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The Role of Hypoxia-Inducible Factor 1 in Mild Cognitive Impairment

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Abstract

Neuroinflammation and reactive oxygen species are thought to mediate the pathogenesis of Alzheimer's disease (AD), suggesting that mild cognitive impairment (MCI), a prodromal stage of AD, may be driven by similar insults. Several studies document that hypoxia-inducible factor 1 (HIF-1) is neuroprotective in the setting of neuronal insults, since this transcription factor drives the expression of critical genes that diminish neuronal cell death. HIF-1 facilitates glycolysis and glucose metabolism, thus helping to generate reductive equivalents of NADH/NADPH that counter oxidative stress. HIF-1 also improves cerebral blood flow which opposes the toxicity of hypoxia. Increased HIF-1 activity and/or expression of HIF-1 target genes, such as those involved in glycolysis or vascular flow, may be an early adaptation to the oxidative stressors that characterize MCI pathology. The molecular events that constitute this early adaptation are likely neuroprotective, and might mitigate cognitive decline or the onset of full-blown AD. On the other hand, prolonged or overwhelming stressors can convert HIF-1 into an activator of cell death through agents such as Bnip3, an event that is more likely to occur in late MCI or advanced Alzheimer's dementia.

Keywords

Mild cognitive impairment; Hypoxia-inducible factor 1; Glucose; Glycolysis; Alzheimer's disease; Reactive oxygen species; Inflammation

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Introduction

Mild cognitive impairment (MCI) in the elderly is generally acknowledged to be a prodromal phase of Alzheimer's disease (AD), since most MCI cases evolve to AD within a decade or more (Flicker et al. 1991; Palmer et al. 2002). For this reason, experimental and clinical data derived from studies of MCI models and subjects are likely to be instructive on the early aspects of cognitive decline. In the transition from MCI to AD, several molecules, whose concentrations may directly correlate with the severity of pathology, are increased in the MCI-AD brain (Pater 2011; Price and Morris 1999; Vlassenko et al. 2011). These include, amongst others, extracellular beta amyloid (A β , a proteolytic product of amyloid precursor protein), tau, hyperphosphorylated tau, and microtubule-associated (intracellular) neurofibrillary tangles (Huang and Jiang 2009; Pater 2011).

The free-radical theory of aging is a prevailing hypothesis which highlights the roles of reactive oxygen species (ROS) and free-radical products in aging (Barja 2004; Harman 1956). MCI and AD correlate positively with age, and consistent with the free-radical theory is the finding that MCI and AD subjects are under relatively high oxidative stress compared to controls (Pratico et al. 2002; Retz et al. 1998). A β , a likely culprit in MCI/AD, is known to facilitate the generation of ROS (Hensley et al. 1994; Retz et al. 1998; Zhang et al. 2007b). In addition, increased circulating cytokines, which represent inflammation, are primary players in MCI/AD, and such elevations may contribute as diagnostic markers (Flicker et al. 1991; Olson and Humpel 2010). Overall, elevated ROS and cytokines (in MCI/AD subjects) lead to increased oxidative stress and inflammation, respectively, which work in concert to promote cognitive decline.

The oxygen sensor and transcription factor, hypoxia-inducible factor 1 (HIF-1), is upregulated in AD and also in response to A β and inflammation (see below). The expression of HIF-1 might have a neuroprotective role in response to ROS and inflammation, and indicates that viable neurons are likely to upregulate other neuroprotective mechanisms in the setting of MCI/AD in order to diminish the toxic effects of ROS and inflammation. In addition, HIF-1 may also activate death signals in excessively toxic settings. This article briefly discusses the contribution of HIF-1 to neuroprotection in MCI and, by extension, in AD where this factor may contribute to cell death. Consistent with the general body of knowledge on MCI/AD, we also provide evidence suggesting that HIF-1 target genes (for example, those that are involved in glucose metabolism) are upregulated in platelets obtained from MCI subjects compared to age-matched controls.

