarily glutamate. Many studies indicate a role for glutamate excitotoxicity in delayed slowly-evolving neurodegeneration. The glutamate uptake and recycling system is an important factor that determines the availability of glutamate for signaling processes. This system can be severely weakened in AD. Furthermore, EAAT 2, excitatory amino acid transporter 2, which is critical in glutamate removal, that is primarily located in perisynaptic astrocytes (Fine leaflets that are critical for modulating synaptic function), was reported to have impaired function in AD. Studies using several species of Aβ peptides (The main component of the amyloid plaques found in the brains of people with Alzheimer's disease) in neuronal cell culture also support the idea that toxic Aβ may allow more glutamate availability by impairing glutamate uptake/recycling mechanisms. This overflowing glutamate supply is likely to contribute to AD-associated excitotoxicity and neurodegeneration (Wang, Reddy, 2018).

The integrity of the presynaptic neurotransmitter release machinery also contributes to the availability of glutamate. Aβ can significantly reduce the expression of presynaptic proteins such as synaptophysin, syntaxin, and synaptotagmin, many of which are active components of the neurotransmitter release machinery. AD may also enhance NMDAR signaling through the modulation of the receptor itself. Various studies have demonstrated that Aβ directly modulates the electrophysiological function of NMDARs. Aβ could possibly even physically interact with NMDARs, either directly or via synaptic proteins such as PSD95 which participate in important signaling pathways within synapses. AD also affects the level of NMDAR coagonists which bind with and activate a response from NMDARs. Complete activation of NMDARs by glutamate requires the continuous binding of coagonist D-serine or glycine, and therefore these coagonists play an important modulatory role in NMDAR function. The role of NTs/receptors in the processes discussed in this section illustrates their significance in AD pathogenesis (Wang, Reddy, 2018).

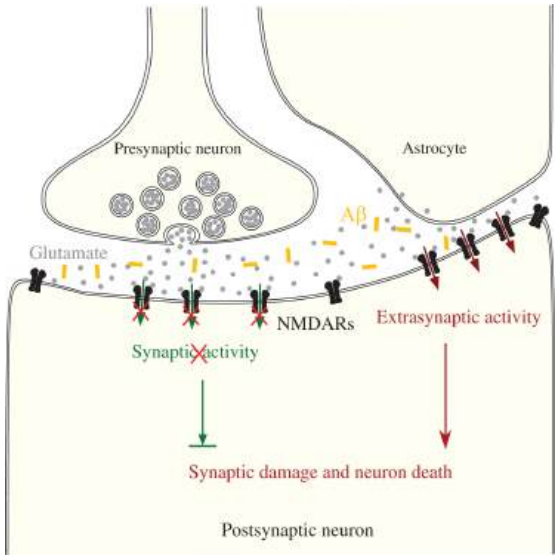

Figure 1: Model of NMDAR dysfunction causing synaptic damage or neuronal death which marks the development of AD (Wang, Reddy, 2018).

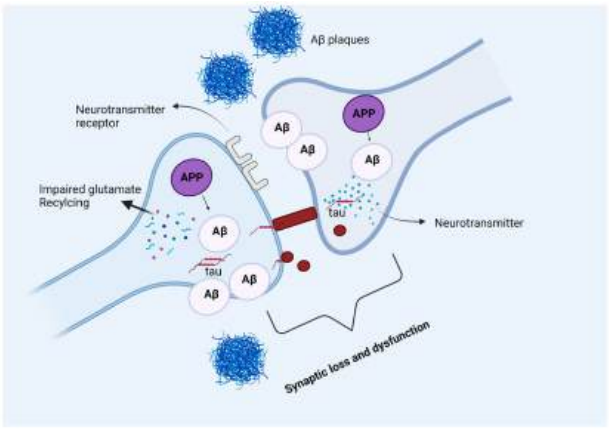

Figure 2: Model of AD hallmark Aβ plaques impairing glutamate recycling, causing synaptic loss and dysfunction (Sehar et al, 2022).

Hormones and AD

Leptin is a pro-inflammatory adipokine, which is a Signaling molecule that promotes inflammation and is secreted by White Adipose Tissue (WAT) and found to be increased in people with a high body mass index. This hormone acts centrally at the level of the hypothalamic region through anorexigenic (suppresses appetite) proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and orexigenic (stimulates appetite) neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. These neurons play a major role in controlling food intake and energy expenditure. It is suggested that leptin may be the link between obesity and dementia through the development of inflammation.

