Review

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Nerve growth factor metabolic dysfunction in Alzheimer's disease and Down syndrome

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Alzheimer's disease (AD) is a devastating neurodegenerative condition and the most common type of amnestic dementia in the elderly. Individuals with Down syndrome (DS) are at increased risk of developing AD in adulthood as a result of chromosome 21 trisomy and triplication of the amyloid precursor protein (APP) gene. In both conditions, the central nervous system (CNS) basal forebrain cholinergic system progressively degenerates, and such changes contribute to the manifestation of cognitive decline and dementia. Given the strong dependency of these neurons on nerve growth factor (NGF), it was hypothesized that their atrophy was caused by NGF deficits. However, in AD, the synthesis of NGF is not affected at the transcript level and there is a marked increase in its precursor, proNGF. This apparent paradox remained elusive for many years. In this review, we discuss the recent evidence supporting a CNS deficit in the extracellular metabolism of NGF, both in AD and in DS brains. We describe the nature of this trophic disconnection and its implication for the atrophy of basal forebrain cholinergic neurons. We further discuss the potential of NGF pathway markers as diagnostic indicators of a CNS trophic disconnection.

Alzheimer's disease and Down syndrome

Alzheimer's disease (AD) is one of the most common – and feared – age-related neurodegenerative diseases affecting world health [1]. The clinical onset of AD is characterized by the gradual loss of short-term memory followed by a progressive deterioration of cognition and behavior which may affect thinking, planning, judgment, and social skills [2]. In the end, the degree of cognitive dysfunction and physical deterioration is so pronounced that the person exhibits a profound dementia, being unable to carry out normal activities of everyday life.

Pathologically, AD is defined by the presence of extracellular amyloid plaques surrounded by dystrophic neurites and neurofibrillary tangles within neuronal cell bodies [3–5]. Amyloid plaques are insoluble deposits of a 4 kDa peptide of ~40–42 amino acids in length, known as amyloid β (Aβ), which has a high propensity to aggregate [6,7]. Neurofibrillary tangles are intracellular inclusions consisting of abnormally phosphorylated filaments of a protein called tau [8]. These pathological aggregates build up in substantial numbers within the entorhinal cortex, hippocampus, amygdala, and throughout the rest of the cortex; and their presence within these brain regions contributes to the learning and memory deficits that characterize AD [9]. However, it would be misleading to define AD as a disorder of plaques and tangles alone, considering the many other complex structural and functional deficits that coexist (e.g., synaptic dysfunction, neurotransmitter deficits, neuroinflammation, and oxidative stress); for comprehensive reviews on these additional aspects of AD pathology, see [10–13].

Impaired memory function is not exclusive of AD and is fairly common in people with mild cognitive impairment (MCI), a condition which is increasingly recognized as being prodromal to AD dementia [14]. Pathologically, a brain with MCI may be almost indistinguishable from a brain with AD [15], and individuals with MCI exhibit a 5–10 times higher risk of developing dementia than the normal aging population [16]. In addition, converging evidence from cognitive and pathological studies indicates that AD exhibits a long asymptomatic phase, during which degenerative changes develop in the brain (over decades), in the absence of clinically detectable symptoms [17–19]. During this phase, referred to as presymptomatic or preclinical AD, Aβ and tau pathology may develop while the person remains cognitively healthy, and before an eventual transition to MCI/AD [20–23]. Understanding the link between the development of these pathological changes and the onset of clinical disease will be central to develop strategies that halt disease progression and preserve cognition.

Unfortunately at present, there is no diagnostic evaluation that can 'unequivocally' identify individuals with 'latent' AD prior to the development of memory loss and dementia symptoms [24]. In contrast to AD, the study of Down syndrome (DS) brains offers the unique opportunity to investigate the temporal sequence of AD pathology development. Triplication of chromosome 21 in DS results in overexpression of the amyloid precursor protein (APP),

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the parent protein from where Aβ is produced [25]. As a result, DS individuals are at increased risk of developing premature aging and AD dementia compared with the general population [26].

Aβ pathology progressively evolves in DS brains since early life [27,28]. Soluble Aβ peptides are already significantly elevated in the DS fetal cortex, compared with normosomic fetuses [29,30]. Diffuse amyloid plaques may appear as early as 8 years of age [31] and recent studies with positron emission tomography (PET) have shown accumulation of ^{11}C-PiB-positive mature amyloid plaques in DS subjects already in their 30s [32]. By middle age (40–60 years), virtually all DS individuals will have advanced AD pathology, including neuritic amyloid plaques, neurofibrillary tangles, and overt gliosis [33].

