

Neurotransmission

Subjects: Clinical Neurology

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Definition

Neurotransmission is the process by which a signal is conveyed between neurons via endogenous signaling molecules called neurotransmitters. Neurotransmitters released from the axon terminal of one neuron cross the synaptic cleft and bind to receptors on the dendrites of another neuron, which are then converted into electrical signals. Synapse, the junction between neurons, has a tripartite structure that consists of presynaptic and postsynaptic nerve terminals along with the intimate association of glial cells.

1. Introduction

It is well established that neurotransmission is affected in patients with AD, particularly the chemical neuroanatomy of monoaminergic systems including serotonergic and dopaminergic systems, cholinergic systems including acetylcholine and GABA, and glutamatergic systems [1]. Neurotransmission dysfunction mainly arises from the degeneration of neurons as a result of the toxic accumulation of A β plaques (see **Figure 1** and **Table 1**).

Figure 1. Dysfunction of neurotransmission in AD. Accumulation of A β plaques and NFT in AD cause impairment of the circadian rhythm, cognition, learning, memory, motor function, mood, sleep and stress response. These pathologies are toxic to neurotransmission systems, affecting cholinergic, glutamatergic, serotonergic and dopaminergic systems. Amyloid-beta plaques and NFT can inhibit the release of ACh and choline acetyltransferase, an enzyme that regulates ACh synthesis, which reinforces the inhibition effect of ACh. Amyloid-beta plaques and NFT can cause mitochondrial damage in glutamatergic neurons. The mitochondrial damage leads to inflammation due to excessive influx of Ca²⁺ and excessive efflux of Mg²⁺ that affect the activation of glutamatergic neurons and decreases the activation of NMDA receptor. The excessive influx of Ca²⁺ in glutamatergic neurons leads to inhibition of choline acetyltransferase and further inhibits the synthesis of ACh. However, the detailed mechanisms are not yet understood, as some studies showed the upregulation of GABA in certain regions but downregulation of GABA in other regions. Amyloid-beta plaques also disrupt the homeostasis of serotonin (5-HT) by inhibiting the binding of serotonin receptor (5-HT_{2A}) and disrupting the dopaminergic system. Abbreviations: A β , Amyloid-beta; NFT, neurofibrillary tangle.

Table 1. In vivo studies related to neurotransmission in AD. Abbreviations: 5 HT, 5-hydroxy-tryptamine, Serotonin; ACh, Acetylcholine; AChE, Acetylcholinesterase; APP^{swe}, Amyloid-beta precursor protein with Swedish mutation; A β , Amyloid-beta; A β O, Amyloid-beta oligomers; A β PP, Amyloid-beta precursor protein; ChAT, Choline acetyltransferase; DA, Dopamine; DAergic, Dopaminergic; GABA, Gamma-aminobutyric acid; MAergic, Monoaminergic; mGlu₂, Metabotropic glutamate receptor 2; NA, Noradrenergic; NMDAR, N-methyl-D-aspartate receptor; PS, presenilin transgenic; SN, Substantia nigra; TH-, Tyrosine hydroxylase negative; TH+, Tyrosine hydroxylase positive; VTA, Ventral tegmental area.

Animal Model.	Gender	Age	Pathology Involved	Neurotransmission Dysfunction	Behavioral Effects	References
APP ^{swe} /PS1dE9 mice	N/A	4-18 months old	Degeneration and loss of forebrain 5-HT and NA axons after A β deposits	Monoaminergic neurodegeneration	Anxiety-related behaviors in 18 months	[2]

Animal Model.	Gender	Age	Pathology Involved	Neurotransmission Dysfunction	Behavioral Effects	References
Swiss mice treated with A β O	N/A	3 months old	Development of A β plaques	A β O disrupts 5-HT homeostasis	Depressive-like behavior	[3]
APP ^{swe} /PS1 ^{dE9} mice	Male	4, 8, 11 months old	Progressive accumulation of A β protein.	Significant decrease in 5-HT _{2A} receptor binding	Memory impairment	[4]
5xFAD mice	Male	6 months old	Significant decrease of both TH+ and TH- cells in DA-producing areas	SN-VTA networks are enhanced to the synchronization of neuronal firing activity in DA-producing nuclei	<ul style="list-style-type: none"> • Cognitive malfunction • Synaptic malfunction 	[5]
Tg2576 mice	Male	2 and 6 months old	Degeneration of VTA DAergic neurons	Reduced noradrenergic transmission in dorsal subiculum	Age-related impairment of memory and non-cognitive functions	[6]
Tg2576 mice	N/A	4-6 and 9-11 months old	A β were prominent in 20-month-old mice	Reduced ACh release from hippocampus in 9- to 11-month-old mice	Memory impairment present in 9- to 11-month-old mice	[7]
APP/PS1 mice	N/A	3 and 7 months old	A β plaques deposition after cholinergic degeneration	<ul style="list-style-type: none"> • Dramatically reduced cholinergic neurons • Neuronal loss in nucleus basalis 	<ul style="list-style-type: none"> • Early memory impairment • Progressive impairment 	[8]
APP/PS1 and 5xFAD mice	N/A	8 and 13 months old	A β plaques deposition and reactive astrocytes	Aberrant increase in GABA release from reactive astrocytes	Impaired learning and memory	[9]
A β PP/PS mice	Male	2-4 months old	Abnormal glutamate release precedes cognitive decline	Significantly increased potassium-evoked glutamate release in CA1	Cognitive decline	[10]

