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Neurology 2018 -Novel basic cell biological approaches to prevent the neuropathological disease symptoms and behavior-Harish C Pant- National Institutes of Health

Harish C Pant
National Institutes of Health, USA

Abstract
Novel basic cell biological approaches to prevent the neuropathological disease symptoms and behavior However, during neuronal insults, it is deregulated induces neuropathology. During our course of studies to understand the biology of this regulation we identified cyclin dependent kinase5 (Cdk5); a neuron specific kinase involved in the nervous system development, function and survival. It was recognized that in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's (PD) and Amyotrophic lateral sclerosis (ALS) the pathology was characterized by aberrant and hyper activation of Cdk5 and accumulation of aberrantly hyper phosphorylated cytoskeletal proteins in cell bodies, suggesting that topographic regulation had been compromised. This led inevitably into studies of neurodegeneration in cell culture and model mice with emphasis on Cdk5 that targets numerous neuronal proteins including cytoskeletal protein regulation by phosphorylation, which when deregulated, is responsible for the pathology seen in neurodegenerative diseases. In cell systems, neuronal stress results in deregulated kinases. Recently we've discovered peptides derived from, p35, and a neuron specific activator of Cdk5, which rescue cells in vitro from stress induced pathology. The questions currently being investigated are (1) how is cytoskeletal protein phosphorylation topographically regulated in neurons? (2) What factors are responsible for the deregulation of Cdk5 in neurons? (3) Can mouse models of AD, PD and ALS be treated therapeutically with peptides that inhibit deregulated Cdk5?

Therapies targeted at amyloid

According to the amyloid cascade hypothesis, AD-related pathology typically begins with asymptomatic cerebral amyloidosis many years before the onset of clinical symptoms. Accumulation of Aβ within the brain starts with monomeric Aβ leaving its reservoir within the spinal fluid (CSF) to make toxic aggregates followed by deposition on neuronal surface and synaptic terminals. Therefore, the majority of AD treatment strategies targeted at the amyloid cascade in the past 30 years or so has been focused on reducing Aβ generation through development of β- and γ-secretase inhibitors, accelerating Aβ clearance through active and passive immunotherapy's, as well as preventing formation of toxic amyloid aggregates.

Reducing Aβ generation
Amyloid Aβ is derived from APP cleaved by two membrane-bound enzymes, β-secretase and γ-secretase complex. Therefore, modulation of those enzymes to inhibit Aβ production has been a serious focus in developing AD therapies. The development of β-site APP cleaving enzyme 1 (BACE1) inhibitors was limited at the start thanks to difficulties in drug delivery. Later brain-penetrant BACE1 inhibitors have been developed with data showing promising efficacy at reducing Aβ in animal models . However, most BACE1 inhibitors tested today did not survive beyond phase II/III clinical trials thanks to either lack of efficacy, or undesirable long-term side effects. For example, Merck halted its ongoing clinical trials of verubecestat (MK-8931) in mild to moderate AD patients, and most recently in people with prodromal AD (the APECS: β amyloid Production and Effects on Cognition Study. However, despite the disappointing results from current clinical trials of BACE1 inhibitors, a recent study demonstrated that conditional knockout of BACE1 was capable of completely reversing pre-formed amyloid deposition and improving cognitive function in a mouse model with 5× Familial AD (FAD) transgenic background, suggesting sequential and gradual inhibition of BACE1 could be beneficial for AD patients . It was pointed out that BACE1 is necessary to maintain optimal cognitive function and that the BACE1 inhibition is not without concerns . More studies are needed to clarify the mechanism(s) of BACE inhibitors in AD, to determine optimal timing for BACE1 inhibition in adult AD patients, and to search for drug candidates without unwanted and off-target toxicities.
The γ-secretase complex is comprised of four subunits, with presenilin (PS) exhibiting catalytic activities of γ -secretase. There is a long list of γ-secretase substrates with APP and Notch among the most well-known due to their implications in AD and cancer. Substantial effort has been invested into developing small-molecule inhibitors of γ-secretase for AD therapies. Non-selective γ-secretase inhibitors led to a decrease in brain Aβ, and reduced Notch signaling at the same time causing gastrointestinal (GI) symptoms and compromised immune system. Despite the concerns, non-selective γ-secretase inhibitors like semagacestat were tested in clinical trials but discontinued at phase III clinical trial stage due to lack of efficacy or maybe worsened cognitive performance, and patient intolerance thanks to severe off-target side effects like GI irritation and carcinoma.

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Selective γ-secretase inhibitors include Notch-sparing γ-secretase inhibitors and γ-secretase modulators. Gleevec, the abl kinase inhibitor was found to scale back Aβ production but spare Notch cleavage by γ-secretase in primary neuronal cells and animals. Avagacestat was reported to inhibit APP processing more preferably than Notch cleavage. However, clinical test |phase II|clinicaltrial|clinical test"> phase II clinical trial clinical trial of Avagacestat was discontinued thanks to adverse side effects suggesting possible Notch inhibition a bit like Semagacestat A recently developed Notch-sparing γ-secretase inhibitor pinitol (NIC5–15) was derived from natural product and reported to have insulin sensitization property. It is currently in Phase II trial for the treatment of AD Non-steroidal anti-inflammatory drugs (NSAIDs) were the first γ-secretase modulators shown to shift Aβ production from the aggregable form (Aβ42) to a more soluble form (Aβ38) One of these NSAIDs, R-flurbiprofen failed to exhibit any efficacy in Phase III trial of mild AD subjects A γ-secretase modulator EVP-0962 showed potency in preclinical stage but no efficacy in Phase II trial of mild cognitive impairment (MCI) or early AD subjects.

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