Leptin signalling regulates different processes such as: food intake, energy expenditure, cognition, learning, memory, and mood. In addition, leptin regulates neurogenesis (neuron formation), synaptogenesis (synapse formation), neuronal excitability, and neuroprotection. The mechanisms of long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission are crucial for the formation and consolidation of hippocampal memory. Leptin is involved in these processes at the level of the hippocampus where leptin and glutamate receptors {N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors} are key players. Leptin also regulates the configuration, or physical structure, of neurons. As a result, plasma leptin levels (leptin concentration in the bloodstream) have been associated with grey matter volume in various brain regions. Grey matter is crucial for information processing and various cognitive functions. Studies show leptin is secreted by adipocytes (fat cells) and circulates in plasma in proportion to fat mass, and changes in body weight are associated with the possibility of developing AD. These studies suggest that plasma leptin deficiency could indicate a possible CNS leptin deficiency and thus serve as a diagnostic marker for MCI or AD. This information reveals leptin's significant role in diagnosing and analyzing AD (Flores-Cordero et al, 2022).

Another important hormone associated with AD is Melatonin. Melatonin (N-acetyl-5-methoxytryptamine), is a tryptophan metabolite (metabolized from tryptophan) and synthesized mainly in the pineal gland. This hormone has a number of physiological functions, including regulating circadian rhythms, clearing free radicals (highly unstable molecules), improving immunity and generally inhibiting the oxidation of biomolecules (electron loss that leads to damaged biomolecule functioning). Decreased melatonin in serum (The fluid component of blood) and cerebrospinal fluid (CSF) and the loss of melatonin diurnal rhythm (melatonin level regulation based on time of day) has been observed in AD patients. In addition, the level of melatonin in CSF decreases with the progression of AD neuropathology. Melatonin levels in both CSF and postmortem human pineal gland are already reduced in preclinical AD subjects, who are cognitively intact at the time and have only the earliest signs of AD neuropathology. There is a strong correlation that exists between pineal content and CSF level of melatonin and between CSF and plasma melatonin levels, which suggests that a reduced CSF melatonin level may serve as an early marker for the very first stages of AD. Since increasing melatonin levels improves some of the clinical symptoms of AD, and since the level of melatonin decreases dramatically during AD, studies on the relationship between melatonin and AD pathology will be helpful to assess its potential in the prevention or treatment of AD These studies show that leptin and melatonin are major risk factors for the development of AD through neurodegeneration.

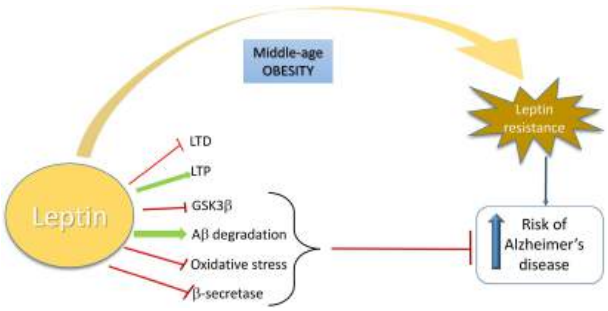

Figure 3: Model of the role of leptin resistance in increasing the risk of contracting AD (Lloret et al, 2019).

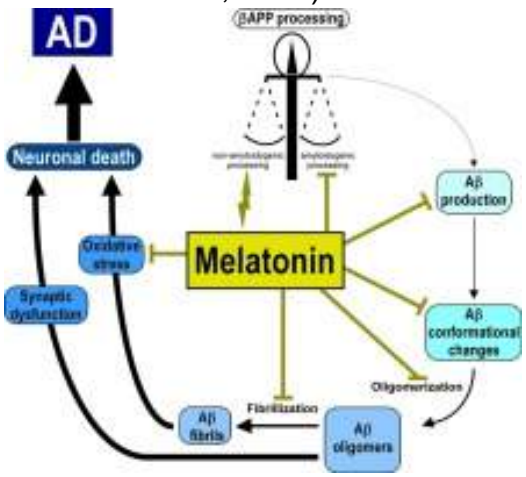

Figure 4: Model of the role melatonin in causing neuronal death, which in turn leads to AD (Vincent, 2018).

Lewy Body Dementia

NTs/Receptors and LBD

Dementia with Lewy Bodies (DLB) is characterized by cholinergic (relating to the NT system of Acetylcholine (ACh) deficits. Cholinergic input from the Nucleus Basalis of Meynert (NBM), a key structure in the basal forebrain, is required for cognitive functions (including memory), and degeneration of the NBM in DLB contributes to the decline in cognitive function observed in patients with this disease. Analysis of cholinergic activity in the brains of DLB patients showed that deficits are greater in some regions of the temporal cortex of those with visual hallucinations vs those without visual hallucinations. Visual hallucinations are a hallmark symptom of DLB. There are abnormalities in ACh receptors in DLB patients, specifically muscarinic receptors. The neurochemistry of muscarinic receptors is complex because different muscarinic receptor types control the stimulation and inhibition of ACh released by the presynaptic cell. In addition, the presence of more than one type of muscarinic receptor on the postsynaptic cell can result in a complex response in the postsynaptic neuron to ACh release by the presynaptic cell. The prevalence of the cholinergic system is further exhibited by other receptors that act as components of the system (Perry, Perry, 1993).

