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Review Article

c-Fos Expression Differentially Acts in the Healthy Brain Compared with Alzheimer's Disease

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Abstract

The proto-oncogene c-Fos is known as a reliable marker of cell activation, which is immediately induced after a new stimulus in specific brain regions, depending on the nature of the stimulus applied. However, the expression of c-Fos is increased in Alzheimer's disease (AD) and contributes to amyloid β-peptide-induced neurotoxicity. This review attempted to focus on the role of c-Fos in learning and memory in both healthy brain and AD, emphasizing on possible mechanisms. Comparing the available findings, regarding learning and memory, c-Fos expression leads to memory formation through ERK (extracellular signal-regulated kinase)/CREB (cAMP response element-binding protein) and long-term potentiation, while it is down regulated after the repetition and habituation of stimuli. However, its overexpression in neurons and glia of AD, contributes to cognitive deficits and neuronal loss, which represents a defect in its ability to habituate to repeated stimuli. Also, expression pattern in glial is associated with constitutive CREB activation following increasing amyloid beta (Aβ), activation transcription factor (ATF3), and cytochrome c in apoptosis pathways. Thus, two contradictory roles of c-Fos in the healthy brain and AD, reveal more complexity in c-Fos up and down stream signaling pathways, bioavailability, and sensitivity. Future studies focusing on c-Fos modulation, might offer promising strategies to mitigate cognitive decline in AD.

Introduction

Immediate-early genes (IEGs) constitute the early genomic response to various stimuli, either directly by encoding transcription factors or through their protein products, which modify cell functions.[1] More than seventy IEGs have been identified, including the most well-known and well-characterized IEG: c-Fos.[2] The c-Fos gene was first introduced as a proto-oncogene responsible for the induction of bone tumors encoded by the Finkel–Biskis–Jinkins murine osteogenic sarcoma virus.[3] Basal expression of c-Fos is low, but it rapidly peaks between 30 and 45 m, producing a 380-amino acid protein called "Fos," which influences target genes.[4] Other members of the Fos family consist of four proteins: FOS, FOSB, FOSL1, and FOSL2.[1,5]

During development, c-Fos is involved in proliferation and differentiation, while in the adult brain, it contributes to neural activity,[6] and responses to stress across various regions, including the hippocampus, cerebral cortex, and medial prefrontal cortex,[1,5,7] as well as long-term memory and synaptic plasticity,[6,8] and activity maturation in the hippocampal–entorhinal under physiological conditions.[9,10] Its rapid, sensitive, and synchronized response to various stimuli has made it a marker for neuronal activation.[11] Notably, c-Fos expression shows distinct patterns depending on the novelty and intensity of the stimulus, in such a way that acute neuronal activity triggers a strong response.[12–14]

On the other hand, recently, dysregulation of c-Fos expression has been implicated in numerous neurological disorders, including Alzheimer's disease (AD).[1,15,16] AD is a chronic neurodegenerative disorder characterized by cognitive decline, inflammation, and memory loss, and it still remains as an incurable disorder.[17–19] Various combined actions of signaling pathways, including c-Fos, have been reported to be activated during AD.[17] Therefore, it is important to investigate these signaling pathways to better understand the etiology and treatment of this disease.

Studies have revealed increased c-Fos expression in the amygdala and hippocampus of AD patients, which correlates with cognitive decline and cellular apoptosis.[20,21] The elevation of Fos protein appears to participate in a destructive cycle by promoting amyloid beta (Aβ) accumulation,[21] expression of apoptotic

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genes,[22] and neuronal loss.[22,23] These findings, together with the detection of c-Fos in inflammatory subtypes of glia, suggest that c-Fos might be involved in neuronal death and the inflammatory response, exacerbating the progression of AD.

The objective of this narrative review was to answer the question of whether c-Fos alterations and responsiveness are the same in the normal and AD brain. Thus, we summarized studies on AD postmortem brains, rodent AD models, and cell cultures. Next, we explore the main data linking mechanisms underlying c-Fos expression in both neurons and astrocytes.

Expression of the c-Fos gene in brain regions

Expression of c-Fos in the brain is induced by physiological synapses and is closely related to the neural activity of the brain in various models of stress and pain,[24–26] passive avoidance learning,[27] and emotional stress.[13] It seems that the pattern of expression occurs within specific brain regions, confirming a mapping pattern of the brain areas involved in response to those stimuli,[28] during either physiological or pathological states.[29] However, it can be difficult to determine the specificity of expression when a stimulus consists of various components such as stress, emotion, motivation, anxiety, learning, and pain.

