Medical Hypotheses (2005) **65,** 1106—1119

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Neuro-modulation, aminergic neuro-disinhibition and neuro-degeneration. Draft of a comprehensive theory for Alzheimer disease ☆

H. Peter Schmitt *

Institute of Pathology, Department for Neuropathology, University of Heidelberg, Im Neuernheimer Feld 220-221, 69120 Heidelberg, Germany

Received 18 June 2005; accepted 23 June 2005

Summary A comprehensive theory for Alzheimer disease (AD) which can provide a clue to the neuronal selective vulnerability (pathoklisis) is still missing. Based upon evidence from the current literature, the present work is aimed at proposing such a theory, *namely the 'aminergic disinhibition theory' of AD*. It includes data-based hypotheses as to the pathoklisis, mechanisms of neuro-degeneration and dementia as well as the aetiology of the disease. Alzheimer disease is regarded as a disorder of neural input modulation caused by the degeneration of four modulatory amine transmitter (MAT) systems, namely the serotoninergic, the noradrenergic, the histaminergic, and the cholinergic systems with ascending projections. MATs modulate cognitive processing including arousal, attention, and synaptic plasticity in learning and memory, not only through direct, mostly inhibitory impact on principal neurones but also partially through interaction with local networks of GABA-ergic inter-neurones. The distribution and magnitude of the pathology in AD roughly correlate with the distribution and magnitude of MAT modulation: Regions more densely innervated by ascending MAT projections are, as a rule, more severely affected than areas receiving less MAT innervation. Because the global effect of MATs in the forebrain is inhibition, the degeneration of four MAT systems, some related peptidergic systems and a secondary alleviation of the GABA-ergic transmission means a fundamental loss of inhibitory impact in the neuronal circuitry resulting in neuronal (aminergic) disinhibition. Clearly, the basic mechanism promoting neuronal death in AD is thought to be a chronic disturbance of the inhibition—excitation balance to the advantage of excitation. Chronic over-excitation is conceived to result in Ca^{2+} dependent cellular excito-toxicity leading to neuro-degeneration including amyloid-β production and NFT formation. Disinhibited neurons will degenerate while less excited (relatively

Abbreviations: APP, amyloid precursor protein; Aβ, amyloid β; ATP, adenosine triphosphate; CaMK, calcium/calmodulin-dependent (protein) kinase; COX, cytochrome oxidase; ERK, extra-cellularly regulated kinase; GSK, glycogen synthase kinase; HIT, molecular change of receptor; MAC, membrane attack complex; MAPK, mitogen-activated protein kinase; KDHC, ketoglutarate dehydrogenase complex; PDHC, pyruvate dehydrogenase complex; GVD, granulo-vacuolar degeneration; PHF, paired helical filaments; PK, protein kinase; R, receptor; TKC, transketolase complex; Tpk, τ protein kinase.

☆ Presented as a poster (No. P3-282) at the Ninth International Conference on Alzheimer's Disease and Related Disorders, 17—22 July 2004, Philadelphia, PA, USA.

* Tel.: +49 6221 562629; fax: +49 6221 564566.
E-mail address: horst.schmitt@med.uni-heidelberg.de.

0306-9877/$ - see front matter
doi:10.1016/j.mehy.2005.06.018

over-inhibited) neurones will survive. Because the decline of aminergic transmission in AD is likely to start at the receptor level, it is hypothesized that early impairment by a molecular 'hit' to an MAT receptor (or a group of receptors) initiates a pathogenetic cascade that develops in an avalanche-like manner. Based on experimental evidence from the literature, the 'hit' might be the attachment of a targeted pathogen like a small roaming amino acid sequence to the receptor(s), e.g., the serotoninergic 5-HT_{2A}-R. Referential sequence analysis could be a means to identify such a small pathogen hidden in a large receptor molecule.

Introduction

The current discussion of both the aetiology and the pathogenesis of the dementia in Alzheimer disease (AD) center around the hallmarks of AD histo-pathology, i.e., amyloid-β (Aβ) [84] and protein τ (tau) [46]. However, neither hypothesis, whether based on Aβ [51] or on protein τ [56], can offer a clue to the aetiology of that devastating disorder. Moreover, they provide vague and controverse ideas to the mental decline, the neuro-degeneration and the cell death in AD. None of both hypotheses duely considers the great variability of Aβ and protein τ as histological markers of AD. Clearly, while Aβ hypotheses cannot explain the ''tangle-only'' cases [59], the τ hypotheses fail to explain the ''amyloid-predominant'' cases [134].

Of note, as early as in 1911, Alzheimer [9] already concluded that the amyloid deposits, the amounts of which were found to vary considerably in the individual case, could not be the cause of the senile dementia but only a byproduct (''Begleiterscheinung''). At the same time, other experts found that the amounts of Alzheimer neurofibrillary tangles (NFT) were individually almost as variable as the Aβ deposits. This prompted von Braunmühl in his summary of 1957 [27] to conclude that NFT were to be regarded as secondary phenomena occurring in the course of the disease, without any significance for either the aetiology of the disease or the origin of the dementia. This is further underscored by the fact that brains of non-demented aged subjects may also exhibit considerable amounts of NFT in the hippocampus and Aβ amyloid deposition in the allo-and neocortex [77].

In current discussions special emphasis is put on the neuro-toxicity of Aβ [85]. However, other reports also stress neuro-protective effects of Aβ [14]. Up to now it has remained completely undecided which kind of Aβ effects prevail in vivo. The therapeutic benefits of the elimination of Aβ from the AD brain or the prevention of its formation have been seriously called in doubt [14].

Remarkably, both the Aβ and the τ hypotheses fail to provide a clue also to the basic phenomenon of the distinct distribution of the pathology or the selective vulnerability (pathoklisis) in AD.

The distributional pattern of the neuronal vulnerability was found to prefer allo-cortical and limbic structures [24,25], neo-cortical association realms [139] as well as some distinct ponto-mesencephalic [123,146], diencephalic [26] and basal forebrain nuclei [92] with ascending projections supplying the forebrain with aminergic neurotransmitters.

One basic yet unanswered question in AD is: How and why do some select sets of neurones become dysfunctional or die while others survive [66]? Why are particular regions of the brain and specific populations of neurons selectively vulnerable [115].

Clearly, whether based on Aβ or τ or other mechanisms, any hypothesis or theory that spares the pathoklisis can be neglected.

A comprehensive theory for Alzheimer disease

Based on facts and evidences from the relevant literature I want to propose the following comprehensive theory for Alzheimer disease:

Alzheimer disease is a disorder of neural input modulation in cognitive processing, neuronal disinhibition representing the basic mechanism that initiates and promotes neuro-degeneration and dementia. The disease develops in an avalanche-like manner from a molecular micro-event to a biological macro-event.

In Alzheimer disease, neuronal disinhibition is the result of receptor-mediated degeneration of four aminergic neuro-transmitter systems and associated peptidergic systems, causing a profound decline of aminergic, peptidergic and subsequently GABA-ergic inhibitory impact. This results in neuronal disinhibition (aminergic disinhibition) leading to chronic Ca^{2+}-dependent excito-toxic cell