Research on the Role of Dopamine and Noradrenaline in Alzheimer’s Disease and Their Changes in the Aging Brain

Guangmiao Jin
Department of Life Sciences, Imperial College London, SW7 2AZ, U.K.

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Abstract: Alzheimer’s disease (AD) particularly affects the aged generations on a global scale. Dopamine (DA) and noradrenaline (NA) are the two essential components in regulating human behaviours, cognition and memory formation. The correlation between the two neuromodulators and AD was intensively studied in this paper. A wide range of genetically modified animal models were adopted in combination with monitoring methods. Because AD occurs more frequently in older age, it is suspected that the aging might be a potential factor of AD. In this review, abundant literatures regarding AD, NA, DA and aging were summarized to generate an insight. Although the relationship between AD and the NA system remains vague, AD is a long-term affecting disease and may not be induced simply by aging.

1 INTRODUCTION

According to Global Health Estimates of World Health Organization (WHO) in 2019, Alzheimer’s disease (AD) and other dementias rated sixth place among all the diseases with the highest mortality rate, causing 814,000 deaths annually. For high-income countries, neurodegenerative diseases overtook stroke and became the second most lethal disease (World Health Organization. (2020). Past research has identified that beta-amyloid (Aβ) plaque has strong association with AD and is often regarded as a histopathological hallmark (Jack 2013). Genetic studies revealed that the presence of Aβ is frequently associated with synaptic dysfunction, interrupting neuronal connectivity and neuronal death in a region-specific manner (Murphy, & LeVine 2010). AD onset is often diagnosed in the older age. Similar to AD, aging is accompanied by the changes in neural circuits. To reveal the mechanism of how AD is gradually developed and if there is similarity between the two factors, some studies related to dopamine (DA) and noradrenaline (NA) are listed, analysed and compared. The review aims to guide readers to a more comprehensive view of NA and DA functioning and their potential roles in regulating AD and aging. As a consequence, the clinical trials based on the two neuromodulator might be attempted, benefiting the AD patients. In the following text, dopaminergic and noradrenergic systems with linkage to aging will be discussed in more detail.

2 DA PATHWAY

Tyrosine is the precursor amino acid in DA biosynthesis. Tyrosine hydroxylase (TH) catalyzes the conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). Consequently, the decarboxylation reaction catalyzed by DOPA decarboxylase (DDAP) removes one molecule of carbon dioxide from the L-DOPA molecule and converts L-DOPA to dopamine (Pan, Kaminga, Wen, Wu, Acheampong, & Liu 2019). Synthesized DA is immediately transported out from the cytosol of the dopaminergic neurons into the monoaminergic synaptic vesicles by vesicular monoamine transporters (VMAT-2). VMAT-2 is located at the membrane of the vesicle. DA uptake into monoaminergic vesicles prevents the accumulation of free DA and the oxidation of DA to o-quinone, as VMAT-2-coupled ATPase actively pumps protons into the vesicles to build up a high proton gradient. DA stored in the dopaminergic vesicle is released into the synaptic cleft and binds onto the DA receptor on the postsynaptic neuron membrane. DA remained in the cleft is cleaved by a DA transporter which...

DA neuron loss has been a widely accepted concept in explaining AD progression. Hippocampus which controls the memory formation and voluntary movement receives input from both cortical and subcortical regions. Consistent with the observation, hippocampal DA is released from the ventral tegmental area (VTA) which contributes to the subcortical input. Decreased levels of DA neurons and DA receptors are often detected in AD patients’ brains, in agreement with the changes in the midbrain-located DA system of Tg2576 mouse model. Tg2576 mice were genetically modified to overexpress mutated amyloid precursor proteins (APPs). Also, DA is a well-recognized modulator for hippocampal plasticity. The memory formation is encoded by the binding of DA at the hippocampal DA receptors (Nobili 2017). In addition, previous studies applying the 18F - fluorodeoxyglucose Positron Emission Tomography indicated that human neuronal function loss occurs prior to the onset of AD. Synaptic dysfunction is one of the early indicators, marking the initiation of pathology. Spine loss in mice harboring the human familial gene mutation is positively correlated with the appearance of cognitive impairment. Synaptic connectivity determines the signal transmission efficiency, further impacting on the learning and memory (Kashyap, Bapat, Das, Gowaika, Amritkar, Rangaranjan, Ravindranath, & Ambika 2019). In line with these finding, aging is positively correlated with neuronal degeneration. Noda et al. reported the age-dependent DA neuronal loss and mitochondrial dysfunction in DA neurons of C57BL/6 mice (Noda, Sato, Fukuda, Tada, & Hattori 2020). Wang et al. in 2019 also demonstrated that normally aged rat brains contained fewer DA neurons, as the number of TH positive neurons declined significantly in 18-month and 28-month than their younger counterparts which were 2- and 6-month-old (Figure 1) (Wang, Zhou, Wang, Li, Liu, & Zhang 2019).

