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Review

Ascending monoaminergic systems alterations in Alzheimer's disease. Translating basic science into clinical care

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ABSTRACT

Extensive neuropathological studies have established a compelling link between abnormalities in structure and function of subcortical monoaminergic (MA-ergic) systems and the pathophysiology of Alzheimer's disease (AD). The main cell populations of these systems including the locus coeruleus, the raphe nuclei, and the tuberomamillary nucleus undergo significant degeneration in AD, thereby depriving the hippocampal and cortical neurons from their critical modulatory influence. These studies have been complemented by genome wide association studies linking polymorphisms in key genes involved in the MA-ergic systems and particular behavioral abnormalities in AD. Importantly, several recent studies have shown that improvement of the MA-ergic systems can both restore cognitive function and reduce AD-related pathology in animal models of neurodegeneration. This review aims to explore the link between abnormalities in the MA-ergic systems and AD symptomatology as well as the therapeutic strategies targeting these systems. Furthermore, we will examine possible mechanisms behind basic vulnerability of MA-ergic neurons in AD.

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Abbreviations: Aβ, amyloid β; AADC, L-amino acid decarboxylase; ACC, Anterior cingulate cortex; AD, Alzheimer's disease; aMCI, Amnestic mild cognitive impairment; APP, Amyloid precursor protein; AR, Adrenergic receptor; ATMX, atomoxetine; BDNF, Brain-derived neurotrophic factor; BPSD, Behavioral/psychological symptoms in dementia; CA, Cornus ammonis; COMT, Cathechol-O-methyltranferase; DA, Dopamine; DA-ergic, Dopaminergic; DAT, DA transporter; DBH, DA β-hydroxylase; DG, Dentate gyrus; DLPFC, Dorsolateral prefrontal cortex; DOPAC, 3,4-Dihydroxyphenylacetic acid; DRN, Dorsal raphe nucleus; DS, Down syndrome; EC, Entorhinal cortex; GPCR, G protein coupled receptor; GWAS, Genome-wide association studies; HA, Histamine; HMT, Histamine-N-methyl-transferase; HDC, Histidine decarboxylase; HVA, Homovanillic acid; 5HIAA, 5-Hydroxyindoleacetic acid; IDE, Insulin-degrading enzyme; IDO, Indoleamine 2,3-dioxygenase; LC, Locus coeruleus; L-DOPA, L-3,4-dihydroxyphenylalanine; L-DOPS, L-threo-dihydroxyphenylserine; MA, Monoamine; MA-ergic, Monoaminergic; MAO, Monoamine oxidase; MAO-B, Monoamine oxidase B; MMSE, Mini-Mental State Exam; MHPG, 3-Methoxy-4-hydroxyphenylglycol; MRN, Median raphe nucleus; MS, Medial septum; mtDNA, Mitochondrial DNA; NAD, Nicotinamide adenine dinucleotide; NADP, Nicotinamide adenine dinucleotide phosphate; NBM, nucleus basalis magnocellularis; NFT, Neurofibrillary tangle; NGF, Nerve growth factor; OFC, Orbitofrontal cortex; PD, Parkinson's disease; PFC, Prefrontal cortex; PLC, Phospholipase C; PP, Perforant path; SAMP8, Senescence-accelerated prone mouse; SNpc, Substantia nigra pars compacta; SNP, Single nucleotide polymorphism; SSRI, Selective serotonin reuptake inhibitor; 5-HT, 5-Hydroxytryptamine; 5-HTT, 5-HT transporter; 5-HTTLPR, 5-HT transporter gene-linked polymorphic region; t-MeHA, Tele-methylimidazole acetic acid; TPH, Tryptophan hydroxylase; TH, Tyrosine hydroxylase; TMN, Tuberomamillary nucleus; VMA, Vanillylmandelic acid; VTA, Ventral tegmental area.

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1. Introduction

Even with the recent slowdown in the economy, the past three decades have witnessed an incredible rate of economic growth around the world. For instance, China, India, and Brazil (comprising around 40% of the world population) have increased their average gross domestic product by 10-fold. The sustained economic prosperity in these countries has been closely linked to an increase in life expectancy. As a result, the world population is becoming increasingly old. In case of China, the number of individuals 60 years and older has increased from 76 million in 1982 to more than 130 million in 2006 (Flaherty et al., 2007).