Another important component of the cholinergic system is the presence of nicotinic receptors. Nicotine receptor stimulation on the presynaptic cell results in the release of ACh and other neurotransmitters involved in cognition and behavior. Nicotine receptors are composed of five protein subunits in combinations of A- or ß-type subunits (heteromeric) or only one type of subunit (e.g. all A). Different subunit combinations display different ligand-binding characteristics and functional activity, and it is presumed that different combinations of subunits have different functions depending on where they are expressed. These subunits overall play a crucial role in

neural and neuromuscular transmission by forming ion channels that allow for rapid communication between nerve cells. Patients suffering from DLB are shown to have significant nicotinic receptor loss, particularly in the dentate granular area, which functions in learning, memory, and spatial navigation. This may have an effect on memory loss in DLB patients Muscarinic and Nicotinic receptors are two important factors in the cholinergic system, and the undeniable prevalence of the cholinergic system in basic cognitive/bodily functions directly links these receptors to DLB pathogenesis (Perry, Perry, 1993).

Aβ Peptides and LBD

Aβ peptides play a significant role in the pathogenesis of DLB. It is suggested that by interacting with the neuronal protein α-synuclein, the amyloid peptides promote aggregation (clumping of proteins into abnormal structures), enhance the accumulation of α-synuclein pathologies, and accelerate cognitive dysfunction. The altered brain processing of Amyloid Precursor Protein (APP), which leads to accumulation of extracellular amyloid deposits throughout the brain tissue of the affected individuals, is also seen in the periphery, for example, CSF and blood derivatives (therapeutic substances derived from human blood/plasma). Hence, the CSF decrease of Aβ peptide 1-42, although characteristic of AD, is also found in DLB. According to one study, the shorter amyloid peptide (Aβ1-40) also appears to be decreased in patients with DLB. In addition, the ratio between the longer and shorter CSF amyloid peptides (Aβ42/Aβ40) appears to be superior in discriminating between AD and other neurodegenerative disorders, including DLB, than the Aβ42 measure alone (P< .01), with the former being equally robust as the combination of Aβ42, p-tau181, and t-tau biomarkers. These ratios reveal the statistical significance of Aβ peptides in DLB. In summary, this evidence shows that Aβ peptides are not just directly linked to DLB pathogenesis but are also important biomarkers for the disease (Mukaetova-Ladinska et al, 2010).

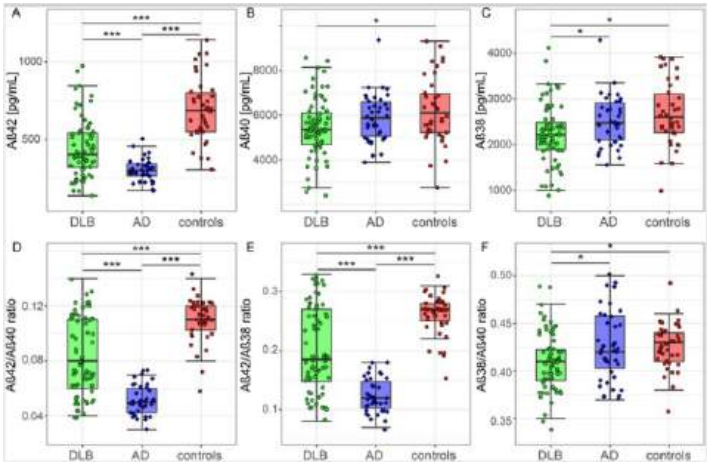

Figure 5: Study comparing CSF Aβ peptides in DLB, AD, and controls. Each graph compares the levels of different Aβ peptides in DLB, AD, and healthy control groups. (Steenoven et al, 2019).

Frontotemporal Dementia

NTs/Receptors and FTD

There is both preclinical and clinical evidence that glutamate is important in the pathogenesis of FTD. An example can be seen in transgenic mice. Transgenic mice that express pathological human tau (abnormal forms of tau protein) have repetitive and disinhibited behaviour, coupled with NMDA receptor hypofunction. NMDA agonist treatment restores their behavior. Several mouse models expressing pathological human tau suggest glutamate mediated excitotoxicity may accelerate neuronal loss in tauopathies such as FTD. Magnetic resonance spectroscopy of patients suffering from FTD has found glutamate/glutamine levels are reduced in the frontal and temporal lobes. Furthermore, ionotropic (function as transmembrane ion channels) and metabotropic (indirectly trigger a chain of intracellular reactions) glutamate receptors are affected in FTD. Through usage of the ligand 11C-ABP688, PET scans of patients with FTD found reduced availability of metabotropic glutamate receptors (mGluR5) in the frontal and temporal lobes, basal ganglia and thalamus. This reduced ability disrupts the modulation of synaptic transmission and neuronal excitability, contributing to neurodegeneration. In addition, other NTs play an equally important role as Glutamate and its receptors in FTD (Murley, Rowe, 2018).

