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NEUROSCIENCE

Amyloid-β and tau in Alzheimer's disease

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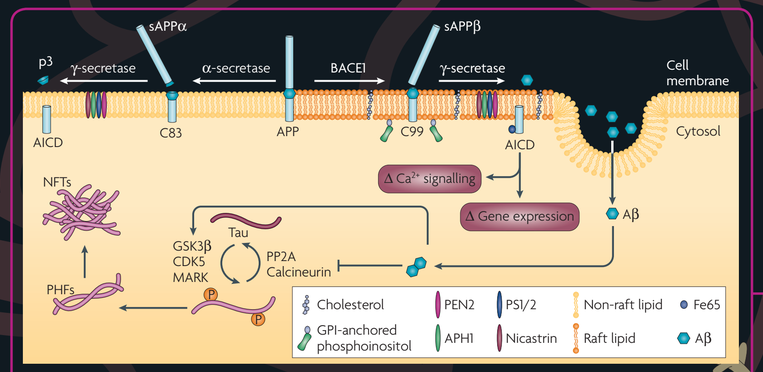
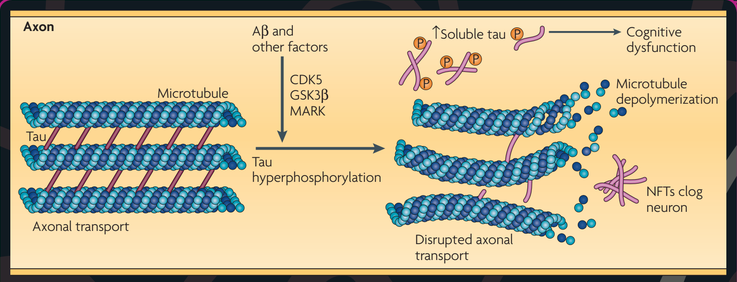
Alzheimer's disease (AD) is a devastating neurodegenerative disorder with a relentless progression. AD pathogenesis is believed to be triggered by the accumulation of the amyloid-β peptide (Aβ), which is due to overproduction of Aβ and/or the failure of clearance mechanisms. Aβ self-aggregates into oligomers, which can be of various sizes, and forms diffuse and neuritic plaques in the parenchyma and blood vessels. Aβ oligomers and plaques are potent synaptotoxins, block proteasome function, inhibit mitochondrial activity, alter intracellular Ca^{2+} levels and stimulate inflammatory processes. Loss of the normal physiological functions of Aβ is also thought to contribute to neuronal dysfunction. Aβ interacts with the signalling pathways that regulate the phosphorylation of the microtubule-associated protein tau. Hyperphosphorylation of tau disrupts its normal function in regulating axonal transport and leads to the accumulation of neurofibrillary tangles and toxic species of soluble tau. Furthermore, degradation of hyperphosphorylated tau by the proteasome is inhibited by the actions of Aβ. These two proteins and their associated signalling pathways therefore represent important therapeutic targets for AD.



