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CREB Signals as PBMC-based Biomarkers of Cognitive Dysfunction: A Novel Perspective of the Brain-Immune Axis

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Abstract

To date, there is no reliable biomarker for the assessment or determination of cognitive dysfunction in Alzheimer's disease and related dementia. Such a biomarker would not only aid in diagnostics, but could also serve as a measure of therapeutic efficacy. It is widely acknowledged that the hallmarks of Alzheimer's disease, namely, amyloid deposits and neurofibrillary tangles, as well as their precursors and metabolites, are poorly correlated with cognitive function and disease stage and thus have low diagnostic or prognostic value. A lack of biomarkers is one of the major roadblocks in diagnosing the disease and in assessing the efficacy of potential therapies. The phosphorylation of cAMP Response Element Binding protein (pCREB) plays a major role in memory acquisition and consolidation. In the brain, CREB activation by phosphorylation at Ser133 and the recruitment of transcription cofactors such as CREB binding protein (CBP) is a critical step for the formation of memory. This set of processes is a prerequisite for the transcription of genes thought to be important for synaptic plasticity, such as *Egr-1*. Interestingly, recent work suggests that the expression of pCREB in peripheral blood mononuclear cells (PBMC) positively correlates with pCREB expression in the postmortem brain of Alzheimer's patients, suggesting not only that pCREB expression in PBMC might serve as a biomarker of cognitive dysfunction, but that the dysfunction of CREB signaling may not be limited to the brain in AD, and that a link may exist between the regulation of CREB in the blood and CREB in the brain. In this Review we consider the evidence suggesting a correlation between the level of CREB signals in the brain and blood, the current knowledge about CREB in PBMC and its association with CREB in the brain, and the implications and mechanisms for a neuro-immune cross talk that may underlie this communication. This Review will discuss the possibility that peripheral dysregulation of CREB is an early event in AD pathogenesis, perhaps as a facet of immune system dysfunction, and that this impairment in peripheral CREB signaling modifies CREB signaling in the brain, thus exacerbating cognitive decline in AD. A more thorough understanding of systemic dysregulation of CREB in AD will facilitate the search for a biomarker of cognitive function in AD, and also aid in the understanding of the mechanisms underlying cognitive decline in AD.

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Keywords

CREB; Alzheimer's disease; biomarker; dementia; inflammation; neuroimmune; PBMC

1. INTRODUCTION

Alzheimer's disease (AD) is a devastating neurological disorder affecting learning and memory. The incidence of AD is on the rise, and an anticipated 14 million persons will suffer from the disease by 2050 in the United States (Hebert et al., 2013). The early onset familial form of the disease is caused by mutations in amyloid precursor protein (*APP*) and presenilin-1,2 (*PSEN-1,2*). The cause of the sporadic disease remains unknown, but is hypothesized to be the result of dysfunction in processing of the amyloid precursor protein (APP) and hyperphosphorylation of the protein tau. These two processes result in the accumulation of beta amyloid (Aβ) plaques and neurofibrilarly tangles, which characterize the postmortem AD brain, and are considered to be the diagnostic hallmarks of the disease. For this reason, the search for a biomarker to aid in the prediction, diagnosis, and treatment of AD has been centered on forms of amyloid and tau. The current most successful biomarkers for AD based on amyloid and tau include measurements of total tau, phosphorylated tau, and $A\beta_{42}$ in the cerebrospinal fluid (Olsson et al., 2016).

However, the severity of cognitive dysfunction in AD may be independent of the extent of amyloid or tau pathology, and indeed, the relationship between postmortem AD pathology and cognitive performance during life is notoriously poor, and therapies targeting amyloid or tau have thus far been largely unsuccessful (Morris et al., 2014). Therefore, a biomarker that can provide information on cognitive function in AD progression is essential, not only to compliment the current diagnostic biomarkers based on amyloid and tau, but also to provide a more sensitive means of measuring the efficacy of therapies meant to ameliorate cognitive dysfunction in AD.

We, and others, have reported that the expression of an important factor in the formation of memory and its retrieval, Cyclic-AMP Response Element Binding Protein (CREB), is diminished in the postmortem AD brain. In this review, we first discuss the evidence supporting the involvement of CREB in cognitive decline in AD. Then we discuss the possibility that CREB signaling in the blood could be an indicator of CREB signaling in the brain, thus serving as a biomarker of cognitive function in AD. Finally, we propose a hypothesis that peripheral CREB deficits may be an early event in AD pathogenesis, perhaps as a result of immune system dysfunction and inflammation, and subsequently modifies CREB signaling in the brain, thereby contributing to cognitive decline in AD (Figure 1).

2. CREB

The exact mechanism underlying synaptic plasticity and memory formation, storage and retrieval remains a topic of investigation, but one of the prevailing hypotheses is that it is dependent on the regulation of key genes and proteins that are modulated as a result of neuronal activity. One of the signaling pathways implicated in this process is the CREB pathway. In the brain, the CREB pathway responds to the increased calcium that results from

neuronal activity. CREB itself can be phosphorylated by a number of kinases that respond directly or indirectly to calcium, such as protein kinase A (PKA), protein kinase C (PKC), the calcium/calmodulin-dependent protein kinases CaMKII and CaMKIV, the extracellular signal-regulated kinase (ERK)-activated kinases mitogen- and stress-activated protein kinase (MSK) and the 90 kDa ribosomal S6 kinase (RSK) (Lonze and Ginty, 2002), as well as in response to nitric oxide (NO) through cGMP activation of PKG (Teich et al., 2015). Following phosphorylation at Ser133 and recruitment of cofactors, such as CREB binding protein (CBP) and p300, CREB can bind to a CRE sequence in the promoter region of downstream genes implicated in synaptic plasticity, including immediate early genes like *Egr-1* (Figure 2) (Jones et al., 2001; Kandel, 2012; Lakhina et al., 2015; Yin et al., 1994). The critical nature of CREB for learning and memory has been demonstrated by studies showing that decreasing the expression or function of the CREB signaling pathway results in impairments in learning and memory. For example, CREB mutant mice that lack the major α and δ isoforms of CREB (though they retain small amounts of CREB activity due to the β isoform) have been generated (Lonze and Ginty, 2002). These CREB mutant mice exhibit impairments in LTP and in memory-based behavior tests, such as fear conditioning and water maze (Bourtchuladze et al., 1994). Importantly, CREB regulates formation of long-term memory in other species, as demonstrated by studies in olfaction long-term associative memory in *C. elegans*, indicating that this pathway is evolutionarily conserved (Lakhina et al., 2015; Yin et al., 1994). In addition, the effects of CREB signaling impairments may not be limited to the hippocampus, as CREB mutant mice also have impaired cortical plasticity (Glazewski et al., 1999). The importance of CREB in long term memory has been additionally demonstrated in mice by the use of genetic methods including a CREB repressor (Kida et al., 2002), and expression of a dominant negative form of CREB (Pittenger et al., 2002). Experiments using viruses to enhance CREB signaling in the rodent hippocampus have been shown to improve performance in a water maze task (Brightwell et al., 2007; Yu et al., 2017). However, indiscriminate upregulation of CREB, particularly of basal CREB, is problematic for memory formation and retrieval, and a dominant active form of CREB expressed in the mouse hippocampus has been reported to impair performance in a water maze task and cause neuronal death (Lopez de Armentia et al., 2007; Viosca et al., 2009). The difference in these outcomes may be partially due to the magnitude of increase in CREB activity, with a more moderate or transient enhancement in activity providing the optimal benefits for learning and memory, or the differences may depend on the mechanism of action of the enhancement of CREB activity, with forms that mimic the downstream effects of wild-type CREB conferring a greater benefit (Suzuki et al., 2011).