Other important neurotransmitters related to FTD are dopamine and serotonin. The areas of the cortex degenerated in FTD receive strong dopaminergic projections. There exists clinical evidence of basal ganglia dopamine dysregulation (i.e. parkinsonism) in FTD and FTD variants such as frontotemporal dementia and parkinsonism (FTDP-17). This observation is supported by a PET study that showed decreased presynaptic dopamine transporter in the putamen (a rounded subcortical nucleus) and caudate (involved in several motor/nonmotor functions) of patients with FTD. The anatomic and clinical presentation of FTD also corresponds well to serotonergic dysfunction: There are strong serotonergic projections to the frontal cortex from the raphe nuclei (a series of nuclei in the midline of the brainstem), low brain levels of serotonin have been associated with aggression and impulsiveness, depressive symptoms, and alterations in frontal cortex metabolism. The symptoms of FTD also overlap considerably with those of psychiatric disorders treated with serotonin augmentation such as depression and obsessive-compulsive disorder. These connections through anatomy and clinical similarities prove that NTs/receptors are rather influential in the development/severity of FTD (Huey et al, 2006).

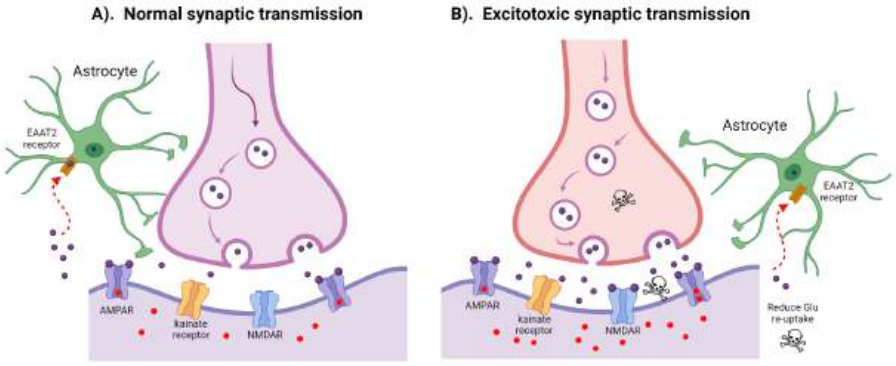

Figure 6: A model comparing normal synaptic transmission with excitotoxic synaptic transmission in FTD and other variations of dementia (Arnold et al, 2024).

Progranulin and FTD

Human Progranulin (PGRN) is an evolutionarily conserved 593–amino acid glycoprotein. PGRN has 593 amino acids in its polypeptide chain and has one or more carbohydrate (sugar) chains attached to it with an apparent molecular weight of ~88kDa. This glycoprotein can be secreted and is enriched in lysosomes (contains degradative enzymes in a membrane). This protein is ubiquitously expressed (produced in all cell types), and, in the CNS, it is highly expressed in microglia and, to a lesser extent, in neurons and other cell types. Traumatic brain injury (TBI) can actually be linked to a PGRN deficiency which increases the risk of FTD. Evidence suggests that the CNS levels of elastase (enzyme that breaks down elastin, a protein that provides elasticity to connective tissues) increase after spinal cord trauma and stroke. Increasing elastase levels are also likely after TBI as it leads to activation of microglia, which in turn secrete multiple cytokines including elastase. This reveals the possibility that TBI may cause an increase in elastases, which would result in a reduction in the levels of PGRN and an increase in the proinflammatory GRNs. Reduced PGRN levels in turn impair lysosomal function which leads to the accumulation of cellular waste, contributing to the development of FTD. TBI is not the only cause of PGRN deficiency, however. Mutations in the GRN gene, which encodes for PGRN, can disrupt and impair PGRN function. These mutations are a major cause of FTD. In summary, PGRN is one of the most important non-NT substances involved in FTD pathogenesis due to its presence in all cell types and the CNS (Jawaid et al, 2010).

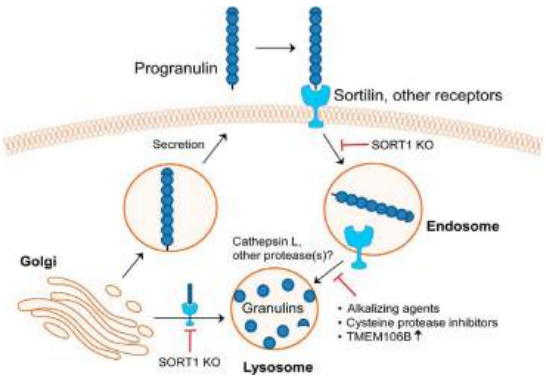

Figure 7: A model portraying the function of PGRN and its enrichment by lysosomes (Holler et al, 2017).