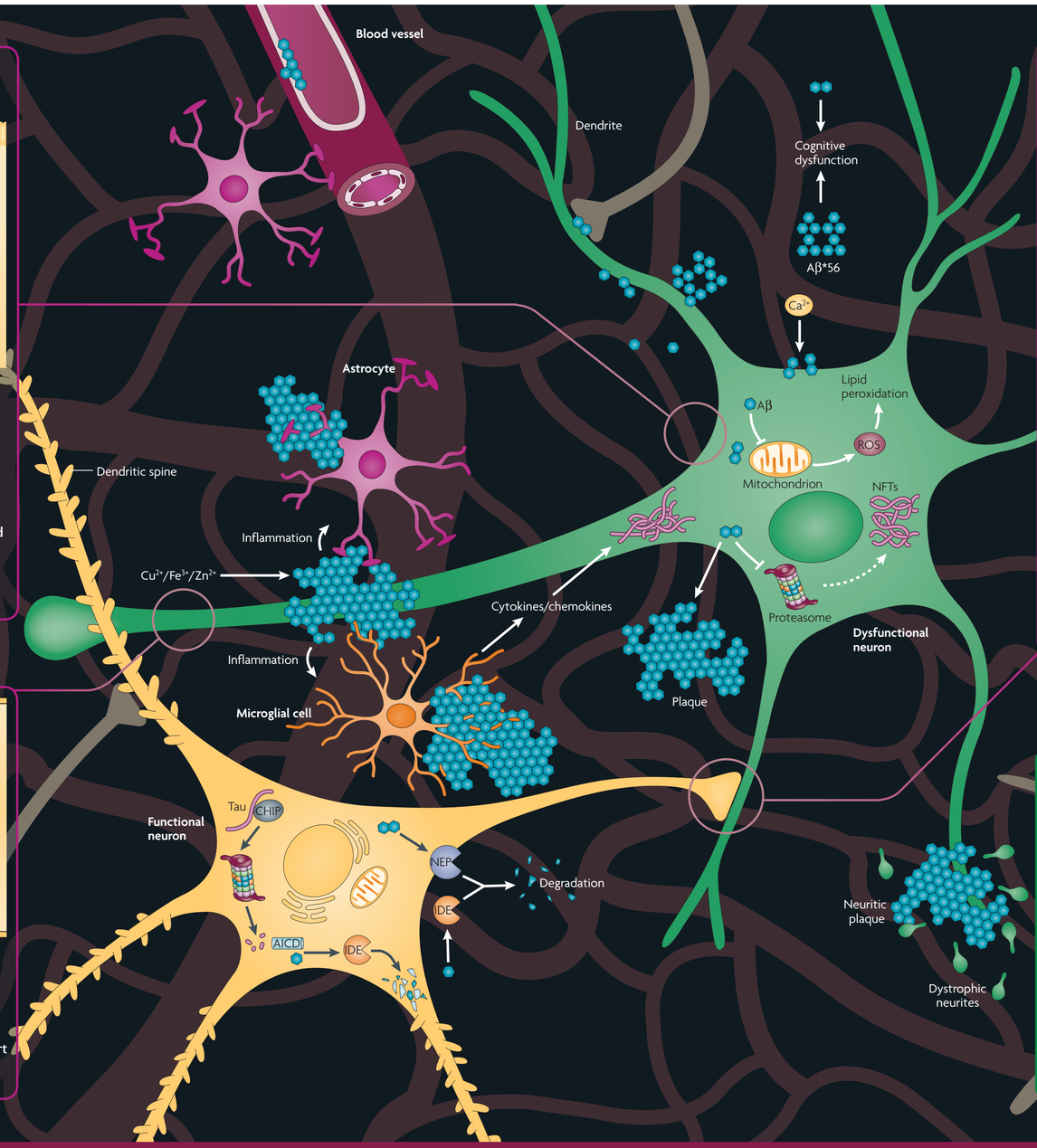
APP and tau processing in neurons

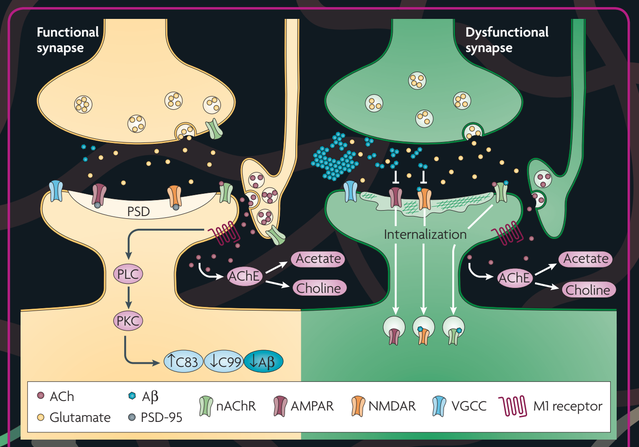
APP is processed by two pathways. In the non-amyloidogenic pathway, APP is cleaved by α-secretase (one of ADAM9, ADAM10 or ADAM17), to generate sAPPα and C83. In the amyloidogenic pathway, which is localized to lipid rafts, BACE1 liberates sAPPβ and generates C99. Cleavage of C99 by γ-secretase (which consists of PS1 or PS2, nicastrin, APH1 and PEN2) releases Aβ and liberates the intracellular domain, AICD, which can modulate gene expression and Ca^{2+} signalling. Aβ oligomers are generated intraneuronally and have numerous adverse consequences, including the facilitation of tau pathology. Certain species of amyloid oligomers, such as Aβ dimers and Aβ*56 (see central figure), are associated with cognitive impairments. In functional neurons, Aβ, Aβ oligomers and AICD are degraded by IDE and NEP. Tau is abnormally hyperphosphorylated in AD, leading to the formation of NFTs. Numerous kinases have been implicated in tau hyperphosphorylation, including GSK3β, CDK5 and MARK. By activating these kinases, certain inflammatory cytokines can also trigger tau hyperphosphorylation. Phosphorylated tau is degraded by the proteasome system.



Effects of tau hyperphosphorylation on axonal function

Tau is a highly soluble microtubule-binding protein. Mutations in tau have not yet been linked to AD, although tau mutations cause frontotemporal dementia with Parkinsonism linked to chromosome 17. Hyperphosphorylation of tau, particularly that mediated by MARK, CDK5 and GSK3β, destabilizes microtubules, causing impairments in axonal transport and neuronal dysfunction. Self-assembly of hyperphosphorylated tau results in the formation of NFTs. However, soluble tau species might also exert potent pathological effects. Targeting the tau pathology might help to attenuate the cognitive decline that occurs in AD.