Another consistent feature of AD and DS pathology is the preferential vulnerability of cholinergic neurons in the basal forebrain [11], cells which undergo atrophy (and later loss) as AD and DS progress [34,35]. This neuronal network is tightly dependent on the day-to-day offer of nerve growth factor (NGF) [36]. In addition, these neurons are key in the modulation of memory, learning, and attention [37], and their demise contributes to the manifestation of cognitive decline and dementia in both conditions [38]. A major unresolved issue had been how this trophic dependency affects the phenotype of basal forebrain cholinergic neurons in AD and DS.

In this review, we describe the recent evidence supporting a central deregulation of NGF extracellular metabolism in AD and DS. We discuss the impact of this trophic disconnection on the basal forebrain cholinergic neuronal phenotype. We further highlight potential avenues for the identification of novel biomarker candidates signaling a central nervous system (CNS) trophic disconnection.

Cholinergic deficits in AD and DS

Although its pathology is complex and various transmitters are affected in end-stage AD, a consistent and well-established feature of all AD brains is the presence of severe cortical cholinergic deficits, including a loss of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity, in the magnitude from 50% to 90% [39–45]. Such changes are also accompanied by loss of cholinergic fibers throughout the association cortex and subcortical nuclei [44,46]. As the disease progresses, considerable shrinkage (and later loss) of projecting nucleus basalis cholinergic neurons develops [34,35,47–49]. Notably, most of these cells persist in a shrunken state and only a small minority dies in end-stage AD [47,48], suggesting that their atrophy may be amenable to rescue with cholinergic neuroprotective therapies. Nucleus basalis neurons, together with septal cholinergic neurons – both located in the basal forebrain – constitute the major source of cholinergic innervation to the neocortex and hippocampus, respectively [50–52]; for a review, see [53].

The impact of such cholinergic deficits in AD can be best recognized in view of the important role of the cholinergic system in learning, memory, and attentional functions [37,54,55], aspects which have been recently reviewed [56,57]. A corollary of the above-mentioned studies was the establishment of the 'cholinergic hypothesis of geriatric memory dysfunction' by Bartus and colleagues, which linked the global cognitive deterioration in AD (and in normal aging) to deficits in cholinergic neurotransmission [38]. The fact that cholinergic dysfunction has a significant impact on clinical outcome is evidenced by the benefit of cholinergic therapy to slow cognitive decline in patients with mild-to-moderate AD [58].

How early during the progression of AD is the cholinergic system affected? *In vivo* PET studies have found slight reductions (~20–30% downregulation) in cortical AChE activity in MCI and AD subjects with mild dementia [59–61]. More recently, Grothe and colleagues, through the use of magnetic resonance imaging (MRI), have shown reductions in basal forebrain volume in individuals with MCI (which correlated with amyloid deposition and cognitive impairment) and higher annual rates of basal forebrain atrophy in subjects at the predementia stage of AD [62–64]. Paradoxically, despite the evidence for memory decline in MCI, ChAT activity was found to be increased in the hippocampus and frontal cortex of MCI postmortem brain tissue [65]. A similar early upregulation of cortical presynaptic cholinergic bouton numbers has been reported in APP transgenic mice, followed by a marked decrease as the amyloid pathology advances [66]. The upregulation of cholinergic markers during early disease stages could be interpreted as a compensatory response for the evolving neurodegenerative changes (e.g., early cholinergic synaptic alterations) that result from AD pathology accumulation. In fact, similar compensatory responses have been observed in other transmitter systems, such as glutamate, early in the disease course. Analysis of postmortem MCI brains has revealed a paradoxical upregulation in glutamatergic presynaptic bouton density, which correlated with reduced cognitive function [67].

Interestingly, CNS cholinergic deficits have also been reported in DS, in particular, marked reductions in cortical ChAT activity [68] and loss of nucleus basalis neurons in adult subjects [69]. This raises considerable interest given that all adults with DS will invariably develop the neuropathological hallmarks of AD [27,28,33,70–72] and that the prevalence of dementia in DS increases strongly with age [73]. Therefore, similar pathological mechanisms affecting basal forebrain neurons may operate in AD and DS brains. Despite the vast evidence supporting a marked phenotypic dysfunction of the cholinergic system in AD, MCI, and DS, the cause of the preferential vulnerability of this transmitter system remained elusive for decades; a topic that will be covered in subsequent sections.

NGF dependency of basal forebrain cholinergic neurons

Over 80 years ago, the pioneering work of Viktor Hamburger and Rita Levi-Montalcini led to the development of the 'neurotrophic factor hypothesis', which states that developing neurons in the periphery and in the CNS depend on target-derived trophic factors for survival, which are retrogradely transported from their sites of production to innervating neurons [74]. These significant contributions led to the discovery of NGF [75,76] and the subsequent identification of other members of the neurotrophin family (i.e., BDNF, NT3, NT4/5) and their