Vascular Dementia

Glutamate/Receptors and VaD

Glutamate, being the most abundant amino acid and the primary excitatory neurotransmitter in the central nervous system of vertebrates, is directly involved with the development of several neurodegenerative disorders including VaD. Specifically, the glutamatergic system plays a role in VaD pathogenesis. Inadequate blood supply to the brain

caused by cardiovascular disease is one of the important mechanisms underlying VaD, leading to neuronal death and cognitive and behavioral impairment. Furthermore, when the brain experiences ischemia and hypoxia due to cardiovascular disease, ATP production is reduced, resulting in abnormal function of the Na+/K+ATPase (NKA), Na+/Ca2+ exchange (NCX), and Ca2+ATPase plasma pump (crucial pumps for maintaining cellular ion homeostasis) on the cell membrane. These in turn disrupt ion gradients inside and outside the cell membrane and cause cellular dysfunction, including glutamate metabolism. The metabolic dysfunction of glutamate increases glutamate release and inhibits glutamate recycling, leading to excessive intercellular glutamate accumulation and receptor activation as well as tonic cell excitability, known as "glutamate excitotoxicity." Moving on, neuronal cells, particularly those in the hippocampus, are sensitive to fluctuations in glutamate levels (Wang et al, 2024).

Several studies have suggested that insufficient cerebral blood supply in pre-VaD leads to increased glutamate release. In addition, activation of the two-pore potassium channel (potassium channels characterized by having two pore-forming regions (or "pores") in each subunit) TWIK-related K channel (TREK-1), found in many neuronal cells and astrocytes, can mediate rapid glutamate release and increase cognitive impairment due to glutamate toxicity. AMPARs, or glutamate receptors, also play a role in VaD. AMPARs are expressed in vascular smooth muscle cells and are involved in the control of blood vessels. In a mouse model of VaD, NBQX, an AMPA receptor inhibitor, was administered to the mice, and it was shown to have significantly lessened axonal degeneration. This suggests that AMPA could potentially play a role in synaptic degeneration under VaD pathology. The evidence above reveals the importance of NTs and receptors in VaD pathogenesis and also in major risk factors for VaD (Wang et al, 2024).

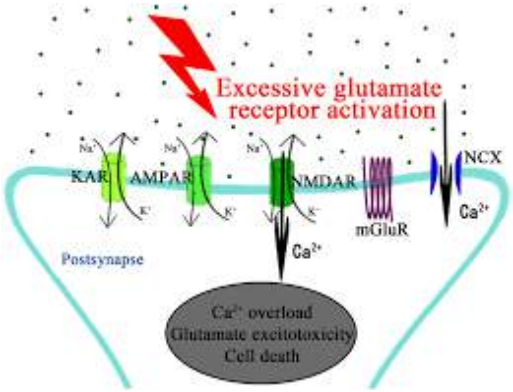

Figure 8: A model of excessive glutamate receptor activation, leading to glutamate excitotoxicity and cell death (Wang et al, 2024).

Hormones and VaD

Studies have been conducted in order to investigate the controversy between correlating estrogen changes to cognitive impairment, which causes VaD. This is due to the sudden downfall of estrogen in women during menopause; this happens to be one of the significant risk factors and the root prevalence of VaD in postmenopausal females. In addition, studies have concluded that estrogen deficiency in postmenopausal women is indeed one of the risk factors, causing cognitive deficit that can lead to VaD. One study focused on the serum sex hormone levels among VaD patients. The study's results revealed that the testosterone and sex hormone-binding globulin (SHBG) levels were lower in male VaD patients, and the estradiol

levels were found to be higher in female VaD patients in comparison to the controls. The final conclusion of the study was that there were no correlations between hormone levels and neuropsychiatric symptoms in male VaD patients, whereas total estradiol (TE2) and testosterone (TT) levels were positively correlated in female VaD patients. One study suggests that estrogens and their receptors may regulate the neuroinflammatory response, and in females, circulating estrogens may play a protective, anti-inflammatory role. Hence, estrogen preserves vascular function and neuroinflammatory response, suggesting that this hormone could be directly relevant to VaD. The results of these studies show that hormones could potentially have a significant role in VaD pathology and development (Akhter, et al).

