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Review article

Monoaminergic neuropathology in Alzheimer's disease

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ABSTRACT

None of the proposed mechanisms of Alzheimer's disease (AD) fully explains the distribution patterns of the neuropathological changes at the cellular and regional levels, and their clinical correlates. One aspect of this problem lies in the complex genetic, epigenetic, and environmental landscape of AD: early-onset AD is often familial with autosomal dominant inheritance, while the vast majority of AD cases are late-onset, with the ε4 variant of the gene encoding apolipoprotein E (APOE) known to confer a 5–20 fold increased risk with partial penetrance. Mechanisms by which genetic variants and environmental factors influence the development of AD pathological changes, especially neurofibrillary degeneration, are not yet known. Here we review current knowledge of the involvement of the monoaminergic systems in AD. The changes in the serotonergic, noradrenergic, dopaminergic, histaminergic, and melatonergic systems in AD are briefly described. We also summarize the possibilities for monoamine-based treatment in AD. Besides neuropathologic AD criteria that include the noradrenergic locus coeruleus (LC), special emphasis is given to the serotonergic dorsal raphe nucleus (DRN). Both of these brainstem nuclei are among the first to be affected by tau protein abnormalities in the course of sporadic AD, causing behavioral and cognitive symptoms of variable severity. The possibility that most of the tangle-bearing neurons of the LC and DRN may release amyloid β as well as soluble monomeric or oligomeric tau protein trans-synaptically by their diffuse projections to the cerebral cortex emphasizes their selective vulnerability and warrants further investigations of the monoaminergic systems in AD.

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1. Clinical and neuropathological criteria for AD diagnosis

Alzheimer's disease (AD) accounts for 60–70% of cases of dementia (World Health Organization, WHO Fact Sheet No. 362, March 2015). The report of Alzheimer's Disease International (ADI, The World Alzheimer Report, 2015) showed that nearly 35.6 million people suffered from dementia in 2012. It is estimated that this number will quadruple by 2050. Therefore, the WHO in 2012 declared AD a global public health priority. There is still no effective treatment to prevent or cure AD. Currently, approved drugs only temporarily alleviate some of the disease symptoms to a limited extent. Cholinomimetics (tacrine, rivastigmine, donepezil, and galantamine) do so by enhancing the cholinergic neurotransmission, whereas memantine (a non-competitive antagonist of *N*-methyl-D-aspartate receptors, NMDAR) is considered to have protective activity against glutamate-induced excitotoxic neuronal death (Yiannopoulou and Papageorgiou, 2013).

1.1. Clues to the etiology of AD

After the milestone discoveries that cerebrovascular amyloid (due to cerebral amyloid angiopathy, CAA) and senile plaques (SP) are composed of amyloid β (Aβ) peptide, that the same antigenic determinants (Glenner and Wong, 1984a; Wong et al., 1985) are shared in both AD and Down's syndrome (Glenner and Wong, 1984b), and that the Val717Ile missense ("London") mutation in the amyloid precursor protein (*APP*) gene on chromosome 21 was found to be causally related to the early-onset autosomal-dominant familial AD (Goate et al., 1991), Hardy, Selkoe and colleagues (Hardy and Allsop, 1991; Selkoe, 1991; Hardy and Higgins, 1992) formulated the amyloid cascade hypothesis, which has become a dominant view of AD pathogenesis ever since. An illustration of amyloid plaques in the brain of an AD case is given in Fig. 1. According to the amyloid theory, excessive production of Aβ (which exists in monomeric, oligomeric, and aggregated forms as