In neurons with high DA concentration, reactive oxygen species (ROS) is often generated by DA autooxidation, including superoxide anion radical (O2−) and hydrogen peroxide (H2O2) which severely damages cellular activities (Linert, Herlinger, Jameson, Kienzl, Jellinger, & Youdim 1996). ROS can bring a series of toxic consequences: such as mitochondrial dysfunction, oxidative stress and protein denaturation. Not only Aβ, ROS is also a potential pathological factor that intertwines with Aβ through numerous routes. Aβ complex binding to metal ions such as Cu (I/II) and Zn (II) facilitates Aβ aggregation and toxic oligomer formation. In addition, the redox-active metal bound Aβ complex

Figure 1. The image shows the stained neurons using anti-TH in four age groups: 2-month, 6-month, 18-month and 28-month-old. Quantitative counting is summarized as a bar chart in which *P < .05 compared with 2-month-old rats (Wang, Zhou, Wang, Li, Liu, & Zhang 2019).
promotes the overproduction of ROS. Consequently, ROS overproduction would impose detrimental effects on nucleic acids, lipids and cellular organelles (Han, Lee, Kim, Lee, Suh, Cho, Chae, & Lim 2018). These factors can individually or mutually contribute to oxidative transformation of DA, bridging the gap between DA and AD pathology. DA is responsible for long-term memory and motor activities, therefore, Aβ-included DA system dysfunction, as well as degeneration of AD-releasing neurons in VTA region were commonly reported in AD-affected brains. In conclusion, DA, along with its oxidative derivatives, would have a potential role in oxidizing metal-bound or metal-free Aβ oligomers and regulating Aβ aggregation pathways (Nam, Derrick, Lee, Kang, Han, Lee, Chung, & Lim 2018).

Despite that aging is reported to be a major risk factor of AD, normal aging still overlaps with AD in terms of pathology and postulated mechanisms. For instance, neurofibrillary tangles (NFTs) and plaques are frequently found in brains of neurologically normal individuals in postmortem studies (Figure 2) (Davis, Schmitt, Wekstein, & Markesbery 1999). Besides, tau pathology which has been confined in LC and entorhinal cortex (EC) is also detected in many aged brains. The deposit of phosphorylated tau was visualized by staining and identified via the immunocytochemistry techniques. The severity of AD develops with aging until the symptoms are diagnosable (Braak, Thal, Ghebremedhin, & Del Tredici 2011). In addition, oxidative balance in brains is disrupted with aging, as the capacity of synthesizing anti-oxidants decreases significantly. Thus, ROS accumulates and inhibits the metabolically important pathways, such as the synthesis of DNA, lipids and proteins. Moreover, inefficient oxidative phosphorylation in mitochondria of older individuals might aggravate the oxidative stress (Sutherland, Chami, Youssef, & Witting 2013). The close association between aging, mitochondrial dysfunction and oxidative burden in AD formation would implicate that antioxidants would be a potential medical target.

3 NA PATHWAY

Noradrenergic pathway initiates from the cell bodies in LC and propagates towards different cerebral regions, spinal cord, and other areas, such as the amygdala, hippocampus, and hypothalamus (Moret, & Briley 2011). Unlike GABA or glutamate which binds to ionotropic receptors in fast action, NA is a neuromodulator and mainly activates metabotropic receptors (Ranjbar-Slamloo, & Fazlali 2020). NA is synthesized from precursor amino acid tyrosine by a series of steps. Dopamine-β-hydroxylase is one of the critical enzymes which catalyze the conversion of dopamine to NA. Once the step is completed, the vesicle packs NA and transports it across the membrane by VMAT2 into the synaptic cleft via exocytosis. Otherwise, catechol-O-methyltransferases (COMT) or monoamine oxidases (MAO) can enzymatically digest the extracellular NA molecules (Figure 3) (Gannon, & Wang 2019). The release of noradrenaline is mediated by adrenoceptors which could generate different effects. For instance, activation of presynaptic α2-adrenoceptors (α2-ARs) and β2-adrenoceptors (β2-ARs) respectively inhibits and promotes NA release. Transporter facilitates the recycling of NA into the presynaptic neuron. The complexity of NA is regulated by the density or distribution of different adrenoceptor subtypes (Gareri, De Fazio, & De Sarro 2002).