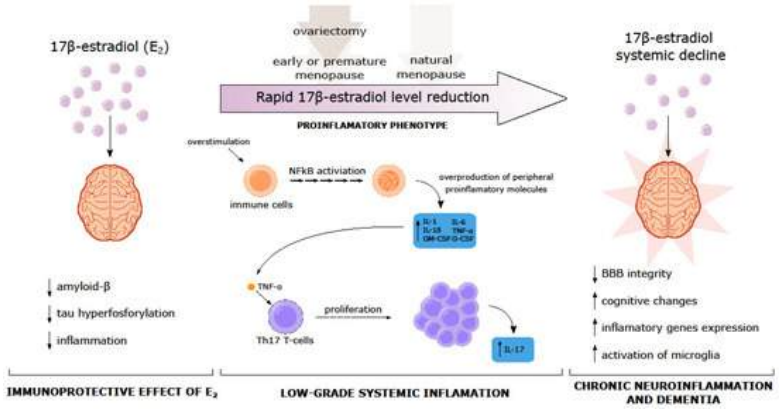

Figure 9: A model of estradiol level reduction, which in turn leads to neuroinflammation and VaD (Sochocka et al, 2023).

Parkinson's Disease (PD)

Dopamine (DA) and PD

The impairment of DA release plays a significant role in the development/pathology of PD. DA release is mediated/controlled by Ca2+ and Rab3-interacting molecule-dependent vesicular exocytosis (process by which cells release molecules stored in membrane-bound vesicles in response to specific molecular signals or machinery) from active zone-like sites. Released DA is thought to act beyond individual synapses at extrasynaptic receptors on many cells and can also be released from the cell body and dendrites through somatodendritic release. The DA release process is highly regulated through a variety of mechanisms, including DA synthesis, cell and vesicular uptake, action potential propagation and local neuromodulatory receptors. *In vivo,* DA release dynamics are thought to be determined by a combination of different DAN firing rates (tonic low frequency pacemaking, sustained increases in firing rate and short intermittent or 'phasic' bursts at high frequencies), as well as by a range of mechanisms operating on DA axons that can locally gate action potential propagation, DA release probability and its dynamics during activity. Several animal and human cell-based models of PD have demonstrated early synaptic dysfunction and intrinsic DA release defects. The mechanisms by which these defects occur can be categorized into six mechanisms: SV exocytosis, SV trafficking and loading, SV endocytosis and recycling, synaptic protein accumulation, damage to the SV pool and non-cell autonomous mechanisms. Most DA release

is mediated by Ca2+-dependent vesicular exocytosis. Disruption to this process will cause impairment in DA release (Cramb et al, 2023).

In addition, normal synaptic functioning in DA axons requires the formation of the SNARE complex (group of proteins crucial for membrane fusion) by vesicular synaptobrevin-2/VAMP-2 and syntaxin-1/SNAP-25 on the plasma membrane. PD proteins such as α-synuclein and LRRK2 directly interact with SNARE proteins and PD-related mutations either alter activity or expression of SNARE complex. Furthermore, the addition of α-synuclein oligomers (proteins that regulate the amount of SNARE complex, which regulates the release of neurotransmitters) inhibits SNARE-complex formation by binding SNARE protein synaptobrevin-2. Exocytosis also requires high energy levels in the form of mitochondrial ATP. PD mutations along with α-synuclein oligomers can impair mitochondrial function or transport leading to an axonal energy deficit and synaptic loss. Defective mitochondria may also disrupt exocytosis through calcium dysregulation, since these organelles are essential for calcium buffering. DA release can also be impaired by unavailability of DA in the readily releasable pool at presynaptic terminals, through defects in synthesis, vesicular loading or trafficking. DA loss in the SVs by disturbed synaptic loading not only leads to a lack of availability of DA for release but the consequent increase in cytoplasmic DA may have toxic effects on the cell as it is rapidly converted to a reactive species (unstable molecules that readily react with other cellular components). In addition, intracellular and specifically axonal and vesicular trafficking is impaired in PD with consequences to synaptic function. DA release deficit could also be a result of direct damage to the SV pool. This could possibly occur through generation of Reactive Oxygen Species (ROS), a common hallmark of PD (Cramb et al, 2023).

Furthermore, cytosolic DA, which is increased in PD models, undergoes auto-oxidation, creating further ROS. An increase in cytosolic DA may be caused by a number of factors, including impaired DA loading into SV or increased DAT activity, both connected to PD. ROS overproduction inhibits SNARE-complex assembly and thus impairs exocytosis. Damage to the SV pool also occurs when protofibrillar α-synuclein and oligomers disrupt the SV membrane allowing DA to spill out into the cytosol (fluid portion of the cytoplasm within a cell) and alter neuron excitability. The ability to reconstitute the vesicular pool for subsequent release events is regulated by vesicle renewal/reuptake, recycling and reloading of the neurotransmitter into SVs.