Animal Model.	Gender	Age	Pathology Involved	Neurotransmission Dysfunction	Behavioral Effects	References
A β PPswe-PS1dE9 mice	N/A	6 months old	Deposition of A β plaques	<ul style="list-style-type: none"> • Significant decrease in cortical glutamate and GABA • Glucose, GABA and glutamate reduced in hippocampus and striatum 	Impairment of cognitive function and memory	[11]
TgAPP23 mice	Male and female	24 months old	Deposition of A β plaques and cholinergic degeneration	<ul style="list-style-type: none"> • Decreased ChAT-positive boutons in neocortex • Significant reduction of ChAT-positive neurons volume in basal forebrain 	N/A	[12]
PS2APP mice	Female	20 or 24 months old	Deposition of A β plaques	Significant reduction of glutamate level in frontal cortex	N/A	[13]
TgAPP23 mice	N/A	7-8 months old	Dysfunction of cholinergic and monoaminergic systems	<ul style="list-style-type: none"> • Decreased AChE and ChAT activity in basal forebrain nuclei • Increased 5-HT levels in parietal cortex and occipital cortex 	N/A	[14]
PDAPP mice	Male and female	4-6 months old	Deposition of A β plaques	Reduced basal and evoked ACh release from hippocampus	Hyper-locomotor function	[15]

Animal Model.	Gender	Age	Pathology Involved	Neurotransmission Dysfunction	Behavioral Effects	References
3xTg-AD mice	Male and female	2-4, 13-15 and 18-20 months old	A β plaques deposition with cholinergic degeneration and alteration of neurotrophic factors	<ul style="list-style-type: none"> Reduced ChAT in medial septum/vertical limb of the diagonal band of Broca in 18- to 20-month-old mice Decreased hippocampal ChAT activity in 13- to 15-month-old mice 	N/A	[16]
hAPP-J20 mice	N/A	6 months old	Altered synaptic plasticity and cognitive function	Significantly decreased phospho GluN2B levels and hippocampal LTP	Impaired learning and memory	[17]
TgCRND8 mice	N/A	2 and 7 months old	A β plaques deposition, oxidative stress, reactive glial cells and neurodegeneration	Reduced ChAT-positive neurons and ACh levels.	Cognitive impairment	[18]
PS2APP mice	Male	5, 9, 13 and 17 months old	Deposition of A β plaques	Significant loss of mGlu2 receptors in entorhinal cortex and lacunosum moleculare regions	N/A	[19]
PS2APP mice	Male	3-4 months old	Altered synaptic plasticity	Aberrant GluN2B-NMDAR function	N/A	[20]
PDAPP mice	Male	2, 4, 12 and 24 months old	A β plaques deposition with cholinergic degeneration	<ul style="list-style-type: none"> Reduced Cholinergic nerve terminals density Significantly decreased ChAT activity 	N/A	[21]
3xTg-AD mice	N/A	9-23 months old	Deposition of A β plaques	Reduced ChAT and AChE-positive neurons	N/A	[22]

Animal Model.	Gender	Age	Pathology Involved	Neurotransmission Dysfunction	Behavioral Effects	References
TgCRND8 mice	Male	3 months old	Deposition of A β plaques and neuronal degeneration	<ul style="list-style-type: none"> • Significantly increased GluN1 in neocortex, hippocampus and cerebellum. • Significantly increased GluA2 in neocortex but decreased in hippocampus 	Cognitive impairment	[23]
TgCRND8 mice	Male and female	2-3 and 12-13 months old	Deposition of A β plaques	<ul style="list-style-type: none"> • Decreased glutamate in hippocampus, cortex, frontal cortex and midbrain • Decreased GABA in hippocampus, cortex and midbrain 	N/A	[24]
TgCRND8 mice	Male	3 months old	Dysfunction of dopaminergic system	<ul style="list-style-type: none"> • Increased dopamine level in the neostriata and frontal cortices • Decreased dopamine level in the hippocampus 	Cognitive impairment	[25]

2. Role of Melatonin on Neurotransmission

The effects of melatonin on neurotransmission primarily involve improvements in cholinergic and glutamatergic systems (see **Figure 2**). As mentioned previously, A β plaques can impair the function of glutamatergic neurons and cause excessive influx of calcium, which lead to overstimulation and unnecessary release of AChE, resulting in reduced choline acetyltransferase and ACh levels.

