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Prion protein antagonists rescue Alzheimer's amyloid-beta-related cognitive deficits

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Abstract

Recent studies revealed that cellular prion protein on neurons bind Alzheimer's amyloid-beta oligomers causing neurotoxic effects. A new article in *Cell Reports* by Gunther and colleagues shows that an orally administered cellular prion protein antagonist can rescue synaptic and cognitive deficits in Alzheimer's mice overexpressing amyloid-beta.

Keywords

Cellular prion protein; Alzheimer's disease; Amyloid-beta oligomers; Antagonist; Cognition

Alzheimer's disease (AD) is the most common form of dementia, characterized by neurovascular dysfunction, accumulation of amyloid-β (Aβ) in brain parenchyma and vasculature, tau pathology, and neuronal loss [1]. Prions are misfolded proteins that have been implicated in several diseases including transmissible spongiform encephalopathies, Creutzfeldt-Jakob disease, and Gerstmann-Sträussler-Scheinker syndrome, and recently in AD [2–4]. The cellular prion protein (PrP^C) is a small, cell-surface glycoprotein that has several physiological functions in brain. For example, PrP^C protects against neuronal stress (e.g., apoptosis, oxidative stress and endoplasmic reticulum stress), maintains myelin, modulates neuronal excitability, and can induce neurite outgrowth and extension [5]. Importantly, PrP^C is one of the cellular receptors for oligomeric form of Aβ (Aβo) [2,3]. Previous studies have shown that PrP^C and Aβo interaction on neurons leads to neuronal dysfunction, suppression of synaptic plasticity and cognitive impairment [6]. It has been also shown that blocking PrP^C-Aβo interactions with peripherally-administered antibodies improves learning and memory in mouse models of amyloidosis [2,7]. Here, we highlight a recent study by Gunther et al. demonstrating that an orally administered PrP^C antagonist rescues synaptic and behavioral deficits in *APP*swe/*PS1*ΔE9 mouse model of Aβ amyloidosis [8], suggesting its potential therapeutic implications for AD.

In search for a novel PrP^C antagonist, Gunther et al. screened 2,560 known drugs and 10,130 diverse small molecules for inhibition of PrP^C interaction with $Aβ_{1–42}$ oligomers [8]. The screen initially identified a promising cephalosporin antibiotic, cefixime, but further validation suggested that the inhibitory action may result from a cephalosporin degradation product. The authors then screened cephalosporin degradation products and discovered

conditions under which ceftazidime degradation resulted in an active antagonist termed compound Z [8]. Compound Z not only disrupted the interaction between PrP^C and $A\beta_{1–42}$ oligomers but also mitigated behavioral deficits in *APP*swe/*PS1*ΔE9 mice when administrated centrally into the brain [8]. While compound Z was effective in reducing cognitive dysfunction, it did not cross the blood-brain barrier (BBB), which limits its therapeutic potential.

To overcome the BBB hurdle, the authors employed a directed approach for inhibitor development with insight from compound Z's chemical nature and sought to identify molecules with greater potential to cross the BBB. A range of negatively-charged polymers were identified with specific PrP^C affinity in the low to sub-nanomolar range, from both biological (melanin) and synthetic (Poly (4-styrenesulfonic acid-co-maleic acid), PSCMA) origins [8]. They identified that polystyrene sulfonate and PSCMA, like compound Z, function to provide potent inhibition of Aβo binding and protection of dendritic spines from Aβo-induced loss [8]. When delivered orally, PSCMA (20 kDa) can cross the BBB and functions to inhibit PrP^C binding to Aβo *in vivo* as shown in 12-month old *APP*swe/*PS1*ΔE9 mice with established Aβ plaque accumulation, synaptic loss and learning and memory deficits. In these mice, PSCMA rescued learning and memory on Morris water maze behavior test. It also repaired synaptic loss as shown by increased expression of presynaptic anti-synaptic vesicle glycoprotein 2A in hippocampus, but did not alter Aβ metabolism or gliosis [8]. A previous study showed that Aβo-induced PrP^C activation of metabotropic glutamate receptor-5 (mGluR5) co-receptors and downstream signaling through Fyn-kinase phosphorylation of N-methyl-D-aspartate receptor subunit NR2B and tau leads to synaptic dysfunction [3]. Whether PSCMA can alter function of other synaptic molecules is presently unknown. Future studies should investigate in greater depth the impact of PSCMA on key synaptic players by electrophysiological, pharmacological and molecular analysis in other mouse models of amyloidosis and AD.

In addition to neurons, PrP^C is also expressed by brain endothelial cells, astrocytes, and oligodendrocytes [5]). This raises the question what is the cellular specificity and/or differential functions of compound Z and PSCMA binding to PrP^C on different cell types in the brain, and could this contribute to the observed improvements in cognition? There are many "good" and "bad" receptors and soluble carrier proteins that can bind Aβo and either regulate Aβo clearance and degradation or initiate and promote Aβo toxicity [3]. An example of a "good" receptor is the low-density lipoprotein receptor-related protein-1 (LRP1) [3]. LRP1 is expressed by several cell types, but at the BBB endothelium LRP1 functions as a major clearance receptor for Aβ [1] and mediates PrP^C-bound Aβ clearance from brain-to-blood [9]. An example of a "bad" receptor is the receptor for advanced glycation endproducts (RAGE) at the luminal side of BBB endothelium that mediates entry of Aβ from blood-to-brain [1,3]. Studies have shown that preventing Aβ-RAGE interaction blocks Aβo-mediated deficits in synaptic strength [1]. Whether compound Z and PSCMA can impact Aβ clearance from the brain across the BBB by blocking PrP^c remains unknown.