In addition to CREB itself, other elements of the CREB signaling complex have also been investigated in regards to learning and memory. CBP and p300 are transcriptional coactivators for CREB that are similar both in sequence and in function, and are necessary for CRE-based gene transcription (Arany et al., 1994; Chrivia et al., 1993). Mice deficient in CBP do not respond to an enriched environment (EE) paradigm in the same way as wild-type mice, in that they do not show enhanced neurogenesis or enhanced performance in spatial navigation and pattern separation tasks following EE (Lopez-Atalaya et al., 2011). Similarly, when p300 is conditionally knocked out in the mouse hippocampus and cortex, the performance of the mice in novel object recognition and contextual fear conditioning

tasks is impaired (Oliveira et al., 2011). In addition to their role as a scaffold for the transcription complex, CBP and p300 may facilitate gene transcription through their intrinsic histone acetyltransferase (HAT) activity (Bannister and Kouzarides, 1996; Ogryzko et al., 1996). The HAT activity of CBP is essential for memory consolidation, as demonstrated by experiments in which the HAT activity of CBP is blocked, while the scaffolding function remains intact (Korzus et al., 2004). In addition, experiments using an activator of CBP/p300 HAT activity that resulted in increased histone acetylation in the hippocampus and cortex, also resulted in a greater duration of memory in a water maze task, suggesting that the HAT activity may be a critical feature of the importance of CBP/p300 in learning and memory (Chatterjee et al., 2013). In support of this idea, poor performance in the novel object recognition task by CBP mutant mice is improved by treatment with an HDAC inhibitor (Stefanko et al., 2009). On the other hand, HDAC inhibition in a CBP conditional knockout was reported not to be sufficient to restore the impairments these mice demonstrated in object recognition, fear conditioning, and spatial memory tasks, even when histone acetylation was rescued by treatment with and HDAC inhibitor (Chen et al., 2010). Therefore, CBP and p300 are likely important factors in learning and memory, but the exact mechanism of their involvement is yet to be fully unraveled.

While it is clear that direct manipulation of the CREB signaling pathway impairs the learning and memory process, the next question is whether CREB signaling plays a role in neurodegenerative diseases characterized by memory impairments, such as in the case of AD.

2.1. CREB IN THE AD BRAIN

The critical nature of CREB signaling for neural plasticity and cognitive performance suggests that this pathway may be dysfunctional in neurodegenerative diseases in which memory and cognitive function are impaired (Cowburn et al., 1992b; Schnecko et al., 1994b; Yamamoto-Sasaki et al., 1999a). Importantly, single nucleotide polymorphisms (SNPs) in *CREB1* and *CREBBP* (which encodes CBP) have been associated with accelerated cognitive decline and impaired episodic memory, semantic memory and executive function (Barral et al., 2014; Wolf et al., 2017). These types of memory, and episodic memory in particular, are disrupted in AD, supporting a link between dysfunctional CREB and the types of memory and cognitive functions impacted in AD (Gold and Budson, 2008). In addition, rare mutations in the *Snf2-related CREBBP* activator protein (*SRCAP*) were identified in individuals with late onset Alzheimer's disease (LOAD), suggesting a causative role for dysfunctional CREB signaling in AD (Vardarajan et al., 2017). However, the underpinnings of CREB dysfunction in persons with AD remain elusive. A few groups, including ours, have reported diminished levels of total and phosphorylated CREB in the postmortem AD brain in the prefrontal cortex (Bartolotti et al., 2016a) and hippocampus (Bartolotti et al., 2016a; Pugazhenthi et al., 2011; Yamamoto-Sasaki et al., 1999b), two brain structures that are thought to be particularly important in episodic and semantic memory (Gold and Budson, 2008). Our group also reported that CBP and p300 are reduced in the postmortem AD prefrontal cortex (Bartolotti et al., 2016a), an observation that is particularly intriguing in light of evidence that p300 may be overactive in the acetylation of tau in the AD prefrontal cortex (Aubry et al., 2015; Min et al., 2015; Min et al., 2010a). The level and

activity of Type I adenylyl cyclase, an enzyme responsible for the generation of cAMP and therefore CREB activation, has been reported to be reduced in the postmortem AD hippocampus (Cowburn et al., 1992a; Schnecko et al., 1994a; Yamamoto et al., 1996; Yamamoto et al., 1997). Similarly, PKA, PKC, CamK, and ERK, which phosphorylate CREB, have been described to be abnormally expressed or activated in the postmortem AD prefrontal cortex or hippocampus (Battaini et al., 1999; Bonkale et al., 1999; Kim et al., 2001; Perry et al., 1999; Reese et al., 2011; Wang et al., 1994). This evidence suggests that there may be multiple points of failure in CREB signaling in the AD brain.

While much work remains to be done investigating the status of CREB in persons with AD, CREB signaling has been extensively studied in mouse models of genetically-linked AD (FAD), although the data from these studies is at times contradictory. For example, decreased basal levels of activated CREB have been reported in the hippocampus of 3-month-old female APPswe/PS1ΔE9 mice (Bartolotti et al., 2016b), 2-month-old male APPswe/PS1ΔE9 mice (Hu et al., 2013), and 6-month-old 3xTg-AD mice (sex unspecified; (Caccamo et al., 2010)). In addition, CREB activation is diminished in the hippocampus following a stimulus, such as environmental enrichment or a learning task such as fear conditioning or novel object recognition in 3-month-old female APPswe/PS1ΔE9 mice (Bartolotti et al., 2016b), or following training for a maze task in 10-week-old male and female TgCRND8 mice (Yiu et al., 2011). On the other hand, increased basal levels of activated CREB expression have been reported in the hippocampus of 4-month-old and 13-month-old Tg2576 (sex unspecified), though these authors observed lower levels of activated CREB in this mouse model at 20 months (Dineley et al., 2001). Similarly, increased basal levels of activated CREB have been observed in whole-brain homogenates from 4- to 6-week-old 3xTg-AD and M146V-$PS1_{ki}$ mice (sex unspecified; (Muller et al., 2011). These contradictory results may be due to a number of factors, including the type of memory tested, the mouse model, the age and sex of the mice, and whether the tissue was harvested at a basal state or following a learning and memory task since it is possible that deficits in CREB signaling may only become apparent as a failure of CREB activation following a learning task in some mouse models of AD. Careful consideration of these factors will be necessary in future experiments to determine the most appropriate mouse model for the study of CREB in AD. It is also important to consider the type of memory task utilized as a function of disease progression. For example, impairments in object recognition tasks [such as in (Dere et al., 2005)] may be apparent at a different disease stage than spatial memory tasks such as mazes. Selecting the appropriate cognitive test for the disease stage and understanding the role of CREB in the formation and retrieval of these types of memory will facilitate the translation of the role of CREB in AD, as well as in the development of therapies meant to restore CREB signaling and enhance cognitive function in AD.

