Novel Combinatorial Therapeutic Targeting of PAI-1 (SERPINE1) Gene Expression in Alzheimer’s Disease

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Summary

Accumulation of neurotoxic amyloid peptides (Aβ) in the brain, generated by β-site proteolytic processing of the amyloid precursor protein (APP), is the hallmark pathophysiologic feature of Alzheimer’s disease. The plasmin-activating cascade, in which urokinase (uPA) and tissue-type (tPA) plasminogen activators convert plasminogen to the broad-spectrum protease plasmin, appears to serve a protective, Aβ-clearing, role in the central nervous system. Plasmin degrades Aβ and catalyzes α-site APP proteolyis generating nontoxic peptides. Plasmin activation in the brain is negatively regulated by the fast-acting clade E serine protease inhibitor (SERPIN) plasminogen activator inhibitor type-1 (PAI-1; SERPINE1) resulting in Aβ accumulation. PAI-1 and its major physiological inducer TGF-β1, moreover, are both increased in Alzheimer’s disease models and implicated in the etiology and progression of human neurodegenerative disorders. Current findings support the hypothesis that targeting of PAI-1 function (by small molecule drugs) and/or gene expression (by histone deacetylase inhibitors) may constitute a clinically-relevant molecular approach to the therapy of neurodegenerative diseases associated with increased PAI-1 levels.

Plasmin-Activating System in Alzheimer’s Disease

Aggregated β-amyloid peptide plaques accumulate in specific areas of the brain in patients with Alzheimer’s disease (AD) by proteolytic processing of the single-pass transmembrane APP [1]. These deposits trigger prolonged inflammation, neuronal death, and progressive cognitive decline [2]. Aβ peptides are produced by aspartic protease (BACE)-induced β-site cleavage of APP creating a membrane-bound COOH-terminal C99 fragment followed by proteolysis (involving presenilin and nicastrin) at the C99 transmembrane-localized γ position [3-5]. There is also an alternative APP processing pathway in which a membrane-proximal (α-site) cleavage, by matrix metalloproteinases (TACE, ADAM 10), replaces β position utilization producing a membrane-anchored C83 fragment. Subsequent γ processing of the C83 product generates the nontoxic p3 peptide [3,6].

Among other targets, the broad-spectrum protease plasmin also degrades Aβ [7-9] and plasmin activation decreases Aβ peptide levels [10]. Plasmin-mediated proteolysis of APP, moreover, involves the α-site (either as a direct or indirect target) resulting in decreased Aβ production, suggesting a protective role for the plasmin cascade in the central nervous system. Indeed, plasmin levels in the brains of AD patients are considerably reduced [10] supporting a causal relationship between deficient activity of the plasmin-generating proteolytic system and accumulation of Aβ in the progression of AD (Figure 1).

Therapeutic Approaches

Several members of the SERPIN superfamily exhibit cell-type neurotrophic, neuroprotective, or neuropathophysiology activities [11]. These include SERPINF1, SERPINI1 (neuroserpin), SERPINE1 (PAI-1), SERPINE2 (nexin-1), and SERPINA3 [11]. PAI-1 (SERPINE1), in particular, has multifunctional roles in the central nervous system as it both maintains neuronal cellular structure and initiates signaling through the mitogen-activated protein kinase pathway [12]. Significantly increased PAI-1 immunoreactivity in the central nervous system of AD patients was associated with development of senile plaques and ghost tangle structures [13] consistent with the earlier colocalization of plasminogen activators and PAI-1 in plaque structures [14] which are sites of sustained inflammation [15]. Tg2576 and TgCRN8 transgenic mice, engineered to express brain-targeted Swedish mutant Aβ and the double Swedish/V717F mutant Aβ, respectively, exhibit age-dependent Aβ plaque development as well as cognitive deficiencies [16]. tPA activity in these mice was significantly decreased specifically in the hippocampus and amygdala correlating with corresponding regional increases in brain PAI-1 expression [17]. Since direct Aβ peptide injection increased PAI-1 expression and Aβ removal from the hippocampal region required both tPA and plasminogen, a functional tPA-plasmin axis appears required for Aβ clearance [17]. While PAI-1 may be neuroprotective in specific acute injury settings (e.g., tPA-triggered neuronal apoptosis) [18,19], chronically elevated PAI-1 levels likely promote Aβ accumulation by inhibiting plasmin-dependent degradation. Genetic evidence clearly indicates that brain PAI-1 expression is increased in Aβ precursor protein presenilin 1 (APP/PS1) mice as well as in AD patients [20] while PAI-1 deficiency in an APP/PS1 transgenic background reduces...
amloid accumulation. These findings have therapeutic implications as a small molecule inhibitor of PAI-1 activity (PAZ-417) partially blocks amyloid deposition in a mouse model of AD. The mechanism, as perhaps expected, suggests that PAI-1 inhibition stimulates tPA/plasmin activity, decreasing brain Aβ levels and reverses cognitive deficits [21]. The development of pharmacologic strategies to prevent and therapeutically manage patients at risk for, and who present with, AD by inhibiting the function of a key contributor (PAI-1) to disease progression has significant translational relevance. Indeed, histone deacetylase inhibitors (HDACi) have potential promise as a therapy for neurodegenerative disease [22]. Sodium butyrate (NaB), a broad-spectrum HDACi, attenuated streptozotocin-induced endothelial dysfunction and improved learning and memory (Morris water maze test) in rats [23]. Butyrate localizes to the cerebral cortex in KCl-induced spreading cortical depression [24] while NaB (as well as TSA and valproic acid) are neuroprotective in the ischemic brain [25]. Most importantly, several HDACi (NaB, TSA, SAHA and to a lesser extent sirtinol) effectively reduced TGF-β1-induced PAI-1 expression [19] (Figure 2). This has translational implications as brain TGF-β1 levels are elevated in the onset and progression of Parkinson’s disease, AD and stroke [19]. Increased expression of TGF-β1 correlates with Aβ angiopathy and transgenic mice that overexpress TGF-β1 in astrocytes exhibit early onset Aβ deposition [26]. TGF-β1, moreover, induces astrocyte APP expression through a TGF-β1-responsive element in the APP promoter while Aβ production was enhanced by TGF-β1 signaling [27]. The coordinate overexpression of PAI-1 and increased Aβ generation in response to elevated TGF-β1 in AD patients is likely to predispose to disease progression [28]. Collectively, these findings raise the possibility that targeting TGF-β1-inducible genes (e.g., PAI-1, APP) will provide a therapeutic benefit in the setting of AD. HDACi coupled with a small molecule central nervous system-accessible PAI-1 functional inhibitor may have efficacy as an approach to reverse the ongoing accumulation of amyloid deposits even after disease development.

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References


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