Interestingly, PrP^C also exists in soluble form in the brain and competes with membrane-anchored PrP^C for binding Aβo. Soluble PrP^C was recently reported to bind Aβo and thereby delay fibril formation [10]. Recent studies revealed the ability of Aβo from

cadaveric pituitary growth hormone to seed and promote the formation of Aβ plaques and cerebral amyloid angiopathy [11]. Do compound Z and PSCMA interact and alter functions of soluble PrP^C and could this affect Aβ seeding and fibril formation remains elusive.

In summary, the new study by Gunther et al. [8], along with other previous publications, strengthens the idea that interfering with the binding of Aβo to PrP^C on neurons could mitigate AD-associated memory loss (see Figure 1). The efficacy of PrP^C antagonists in amyloidosis models should be confirmed, however, by additional studies, since PrP^C-Aβo interactions are differentially affected in different models of amyloidosis, as recently reported [12]. This raises a question whether binding efficiency of PrP^C antagonists varies between different Aβo species and/or if binding is influenced by other receptors or carriers in the vicinity of PrP^C. Nevertheless, this exciting new work has promising therapeutic implications for AD, but the translational potential in humans remains to be seen.

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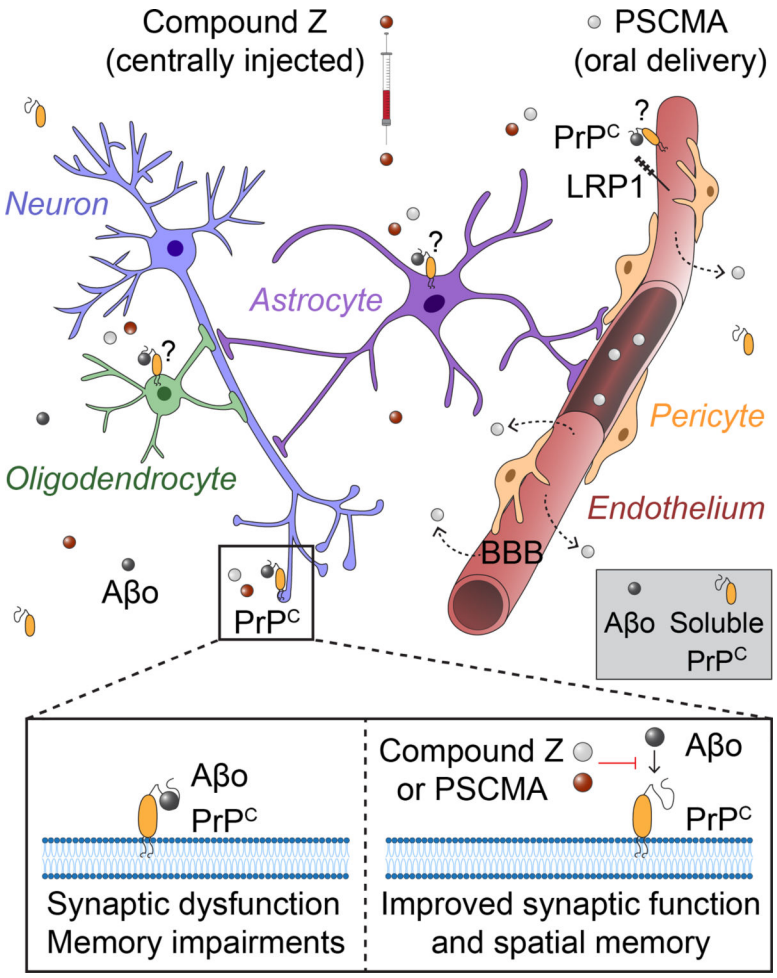

Figure 1. PrP^C antagonists improve synaptic function and spatial memory in a mouse model of Alzheimer's disease.

Binding of amyloid-β oligomers (Aβo, black circles) to neuronal cellular prion protein (PrP^C) leads to synaptic dysfunction and memory impairments. Centrally administered compound Z (red circles) and orally delivered Poly (4-styrenesulfonic acid-co-maleic acid) (PSCMA) that crosses the blood-brain barrier (BBB) (gray circles), both inhibit Aβo binding to PrP^C on neurons (blue). This improves synaptic function and spatial memory deficit in Alzheimer's mouse model of β-amyloidosis. Endothelial cells (red), astrocytes (purple) and oligodendrocytes (green) also express PrP^C. Whether inhibiting PrP^C-Aβo interactions on non-neuronal cell types can affect their function and/or contribute to the observed beneficial effects of compound Z or PSCMA, remains presently unclear. For example, whether compound Z or PSCMA can impact low-density lipoprotein receptor-related protein-1 (LRP1)-mediated clearance of PrP^C-bound Aβ across the blood-brain barrier (BBB) is currently unknown. Do compound Z and PSCMA interact and alter functions of soluble PrP^C interaction with Aβo which can affect fibril formation (gray box) remains elusive.