Among brain regions, c-Fos expression has been extensively reported in hippocampal regions, including CA1, fimbria, dentate gyrus, hilus, and cerebral cortex,[20,30] as well as in the parietal, medial prefrontal, and ventrolateral orbital cortex after noxious stimuli.[27] Previously, we showed significantly more Fos-positive neurons in 92 brain regions after a slight electric foot shock, in rats predisposed to emotional stress, compared with the resistant phenotype.[13] This extensive pattern of c-Fos expression reflects differences in behavioral typologies and the sensitivity of those brain regions in response to components of stress, anxiety, motivation, fear, emotion, pain, and aversive memory.

The c-Fos gene in different brain cell types

It is obvious that c-Fos is induced in neurons of specific brain regions like the hippocampus, amygdala, and cortex, to connect neural information with brain regions as part of a homeostatic response.[24,25] In addition to neurons, it is expressed in the glial cells of adult rat brains.[1,31–37] In astrocytes, it is expressed under the influence of proliferation, differentiation, growth, inflammation, repair, damage,[1,31] stress,[32] cytokines,[33] lipopolysaccharide (LPS),[34] and infection with adenovirus.[35]

Glial cells are important resident cells in the brain that are involved in various functions under both physiological and pathological conditions, including the regulation of immune responses,[1,38] response to stress,[39,40] development of synapses,[41] neurotransmitter uptake,[42] maintaining the ionic balance in synaptic and extrasynaptic spaces,[43] bidirectional communication between neurons and astrocytes,[43] and the generation of action potentials via Ca^{2+} waves.[44]

c-Fos has also been reported to be induced in oligodendrocytes and microglia in response to stress across different subregions of the medial prefrontal cortex.[11] For instance, it has been reported that glutamate activates c-Fos in glial cells via metabotropic glutamate receptor subtype 5,[36] in addition to N-methyl-d-aspartate (NMDA),[45] α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors.[46–48] All these findings indicate that glial c-Fos expression may mediate inflammatory responses and be involved in the mechanisms of neuronal loss in AD.[32]

Taken together, astrocytes play crucial roles in maintaining brain homeostasis, ranging from proliferation to communication, under both physiological and pathological conditions such as trauma, inflammation, and metabolic disturbances partly via c-Fos signaling. This is in contrast to neurons, whose expression is associated with depolarization and neural plasticity.[1]

Roles of c-Fos in learning and memory

Immediate early gene expression in neurons, plays an important role in the neuroplastic mechanisms underlying learning and memory,[7] particularly for consolidation and memory formation.[31,49,50] Among various IEGs, c-Fos has been known to be involved in consolidation, recall,[6] and encoding of long term memory (LTM).[12,51] Several Neuromolecular Labs have reported the immediate and transient expression of c-Fos in various brain regions following training in behavioral tasks, including associative memory,[52] traumatic memory,[53] passive avoidance learning,[13] Morris water maze,[51] socially transmitted food preference,[54] and cued fear memory.[52] These findings are in line with those experiments that disrupted c-Fos function using antisense oligonucleotides and found long-term spatial memory impairment in the water maze,[49] as well as impairments in hippocampus-dependent spatial and associative learning tasks.[55] Therefore, c-Fos expression couples extracellular signals to long-term adaptive gene expression changes in novel learning contexts,[12] while it downregulates after the prolongation of learned behavior,[56] repetition, and habituation.[57]

Collectively, under physiological conditions, it appears that acute neuronal activity, but not chronic and repetitive stimulation, induces c-Fos expression. This indicates a biphasic regulation of c-Fos, governed by hypersensitivity of the c-Fos promoter following exposure to a stimulus, which is followed by fast adaptation in the hippocampus.[6] However, this pattern of expression in acute and chronic stimulation does not mean that the c-Fos neural marker always follows the "all-or-none law," because c-Fos expression is sensitive to both the frequency and intensity of the stimulus, as was evident in our study in the adult rat brain. We showed that 2.5 mA compared with 0.25 mA electrical foot shock caused more c-Fos expression in brain regions related to noxious stimuli in rats.[13,58]

Besides its role as a neural activity marker, the pattern of c-Fos is very complex when considering individual differences in control rats.[13] Significantly more c-Fos expression was reported in rats predisposed to emotional stress compared with resistant ones.[13] Taken together, novelty, as a main component of learning and memory, has a crucial influence on c-Fos expression. Both blocking and activating c-Fos either inhibits or induces memory-associated behaviors, respectively.