Hypoxia-Inducible Factor 1 and its Regulation in MCI/AD

HIF1

HIF-1 is a basic helix-loop-helix heterodimeric transcription factor that is generally expressed in response to hypoxia. In the presence of oxygen or under normoxic conditions, O₂-dependent/sensing prolyl hydroxylase domain (PHD) dioxygenase enzymes, with the help of ferrous iron, hydroxylate key proline residues in HIF-1 α , making this hydroxylated protein eligible for protein degradation via the ubiquitin proteasome pathway, aided by the von Hippel-Lindau ubiquitin ligase (Fong and Takeda 2008; Masson and Ratcliffe 2003;

Semenza 2004). There is data to indicate that a second mode of HIF-1 regulation involves asparaginyl hydroxylation, where this particular biochemical change decreases the efficiency of the interaction of HIF-1 with its transcriptional co-activators (Masson and Ratcliffe 2003). A detailed summary of HIF-1 regulation is reviewed by Zhang et al. (2011).

In hypoxic conditions where oxygen is not abundant, PHD dioxygenase enzymes are less efficient, thus HIF-1 α stability is enhanced, allowing sufficient quantities of this protein to dimerize with HIF-1 β , forming an active transcription complex that promotes the expression of target genes involved in angiogenesis, glycolysis (glucose transport and metabolism), erythropoiesis, and inflammation (Semenza 2004). This way, HIF-1 activity is increased in order to promote cell survival (Semenza 2004; Zhang et al. 2011). As will be explained below, HIF-1 may also facilitate cell death under overwhelming or chronic toxic insults (Zhang et al. 2007b, c).

HIF-1 Activity and Oxidative Stress

Oxidative stress is present in AD (Markesbery 1997). Redox proteomics studies indicate that protein oxidation is significantly increased in the hippocampus of MCI subjects compared to age- and sex-matched controls (Butterfield et al. 2006). Such oxidation, triggered by oxidative stress, contributes to neuronal cell death and cognitive decline (Davies et al. 1997; Hensley et al. 1994; Pratico et al. 2000, 2002). In addition to hypoxia, oxidative stress mediated by ROS stabilizes HIF-1 α (Michiels et al. 2002).

Strong evidence for the possible role of HIF-1 in the early stages of AD has been obtained from cultured neurons and nerve cells (Soucek et al. 2003). In that work (Soucek et al. 2003), the authors observed that amyloid-resistant clones upregulated HIF-1 and its downstream targets such as hexokinase and pyruvate kinase. The hexose monophosphate pathway also appeared to be upregulated in an HIF-dependent fashion since the activity of glucose-6-phosphate dehydrogenase was also increased, consistent with later independent work (Gao et al. 2004). We also indirectly tested for HIF-1 upregulation/stability in platelets of MCI subjects by measuring the mRNA of known HIF-1 target genes, using quantitative real-time polymerase chain reaction (qRT-PCR). Although AD primarily affects the brain and central nervous system, it is possible that peripheral markers may provide useful correlative information (Pratico et al. 2000; Swindell et al. 2013). Peripheral platelets recapitulate several features of AD such as elevated tau (Neumann et al. 2011) and defective processing of amyloid precursor protein (Davies et al. 1997; Rowley et al. 2012). In addition, neutrophils (a type of granulocyte) have been shown to possess elevated oxidative properties in AD patients (Vitte et al. 2004).

In platelets (Fig. 1), we found decreased expression of pyruvate dehydrogenase kinase, isozyme 1 (PDK1, $p = 0.0007$), negligible change in BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3, $p = 0.9$), and non-significant change in the expression of BNIP3-like (BNIP3L, $p = 0.06$). However, significant increases were noted in the glucose transporter, isozyme 1 GLUT1 ($p = 0.008$), hexokinase (HK1, $p = 0.03$), and vascular endothelial growth factor A (VEGF-A, $p = 0.01$) in platelets obtained from MCI cases compared to control. The greatest changes in gene expression were noted in GLUT1, HK1, and VEGF-A, all known targets of HIF-1. This indicates that HIF-1 target genes might be

induced systemically in MCI subjects. PDK1 is an inhibitor of the pyruvate dehydrogenase complex, and serves to limit the amounts of acetyl-CoA available for mitochondrial oxidation, thereby reducing the generation of ROS (Kim et al. 2006), which might explain its decrease in MCI platelets. BNIP3 is known to catalyze selective mitochondrial autophagy under hypoxic conditions, presumably to reduce mitochondria-generated ROS (Zhang et al. 2008). GLUT1 is a uniporter whose expression facilitates the uptake of glucose into cells (Chen et al. 2001) and HK1 commits glucose to glycolysis via substrate phosphorylation to generate glucose-6-phosphate (Marin-Hernandez et al. 2009). Finally, VEGF-A is a vasculogenic mitogen that promotes neovascularization in target tissues (Forsythe et al. 1996) (Fig. 2).