Figure 2. Effects of Melatonin treatment on dysfunction of neurotransmission in AD. Melatonin can ameliorate the formation of A β plaques and NFT, as well as improve the impairments due to these AD hallmarks, including disrupted circadian rhythm, cognition, learning, memory, motor function, mood, sleep and stress response. Melatonin treatment can have beneficial effects on serotonergic and dopaminergic systems, but the exact mechanisms have yet to be determined. Melatonin can also have beneficial effects on the cholinergic system by increasing acetylcholine release and reducing inflammation caused by excessive influx of Ca²⁺ and excessive efflux of Mg²⁺, thereby inhibiting choline

acetyltransferase. Abbreviations: A β , Amyloid-beta; NFT, neurofibrillary tangle.

Melatonin has been hypothesized to alleviate the disruption of the cholinergic system in AD through inhibiting the calcium-induced release of AChE, thus effectively acting as an acetylcholine enhancer [26]. Supporting this hypothesis, a study on a sporadic AD rat model showed that melatonin treatment could significantly decrease the level of inflammation and oxidation, as well as inhibit AChE activity [27]. In addition, it has been shown that as AD progresses, choline acetyltransferase [28] and AChE synthesis begins to decrease, which correlates positively with dementia severity in AD patients. Melatonin has also been shown to promote choline transport, which improved ACh synthesis [29]. In APP695 mice, melatonin treatment significantly decreased ChAT activity in the frontal cortex and hippocampus [30]. In a recent study on sporadic AD mice, melatonin rescued the AChE level and promoted neuroprotection [31].

Melatonin has also been suggested to alleviate the altered glutamatergic system in AD by inhibiting the activity of NMDA receptors. Melatonin was able to reduce excessive Ca²⁺ influx by altering the activity of voltage-gated Ca²⁺ channels, thereby inhibiting the effects of NMDA receptors [32]. This was supported by a study on adult male Wistar rats, which found that melatonin treatment attenuated the glutamatergic-dependent excitatory response in striatal neurons by reducing Ca²⁺ influx in voltage-gated Ca²⁺ channels and NMDA-gated Ca²⁺ channels, resulting in an anti-excitotoxic effect [33]. Even though these findings show melatonin has beneficial effects on cholinergic and glutamatergic systems, the impact of melatonin on the neurotransmission of monoaminergic systems has yet to be demonstrated, which will require more research.

3. Conclusions and Future Perspective

The effects of melatonin on neurotransmission and AD pathologies have been separately investigated in several respective studies. Melatonin is well established as a therapeutic for sleep disorders and jet lag, and has been investigated as an adjunct medication for cancer patients and as a medication for free-radical diseases. In this review, we have explored how melatonin can serve as a therapeutic for AD by inhibiting the pathological progression and restoring cholinergic and glutamatergic neurotransmission. Nevertheless, more research is needed to reveal its effects on other neurotransmitters such as GABA, serotonin, dopamine and histamine. Apart from the study on the direct interaction of melatonin with neurotransmission, the pathway through which melatonin can indirectly clear A β plaques is also worth studying since A β plaques are the fundamental source to cause neurotransmission dysfunction, and melatonin can reinforce the clearing effect of the glymphatic pathway by utilizing melatonin-AQP4 interaction. In addition, recent preclinical studies have indicated that melatonin metabolite N(1)-Acetyl-N(1)-formyl-5-methoxykynuramine, melatonin-derived benzylpyridinium bromides, melatonylvalpromide and melatonin-N,N-Dibenzyl(N-methyl) amine hybrids have neuroprotective effects against AD pathologies [34][35][36][37]. Moreover, melatonin receptor agonists piromelatine and agomelatine were found to be effective against AD [38][39], but their neuroprotective effects against neurotransmission dysfunction in AD are still unknown. Further preclinical research is needed to investigate the detailed role of these compounds on different neurotransmission systems in AD, and further clinical studies on melatonin and its compounds are needed to validate their efficacy in the different stages of AD. To facilitate future studies, the recent advancement of neurotransmitter imaging techniques including positron emission tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) can be taken into consideration. These are useful for accurate real-time neurotransmission detection. Furthermore, the improvement of the melatonin delivery system and the genetic variation of melatonin response can be evaluated by high-throughput screening and computer-aided drug design [40][41]. Finally, by understanding the mechanisms of how melatonin ameliorates AD pathogenesis, we can further ascertain its therapeutic value. Without a doubt, the future of melatonin as a potential treatment for AD is bright.

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