Mechanism of c-Fos induction and functions during learning & memory

During learning and memory, various molecular signaling pathways, including the excitatory neurotransmitter glutamate,[1] bind to NMDA-R and then activate the expression of c-Fos in neurons through various kinases, that are critical to memory and cognition. These include the calcium-dependent phosphorylation of cAMP response element-binding protein (CREB), extracellular signal-regulated kinase (ERK), Janus kinase 1-2, tyrosine kinase 2, mitogen-activated protein kinase (MAPK), calmodulin kinases (hereinafter referred to as CaMKs), protein kinase A,[10,59] and protein kinase C (PKC).[60,61] PKC is involved in the early induction

Table 1. c-Fos-related mechanisms in the normal brain and Alzheimer's disease

Aspect	Key findings	Signaling pathways and mechanisms	Type of specimen	Ref
c-Fos in memory formation	c-Fos is involved in the consolidation, recall, and encoding of long-term memory.	Neural activity and Ca through glutamate receptors, stimulate downstream signaling via ERK, CREB, and CaMKIV, and lead in LTM.	Rat, mouse	6,7,12,49,51,55
c-Fos in synaptic plasticity	c-Fos expression increases with novel experiences and is downregulated with habituation.	ERK/CREB pathway; AP-1 transcription factor complex formation with c-Jun, and then expresses target genes Arc, BDNF.	Rat, mouse	6,12,25,57
c-Fos in Alzheimer's disease (AD)	Elevated c-Fos expression in postmortem AD brain tissue and AD models.	Aβ42-induced c-Fos activation; FOS/ATF signaling and O-GlcNAcylation of c-Fos reduces CREB/BDNF.	Human, mouse, rat	20–22,51,66–68,71,74
c-Fos in neuroinflammation	c-Fos is induced in glial cells by LPS, cytokines, and glutamate.	MAPK, p38, and CREB/ATF-1 pathways; regulation of inflammatory cytokines.	Rat, mouse	1,32–34,36,64
c-Fos in apoptosis	c-Fos promotes apoptosis via AP-1 complex and pro-apoptotic gene activation.	ERK/FOS activates BAX, caspase-3, and ATF. ATF3-mediated inhibition of PINK1; BIM translocation to mitochondria leads in apoptosis.	Human, rat, mouse	22,65,69,77–80
c-Fos in oxidative stress	Oxidative stress upregulates c-Fos via MAPK pathways, contributing to neuronal dysfunction.	ROS activation of ERK and JNK; increased transcription of pro-apoptotic genes; dysregulation of Nrf2, MAPK, PI3K/Akt, and Wnt/β-catenin signaling; mitochondrial dysfunction-induces apoptosis.	Rat, mouse, human	75,76,81–86
c-Fos in normal glial cells	c-Fos is expressed in astrocytes, oligodendrocytes, and microglia in response to stress and inflammation.	Glutamate-induced activation via mGlu5 receptors; MAPK and PKC pathways.	Rat, mouse	1,31–34,36,42
c-Fos in excitotoxicity	c-Fos acts as an excitotoxic marker in AD, contributing to neuronal loss.	NMDA receptor activation; calcium influx and ROS production.	Rat, mouse	70,73
c-Fos expression in glial cells of AD subjects	Glutamate and cytokine stimulation of astrocytes rapidly increases c-Fos expression via calcium and complement factor H and causes neuronal loss.	MAPK and PKC pathways in intervertebral disc cells; p38 MAPK/CREB/ATF-1 signaling in glial cells; activation via LPS and cyclic AMP/calcium response elements.	Rat, mouse	1,32–34,36,64

AP-1, activator protein 1; ATF, activation transcription factor; BAX, Bcl-2–associated X protein; BDNF, brain derived neurotrophic factor; CREB, cAMP response element binding; ERK, extracellular signal-regulated kinase; LPS, lipopolysaccharide; LTM, long term memory; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; ROS, reactive oxygen specious.

phase through phosphorylation of glutamate receptor 1 subunits of AMPA-R, whereas protein kinase A is crucial for the late, protein synthesis-dependent phase through phosphorylated MAPK.[62,63] Some of the important mechanisms underlying c-Fos expression during learning and memory are summarized in Table 1.[1,6,7,12,20–22,25,31–34,36,42,49,51,55,57,64–86]