A β in AD promotes the expression of HIF-1, which in turn helps to facilitate glucose uptake and metabolism, in order to enhance neuron survival through the generation of antioxidants such as NADPH (Soucek et al. 2003). Moreover, increased glycolysis helps to decrease ROS (Brand 1997). The results obtained herein from MCI platelets are consistent with this view since HK1, GLUT1, and VEGF-A are upregulated in MCI compared to cognitively normal controls. The overall sets of studies thus indicate that, similar to AD states, glycolysis is likely elevated in MCI since HIF-1 and target genes that promote glycolysis show elevated expression. Peripheral platelets and neurons in AD share important features such as defective processing of amyloid precursor protein, increased tau, and elevated peroxynitrites (Davies et al. 1997; Veitinger et al. 2014). Such ROS-generating features in platelets serve as models to explain how HIF-1 expression and activity may manifest as elevated expression of glycolytic genes.

Interestingly, similar to previous work where sub-toxic amounts of amyloid beta were beneficial to neurons (Yankner et al. 1990), pre-treatment with sub-toxic doses of amyloid beta upregulated HIF-1 and this pre-treatment protected neurons from larger, toxic doses of amyloid beta (Soucek et al. 2003). The authors concluded that these HIF-1-dependent pathways boost glucose metabolism, and in so doing, generate NADH and NADPH which might help generate antioxidants that are neuroprotective. This antioxidant effect is in agreement with recent work, suggesting that antioxidants can reverse deficient axonal mitochondrial transport/function in neurons transformed with platelet-derived mitochondria from sporadic AD cases (Yu et al. 2016). This study suggests that the ability to generate neuroprotective responses (as in HIF-1 signaling) against neuronal insults may be predictive of the rate of cognitive decline in the early stages of MCI.

While NADPH may protect against ROS, there is evidence that amyloid A β , through CD14 and toll-like receptors 2 and 4, activates NADPH oxidase (PHOX) in microglia, enabling the phagocytic activity of microglia and production of ROS (Reed-Geaghan et al. 2009). Moreover, the authors noted that deletion of these receptors inhibited ROS generation and microglial phagocytosis (Reed-Geaghan et al. 2009). More recent work extended these findings by showing that A β -induced PHOX activation can promote neuronal cell loss, an event significantly attenuated by superoxide dismutase, toll-like receptor antibodies, or PHOX inhibitors such as apocynin and 4-(2-aminoethyl)-benzenesulfonyl fluoride (AEBSF) (Neniskyte et al. 2016). Consistent with literature indicating that protein kinase C (PKC) can activate PHOX (Cosentino-Gomes et al. 2012; Dekker et al. 2000; El Benna et al. 1996),

activation of PKC with phorbol 12-myristate 13-acetate (PMA) was also sufficient to trigger PHOX activity and drive neuronal cell death (Neniskyte et al. 2016). The overall data thus argue that A β can utilize NADPH oxidase in microglia to trigger neuronal cell death and accelerate the incidence of MCI and AD.

Membrane-permeant iron chelation compounds [deferoxamine (DFO) and deferiprone (DFP)] have been recently shown to decrease the production of A β _{25–35}-induced ROS in microglia via down-regulation of gp91PHOX (a subunit of NADPH oxidase) (Part et al. 2015), and p22PHOX in a murine model of inflammation (Li and Frei 2006). Another study documented that after DFO treatment in humans, increases in the expression of HIF-1 target genes (erythropoietin and VEGF) were associated with improved vasoreactivity and cerebrovascular autoregulation, but not neurovascular coupling (the association between cognitive demand and cerebral blood flow) (Sorond et al. 2015). As expected, the benefits of iron chelation were more robust in the elderly compared to younger humans (Sorond et al. 2015). These findings may be explained by the idea that chelation of ferrous iron decreases the efficiency of PHD enzymes (McNeill et al. 2005; Rabinowitz 2013; Schofield and Ratcliffe 2004), leading to the stabilization of HIF1 α and in turn the expression of HIF-1 target genes.