Effects of Aβ on synaptic function

Synaptic dysfunction is triggered by structural changes, such as the loss of dendritic spines and the PSD, and Aβ-induced neurochemical changes. Aβ is thought to have a physiological role in modulating synaptic activity, the disruption of which probably underlies cognitive dysfunction. Furthermore, excess build-up of Aβ and synaptotoxic Aβ oligomers induces neurotransmitter receptor internalization and inhibition. Acetylcholine levels are markedly reduced in AD, and acetylcholinesterase inhibitors are used as therapeutic agents. Levels of nAChR are diminished in the AD brain, in part by Aβ-induced internalization. Activation of muscarinic M1 receptors shifts APP processing towards the non-amyloidogenic pathway; hence, M1 agonists might represent a therapeutic means of reducing Aβ levels.

Selected current and future therapeutic targets

Target	Approaches
Aβ accumulation	Immunotherapy (active or passive immunization or intravenous immunoglobulin; Bapineuzumab, ACC-001, LY2062430, RN1219) | BACE inhibitors (ATG-Z1) | γ-secretase inhibitors/modulators (tarenflurbil, LY450139, MK0752, E2012) | IDE or NEP | Aβ aggregation inhibitors (ELND005) | Metal chelators (clioquinol) | APP translation inhibitors
Tau hyperphosphorylation/ microtubule dysfunction	CDK5 inhibitors | GSK3β inhibitors | Microtubule stabilizers (AL-108) | Tau aggregation inhibitors
Acetylcholine signalling	Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine) | Muscarinic receptor agonists (NGX267, milameline) | Nicotinic receptor modulators (AZD3480, MEM3454, GTS-21)
Glutamate signalling	NMDA receptor antagonists (memantine, neramexane) | Ampakines (AMPAR modulators; CX516)
Other neurotransmitter receptors and ion channels	GABA receptor antagonists (SGS-742) | Serotonin receptor antagonists (xaliproden, lecozotan, PRX-03140) | Calcium channel blockers (MEM1003)
Inflammation	Anti-inflammatories (ibuprofen, naproxen, rofecoxib, PPAR-γagonists)
Oxidative stress	Antioxidants | Calpain inhibition
Preventative measures	Cholesterol-lowering agents (lovastatin, pravastatin) | Stress reduction (mifepristone) | Dietary (DHA, curcumin, vitamins) | Lifestyle (exercise, mental stimulation)
Neuroprotective mechanisms/repair	NGF gene therapy | Neurotrophin support/mimics | Neural stem cell therapy | Hormone replacement therapy

About the Elan and Wyeth collaboration

The Elan and Wyeth Alzheimer's Immunotherapy Program (AIP) includes investigational clinical programmes for bapineuzumab (AAB-001), ACC-001 and other immunotherapeutic compounds. AIP is a 50–50 collaboration whose aim is to research, develop and commercialize an immunotherapeutic approach that could be used for the treatment of mild to moderate Alzheimer's disease and possibly to prevent the onset of the disease. For additional information about Elan, please visit http://www.elan.com. For additional information about Wyeth, please visit http://www.wyeth.com.

Abbreviations

Aβ, amyloid-β; ACh, acetylcholine; AChE, acetylcholinesterase; ADAM, a disintegrin and metalloproteinase domain; AICD, APP intracellular domain; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; APH1, anterior pharynx-defective 1; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme; CDK5, cyclin-dependent kinase 5; CHIP, C-terminus HSP70-interacting protein; DHA, docosahexaenoic acid; GABA, γ-aminobutyric acid; GSK3β, glycogen synthase kinase 3β; IDE, insulin-degrading enzyme; MARK, microtubule-affinity-regulating kinase; nAChR, nicotinic acetylcholine receptor; NEP, neprilysin; NFTs, neurofibrillary tangles; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; PEN2, presenilin enhancer 2; PHFs, paired helical filaments; PKC, protein kinase C; PLC, phospholipase C; PP2A, protein phosphatase 2A; PPARγ, peroxisome proliferator-activated receptor-γ; PS, presenilin; PSD, postsynaptic density; ROS, reactive oxygen species; sAPP, secreted APP ectodomain; VGCC; voltage-gated calcium channel.

Contact information and acknowledgements

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The author thanks C. Glabe, K. Green, M. Blurton-Jones and S. Oddo for helpful suggestions and A. Parachikova for assistance with the figures.
Work supported by grants from the US National Institute of Aging (AG-021982 and AG-027544).

Edited by Katherine Whalley; copy edited by Craig Nicholson; designed by Kirsten Lee.
http://www.nature.com/nrn/posters/index.html

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