Additional evidence supporting the role of CREB dysfunction in AD and in cognitive impairments comes from the improvements in learning in memory that are observed when CREB signaling is enhanced in FAD mice. For example, virus-mediated rescue of CREB signaling in the hippocampus of 10-week-old male and female TgCRND8 mice has been shown to ameliorate memory deficits in a maze task (Yiu et al., 2011). CREB can also be increased through the reduction of phosphodiesterases (PDE), a family of enzymes hydrolze cAMP (PDE4, PDE7, PDE8) or cGMP (such as PDE5, PDE6, PDE9) or both cAMP and

cGMP (PDE1, PDE2, PDE3, PDE10, PDE11), thereby reducing signaling through these molecules (Garcia-Osta et al., 2012). Reducing the expression or activity of PDEs is one way in which CREB can be pharmacologically enhanced, and may serve as an effective therapy for cognitive dysfunction in AD. For example, downregulation of PDE4D in the hippocampus reversed memory deficits induced by $A\beta_{42}$ in male mice, as measured by a novel object recognition and Morris water maze task, as well as rescued pCREB expression in the hippocampus (Zhang et al., 2014). Similarly, treatment of male rats with rolipram, a PDE4 inhibitor, rescued $A\beta_{40}$–induced deficits in memory in rats, as measured by a passive avoidance task, and also rescued the $A\beta_{40}$–induced reduction in hippocampal pCREB (Cheng et al., 2010). Peripheral administration of rolipram was also able to rescue deficits in performance in a contextual fear conditioning task in 3-month-old male and female APP/PS1 mice, and rescued diminished expression of pCREB while not significantly affecting $A\beta_{40}$, $A\beta_{42}$, expression or amyloid plaque burden in the hippocampus (Gong et al., 2004), again emphasizing that the CREB signaling pathway may be able to affect cognitive function independent of regulation of amyloid. Rolipram itself may be limited as a therapeutic due to its side effects (Zhu et al., 2001), but these studies have demonstrated the potential of PDE inhibition as a means of enhancing CREB signaling and cognitive function in AD. Additional support for this idea comes from studies of PDE5 inhibitors. PDE5 inhibitors can increase pCREB by increasing cGMP, which has been shown to be reduced as a result of Aβ-induced reductions in the nitric oxide signaling cascade (Puzzo et al., 2005). Indeed, inhibition of PDE5 has been shown to reverse memory deficits a contextual fear conditioning and water maze, as well as rescue pCREB expression in the hippocampus of male and female 3-month-old APPswe/PS1ΔE9 mice (Puzzo et al., 2009). Amelioration of cognitive dysfunction in a Y-maze task was also shown following treatment with a PDE5 inhibitor in 10-month-old male APPswe/PS1ΔE9 mice (Jin et al., 2014). PDE5 inhibitors are particularly attractive candidates for use in treating AD as data from clinical trials of extended use of PDE5 inhibitors in the treatment of erectile dysfunction suggests they are safe (Fusco et al., 2010). Therefore, in addition to highlighting the importance of CREB signaling in cognitive function in AD, the continued research and development of PDE inhibitors offer a promising means of enhancing this signaling and improving cognitive function in AD (Bischoff, 2004a; Fiorito et al., 2017; Garcia-Osta et al., 2012; Teich et al., 2015).

The cause of CREB impairments in AD is not clear. In FAD mouse models, dysregulation of CREB signaling may result from the mutations in PS1 and or APP that are commonly utilized to generate the model (Chen et al., 2012; Marambaud et al., 2003; Wang et al., 2006). For example, several studies suggest that PS1 regulates CREB expression and function, (Bonds et al., 2015; Marambaud et al., 2003; Muller et al., 2011; Watanabe et al., 2009). In addition, it is thought that normal presenilin may promote CBP-induced transcription, and that FAD mutant PS1 can interfere with this process (Francis et al., 2006; Saura et al., 2004). Mutations in APP may also contribute to CREB signaling dysfunction, possibly through the dysregulation of APP processing or by increasing Aβ toxicity (Dineley et al., 2010b; Dineley et al., 2001; Espana et al., 2010; Ma et al., 2007; Nishimoto et al., 1993). In support of this idea, 5-month-old male C57BL/6 mice treated with Aβ oligomers express lower levels of pCREB in the hippocampus and impaired performance in a fear

conditioning task (Dineley et al., 2010a). Similarly, treatment of 11- to 12-month-old Tg2576 mice (sex unspecified) with anti-Aβ antibodies has been shown to rescue impairments in CREB activation (Ma et al., 2007). Interestingly, overexpression of BACE1, which is thought to be increased in FAD, reduces CREB phosphorylation, PKA activity, and cAMP levels *in vitro*, independent of its effects through Aβ, suggesting that CREB dysfunction may not be exclusively dependent on Aβ levels (Chen et al., 2012). Similarly, virus-mediated enhancement of CBP expression reduced memory impairments in a Morris water maze task without also affecting changes in amyloid or tau pathology in the hippocampus of 6-month-old 3xTg-AD mice (sex unspecified; (Caccamo et al., 2010)). Indeed, we have observed deficits in CREB signaling in the hippocampus of both male and female APPswe/PS1ΔE9 mice as early as 2-3 months of age (Hu et al., 2013), though these mice do not typically demonstrate wide-spread plaque deposition until 4 to 6 months of age (Jankowsky et al., 2004; Jankowsky et al., 2005). However, these mice do still have aberrant APP processing and increased levels of soluble Aβ at this age, indicating that more study is needed to determine the contribution of the different forms of Aβ on CREB signaling (Bonardi et al., 2011; Min et al., 2010b; Zhang et al., 2012). Therefore, while the mutations in APP and PS1 in mouse models of FAD are clearly the original source of CREB impairments, the proximate cause remains unclear and CREB may be regulated independently of amyloid and tau in FAD mice.

