Chronic Inhibition of phospholipase D1 overexpression using small molecule inhibitors prevents synaptic dysfunction and memory deficits in a mouse model of Alzheimer’s Disease

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Introduction

- Alzheimer’s disease (AD) is the most common form of dementia
- 6th leading cause of death with no cure
- Diagnosed later in life, but initial disease events, notably synaptic dysfunction, occur decades earlier
- We have reported dysregulation of phospholipaseD (PLD1) expression in AD synaptic dysfunction (Krishnan et al., 2018)
- Synaptic expression of PLD1 was reduced in AD hippocampus compared to age-matched controls
- PLD1 signaling mechanisms include membrane trafficking, cytoskeletal reorganization and autophagy
- Our previous studies (Krishnan et al., 2018,11,16) have also demonstrated that PLD1 is a convergent second messenger for dopaminergic, serotonergic and glutamatergic neurotransmission, and affects pre- and post-synaptic function
- Using 3XTg-AD transgenic model of Alzheimer’s disease, we demonstrated here the importance of PLD1 signaling in mediating the synaptic vulnerability thus making the synapses susceptible to amyloidogenic protein insults
- We also studied potential signaling partners such as the axonal target of rapamycin (mTOR), protein kinase C alpha (PKCa) and Cofilin that are known signaling partners for PLD1 isoform and have a role in synaptic neurotransmission deficits in AD
- Due to the availability of well-tolerated PLD1 small molecule inhibitors that we and others have characterized before, we tested acute and chronic treatment in aged 3XTg-AD mice. Synaptic (electrophysiology) and memory (behavior) were improved following chronic treatment, suggesting that PLD1-mediated synaptic vulnerability plays a crucial role in AD and related dementia.

Abstract

Alzheimer’s disease (AD) is the most common form of dementia and the 6th leading cause of death in America for which there is no resolving cure. While diagnosed later in life, initial disease events occur decades earlier. Among these early events, we have reported earlier dysregulation of phospholipaseD1 (PLD1) expression contributing to synaptic dysfunction and underlying memory deficits. Synaptic expression of PLD1, an inducible isoform, was elevated in AD hippocampus compared to age-matched controls. PLD1 signaling mechanisms include membrane trafficking, cytoskeletal reorganization and autophagy, all of which could play an important role in synaptic integrity. Our previous studies have demonstrated that PLD1 is a convergent second messenger for dopaminergic, serotonergic and glutamatergic neurotransmission, and affects pre- and post-synaptic function.

Recently, our functional studies using a mouse model, 3XTg-AD, of AD-like memory deficits and synaptic dysfunction highlighted the importance of PLD1 signaling in mediating the synaptic vulnerability thus making the synapses susceptible to amyloidogenic protein insults. We also studied potential signaling partners such as the neuronal target of rapamycin (mTOR), protein kinase C alpha (PKCa) and Cofilin that are known signaling partners for PLD1 isoform and have a role in synaptic neurotransmission deficits associated with AD. Due to the availability of well-tolerated PLD1 small molecule inhibitors that we and others have characterized before, we tested acute and chronic treatment in aged 3XTg-AD mice. Synaptic (electrophysiology) and memory (behavior) were improved following chronic treatment, suggesting that PLD1-mediated synaptic vulnerability plays a crucial role in AD and related dementia.

Materials and Methods

PLD1 inhibitor (VE0155069) was obtained from Tocris Bioscience (Bristol-Myers, Minneapolis, NE).

Mouse hippocampal long-term potentiation of PLD1-dependent changes was studied using pharmacological approaches in ex vivo slice preparations from wild-type and transgenic mouse models.

PLD1-dependent changes in novel object recognition memory and freezing behavior were assessed following PLD1 inhibition. Co-immunoprecipitation was used to study associations between PLD1 and PKC alpha/mTOR/cofilin.

Results

1. PLD1 inhibition corrects novel object memory deficits in 6-month 3XTg-AD female mice compared to age-matched siblings in novel object recognition tests
2. PLD1 inhibition prevents memory dysfunction in 6-month 3XTg-AD female mice in contextual and cued fear conditioning test

Conclusion

Synaptic PLD1 overexpression may contribute towards memory deficits by affecting (a) neuritic/dendritic branching and spine formation, (b) autophagy and (c) postsynaptic amplification of excitatory responses associated with increased mTOR, PKCa and cofilin signaling. Both synaptic (electrophysiology) and memory (behavior) were improved following chronic treatment, suggesting that PLD1-mediated synaptic vulnerability plays a crucial role in AD and related dementia. Noted was an increase in motor activity of PLD1 inhibitor treated mice. Further studies are needed to determine if there is a motor effect of the dual treatment. Additional studies elucidating these mechanisms will be crucial in pushing the therapeutic value associated with PLD1 inhibition.

References

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