Figure 2. The process of NA synthesized in the presynaptic neuron and different fates of NA (Reprinted from “NA synthesis and export”, by BioRender.com (2021).
As NA is mainly supplied from LC, the degeneration of NA is marked as an early sign of neurodegeneration. One of the most obvious changes in the LC region is the decline in the number of NA neurons. A significant NA neuron loss can lead to AD progression (Holland, Robbins, & Rowe 2021). The remaining NA neurons would initiate changes in activity as a compensation. For instance, the mRNA level of TH would increase in the remaining NA neurons, since TH is involved in the rate-limiting step. According to TH-immunoreactivity (TH-IR) quantification, the number of TH-IR-positive neurons reduced significantly in AD subjects (Figure 3). The evidence further emphasizes the importance of NA in maintaining the normal functioning of human brains.

In post-mortem studies of AD patients’ brains, tissue separation and oligonucleotide probe which targets at the AR of interest were performed individually. It was found that various AR subtypes undergo different changes. The expression level of α1A- and α2A-AR mRNA in the hippocampus remains constant, whereas the expression level of α1D- and α2C-AR mRNA reduces profoundly (Szot, White, Greenup, Leverenz, Peskind, & Raskind 2006). Alterations in the AR are constantly observed with the changes in receptor expression and density, affecting sensitivity and amplitude of the NA modulating abilities (Gannon, & Wang 2019). Furthermore, AR subtypes were proved to be related to the formation of Aβ. For instance, α2A-AR activation interprets the interaction of APP with a Vps10 family receptor which mediates the APP sorting. Therefore, activation of imt2A-AR promotes the amyloidogenic process (Chen, Peng, Che, Gannon, Liu, Li, Bu, van Groen, Jiao, & Wang 2014). Similarly, β2-AR up-regulates the γ-secretase activity. Activated γ-secretase, along with β-secretase, cleaves APP to produce Aβ. Thereby β2-AR accelerates the pathology of AD by stimulating more Aβ plaques formed in the brains (Ni, Zhao, Bao, Zou, Teng, Wang, Song, Xiong, Bai, & Pei 2006). The β2-AR also functions to influence the microglial dynamics. Strikingly, the effect of β2-AR imposed on microglia depends on the stress level. By comparing mice during wakefulness and sleeping, β2-AR was found to diminish the activity and clearance ability of microglia for awake mice. In contrast, β2-AR inhibitors down-regulate the stress-induced activities of microglia (Mather 2021).

Even though a clear relationship between the postmortem LC neuron count and aging has not been established, several other indicators have implied the decline in the LC-NA system. One of the indicators is the decreased NA level with aging in some brain regions, such as the cingulate gyrus, hippocampus, hippocampus and hindbrain (Mather, Gutchess, & Thomas 2019). Complementarily, NA level in cerebrospinal fluid and blood grows with age progression. Seals & Esler estimated that a 15-20% increase per decade in plasma NA would be observed over the adult range. More NA spillover into plasma was reported in accord with aging (Seals, & Esler 2000). The degree of increase is even more obvious
in AD patients than in healthily aged adults (Elrod, Peskind, DiGiacomo, Brodkin, Veith, & Raskind (1997). Strikingly, hyperactivation of LC-NA systems would also occur in the early AD stage. LC hyperactivation promotes the Ca2+ influx and mitochondrial toxicity. Furthermore, the pacemaker activity is interpreted, associated with an elevation in bioenergetic demand which would potentially induce a significant level of oxidative stress (Weinshenker 2018). Moreover, tau pathology continues to progress in LC with aging. Increasing tau proteins are hyperphosphorylated and integrate as oligomers. The tubulin-binding affinity of hyperphosphorylated tau decreases. Instead, tau proteins tend to aggregate. Consistently, aggregated tau is often involved in the initial phase of AD and other neurodegenerative diseases (Iqbal, Liu, & Gong 2016). At least, by current studies, clinical signs of AD are detectable in an early age but can also be symptomless, since pre-tangles and NFTs in nerves can exist for decades. Although AD is not likely to be age-dependent, it develops in a long-term mode and extends in old ages (Braak, & Del Tredici 2011).

4 CONCLUSIONS

The article reviews the past investigations on the DA and NA. In conclusion, DA and NA, being provided from VTA and LC, are both crucial neuromodulators in terms of modulating brain states and memory formation. They influence the brain functioning from several mechanisms: (1) reduction or lack of neurons synthesizing DA or NA; (2) adding burden to oxidative stress in the neurons; (3) variation in the density and expression levels of different AR subtypes. These findings provide new strategies for designing drugs which target specifically at AD patients in the hope that their brains’ normal functions could be recovered. Although brain changes during normal aging overlap partially with changes in AD patients’ brain, there is still no clear evidence to prove that aging is directly correlated to AD progress. But instead, AD is more likely to affect an individual from an early age until the symptoms reveal in a relatively older age. Thus, it would be worth exploring if there is any other factors correlated to aging.

REFERENCES


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