In sporadic AD, the mechanism underlying CREB dysfunction is even less clear. If CREB impairments are simply the result of increased plaque load or NFTs, as might be concluded from the FAD mouse data, a relationship between CREB expression and these pathological hallmarks should be observed. However, in our recent study in which we examined CREB signaling components in the postmortem AD prefrontal cortex, we did not observe a relationship between pCREB and the extent of plaque deposition or NFTs in the prefrontal cortex (Bartolotti et al., 2016a), suggesting that CREB dysfunction may not be simply a result of advanced neurodegeneration and AD pathology.

Aging is one of the primary risk factors for sporadic AD. It is therefore interesting that CREB decreases as a function of age in both the human (Yamamoto-Sasaki et al., 1999b) and rat hippocampus, both at a basal level (Foster et al., 2001), and following training on a contextual fear conditioning task in which the older rats exhibited poorer performance (Kudo et al., 2005). While the mechanism responsible for reduced CREB in the hippocampus during aging is unclear, reactive oxygen species may play a role (Bevilaqua et al., 1999; Ozgen et al., 2009; Ryu et al., 2005; Waldron and Rozengurt, 2000). Another hypothesis is that dysregulated inflammation during aging may underlie cognitive decline (Franceschi et al., 2007). This explanation is particularly attractive in that it provides a link between alterations in CREB signaling in the brain and the periphery, which we review next. However, it is important to note that the reductions in CREB signaling components observed in AD are typically age-matched, indicating that age alone is not responsible for the further reduction of CREB signaling observed in AD.

2.2. CREB IN PBMC

As CREB is a critical component of memory and cognitive function in the brain, its accessibility in the periphery could offer valuable and relevant insight into cognitive decline during AD, as well as serve as an indicator of the efficacy of therapies intended to enhance cognitive function. In addition, our work in APPswe/PS1ΔE9 mice suggests that CREB dysfunction in the hippocampus may precede plaque deposition (Bartolotti et al., 2016b; Hu et al., 2013), suggesting that CREB dysfunction is an earlier event than disease pathological hallmarks. In that regard, a peripheral marker would also aid in understanding the timescale of CREB impairments in AD, rather than depending on an end-state, postmortem analysis.

In our recent paper, we showed that levels of pCREB in PBMC samples isolated during life were temporally correlated with levels of pCREB in the postmortem AD prefrontal cortex (Bartolotti et al., 2016a). This observation suggests the interesting possibility that analysis of peripheral CREB signaling components, and pCREB in particular, could be used as a marker for CREB signaling in the brain. Others have previously investigated the potential of CREB signaling components in PBMC as markers for CREB signaling in the brain. For example, CREB and pCREB are reduced in the postmortem prefrontal cortex and hippocampus of individuals suffering from mood disorders (Dwivedi et al., 2003), and a reduction in pCREB has been observed in peripheral blood T lymphocytes of individuals suffering from depression (Koch et al., 2002), supporting the idea that abnormal CREB function may be apparent in the PBMC when it is occurring in the brain.

CREB plays important roles in regulating immune function and a detailed description of its roles in that regard are described elsewhere (Wen et al., 2010). In PBMC, CREB is primarily thought to be important fo survival, cell cycle and proliferation, and cytokine production (Wen et al., 2010). Here we will briefly review the current understanding of CREB signaling in different subtypes of PBMC (Table 1), and the evidence supporting the hypothesis that these processes are dysfunctional in AD.

Lymphocytes make up the greatest percentage of PBMC and include T cells, B cells and natural killer (NK) cells. T cells, particularly CD4+ T cells, in turn make up the greatest percentage of lymphocytes. Therefore, it is likely that detectable changes in CREB expression in a pool of PBMC come from CD4+ T cells, but CREB may also be dysfunctional in other PBMC.

Several cytokines and immune-related factors, including interleukin 2 (IL-2), IL-6, IL-10, tumor necrosis factor alpha (TNF-r), cyclooxygenase-2, and macrophage migration-inhibitory factor possess a CRE element (Wen et al., 2010). In addition, CREB is thought to be important for the expression of interferon γ (IFN-γ), and interleukin 4 (IL-4) by CD4+ T cells (Zhang et al., 2000), and the expression of these cytokines is thought to be dysfunctional in, and perhaps contribute to the pathogenesis of, AD (Zheng et al., 2016). Data from CREB mutant mice suggests that CREB is important for regulating Th17 differentiation and regulatory T cell (Treg) differentiation, and may be a particularly important factor in maintaining balance between Th17 and Treg cells (Wang et al., 2017). While the role of Th17 and Treg cells in AD is controversial and remains an important topic for investigation (Baruch et al., 2015; Dansokho et al., 2016; Flego et al., 2015; He and

Balling, 2013; Kim and Leonard, 2007; Larbi et al., 2009; Saresella et al., 2010; Tahmasebinia and Pourgholaminejad, 2017), there is some evidence that a dysfunction in CREB signaling in these cells could be present in AD. For example, an imbalance between Th17 and Treg cells has been reported in AD PBMC (Oberstein et al., 2018). In addition, CREB and CBP are important for the expression of interleukin-17 (IL-17) by Th17 cells (Hammitzsch et al., 2015; Hernandez et al., 2015), which has been shown to be altered in the serum of mice in response to hippocampal administration of $A\beta_{1\text{-}42}$. Similarly, CBP and p300 are thought to be important in mediating Treg function, which is an important part of appropriate regulation of the inflammatory response (Klatzmann and Abbas, 2015), and deletion in CBP and p300 leads to aberrant expression of inflammatory genes (Liu et al., 2014).

In addition to T cells, other PBMC subsets may be impacted by dysfunctional CREB signaling in AD. For example, NK cells isolated from AD patients have been shown to be less responsive to stimulation including stimulation by IL-2 (Araga et al., 1991). In addition, numbers of NK cells have been reported to be diminished in AD, possibly as a result of increased apoptosis (Schindowski et al., 2006, but the important role of CREB signaling in NK cell function in response to IL-2 (Ponti et al., 2002) suggests that impaired CREB signaling may contribute to the dysregulation of NK cells in AD.

In addition to lymphocytes, macrophages and small numbers of dendritic cells (DCs) can also be found in PBMC. As in the case of lymphocytes, CREB may play a role in the survival of monocytes (Roach et al., 2005). CREB is thought to mediate interleukin 10 (IL-10) expression by macrophages (Ananieva et al., 2008) and DCs (Alvarez et al., 2009). Specific knockout of CREB in DCs leads to an impairment in immune processes related to DC function, specifically the expression of B cell lymphocytes in germinal centers (Ohl et al., 2018).

Finally, CREB is thought to be important in the proliferation of B cells (Yasuda et al., 2008). B cells have been reported to be decreased in AD PBMC (Richartz-Salzburger et al., 2007; Speciale et al., 2007), which might be interpreted as a result of impaired CREB signaling in AD PBMC, but further experiments are necessary to support this idea.

