Regulation of BACE1 transcytosis in hippocampal neurons

https://neurodegenerationresearch.eu/survey/regulation-of-bace1-transcytosis-in-hippocampal-neurons/

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Research Abstract

? DESCRIPTION (provided by applicant): BACE1 is a type I transmembrane protein that initiates Alzheimer’s disease Aß production by cleavage of amyloid precursor protein (APP). Accumulating evidence demonstrates that synaptic activity dynamically regulates Aß release production near synapses. The molecular and cellular mechanisms underlying activity-

dependent increase of Aß production remain largely unknown. In addition to APP, BACE1 cleaves a number of synaptic transmembrane substrates. Recently, we discovered unidirectional dendritic retrograde transport of internalized BACE1 in hippocampal neurons and found evidence that BACE1 undergoes long-range transport from somatodendritic compartment to axon, in a process termed transcytosis. Very few studies have been published on the regulation of neuronal BACE1 trafficking, and also on protein transcytosis in neurons. BACE1 undergoes post-translational S-palmitoylation, phosphorylation, and ubiquitylation. These modifications on synapse-associated proteins occur in response to synaptic activity, which, in turn, regulate dynamic protein trafficking. We hypothesize that synaptic activity modulates dynamic trafficking at the synapse and transcytosis of internalized BACE1, thus providing a crucial mechanism by which synaptic activity could promote amyloidogenic processing of APP at or near synaptic sites. The Specific Aims of this proposal are: Aim 1) To test the hypothesis that synaptic activity regulates BACE1 trafficking and transcytosis. We will use advanced live-cell imaging and FRAP methods to characterize how synaptic activity affects BACE1 localization in dendritic spines and presynaptic terminals and the local dynamics of BACE1 internalization and recycling at the synapse. In parallel, we will assay transcytosis of internalized BACE1 using microfluidic culture system. Aim 2) To test the hypothesis that synaptic activity dynamically modulates BACE1 post-translational modifications. We will investigate how synaptic activity modulates dynamic modifications within the cytosolic tail of endogenous BACE1. We will confirm and extend the findings by performing trafficking studies (as in Aim 1) in neurons expressing BACE1 bearing mutations within the sites of S-palmitoylation, phosphorylation, and ubiquitylation. Our proposal is timely, unique, and highly innovative because we were the first to describe BACE1 transcytosis in recycling endosomes. We now propose to extend our findings to study how synaptic activity modulates this highly unusual mode of protein trafficking. Our goal to investigate synaptic regulation of BACE1 is also highly significant because endogenous BACE1 and transgene expressed BACE1-YFP predominantly localize to presynaptic terminals in vivo, and BACE1 accumulates in dystrophic presynaptic terminals near senile plaques in the brains of individuals with AD. Thus, investigating how synaptic activity is coupled to BACE1 trafficking and axonal targeting is highly relevant to mechanisms underlying Alzheimer’s disease pathogenesis as well as for BACE1 processing of its multiple neuronal substrates under physiological and pathological conditions.

Further information available at:

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