Dementia, primarily caused by Alzheimer's disease (AD), is one of the most important health challenges linked to aging (Savva et al., 2009). In 2001, a report by AD International estimated that there were 24.3 million cases of dementia worldwide, of which, 60% reside in developing countries (Prince et al., 2004). Currently, there are 5.4 million people with AD in the US and this figure is expected to reach 16 million by 2050. In addition to the incredible human toll (Minino, 2011), AD has also been proven to be economically expensive. The cost of providing care for AD patients has been shown to be three times higher than other disorders affecting people 65 years and older (Thies and Bleiler, 2011). In 2010, the annual economic cost of dementia in the world was estimated to be around US$ 604 billion (Wimo and Prince, 2010).

AD is a neurodegenerative disorder leading to both macroscopic and microscopic structural alterations and dysfunction of multiple neuronal circuits in the brain. Macroscopically, AD is associated with brain atrophy particularly in the hippocampus and cortical regions along with widening of lateral ventricles (Kim et al., 2012). At the microscopic level, AD has been linked to senile plaques, neurofibrillary tangles (NFT), as well as synaptic and neuronal loss particularly in the hippocampus and temporal cortex. Senile plaques are characterized by dystrophic neurites containing abnormal mitochondria, lysosomes, and microtubules in the periphery and amyloid β (Aβ) in the core region. Neurofibrillary alterations (i.e. NFTs, dysmorphic neurites surrounding Aβ, and neuropil threads) are mostly intracellular accumulations of paired helical filaments. Among cortical regions, the entorhinal cortex (EC) has been shown to be the first region to display AD changes while primary sensorimotor areas are generally spared (Braak et al., 1993).

In addition to the occurrence of plaques and tangles in the cortex, AD is associated with degeneration of subcortical populations, particularly cholinergic and monoaminergic (MA-ergic) systems (Wenk, 2003). The affected neurons are generally characterized by long and poorly myelinated axons, extensively projecting to hippocampal and cortical regions. Through vast innervation, these numerically sparse subcortical regions impose a strong modulatory influence on hippocampal and cortical cells. Neuroanatomical studies in animal models of neurodegeneration have indicated that all these regions play significant roles in attention and memory acquisition and retrieval. A question has been raised regarding the role of degeneration of these subcortical regions in the pathophysiology of AD. We have previously reviewed the role of degeneration of the cholinergic system in AD (Salehi et al., 2007b). Here, we aim to review the status of MA-ergic systems in the brainstem and hypothalamus and their ascending projections in the pathophysiology of AD. In AD, as in Down syndrome (DS), there is a degeneration of ascending cholinergic fibers arising from basal forebrain cholinergic neurons. In our previous studies, we were able to link the loss of cholinergic neurons in the Ts65Dn mouse model of DS to a defect in the retrograde transport of nerve growth factor (NGF) associated with abnormal early endosomes. Interestingly, failed NGF axonal transport in Ts65Dn mice was linked to the over-expression of amyloid precursor protein (App) in these mice (Salehi et al., 2007b; Millan Sanchez et al., 2011). We also found similar relationship between *App* over-expression and degeneration of MA-ergic neurons in the locus coeruleus (LC) in the Ts65Dn mouse model of DS (Salehi et al., 2009a).

It has been known for long that MA-ergic systems are widely affected in AD. Mann and colleagues reported significant reduction in the nucleolar volume and total RNA levels in both serotonergic (5-HT-ergic) and norepinephrinergic (NE-ergic) neurons in the brainstem of AD patients (Mann et al., 1982, 1984). Several new studies including our own, confirmed MA-ergic neuron degeration (Himeno et al., 2011; Jurgensen et al., 2011; Kalinin et al., 2011; Salehi et al., 2009a) and have successfully targeted these systems for the treatment of cognitive dysfunction in mouse models of neurodegeneration. In light of these new findings – as well as of reports that polymorphisms in MA-ergic related genes are associated to behavioral and cognitive features of AD (Borroni et al., 2004; Witte and Floel, 2012) – it has become necessary to revisit the current status of knowledge about the role of MA-ergic systems in the pathogenesis of AD.

The positive effects of improving NE-ergic system on cognition in mouse models of neurodegeneration (Salehi et al., 2009a) have now been complemented by additional exciting studies indicating