From this discussion it is clear that a more thorough understanding of the cell type responsible for CREB dysfunction in AD PBMC is critical to understanding this phenomenon. Future experiments should examine CREB signaling expression in the different subpopulations of PBMC. In addition, the cause of impaired phosphorylation of CREB in AD PBMC will be the topic of future study, but we will consider a few possibilities here. One possible mechanism for the impairments in CREB phosphorylation could be through kinase function. CREB in PBMC responds to many of the same kinases as neuronal CREB (for review (Kuo and Leiden, 1999)), suggesting the possibility of common regulatory pathways. For example, Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) activates CREB in leukocytes via RSK (Mitton et al., 2014), and peripheral administration of GM-CSF to 12-month-old male and female AβPPswe mice has been shown to improve cognitive function as measured by a radial-arm water maze (Boyd et al., 2010). Similarly, mice deficient in CaMKIV not only demonstrate memory impairments in

fear conditioning and Barnes circular maze experiments (Takao et al., 2010), but also exhibit impaired phosphorylation of CREB in T cells (Anderson and Means, 2002). Mitogen and stress activated protein kinase (MSK) has also been shown to activate CREB in T cells, and is thought to have an anti-inflammatory role in the cells of the immune system (Kaiser et al., 2007; Reyskens and Arthur, 2016). Therefore, a common, system-wide impairment in the function of one or more kinase could be a mechanism underlying the diminished CREB phosphorylation in both brain and blood. We next consider the hypothesis that CREB dysfunction actually begins in the periphery and is transferred to the brain, thus contributing to cognitive decline in AD.

3. PERIPHERAL CREB DYSFUNCTION AS AN EARLY EVENT IN AD PATHOGENESIS

Dysregulation of the immune system is a hallmark of age-related cognitive decline and neurodegenerative diseases characterized by dementia (Franceschi et al., 2007). It is thought that the aged brain expresses higher levels of pro-inflammatory chemokines and cytokines like TNFα and IL-6, as well as lower levels of anti-inflammatory cytokines like IL-2 (Chung et al., 2009)). Aged individuals with greater expression of circulating pro-inflammatory cytokines are more likely to suffer from cognitive impairments, and this correlative observation leads to the hypothesis that pathological neuroinflammation may be playing a causative role in cognitive decline observed in aging (Marsland et al., 2015; Wyss-Coray, 2006). It has also been proposed that dysregulated inflammation during aging may act as a prodromal form of AD (Giunta et al., 2008). In support of this idea, it has been reported that increased expression of inflammatory proteins in the plasma precedes onset of AD (Engelhart et al., 2004). CREB signaling is a key component of appropriate regulation of the inflammatory response, particularly in its role of regulating cytokine production by PBMC (Raker et al., 2016), which suggests that peripheral CREB signaling may play a role in systemic aging. Intriguingly, exposure of old mice to young blood increases pCREB expression in the hippocampus of the old mice (Villeda et al., 2014), indicating that the effects of aging on peripheral blood may influence CREB signaling in the brain, and thus cognitive function. How altered CREB signaling in the aging peripheral blood might relate to altered CREB signaling in the brain remains unknown, but elucidating this connection may shed light on the connection between peripheral inflammation and cognitive decline in AD. Common indicators of inflammation, such as levels of cytokines and chemokines, have been repeatedly shown to be altered in AD compared to age-matched controls, both in the brain and in the peripheral fluids (for review see (Wyss-Coray and Rogers, 2012)), indicating that while increased inflammation may be a part of the aging process, the dysregulation of inflammation in AD may be more pathogenic. In our recent paper, we observed modest increases in pCREB, Total CREB and CBP in PBMC isolated from persons with mild cognitive impairment, the prodromal form of AD (Bartolotti et al., 2016a). We hypothesized that this increase could be an early attempt at compensating for impairments in CREB signaling in PBMC, or it could be indicative of increased CREB-dependent inflammation typical of MCI (Bonotis et al., 2008; Magaki et al., 2007). Indeed, peripheral expression of cytokines, including the CREB-driven cytokines IL-2 and IL-10, is reported to be especially high in MCI (King et al., 2018), suggesting that alterations in CREB signaling

in PBMCs correspond to alterations in inflammation that occur with AD progression different from what is occurring in aging without AD.

While the issue of whether peripheral inflammation is a cause or effect of AD remains unclear, there is some evidence supporting a causative role. For example, stimulating an immune response through peripheral administration of LPS has been shown to cause cognitive impairment, as measured by a water maze task, and induce expression of $A\beta_{1\text{-}42}$ in the hippocampus and cortex of male mice (Lee et al., 2008), supporting the idea that alterations in the periphery can influence cognitive function and AD pathology. In addition, a recent meta-analysis reported that increased peripheral inflammation increased risk for dementia (Koyama et al., 2013). These studies suggest that dysregulation of the immune system may be at least an early event in AD, and may even contribute to the disease in a causative way.

Importantly, clinical trials of non-steroid anti-inflammatory drugs (NSAIDs) have largely failed thus far as a therapy for AD (Aisen et al., 2003). While this failure may be due to many factors, such as initiation of treatment too late in the disease course, or lack of strength or specificity, this result does suggest that non-specific lowering of peripheral inflammation may not be sufficient to improve cognitive function in AD, and further work needs to be done to identify the mechanism of inflammatory dysfunction in AD. Recent evidence suggests that inflammasomes may respond to, as well as exacerbate, AD pathology, potentially resulting in a cycle of increased inflammation and increased pathology, thus emphasizing the contribution of the immune system to AD pathogenesis (Venegas et al., 2017). We propose that the dysregulated peripheral CREB signaling is a component of immune system dysfunction in AD, and that this dysfunction may be communicated to the brain, exacerbating cognitive decline in AD.

3.1. MOLECULAR MEDIATORS

Perhaps one of the best-supported mechanisms for neuro-immune communication is via cytokines, particularly those expressed by PBMC. In AD, it is thought that the blood brain barrier (BBB) exhibits increased “leakiness”, which may allow abnormal trafficking of immune cells and increased communication between the blood and brain (Martorana et al., 2012). For example, activated T cells are able to cross the BBB from the periphery into the CNS, and increased levels of infiltrating T cells have been observed in the postmortem AD hippocampus (Togo et al., 2002). However, even in the absence of direct contact, brain cells and PBMC both produce and respond to cytokines (Bartfai and Schultzberg, 1993), offering another potential mechanism for transference of CREB-related signaling deficits (Figure 3).

As mentioned above, CREB regulates both the production of and response to many interleukins in the PBMC, including IL-2, IL-4, IL-6, IL-10, and IL-17 (Acarin et al., 2000; Avni et al., 2010; Erta et al., 2012; Guyot et al., 1998; Hammitzsch et al., 2015; Hernandez et al., 2015; Jansky et al., 2003; Rigano et al., 1996; Zhang et al., 2000). A recent meta-analysis suggested that the peripheral expression of these and other cytokines is associated with AD and cognitive function (Lai et al., 2017). IL-2 has been reported to be both decreased (Beloosesky et al., 2002) and increased (Huberman et al., 1994) in AD PBMC, though more work needs to be done to determine the exact nature of this dysfunction.