Although regulatory mechanisms linking iron chelation, HIF-1 activity, and PHOX regulation are not entirely clear, some studies on the effects of intermittent hypoxia suggest that iron chelation and ROS can increase HIF-1 α levels, which can, in turn, increase the expression of NADPH oxidase 2 (Nanduri et al. 2015; Yuan et al. 2011; Yuan et al. 2008). This view supports the role of HIF-1 during excessive cellular insults and cell death (Zhang et al. 2007a, b).

HIF-1 α has been reported to be reduced in mitochondrial DNA-depleted SH-SY5Y cells transformed with mitochondria derived from platelets of MCI and AD subjects, compared to controls (Silva et al. 2013). Moreover, the authors documented a decrease in the NAD⁺/NADH ratio of MCI and AD samples as well as reduced glycolysis, and an increased ADP/ATP ratio compared to controls (Silva et al. 2013). Although not fully understood, reduced rates of glycolysis in association with decreased NAD⁺/NADH and increased ADP/ATP ratios likely reflect dysregulation of bioenergetics in these subjects. NADH-dependent decrease in glycolytic flux is likely not a major regulatory event in MCI/AD, except if it occurs as part of larger biochemical derangements. The decreased NAD⁺/NADH ratios are also in agreement with work documenting compromised electron transport chain/oxidative phosphorylation in MCI/AD (Valla et al. 2006), which is in agreement with the idea that cells can increase aerobic glycolysis in order to decrease oxidative stress (Brand 1997). These findings are consistent with glucose hypometabolism seen in PET neuroimaging of brains of patients with prolonged MCI or advanced AD (Silverman et al. 2001), as opposed to the early stages of MCI where glucose metabolism might be enhanced, particularly in surviving neurons (Soucek et al. 2003).

HIF-1 Activity and Inflammation

Inflammation characterizes MCI/AD (Fillit et al. 1991; Ishii and Haga 1975; McCaulley and Grush 2015), and may also involve disruption of the blood–brain barrier, especially in

APOε4 homozygotes (Bell et al. 2012). In this environment, inflammatory cytokines, such as macrophage-derived tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β), upregulate HIF-1α likely by mechanisms that inhibit PHD enzymes and enhance HIF-1 stability and transcriptional activity (Dehne and Brune 2009; Hellwig-Burgel et al. 1999; Zhou et al. 2003). In a second mechanism, HIF-1 also downregulates receptors for inflammatory cytokines in the hippocampus, attenuating the toxicity of excessive neuroinflammation during cerebral ischemia (Xing and Lu 2016). Since inflammatory cells and their underlying toxic mechanisms generate free radicals similar to the scenario of amyloid beta-induced neurotoxicity, it is reasonable to infer that HIF-1 activity is also upregulated in this setting. Therefore, amyloid beta acts as a trigger for oxidative stress (Hensley et al. 1994) and inflammatory processes which generate ROS and consequent activation of HIF-1 (Haddad and Land 2001).

Studies in rat cortical neurons have provided direct evidence for a causal role of inflammation in triggering HIF-1 expression. Chronic lipopolysaccharide (LPS) administration into rat brains was associated with inflammation by promoting reactive astrocytes and microglia, increased TNF-α and IL-1β, hippocampal atrophy, and worsened cognitive performance (Hauss-Wegrzyniak et al. 1998). LPS was shown to enable the expression of NR1, an NMDA glutamate receptor (NMDAR) subunit, while small interfering RNAs against HIF-1α reduced NR1 expression during LPS tests (Yeh et al. 2008). In concordance with the view that LPS can promote HIF-1α expression (Frede et al. 2006), others have reported that neuronal survival was also decreased when NR1 and HIF-1α were knocked down prior to an LPS insult (Yeh et al. 2008). In sum, these studies indicate that HIF-1α mediates a neuronal survival pathway during inflammatory neurological insults, particularly in the early stages of such cellular assaults.

In humans, microvessels derived from AD subjects, compared to cognitively normal age-matched controls, show elevated levels of potentially neurotoxic and inflammatory molecules such as thrombin protease, interleukin 8 (IL-8), alphaVbeta3 and alphaVbeta5 integrins (Grammas et al. 2006). Increased HIF-1α in the microcirculation was also associated with the increases of inflammatory markers in the aforesaid proteins in that study. These reports are consistent with the notion that HIF-1 activity is enhanced in MCI/AD, and data from cellular and animal models argue that this enhanced activity may be neuroprotective.

