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NEUROTRANSMITTERS AND BRAIN DEGENERATION

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ABSTRACT

Neurodegeneration is characterized by the death of neurons which leads to progressive damage with the loss of cognitive abilities. Neurotransmitters are divided into neuropeptides, amino acids, purines, amines, and many other molecules, and mediate information in the central nervous system (CNS). Additionaly, these neurotransmitters mediate many brain disorders, including Alzheimer's Disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), amongst others. Monoamine neurotransmitters include the catecholamines, dopamine, norepinephrine, and epinephrine, which are vital to the CNS where they indirectly or directly influence most physiological brain functions. Dopamine modulates glutamate-induced excitation in the basal ganglion and cortex, while serotonin or 5-hydroxytryptamine (5-HT) regulates several higher brain functions such as cognitive control and learning. In addition, acetylcholine (ACh) regulates blood pressure, muscle and cardiac contractions, and intestinal peristalsis, amongst other functions. The regulation of neuropeptides could represent a promising target for the therapy of neurodegenerative diseases.

KEYWORDS: *neurotransmitter, CNS, brain degeneration, neuron*

INTRODUCTION

Neurodegeneration is the progressive damage of the central nervous system (CNS) caused by the decline and death of neurons. The damage gradually worsens over time with increasing death of nerve cells, leading to the loss of cognitive abilities and memory impairment.

The CNS controls muscle and organ functions of the body through the synaptic transmission of signals from the brain to the peripheral nervous system (PNS). Neurotransmitters are neurochemicals that play a vital role in the transmission of information in the nervous system, sending signals from pre- to post-synaptic neurons. They are chemicals stored in the axon terminal in synaptic vesicles which are released across the synapse cleft to be bound to post-synaptic receptors, and are vital for the communication of sensory, motor, and integrative neuronal messages, and for functioning of the brain. These small molecules include amino acids, purines, amines, and neuropeptides, among other types. To date, more than a hundred neurotransmitters have been identified, however, more research is continuing to unveil others (1). These neurotransmitters have excitatory, inhibitory, or modulatory effects and are involved in cognition and behavior.

Aberrant levels of neurotransmitters affect the proper functioning of the brain and cause mental illness and physical and neurodegenerative diseases (2,3). Neurotransmitters have been implicated in different neurodegenerative diseases including Alzheimer's disease (AD) (4,5), Parkinson's disease (PD) (6,7), Huntington's disease (HD) (8), multiple

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sclerosis (MS) (9), and amyotrophic lateral sclerosis (ALS) (10) and continue to be studied for their effects on the health of the brain.

The neurotransmitters can be categorized chemically into three groups: amino acids, amines, and peptides. The main neurotransmitters in the brain include the dopaminergic, cholinergic, glutamatergic, and GABAergic systems, all of which have been shown to be implicated in the complex process of neurodegeneration (11).

This short review aims to serve as an update on the involvement of these as well as other neurotransmitters in major neurodegenerative diseases.

Amino Acid neurotransmitters

The amino acid neurotransmitters are an important class that is common in the CNS, playing a role in fundamental processes of brain functioning, and are implicated in the pathogenesis of different neurodegenerative diseases. The amino acids include neurotransmitters such as glutamate, glycine, and γ-aminobutyric acid (GABA), which play roles in essential brain processes. These neurotransmitters are small molecules with a simple structure; there is an anionic carboxylate group at one end, with a cationic ammonium group at the other.

Raised levels of glutamate, which is produced from glutamine and is the precursor of GABA, can cause the activation of N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to an excess of calcium ions in the postsynaptic neuron that can cause hyperexcitability, excitotoxicity and cytotoxicity (12-14). Animal studies have shown that in the hippocampus, excitotoxicity induced by glutamate has been associated with dendritic branching and limited neuronal regeneration, with subsequent impairment in spatial learning (15). Furthermore, this excitotoxicity may potentially be involved in MS (16), ALS (17), and PD (18). Evidence has also shown that there is an excitotoxic component at work in the pathology of AD (19). Glutamate receptors, which are complex and numerous in the CNS, include twenty different types that are categorized as ionotropic or metabotropic, and then further subdivided into groups. Metabotropic group II glutamate receptors (mGluR2 and 3) have been shown to play a role in AD, while group III receptors (mGluR4, 6, 7 and 8) may be implicated in PD (20). It has been reported that disrupted glutamate homeostasis may be involved in neurodegenerative diseases including ALS, MS, AD, PD, and HD (21,22).

Astrocytes are vital for regulating glutamate homeostasis, as they control extracellular levels of glutamate through uptake and release mechanisms (23). Reduced glutamate uptake by astrocytes has been detected in HD patients (24) and astrocyte reactivity is implicated in other neurodegenerative diseases as well, such as AD, PD, and ASL (25).

The amino acid neurotransmitter GABA is formed through glutamate decarboxylase and has inhibitory effects in the adult brain, where it is the main inhibitory neurotransmitter within CNS, PNS, and enteric nervous systems. Low levels of GABA lead to neuronal hyperexcitability and, therefore, an equilibrium is important for brain functioning. Disruption of GABA homeostasis is associated with different neurological and neurodegenerative disorders including AD, PD, HD, and possibly MS, where lower levels of sensorimotor GABA concentration have been seen correspondence with the worsening of motor function (26-28).