Similarly, the reports concerning production of IL-6 are also conflicting and has been reported to be both increased (Reale et al., 2005) and decreased (Bergman et al., 2002) in AD PBMC. IL-4 and IL-10 have both been reported to be reduced in AD PBMC (Reale et al., 2008; Speciale et al., 2007).

Interleukins are thought to have some permeance through the BBB (Alves et al., 2017; Banks et al., 2004; Waguespack et al., 1994). IL-2 has been reported to be decreased in the postmortem AD hippocampus (Alves et al., 2017), which is likely a result of decreased production from the resident cells of the brain, but could be partially due to decreased transfer from the periphery. IL-2 receptors are expressed on neurons and IL-2 knockout mice exhibit impaired performance on a Morris water maze task (Petitto et al., 1999). Importantly, specific knockout of brain-derived IL-2 does not worsen memory impairments as measured by a Morris water maze task, indicating a key role for peripherally-derived IL-2 on cognition (Petitto et al., 2015). Interestingly, treating 8-month-old male APPswe/PS1ΔE9 mice peripherally with IL-2 was found to rescue neurodegeneration and memory impairments in a Morris water maze task, as well as increasing the presence of IL-2 and Tregs in the brain (Alves et al., 2017). The expression of other CREB-driven interleukins in the AD brain also requires more study. The nature of IL-6 dysfunction in the AD brain, for example, remains unclear (Chakrabarty et al., 2010; Chong, 1997; Han et al., 2011; Hull et al., 1996a; Hull et al., 1996b; Ringheim et al., 1998). While IL-10 is thought to be reduced in AD PBMC, recent experiments in mice suggest that increased IL-10 in the brain of mice overexpressing APP may worsen cognitive impairments as demonstrated with a contextual fear conditioning task in 5-month-old male and female CRND8 mice (Chakrabarty et al., 2015). Similarly, a reduction in IL-10 was shown to be beneficial for cognitive function in 12- to 13-month-old male and female APP/PS1 mice, as demonstrated by improved performance on a novel object recognition task, and the same study reported that IL-10 may be increased in the AD brain (Guillot-Sestier et al., 2015). IL-10 may be differentially regulated depending on the disease course (Asselineau et al., 2015). Treatment with rolipram, a compound that increases phosphorylation of CREB, increases IL-10 levels and decreases TNF-α (a cytokine suppressed by CREB (Avni et al., 2010)) in the brain, while improving cognitive functioning in an animal model of diabetes, as measured by a Morris water maze task, (Miao et al., 2015), suggesting a link between these pathways.

It is important to note that the canonical interleukin signaling pathway acts via JAK/STAT, and though cytokine signaling via JAK/STAT has been implicated in the formation of LTM (Petitto et al., 2015), the relationship between this process and CREB signaling remains to be investigated and indicates that deficits in interleukin expression or activity resulting from CREB deficits in the periphery may indirectly affect CREB expression in the brain. One study demonstrated that JAK2 prevents degradation of pCREB, thus stabilizing it in adrenocortical cells, suggesting one potential mechanism by which JAK/STAT signaling might be linked to CREB signaling (Lefrancois-Martinez et al., 2011). In addition, the ERK and Akt pathways can respond to JAK/STAT signaling, and CREB could in turn respond to alterations in ERK or Akt (Kristiansen and Mandrup-Poulsen, 2005), which could lead to phosphorylation of CREB. In addition to CREB activation, interleukins may affect the expression or activity of CBP/p300. For example, IL-4 has been shown to increase the HAT activity of CBP in epithelial cells (Shankaranarayanan et al., 2001). Therefore, while

interleukins are a promising candidate to mediate the communication of disrupted CREB signaling from the periphery to the brain, more work is needed to demonstrate a mechanistic link.

Other potential mediators of CREB deficits from the periphery from the brain include neurotrophic factors. PBMC can produce neurotrophic factors, which are BBB-permeable and are an important means of communication between the blood and brain (Otten et al., 2000). Production of neurotrophins by T cells is thought to be an important neuroprotective factor for injured neurons (Moalem et al., 2000), suggesting that communication from PBMC to the brain by neurotrophins is a plausible mechanism by which a dysfunction in CREB might be communicated. CREB is an important mediator both of the transcription of neurotrophic factors and of the response to neurotrophic factor signaling. Neurotrophic factors have been demonstrated to be dysfunctional in AD, both in peripheral fluids and postmortem tissue (Du et al., 2018), supporting the idea that the communication of CREB dysfunction may be mediated by neurotrophic factors. For example, brain-derived neurotrophic factor (BDNF), which possess a CRE region, has been reported to be decreased in AD peripheral blood samples (Qin et al., 2017), and higher levels of BDNF in serum have been linked to slower cognitive decline in AD (Laske et al., 2011). Therefore, it is possible that CREB dysfunction in PBMC could lead to reduced BDNF production by the PBMC, thereby reducing the contribution of circulating BDNF to signaling in the brain, a deficit that could presumably accelerate cognitive decline. In addition to BDNF, other neurotrophic factors are also potential candidates for the communication of CREB deficits from PBMC to the brain. For example, CREB also facilitates expression of NGF (McCauslin et al., 2006) and VEGF (Jeon et al., 2007), but the data concerning the expression of these neurotrophic factors in AD is conflicting (Du et al., 2018), and requires further study before these factors can be supported as a link between dysfunctional CREB in PBMC and in the brain.

Catecholamines (e.g., dopamine, epinephrine, and norepinephrine) are hormones that could also contribute to the communication of CREB deficits between the blood and brain. T cells can produce catecholamines (Flierl et al., 2008). CREB is important for tyrosine hydroxylase, which is a critical enzyme in the biosynthesis of catecholamines (Lewis-Tuffin et al., 2004; Piech-Dumas and Tank, 1999), and therefore disrupted CREB signaling could impair production of catecholamines. CREB is a mediator of the signaling response of catecholamines (Beck et al., 2004; Lorton and Bellinger, 2015) and could therefore be impacted by altered peripheral catecholamine signaling. Indeed, catecholamines are thought to be dysfunctional in the AD brain and may lead to neurodegeneration and cognitive dysfunction (Gannon et al., 2015). However, the role of CREB in the regulation of catecholamines in PBMC and the effect this alteration may have on CREB signaling in the brain still requires more study.