There is substantial evidence that links PD with defects in SV endocytosis and recycling. Both complete DJ-1 knockout as well as PD-related DJ-1 mutations disrupt SV endocytosis. Further evidence supports that defective SV recycling and decreased reuptake of DA leading to lack of SV replenishment could be an important contributing factor to disruption of DA release in PD. Another major hallmark of PD is protein aggregation. A-synuclein aggregation in particular may induce DA release defects by physically blocking cell processes caused by the aggregate itself or rather through sequestration of the functional protein, leading to disruption of synaptic processes by loss of protein function. Autophagy, a major protein degradation pathway, is crucial for regulation of protein turnover in neurons and has been connected to Parkinson's disease-related mutations including SNCA, LRRK2, VPS35, parkin, Pink1 and DJ-1. This particular pathway appears to be specifically important for synaptic homeostasis in DA systems. Thus, protein aggregation may disrupt DA release through sequestration of essential proteins or by physical interference in critical processes for release. These essential processes involving DA prove its importance in the development and diagnosing of PD (Cramb et al, 2023).

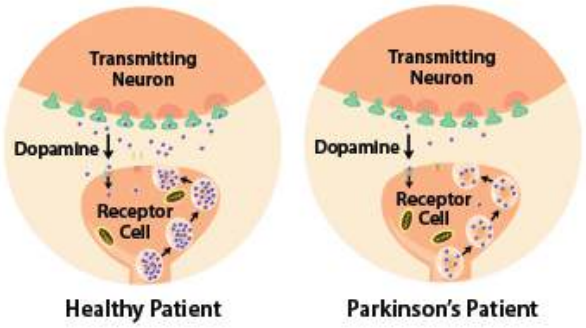

Figure 10: A model comparing the DA pathway in a healthy patient to that of a PD patient (OHSU, 2025).

Hormones and PD

Cortisol and other Glucocorticoids (GCs) also play a role in the development/pathology of PD. Glucocorticoids are essential to homeostasis and a normal response to stress. Chronic stress and elevated cortisol are implicated in many of the mechanisms that are implicated in the progression and, potentially, development of PD including metabolic changes, mitochondrial dysfunction, and neuroinflammation. Excessive cortisol secretion promotes neuroinflammation through the mechanism in which glucocorticoid receptors or GR (anti-inflammatory actions) are downregulated as a compensatory response to excess cortisol production and GC resistance, which further promote the release of GCs. Catecholamines and glucocorticoids under normal conditions regulate inflammation through the inhibition of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, and the stimulation of anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13 [38], by exerting action in the cytoplasm of immune cells. However, through an interplay of inflammation due to immune response and subsequent cytokine release and a lack of downregulation normally executed by GCs, neuroinflammation persists, leading to the atrophy of neurons in critical brain areas, such as the hippocampus. Neuroinflammation is prominent neurodegenerative diseases including PD, and may be the driving factor in both the progression of and contribution to disease development. Thus, dysfunctional hormone level regulation may be linked to PD as such dysfunction allows neuroinflammation to persist (Knezevic et al, 2023).

Discussion

The important role of NT/receptor and hormone dysregulation in Alzheimer's Disease, Lewy-Body Dementia, Frontotemporal Dementia, Vascular Dementia, and Parkinson's Disease has been thoroughly reviewed in the results section. Most often the NTs involved have specific metabolic functions, contribute to basic cognitive functions, and/or are crucial to maintaining synaptic plasticity. The neuroreceptors are mainly involved in the functioning of specific NT systems. The hormones have several functions varying from reproductive development to maintaining homeostasis. It is important to discuss the comparison of NTs and hormones in detail due to the complex nature of their involvement in these variations of dementia.

Glutamate and Dopamine both have significant effects in dementia pathogenesis and are two of the most common NTs associated with dementia. However, the roles they play in the disease are rather different. Glutamate's main connection to dementia is the process of glutamate excitotoxicity, while dopamine's main connection is through dopamine transporter

dysregulation, which in turn leads to decreased dopamine levels, finally leading to neurodegeneration and dementia. Despite these differences, glutamate receptors and dopamine protein degradation pathways function similarly. iGluRs (glutamate receptors) are extremely important in synaptic plasticity/homeostasis, the underlying molecular mechanism behind learning and memory. Autophagy, a major protein degradation pathway, is crucial for regulation of protein turnover in neurons and also appears to be specifically important for synaptic homeostasis in dopamine systems. These NTs and their roles in the brain prompt further research into the maintenance of NT systems/pathways in order to prevent NT level dysregulation. Other important processes including synaptic homeostasis are also heavily regulated/influenced by hormones. (Wang, Reddy, 2018), (Cramb et al, 2023).