Abbreviations: 2OG, 2-oxoglutarate; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; 5mC, 5-methylcytosine; 6-OHDA, 6-hydroxydopamine; α-KG, α-ketoglutarate; AAAD, aromatic-L-amino acid decarboxylase; AANAT, aralkylamine N-acetyltransferase; AAS, ascending arousal system; Aβ, amyloid β; AChE, acetylcholinesterase; AChEI, acetylcholinesterase inhibitors; AD, Alzheimer's disease; ADAM10, adisintegrin and metalloprotease 10; ADI, Alzheimer's Disease International; ADL, activities of daily living; AgD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; *Alu*, Alu (repetitive) element; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, amyloid plaques; APOE, apolipoprotein E; APP, amyloid precursor protein; ASMT, N-acetylserotonin *O*-methyltransferase; ATP, adenosine triphosphate; BACE, β-site APP cleaving enzyme; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BF, Bayes factor; BMAA, β-methylamino-L-alanine; BNST, bed nucleus of the stria terminalis; BPSD, behavioral and psychological symptoms of dementia; BuChE, butyrilcholinesterase; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CaMKII, calcium/calmodulin-activated protein kinase II; cAMP, cyclic adenosine monophosphate; CBD, cortico-basal degeneration; CBP, cAMP response element binding protein; CDK5, cyclin-dependent kinase 5; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's disease; ChAT, choline acetyltransferase; CHIP, carboxyl-terminus of Hsp70 interacting protein; CK1, casein kinase 1; CpG, island, region of DNA where a cytosine nucleotide is followed by a guanine separated by only one phosphate (5'-cytosine-phosphate-guanine-3'); CNS, central nervous system; COMT, catechol-*O*-methyltransferase; CSF, cerebrospinal fluid; CVD, cerebrovascular diseases; DBH, dopamin-β-hydroxylase; DLB, dementia with Lewy bodies; DMN, default-mode network; DNMT, DNA methyltransferase; DOPAC, dihydroxyphenylacetic acid; DRN, dorsal raphe nucleus; DSM, Diagnostic and Statistical Manual for Mental Disorders; DYRK1A, dual specificity tyrosine-phosphorylation-regulated kinase 1A; EHT, eicosanoyl-5-hydroxytryptamide; ELISA, Enzyme-Linked Immunosorbent Assay; EOAD, early-onset Alzheimer's disease; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GSK, glycogen synthase kinase; GWAS, genome-wide association study; HCHWA-D, hereditary cerebral hemorrhage with amyloidosis – Duch type; HDAC, histone deacetylase; HDC, histidine decarboxylase; HLA, human leukocyte antigen; HMT, histamine *N*-methyltransferase; JNK, c-Jun N-terminal kinase; LBD, Lewy body disease; LC, locus coeruleus; L-DOPA, L-3,4-dihydroxyphenylalanine; L-DOPS, L-threodihydroxyphenylserine; *LINE-1*, long interspersed (repetitive) element 1; LOAD, late-onset Alzheimer's disease; LTD, long-term depression; LTP, long-term potentiation; LXR, liver-X receptors; MAO-A, monoamine oxidase A; MAPK, mitogen-activated protein kinase; MAPT, microtubule-associated protein tau; MARK, microtubule affinity-regulated kinase; MCI, mild cognitive impairment; MFB, medial forebrain bundle; MHPG, 3-metoxy-4-hydroxyphenylglycol; miRNA, microRNA; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NFT, neurofibrillary tangles; NIA/AA, National Institute on Aging and the Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NMDAR, *N*-methyl-D-aspartate receptors; NP, neuritic plaques; NRC, nucleus raphe centralis; NRD, nucleus raphe dorsalis; NRL, nucleus raphe linearis; NRM, nucleus raphe magnus; NRO, nucleus raphe obscurus; NRP, nucleus raphe pallidus; NT, neuropil threads; PAG, periaqueductal gray; PART, primary age-related tauopathy; PD, Parkinson's disease; PDPK, proline-directed protein kinases; PET, positron emission tomography; PFC, prefrontal cortex; PHF, paired helical filaments; PKA, protein kinase A; PP2A, protein phosphatase 2A; PSD-95, postsynaptic density protein 95; PSEN, presenilin; PSP, progressive supranuclear palsy; *PTK2B*, protein tyrosin kinase 2β; RCT, randomized controlled trial; REM sleep, rapid eye movement sleep; rs, reference single nucleotide polymorphism; rTMS, repetitive transcranial magnetic stimulation; SCN, suprachiasmatic nucleus; SERT, serotonin transporter; SF, straight filaments; SIRT1, sirtuin 1; SN, substantia nigra; SNc, substantia nigra pars compacta; SNP, single nucleotide polymorphism; SP, senile plaques; SPECT, single-photon emission computed tomography; SSRI, selective serotonin reuptake inhibitor; SWS, slow-wave sleep; TACE, TNF-α converting enzyme; TARDBP, transactive response DNA-binding protein; TH, tyrosine hydroxylase; t-MeHA, tele-methylhistamine; TNF-α, tumor necrosis factor α; TOR, target of rapamycin; TPH, tryptophan hydroxylase; TPSD, tangle-predominant senile dementia; VBI, vascular brain injury; VTA, ventral tegmental area; WHO, World Health Organization.