Though microRNAs (miRs) are typically thought of for their ability to regulate translation within a cell, evidence suggests that miRs can exist extracellularly and may be a form of cell-cell communication (Valadi et al., 2007). Indeed, trends of expression of miRs in peripheral circulation often mirror trends of expression in the brain, which has made them an attractive candidate for biomarkers. miRs known to regulate or be regulated by CREB, such as miR-9 (Tan et al., 2012a; Tan et al., 2012b), miR-124 (Rajasethupathy et al., 2009; Wu

and Xie, 2006), miR-132 (Majer et al., 2012; Vo et al., 2005; Yi et al., 2014), miR-134 (Gao et al., 2010; Zhao et al., 2013), miR-212 (Hollander et al., 2010; Vo et al., 2005), could also serve as mediators of communicating CREB signaling dysfunction between the blood and the brain, and idea supported by evidence that these CREB-linked miRs are abnormally regulated in AD (An et al., 2017; Cogswell et al., 2008; Hebert et al., 2008; Lau et al., 2013; Lukiw, 2007). However, much work needs to be done to demonstrate not only that these miRs respond to CREB in PBMC, but also that the miRs are released from the PBMC, traffic to the brain, and impact CREB signaling in the brain and that this process is altered in AD for this to be a plausible mechanism of communication of CREB signaling dysfunction in AD.

4. CONCLUSIONS

Here we have discussed possible mechanisms underlying systemic and central CREB impairments. These mechanisms are important because they may underlie impaired CREB signaling as a cause of cognitive decline in AD and potentially other brain disorders characterized by cognitive deterioration. Focusing on mechanisms in AD, we have provided evidence that CREB signaling in PBMC is related to CREB signaling in the brain, and considered the possibility that the expression of CREB signaling components in PBMC may be a more faithful biomarker of cognitive function in AD than markers directly reliant on pathological hallmarks. We have proposed the hypothesis that CREB dysfunction in PBMC is an early event in AD pathogenesis, perhaps as a result of immune system dysfunction, and is communicated to the brain, causing dysregulation of CREB signaling in the brain and exacerbating cognitive dysfunction in AD. Finally, we have considered potential molecular mediators of this communication, with the acknowledgement that the data on immune to brain communication is still relatively underexplored and much more research is needed to fully elucidate the mechanism. However, a more thorough understanding of CREB in the immune system and CREB in the brain and the relationship between these two may shed light on the elusive nature of dementia and lead to more effective therapeutics.

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Highlights:

- There is no reliable biomarker for cognitive dysfunction in AD.
- CREB signaling is critical to learning and memory and may be dysfunctional in AD.
- Expression of CREB components in PBMC may provide a biomarker for CREB in the brain.
- CREB dysfunction in PBMC may be a result of immune dysfunction.
- PBMC CREB dysfunction may affect neuronal CREB, worsening cognitive decline in AD.

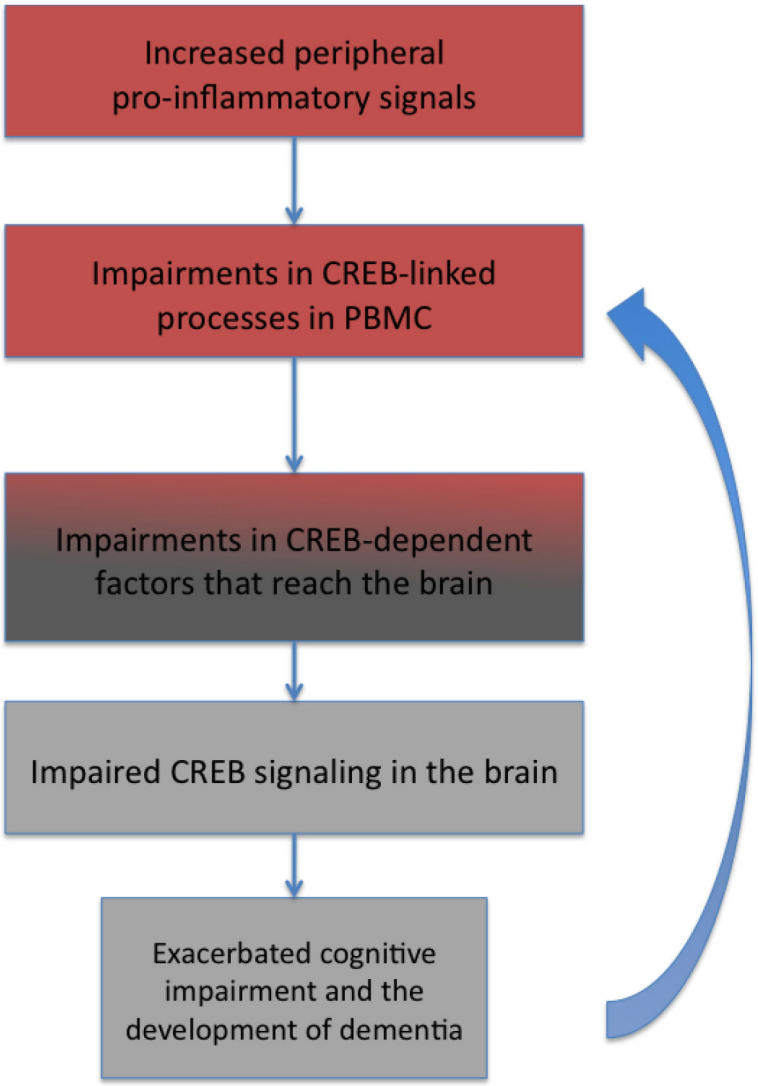

Figure 1.

Hypothesis for the mechanism by which CREB signaling defects in the periphery might affect CREB in the brain in AD. Following dysregulation of the immune system that accompanies AD, CREB signaling in PBMC is disrupted. This deficit may be imparted to the brain through mediators such as cytokines, neurotrophic factors, or hormones. Deficits in CREB signaling in the brain may accelerate cognitive decline in AD, and may in turn influence CREB signaling in the periphery through similar mediators, resulting in a cycle of CREB dysfunction and further cognitive decline.

