A potential pathogenetic role of iron in Alzheimer's disease

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Abstract

The role of iron in the pathogenesis of Alzheimer's disease (AD) is still unclear, despite the evidence that it accumulates in the same brain regions characterized by the amyloid β peptide ($A\beta$) accumulation. Here we propose that iron directly influences the $A\beta$ production through the modulation of furin, a proconvertase involved in the regulation of the α -secretase-dependent processing of the amyloid protein precursor (APP).

Keywords: iron • furin • Alzheimer's disease

Medical hypothesis

The major pathological hallmark of Alzheimer's disease (AD) is the presence of senile plaques, *i.e.* proteinaceous brain deposits whose main component is the amyloid β peptide ($A\beta$) derived by the proteolytic cleavage of the amyloid protein precursor (APP). APP is cleaved by three types of proteases: α -, β - and γ -secretases. Processing by β - and γ -secretases cleaves the N- and C-terminal ends of the $A\beta$ region, respectively, releasing $A\beta$, whereas α -secretase cleaves within the $A\beta$ region, destroying the $A\beta$ sequence and producing the neuroprotective sAPP α fragment (Fig. 1). α - and β -secretases may compete for the APP cleavage since they cleave sequences of APP that are proximally located. For this reason, stimulation of α -secretase pathway attenuates $A\beta$ accumulation in the brain and amyloid formation [1].

Furin, a ubiquitously expressed proconvertase whose proteolytic activity is required for many cellular processes, modulates both α - and β -secretases processing.

In AD, the role of furin in sAPP α production has been demonstrated both *in vitro* [2] and *in vivo* [3]. In particular, furin enhances α -secretase activity *via* the cleavage of ADAM10 and TACE/ADAM17, two metalloproteases that show α -secretase activity. The role of furin in regulating sAPP α production is strengthened by the evidence that furin mRNA level is significantly reduced in the brains of both AD patients and Tg2576 transgenic mice [3]. When furin levels

are restored by furin adenovirus injection in mice, the α -secretase activity and sAPP α levels are rescued, and the amyloid $A\beta$ production decreases [3]. The control of β -secretase production is in some way redundant since pro-BACE (Beta-site APP Cleaving Enzyme) is cleaved *in vivo* by furin [4] but also by other proconvertases as PACE4, LPC, PC6A and PC6B [5]. Indeed, BACE activity on APP is not significantly affected by the absence of furin or by PC inhibitors, suggesting that also pro-BACE processes APP [5].

Another important pathological finding of AD is the iron accumulation that occurs in the same brain regions characterized by $A\beta$ deposition [6]. Although iron-mediated damage likely occurs through the increased oxidative stress due to the Fenton reaction, the functional link between iron and $A\beta$ accumulation remains unclear.

Recently, we reported that furin modulates systemic iron homeostasis through the production of soluble hemojuvelin (HJV) [7], an antagonist of bone morphogenetic protein (BMP)-mediated activation of hepcidin [8], which strongly regulates iron homeostasis. Furin transcription is modulated by iron concentration and chemical-induced hypoxia [7, 9]. We showed that in the presence of excess cellular iron, furin protein level decreases and, as a consequence, soluble HJV production is impaired. In contrast, when the iron concentration decreases, or in hypoxia, the up-regulation of furin protein increases the production of soluble HJV, blocking hepcidin activation [7].

Based on these observations, iron-regulation of furin might have an important role also in AD. Although the mechanisms underlying the initial iron accumulation remain unclear, once iron concentration increases in the brain, it could down-regulate furin protein level, impairing the ability of α -secretase to produce the sAPP α neuroprotective form.

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We suggest that iron could increase β -amyloidogenic peptide through different mechanisms: first, iron down-regulates furin transcription and decreases furin protein levels (Fig. 1); second, the iron-dependent reactive oxygen species (ROS) production shifts the aconitase to the iron regulatory protein 1 (IRP1) form, which translates into an abnormal signal of iron deficiency, increasing the cellular iron uptake [10]. These conditions would initiate a vicious circle that progressively increase the intracellular labile iron pool (LIP) and further down-regulates furin, shifting the secretase equilibrium towards the $A\beta$ formation.

A previous observation has strengthened the role of iron in AD showing that APP is post-transcriptionally regulated by the iron regulatory proteins (IRPs) through a 5'UTR iron-responsive element (IRE) [11]. Although the structure of APP 5' IRE appears non-canonical (Type II-IRE), the authors demonstrated that excess iron is able to increase APP production through the stabilization of its messenger RNA, whereas iron chelation reverted this effect [11]. Increased APP formation in the presence of inhibition of the α -secretase activity would further favour the $A\beta$ deposition.

In addition to the furin down-regulation mediated by iron, another mechanism could decrease the α -secretase activity (Fig. 1). It has been demonstrated that TIMP-3, a metalloprotease inhibitor that blocks ADAM10 and TACE/ADAM17 activities, is up-regulated *in vivo* in brain from AD patients and from Tg2576 transgenic mice [12], during ROS production [13].

According to the proposed mechanisms, iron would influence α -secretase activity both directly through the down-regulation of furin, and indirectly through TIMP3 up-regulation, mediated by iron-dependent ROS production.

If our hypothesis is experimentally confirmed, stimulating furin activity or interfering with the related molecular mechanisms could become a therapeutic target to increase production of the sAPP α neuroprotective peptide. Alternatively, new protocols of iron chelation could be set up for patients in early phase of the disease. Indeed reduction of brain iron by chelation was recently

Fig. 1 Schematic representation of the proposed mechanisms leading to increased iron and iron mediated mechanisms of $A\beta$ upregulation. The initial iron accumulation downregulates furin, impairing the processing of ADAM10 and TACE, the two α -secretases involved in sAPP production. Since the activity of α - and β -secretases are tightly balanced, due to the close proximity of their consensus cleavage sites, reduction in α -secretase activity increases the $A\beta$ production, through β - and γ -secretases. Iron accumulation in the cell increases the reactive oxygen species (ROS) production, which upregulates TIMP2, an inhibitor of α -secretase, and shifts the cytoplasmic aconitase to IRP1, giving a wrong signal of iron deficiency and stimulating the cells to enhance iron uptake. The effects mediated by ROS create a vicious circle, which amplify the α -secretase activity reduction and increment the $A\beta$ production.

shown to produce some clinical improvement in a pilot protocol in Friedreich ataxia [14].

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