Alzheimer's disease: A positive feedback-loop induced by oxidative stress

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Abstract

Alzheimer's disease (AD), the primary form of dementia, is hallmarked by the extraneuronal deposition of amyloid β (Aβ) plaque and intraneuronal tau neurofibrillary tangles (NFTs). The former is believed to induce microglial cell activation, triggering the release of reactive oxygen species (ROS). Here we explore the highly associative nature of Poly [ADP-ribose polymerase-1] (PARP-1) with Aβ, oxidative stress, and other hallmarks of AD. We hypothesize that PARP-1 induces the formation of Aβ plaque through the activation of Glycogen Synthase Kinase 3 (GSK-3). This promotes the release of ROS from microglial cells, which has been shown to activate PARP-1, therefore creating a positive feedback-loop. Additionally, GSK-3β isoform has been shown to inhibit the binding of heat shock factor 1 (HSF-1) to DNA, impeding the transcription of heat shock protein (HSP) encoding genes, thought to prevent Aβ aggregation. Furthermore, recent studies have shown that activation of PARP-1 induces neuronal parthanatos, a form of programmed cell death. This hypothesis provides an explanation for the various features of AD patients: increased tau hyper-phosphorylation, the high levels of PARP-1 and GSK-3 exhibited in AD sufferers, and the formation of Aβ plaque. Consequently, inhibition of multiple factors, including PAPR-1, may represent an exciting new therapeutic method to delay or prevent AD progression.

Keywords: ROS, PARP-1, Aβ, tau, GSK-3, HSF-1

1. Introduction

PARP-1 is a nuclear enzyme activated in response to ROS-induced DNA damage [1] and is implicated in several DNA repair pathways and the conservation of genome stability [2]. However, multiple studies have reported the overexpression of PARP-1 in AD patients [3][4]. Its highly associative nature with AD provides a strong incentive to explore its therapeutic potentials [5].

GSK-3 is considered to be the critical link between the Aβ plaque and NFT formation in AD patients [6]. Its significantly higher activity in the frontal cortex of AD sufferers has also made GSK-3 inhibition a potential therapeutic form of treatment [7]. However, recent studies suggesting the dependence of GSK-3 activity on PARP-1 have prompted the latter to be a more plausible culprit for the progression of AD [8]. One study reports reduced tau phosphorylation upon PARP-1 inhibition in tau441 cells, along with a reduced GSK-3 activity [9]. Another study demonstrates a decrease in oligomeric Aβ in mice brains, upon GSK-3β inhibition [10]. These papers provide evidence for the link between GSK-3 and the hallmarks of AD – Aβ plaque formation and tau hyperphosphorylation.

Furthermore, GSK-3β is believed to inhibit DNA binding and transcriptional activities of HSF-1. This hypothesis is supported by evidence which shows that GSK-3β negatively regulates HSF-1 during heat shock [11]. The repression of HSF-1 by GSK-3β may be an explanation for the reduced activity of the heat shock factor in AD patients [12], while the repression of HSF-1 results in a reduced transcription of target genes encoding HSPs. The Hsp90 promoter, for example, is under the control of HSF-1, which upregulates by binding heat shock elements (HSEs) to the promoter [13]. Hsp90 and Hsp70 have been shown to inhibit Aβ aggregation into plaque by acting as chaperones [14]. This leads

to the hypothesis that in AD patients, the heat shock response (HSR) does not function in a correct manner as it would in a healthy control, leading to neuropathogenesis by the formation of Aβ plaque.

Microglial cells, macrophages of the CNS, have been found in close association with Aβ aggregates. Several studies report the activation of microglial cells, resulting in neuroinflammation, occurs due to an increase in Aβ [15][16][17]. Microglial activation is a neuronal immune response reported in a number of other neurodegenerative disorders, resulting in cytokine and ROS release [18][19]. We hypothesize that this accumulation of cellular ROS creates a positive feedback-loop, where PARP-1 is further activated by an increase in oxidative stress.