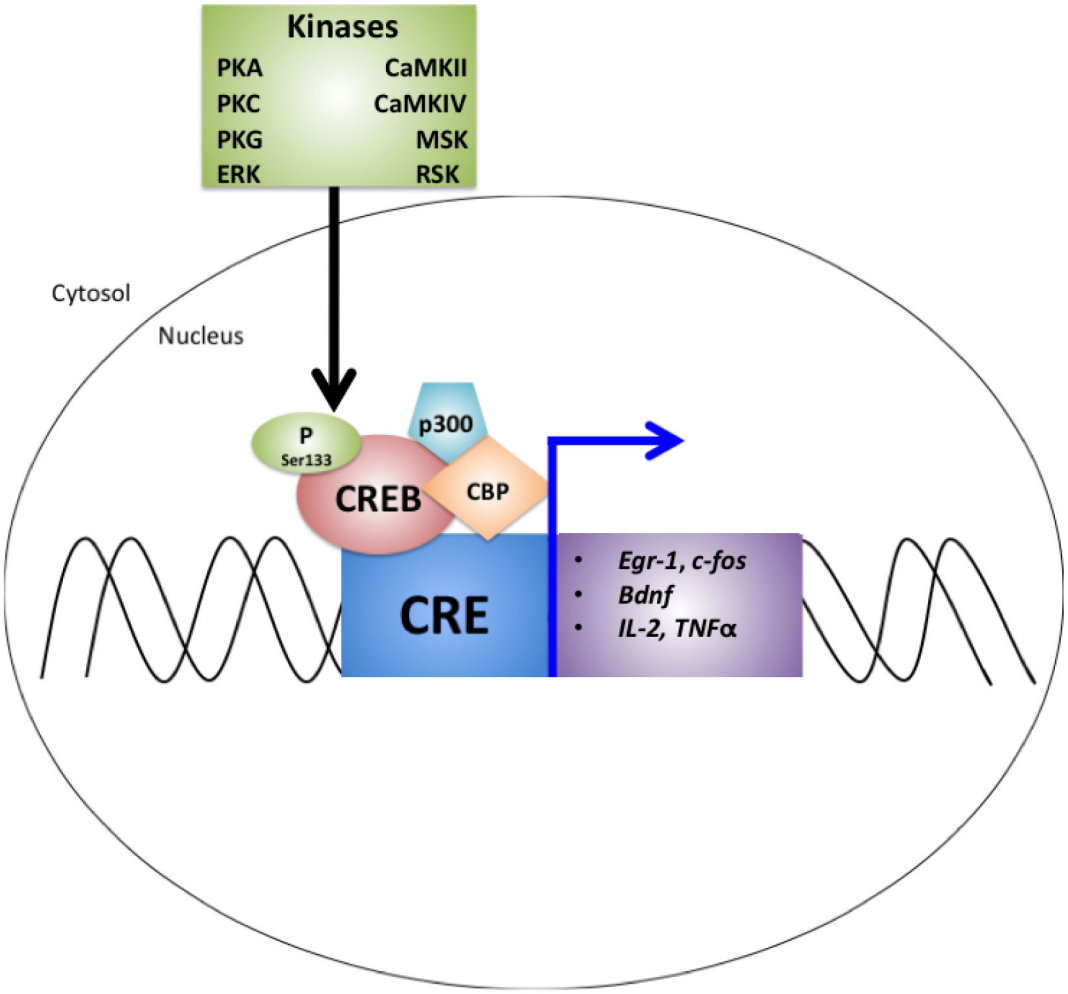

Figure 2.

The components of CREB-based signaling, a process that results in expression of CRE-driven genes thought to be important for the formation of memory. *Egr-1, c-fos,* brain derived neurotrophic factor (*bdnf*) and tumor necrosis factor alpha (*TNFα*) are examples of CRE-driven genes.

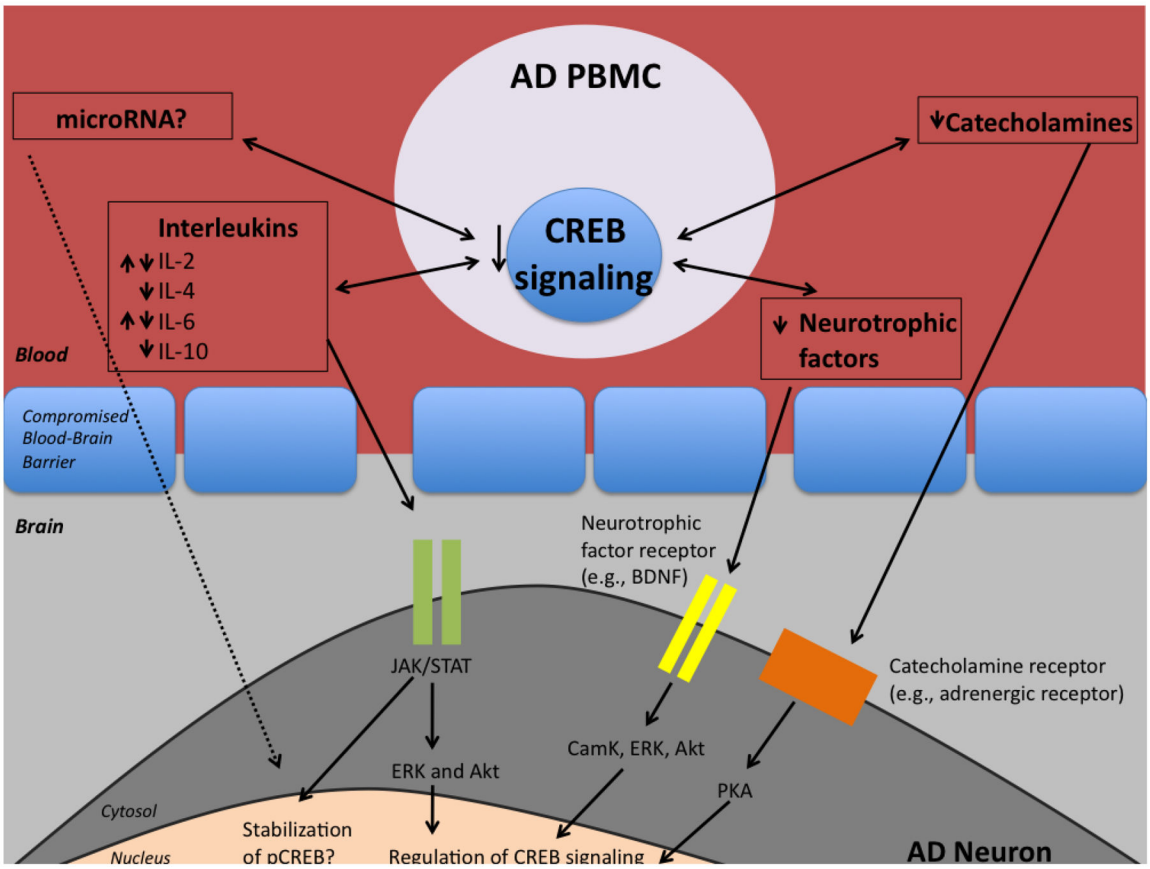

Figure 3.

Hypothesis detailing possible mechanisms by which CREB signaling in PBMC affect CREB signaling in neurons. Deficits in CREB may cause dysfunction in the production of and response to interleukins, neurotrophic factors, catecholamines, or microRNAs. These factors may traffic across the compromised blood brain barrier and signal through neuronal receptors on vulnerable neurons, thus negatively affecting CREB activation and CRE-based transcription, important for learning and memory.

Table 1.

Role of CREB in PBMC.

Cell Type	Role of CREB
T cells	• Proliferation and survival. •Production of IL-2, IFN-γ, and IL-4 by CD4+ T cells. •Regulation of Th17 and Treg differentiation via TGFβ and IL-6. •Production of IL-17 by Th17 cells.
B cells	• Proliferation and survival.
NK cells	• Mediates response to IL-2.
Macrophages	• Production of IL-10.
Dendritic cells	•Maturation. •Production of IL-10.