Leptin and Progranulin are a major hormone and a multifaceted protein, respectively, commonly involved in dementia. Both of these substances have separate roles in the human body but have similar implications in dementia pathogenesis. Leptin, a pro-inflammatory adipokine (Signaling molecules that promote inflammation), is secreted by White Adipose Tissue (WAT) and found to be increased in people with a high body mass index. Leptin signalling regulates various crucial processes including food intake, energy expenditure, cognition, learning, memory, and mood. From a neurocognitive perspective, leptin regulates neurogenesis (neuron formation), synaptogenesis (synapse formation), neuronal excitability, and neuroprotection. In contrast, progranulin is a glycoprotein which is ubiquitously expressed (produced in all cell types), and, in the CNS, highly expressed in microglia and on a smaller scale in neurons and other cell types. On the other hand, both leptin and progranulin deficiencies serve as diagnostic biomarkers/risk factors for dementia. Leptin is secreted by adipocytes (fat cells) and circulates in plasma in proportion to fat mass, and changes in body weight are associated with the possibility of developing dementia. Thus, according to the studies cited, plasma leptin deficiency could indicate a possible CNS leptin deficiency and thus serve as a diagnostic marker for dementia. Similarly, reduced PGRN levels impair lysosomal function which leads to the accumulation of cellular waste, contributing to dementia pathogenesis. The functional stronghold that these hormones have at the cellular level prompts further investigation into the correlation between hormone levels and cell death rates. This research may open windows for the potential usage of hormone/cell regeneration therapy for the treatment of dementia (Flores-Cordero et al, 2022).

Based on the significant information collected from the several studies reviewed in the results section, it is recommended that scientists focusing on this topic delve deeper into the implications of neurological processes involving neurotransmitters/receptors and hormones as risk factors and/or important biomarkers for the several variations of dementia. Understanding these implications may lead to breakthroughs in the research of more well-known, less foundational causes of dementia such as genetic/hereditary causes and risk factors. Fortunately, there are several treatments to mitigate the symptoms/development of dementia.

This section primarily reviews treatments from the studies cited in the results section. One of the most actively explored treatment strategies is the enhancement of cholinergic activity. Cholinergic compounds currently being tested are clinically composed of first generation drugs and second generation drugs. For example, refined cholinesterase inhibitors (whose structural and biological diversity is enormous) with anatomical selectivity, fewer side effects and broader therapeutic ratios are currently being enlisted in new clinical trials. One major byproduct of efforts in designing cholinergic cognitive therapy is the potential application to the so-called mild memory impairment which can occur in normal individuals over the age of

50. There is also scope for applying drugs developed for dementia as cognitive enhancers for younger individuals who feel the need to improve memory performance: The so-called 'smart' drugs. Another potential treatment strategy is hormone replacement therapy (HRT). In a recent study, AD and related dementias were reported less frequently on death certificates among subjects undergoing estrogen replacement therapy (ERT) than among nonusers (relative risk = 0.69, 95% confidence interval = 0.46 to 1.00). The risk levels for dementia and AD decreased with increasing doses of estrogen and with increasing intervals of use. Another observational study demonstrated that estrogen use may delay the onset of AD. Participants in the study included 1124 postmenopausal women who were initially free of cognitive impairment and who had follow-up 1 to 5 years after baseline. AD developed in 5.8% of the women taking estrogen after menopause in comparison with 16.3% of the nonestrogen users (P = 0.001). Again, the risk for Alzheimer's disease decreased with longer duration of estrogen use. Participants using estrogen for 1 year or less showed lower risk for Alzheimer's disease; however, women taking estrogen for over 1 year had the greatest reduction in risk.

Based on the information reviewed in this paper, another potential treatment would be a combination of neurotransmitter level alteration and hormone therapy. Both treatment regimens can either be administered simultaneously or one after the other. The treatment that proves more effective will be continued until the patient either begins showing signs of recovery or until the progression of dementia is significantly decreased. If signs of recovery begin to show, the strength of the treatment will be increased. However, if the progression is simply mitigated, the treatment can either be continued at a similar strength or stopped completely, depending on what the patient/patient's loved ones prefer at that time. An example of a pharmaceutical therapy combination is the combination of Estrogen Replacement Therapy(ERT) and dual-action antidepressants to increase dopamine levels in female PD and VaD patients. An example of a combination of non-pharmaceutical therapies is the administration of Cognitive Behavioral Therapy(CBT) and stress management routines to decrease cortisol/glucocorticoid(GC) levels which hold visible significance in PD pathogenesis.

Ultimately, although dementia is currently a class of several incurable and incredibly varying neurodegenerative syndromes, many of these variations have relations through grassroots causes/risk factors in the form of neurotransmitters/receptors and hormones. This review should be taken into direct consideration during further dementia research because it provides a thorough description of the neurobiological processes that neurotransmitters/receptors and hormones are involved in and how they relate to the development/severity of dementia and supports this description with numerous studies from reputable sources. This review may encourage forward progression towards making a breakthrough in potentially universal cures or treatment plans for the condition as a whole. The next step is to apply this research in more advanced, trial-and-error based scientific studies while also making this key information readily available/understandable to the general public.

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