In neurodegenerative diseases such as Alzheimer's and Parkinson's disease, ATP-dependent PARP-1 is postulated to be responsible for excessive neuronal death [5]. This is because the overactivation of PARP-1 has been shown to lead to parthanatos, a form of programmed cell death occurring in response to extreme genomic stress [20]. Parthanatos prevails over apoptosis due to the depletion of ATP by PARP-1 – the former is an ATP-independent process.

We hypothesize that a positive feedback loop mediated by oxidative stress is a critical contributor of the hallmarks observed in AD patients. Therefore, we propose that inhibitors of PARP-1 could effectively reduce the progression AD in patients.

2. Discussion

2.1 PARP-1 and GSK-3

Proportions of PARP-1 in the frontal and temporal cortices of AD sufferers have been shown to be significantly greater compared to those in control brains [3][4][21]. The additionally elevated levels of GSK-3 reported in the frontal cortex of AD subjects prompted us to research the relationship between these two enzymes. One study shows the inhibition of PARP-1 via 3-aminobenzamide (3-AB) in rats significantly decreased the activity of GSK-3β, suggesting that it is regulated by PARP-1 [8]. This indicates that PARP-1 inhibition could effectively delay or prevent further progression of AD. Another study conducted on tau-441 cells recorded a decrease in phosphorylation of tau-1 at the Ser 195, 198, 199, and 202 sites, along with an increase in GSK-3 activity, upon inhibition of PARP-1 by 3-AB [9]. Since tau is a substrate of GSK-3, this evidence suggests that PARP-1 increases GSK-3 activity, which in turn increases tau phosphorylation. Some have additionally reported that activation of GSK-3β induces not only tau hyper-phosphorylation, but also the formation of NFTs [22][23]. However, other studies indicate that GSK-3β activity does not induce NFT formation [24][25][26]. They report that although an increase in hyper-phosphorylated tau is observed, neither insoluble tau aggregates nor neurofibrillary tangles were detected upon increased activation of GSK-3β. However, one of the studies claims that transgenic mice over-expressing GSK-3β in hippocampal and cortical neurons were more prone to spatial learning deficits [24].

The other hallmark of AD is the formation of Aβ plaque, which has shown reduced levels upon inhibition of GSK-3α by lithium [27][28]. One study claims that mice brains reported reduced oligomeric Aβ when GSK-3β was inhibited [10].

We gather from this that both isoforms of GSK-3 are highly associated with the hallmarks of AD: hyper-phosphorylated tau proteins, Aβ plaques, and possibly NFTs. Numerous studies also show that GSK-3 activation directly induces these neuropathological features in AD.

2.2 HSF-1

HSF-1, the master regulator of the HSR, is repressed by GSK-3, revealing why this heat shock factor is found at such reduced levels in AD patients [11]. Since HSF-1 regulates the activities of various HSPs such as Hsp40, Hsp70, and Hsp90, it is expected that its inhibition in AD will result in reduced levels of HSPs – this has been demonstrated by several times [29][30]. One study shows that rats with AD exhibited reduced levels of HSF-1 along with downregulation of Hsp60, Hsp70, and Hsp90 in their cerebella [30]. An explanation for the negative regulation of HSF-1 in AD is that GSK-3 is able to inhibit the binding of HSF-1 to DNA, as well as reduce its transcriptional activities [11]. This was confirmed when increased binding and transcription occurred upon inhibition of GSK-3. The speculation that reduced HSP level is possibly responsible for the neuropathic features exhibited in AD comes from

studies reporting the important functions of HSPs in regulating Aβ aggregation and tauopathy.

Hsp90 is shown to inhibit the formation Aβ and reduce aggregation through its chaperone activity [14]. Two mechanisms by which Hsp90 achieves this have been proposed. (1) The chaperone can bind to the Aβ, preventing it from interacting with other Aβ peptides and forming aggregates. This mechanism functions independently of ATP. (2) The chaperone binds to the Aβ, inducing a conformational change so that it is less susceptible to aggregation. This mechanism is therefore ATP-dependent [14] [31]. The formation of Aβ plaque in AD can therefore be explained by the reduced levels of HSPs which would otherwise prevent aggregation.