Hypoxia-Inducible Factor, Cerebral Blood Flow, and Memory

Cardiovascular disease risk factors, such as hypertension, diabetes, dyslipidemia, and obesity, contribute to metabolic syndrome and consequently increase the risk of stroke and heart disease (Kaur 2014) and neurological disorders (Farooqui et al. 2012). One study showed a >30% increased risk of subclinical infarcts (detected by brain magnetic resonance imaging) in subjects with mitral or aortic calcific disease of the heart (Rodriguez et al. 2011). This observation is consistent with findings at autopsy showing a correlation between AD cases and damage to the aortic valve or ventricular myocardium (Corder et al. 2005). Stroke, metabolic syndrome and its components (mainly diabetes and hypertension), atrial fibrillation (a risk factor for stroke), hypertension, and heart diseases, are all associated with

cognitive decline, decreased cognitive processing, decreased neurovascular coupling, and dementia (Alonso and de Larriva 2016; Hochstenbach et al. 1998; Obisesan 2009; Tsai et al. 2016). Notably, control of hypertension decreases the risk of dementia (Obisesan 2009). These studies strongly suggest that cerebral hypoperfusion and ischemia, and decreased delivery of oxygen and nutrients to the brain are major contributors to dementia and its molecular drivers such as mitochondrial dysfunction, amyloid beta deposition, and increased inflammatory cytokines (Daulatzai 2016; Shiota et al. 2013; Zhang et al. 2007c). This is also consistent with glucose hypometabolism seen in the brains of individuals with advanced AD (Daulatzai 2016; Silverman et al. 2001). It is important to note that these mechanisms are shared by both vascular dementia and AD (Nagata et al. 2016).

Cerebral blood flow is thought to decrease during aging (Brodie et al. 2009; Oudegeest-Sander et al. 2014), and the presence of risk factors as outlined above may catalyze cognitive decline in this vulnerable state. As discussed earlier, upregulation of HIF-1 α and its target genes through, for example, iron chelation by DFO can improve memory (Fine et al. 2012) and increase cerebral vasoreactivity and autoregulation, as ascertained from transcranial Doppler ultrasound measurements of cerebral blood flow velocity in the middle cerebral artery (Sorond et al. 2009, 2015). This is particularly relevant since cerebral blood flow is decreased in late MCI and AD (Wang et al. 2013).

Several studies suggest that upregulation of HIF-1 activity or expression of its target genes may contribute to improved memory. Earlier work showed that VEGF, an HIF-1 target gene, drives neurogenesis and improves memory in mice, a phenomenon abrogated by RNA interference or inhibition of VEGF (Cao et al. 2004). This classic finding is supported by recent work indicating that HIF-1 is necessary for maintaining neural stem cells (Li et al. 2014) which are critical for neurogenesis (Goritz and Frisen 2012). In the context of acute exercise, VEGF is upregulated in the hippocampus (Tang et al. 2010); moreover, angiogenesis (which is influenced in part by VEGF), neurogenesis, hippocampal cerebral blood volume (measured by magnetic resonance imaging), and improved VO_{2max} (in humans) have all been associated with enhanced cognitive performance in rodents and humans after exercise (Pereira et al. 2007). Enhanced hippocampal memory has also been noted in mice after administration of erythropoietin (Adamcio et al. 2008) or after HIF-1-dependent elevation of VEGF-A and erythropoietin, caused by treatment with PHD inhibitors (Adamcio et al. 2010). These studies highlight the role of HIF-1 in cerebral blood flow, oxygen delivery, cognitive function, and memory.