Monoamine neurotransmitters

The monoamine neurotransmitters are a class of neurotransmitters involved in diverse physiological and mental functions containing one amino group which is connected to an aromatic ring by a two-carbon chain. This group of neurotransmitters includes the catecholamines, which contain the chemical structure catechol, with the amino acid tyrosine as the precursor. The category of catecholamines includes dopamine, norepinephrine, and epinephrine.

Dopamine (4-(2-aminoethyl)-1,2-benzenediol) is a vital neurotransmitter in the CNS that indirectly or directly affects most physiological functions in the brain (29).

The important enzyme monoamine oxidase (MAO) is involved in the catabolism of monamine neurotransmitters and xenobiotic amines and has been established to play an important role in the neurodegenerative disorders of PD and AD (30,31). In PD, MAO is involved with the degeneration and death of dopaminergic neurons in the substantia nigra (32) and the administration of dopa therapy can be proactive for increasing levels of dopamine and reducing the production of ROS and oxidative stress (33). In AD, the elevation of type B monoamine oxidase (MAO-B) has been linked to dysregulated equilibrium that includes impaired mitochondrial function, increased oxidative stress, with excitotoxicity and apoptosis that leads to the death of neurons (30,34).

Dopamine dysfunction affects HD as well; striatal levels of the neurotransmitter are initially increased, causing increased hyperkinetic movements, with a decrease seen in the later stages of the disease that results in hypokinesia (35). Moreover, dopamine modulates glutamate-induced excitation in the basal ganglion and cortex, so dopamine dysregulation may contribute to excitotoxic cascades (35).

The neurotransmitter serotonin (5-hydroxytryptamine) also regulates many physiological functions including the regulation of different higher brain functions such as cognitive control, learning, and affect (36,37). Serotonin also has direct effects on other neurotransmitters, inhibiting the release of dopamine, and modulating GABA and glutamate transmission (38).

Serotonin is implicated in the pathogenesis of AD, with serotonergic denervation and alteration having been suggested to play a role, and improved serotonergic functioning has been seen with modified and improved symptoms concerning memory and cognition in AD patients (39). In fact, modulation of the serotonergic system could represent a promising target for AD therapy (40).

Additionally, serotonin may play a role in PD, which was believed to be predominantly affected by the dopaminergic system. Serotonergic dysfunction has been shown in PD animal studies (41), as well as imaging studies (42), and may affect the nonmotor symptoms of the disease, such as fatigue (43), depression (44), visual hallucinations (45), and changes in weight (46).

Epinephrine and norepinephrine act as hormones as well as neurotransmitters in the autonomic nervous system. Elevated concentrations of these neurotransmitters are thought to be involved in AD (47), with most evidence showing changes in the noradrenergic system and loss of noradrenergic innervation contributes to the pathogenesis and progression of the disease (48-50). At the start of the disease, this affects the noradrenergic neurons of the locus coeruleus, together with formation of tau protein, and at later stages there is a loss of noradrenergic neurons and affects in neuronal anatomy, neurotransmitter systems, and the noradrenergic receptors (51,52).

In the CNS, histamine acts as a neurotransmitter where it is released by histaminergic neurons in the hypothalamus. It is involved in a variety of physiological functions including arousal, cognition, circadian rhythms, and neuroendocrine regulation (53). Analysis of postmortem brains from AD patients have shown increased histamine levels (54), and other studies have indicated an association of the disease with histaminergic dysfunction (53,55,56).

Acetylcholine

Acetylcholine (ACh), the first neurotransmitter that was discovered, plays a role in numerous physiological processes in the PNS and the CNS. In the PNS, ACh regulates blood pressure, muscle and cardiac contractions, and intestinal peristalsis, amongst other functions. In the CNS, it is involved in the control of voluntary movements and sleep, as well as cognitive processes such as learning, attention, and memory. The chemical structure of ACh is reflected in its name; it consists of an ester of acetic acid and choline.

Cholinergic alterations can result in neurodegenerative diseases such as AD, PD, and HD, with effects concerning the cognitive, behavioral, and motor disabilities of these pathologies (57). Memory impairments are related to the degeneration of central cholinergic neurons, and neuroinflammation, a trademark of neurodegenerative diseases, may result, as cholinergic signaling has anti-inflammatory effects and modulates inflammation (58).

Pathological disruptions have been seen in the cholinergic system of AD patients and it is believed that disruption of this system indirectly leads to the impairment of cognitive function (5 Francis). Additionally, the hallmark characteristics of AD, amyloid-β plaques and neurofibrillary tangles of hyperphosphorylated tau, have direct and indirect cytotoxic effects on neurotransmission, impairing synaptic integrity and altering the release of neurotransmitters (59).

CONCLUSIONS

In the last century, hundreds of neurotransmitters have been discovered, with intense investigation continuing for the identification and elucidation of their roles in the body. Altered homeostasis of neurotransmitters and dysfunctional neurotransmission leads to severe pathology, and thus far, research has shown that neurotransmitters play key roles in neurodegenerative disorders such as AD, PD, HD, and ALS.

Further research is necessary to better understand the complex mechanisms of neurotransmitters in neurodegenerative disease and their actions on brain health, with the goal of improving the treatment and early monitoring of these disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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