Rapamycin, also known as sirolimus, is shown to reduce Aβ by inducing autophagy of amyloid precursor protein (APP). The reason for its interest is that rapamycin-fed mice expressed large quantities of molecular chaperones, along with increased levels of HSF-1 [32]. It is believed that these chaperones are responsible for inducing APP autophagy and are activated by HSF-1 [29]. Since rapamycin plays a role in the proteostasis of Aβ, while inducing the activation of HSF-1, we gather the importance of HSF-1 in the regulation of Aβ.

The formation of NFTs in AD can also be explained by the reduced activity of the Hsp70 chaperone. One study indicates that the binding of the chaperone to the tau microtubule-binding domain prevents tau proteins from interacting with each other and forming aggregates [33].

2.3 Aβ and oxidative stress

The clearance of Aβ can also occur through the activation of microglial cells, which induce an immune response [15]. Microglia are believed to produce this response through the release of neurotoxic cytokines accompanied by ROSs, resulting in neuropathy. Therefore, although microglial cell activation prompts the clearance of plaque by generating anti-Aβ antibodies, it also induces neuroinflammation by the release of toxic substances [16]. Additionally, activation of microglial cells has been shown to correlate with tau aggregation [17]. Since ROS induced DNA damage results in the activation of PARP-1 [1], we hypothesize that a positive feedback-loop is established. In other words, the activation of PARP-1 induces oxidative stress, which further activates PARP-1.

2.4 PARP-1 and parthanatos

Recent studies have shown that activation of PARP-1 induces neuronal parthanatos, a form of programmed cell death. When ATP-dependent PARP-1 repairs DNA during oxidative stress, the cell is depleted of ATP and NAD^+ [20]. With the accumulation of DNA strand breaks due to ROS, the cell is selected to die [34]; however, apoptosis cannot occur, since it is dependent on ATP. Instead, ATP-independent parthanatos takes over. We believe that parthanatos could be culpable for the brain tissue deterioration in exhibited in AD patients.

3. Conclusion

We conclude that AD could be caused by a positive feedback-loop dependent on multiple factors, where PAPR-1 indirectly induces oxidative stress, and equally, oxidative stress further activates PARP-1 [Fig. 1]. If correct, our hypothesis would explain the formation of Aβ and tau plaque, in addition to the high levels of PARP-1 and GSK-3 occurring in AD patients. It is clear that multiple factors contribute to the pathological hallmarks of this neurodegenerative condition, and that there are almost certainly others which we have not mentioned here. However, our hypothesis suggests that targeting multiple causative agents at once would provide a more effective approach to treating AD.

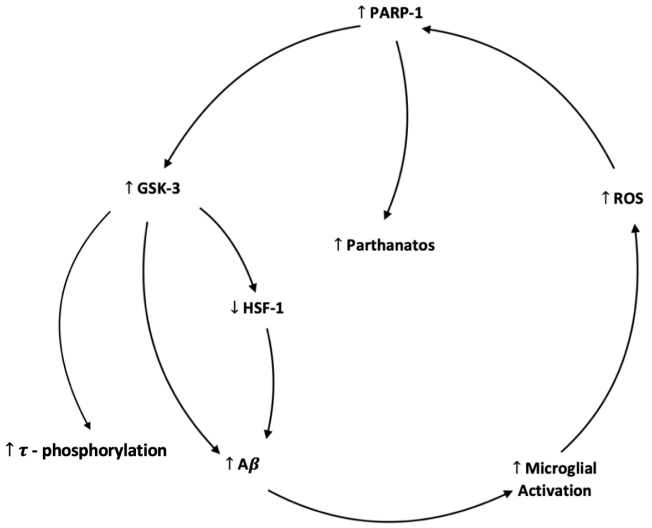

Fig. 1 Diagram depicting our hypothesis that AD is caused by positive feedback.

4. References

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