Hypoxia-Inducible Factor as a Mediator of Programmed Cell Death

Although we have discussed HIF-1 as a transcription factor that is upregulated in order to preserve cell survival (Piret et al. 2005), there is evidence that this same complex might mediate apoptosis and cell death during neuronal injury, especially during chronic inflammation as described above. Prolonged hypoxia/ischemia leads to apoptotic-like neuronal cell death evidenced by mitochondrial degeneration, caspase activation, and DNA laddering (Halterman and Federoff 1999). Like the pro-apoptotic protein Nix which is expressed during chronic hypoxia, Bnip3 is known to be expressed under similar circumstances, driven by HIF-1 binding at HIF-1 response elements (HRE) associated with

this gene (Bruick 2000). In rat primary cortical neurons, A β has been reported to mediate BNIP3 expression in a ROS/hypoxia-inducible factor-1 α (HIF-1 α)-dependent manner, an effect reversed by protective antioxidants vitamins C and E, or small interfering RNAs against HIF-1 α or BNIP3, ultimately leading to increased cellular survival (Zhang et al. 2007b). An independent set of experiments, wherein the toxin cyanide was used as an insult against an immortalized dopaminergic cell line, remarkably replicated the findings of Zhang et al. who worked on rat primary cortical neurons (Zhang et al. 2007a, b).

It appears that HIF-1-mediated programmed cell death occurs when cellular injury is so severe that survival mechanisms are overwhelmed, or when cells fail to adapt to early or subacute toxic challenge. This explains why HIF-1/Bnip3-mediated cell death is a delayed process (Althaus et al. 2006; Halterman and Federoff 1999). This viewpoint is supported by studies showing that sub-lethal concentrations of amyloid beta are protective (Soucek et al. 2003), while higher doses of amyloid beta can trigger cellular death mediated by HIF-1/Bnip3 (Soucek et al. 2003; Zhang et al. 2007b).

Conclusion

The summarized studies show an association between MCI and elevated expression of GLUT-1, VEGF-A, and other HIF-1 target genes that function in glycolysis and vascular flow. In MCI subjects and similar to early AD states, increased expression of pro-glycolytic factors, cerebral autoregulation mediated by HIF-1 in enhancing cerebral blood flow, and antioxidant pathways may be an early adaptation to oxidative and inflammatory stress in order to attenuate neuronal cell death. However, overwhelming and prolonged stressors, such as ischemia or oxidative stress, may undermine the neuroprotective benefits conferred by HIF-1 and other survival pathways, or even convert HIF-1 to an activator of death signals.

Overall, increased HIF-1 α expression counters oxidative stress and/or inflammation in MCI/early AD and is neuroprotective. In late MCI or advanced AD, HIF-1 α likely functions as an activator of cellular death. Systematic studies addressing this bifunctional role of HIF-1 in cell survival and cell death are needed. In addition, targeted modulation of HIF-1 or some of its target pro-glycolytic genes is a likely therapeutic strategy in early cognitive decline.

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Fig. 1.

Criteria for subject selection have been previously described (Iyalomhe et al. 2015). Platelets were obtained from 17 MCI subjects (mean of 69.1 years, standard deviation of 7.4 years) and 10 age-matched controls (mean 69.6 years, standard deviation of 4.1 years). Blood was collected using sterile techniques and stored in heparinized tubes. Samples were centrifuged at $500 \times g$ after which the top two-thirds of the top-most layer with platelet-rich plasma was gently pipetted into a separate tube, and the buffy coat layer containing the leukocyte population was removed and stored in aliquots at -80°C . Approximately 50 ng of platelet RNA, isolated by Tri-Reagent (Molecular Research Center, Cincinnati, OH), was reverse transcribed using superscript[®] VILO[™] Master Mix for qRT-PCR (Invitrogen, Carlsbad, CA), followed by qRT-PCR using TaqMan expression assay. Gene expression was normalized to HPRT1 (hypoxanthine phosphoribosyl transferase 1, 4333768F, Applied Biosystems). Relative gene expression was evaluated using Biogazelle QBasePLUS (Zwijanaarde, Belgium). Gene expression in MCI cases was expressed relative to cognitively normal, non-MCI controls. Errors are standard error measurements. A two-tailed *t* test was used to determine statistical significance for each gene. *HK1* hexokinase 1, *GLUT1* glucose transporter, isoform 1, *VEGF-A* vascular endothelial growth factor A, *PDK1* pyruvate dehydrogenase kinase 1, *BNIP3* BCL2/adenovirus E1B 19 kDa protein-interacting protein 3,

BNIP3L BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

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Fig. 2.
Model of neuroprotective pathways in early MCI and cell death (in late AD) mediated by HIF-1