Among the complex protein kinase cascades, phosphorylated ERK activity is primarily important for c-Fos/CREB cycling and LTM formation.[87] ERK is phosphorylated by MEK, which is previously activated by Raf and Ca^{2+} through glutamate NMDA-R.[88,89] Therefore, based on training conditions, the frequency and duration of kinase/phosphatase activation will determine ERK activity and the establishment of memory engrams.[88–92] Following c-Fos expression, the FOS protein is synthesized and returns to the nucleus, where it acts together with c-Jun by binding and forming the activator protein-1 (AP-1) heterodimer,[57,64,93] playing a significant role in neural plasticity.[65] Although CREB and ERK are required for initial c-Fos induction, c-Fos is later required to increase CREB expression as well.[94] The first c-Fos induction step is required to form LTM, while the second CREB induction is necessary to prolong LTM for at least seven days.[88]

c-Fos expression in AD

AD accounts for 60–70% of all dementia cases, and approximately 10% of affected individuals experience cognitive decline.[95] Pathologically, AD is characterized by the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. These proteins disrupt neuronal function and contribute to neuroinflammation, which is increasingly recognized as a critical factor in the progression of AD.[96] Despite significant research efforts, the etiology and initial molecular signaling events in AD remain unknown, emphasizing the need for further investigation.

According to the literature, c-Fos is involved in age-dependent cognitive decline [12] and various inflammatory processes,[20] which are further accompanied by synaptic loss. Elevated c-Fos expres-

sion has been reported in postmortem brain tissue from AD patients and is positively associated with cognitive impairment.[66,97,98] Moreover, some data show a positive association between AD, Aβ production, and hippocampal hyperactivity,[99,100] in line with experiments on facilitating spikes in hippocampal synapses and stimulation of excitatory CA1 neurons in 5xFAD mice.[101,102]

Amyloid β 1-42 causes a rapid and sustained increase in c-Fos expression in a mouse hippocampal cell line, contributing to neurotoxicity, which was abolished by the administration of c-Fos antisense oligodeoxynucleotides.[22] Supporting this, several animal studies reported elevated levels of c-Fos protein in the hippocampus of rat models of Aβ.[51,67,68] Interestingly, increased neuronal accumulation of Aβ and c-Fos expression were observed in glutamatergic neurons of the motor cortex in hyperactive double-transgenic mice models of Alzheimer's disease expressing both amyloid precursor protein and presenilin 1 (APP/PS1),[103] as well as in APP swe (Swedish mutation of amyloid precursor protein) and α-synuclein transgenic mice.[104–108]

Aβ42 elevation may trigger excessive neuronal c-Fos expression,[109] contributing to apoptotic signaling.[22] In addition, inflammatory markers, such as LPS and interleukins, which are elevated in AD, also induce c-Fos expression in astrocytes.[36] Subsequently, activation of ERK/FOS signaling intensifies the inflammatory response and apoptosis,[110,111] whereas inhibition of the ERK/FOS pathway reduces levels of inflammation and apoptosis.[69,112] In line with this, co-treatment with c-Fos inhibitors and antioxidants showed a positive effect on cognition in neurodegenerative models.[113]

Consistent with these findings, activation of NMDA-R following rat hyperactivity might cause neuronal loss through Ca^{2+} and c-Fos signaling.[70,114] Meanwhile, in an AD mouse model, c-Fos expression in visual cortical networks correlated with impaired visual experience-dependent memory in a pre-amyloid plaque stage.[15]

In amyloid neurotoxicity, abnormal c-Fos expression is likely downstream of Aβ elevation and subsequent Ca^{2+} influx. The expressed c-Fos protein is additionally stabilized by Aβ42-induced O-GlcNAcylation, consequently leading to the activation of pro-apoptotic AP-1.[22] Despite all the aforementioned evidence, the relationship between Aβ and c-Fos, is not straightforward. For instance, APP knockout mice displays elevated c-Fos mRNA expression in the prefrontal cortex, while c-Fos gene mutations are rare in hereditary AD and do not directly drive disease phenotypes.[24,115]

To explain the dichotomy of c-Fos response in normal and AD states, one possibility is that, higher baseline c-Fos levels in hAPP mice may result from a defect in their ability to habituate to repeated everyday experiences, in contrast with normal/control mice, which show lower baseline c-Fos expression.[103–108] Collectively, transient expression under healthy conditions appears to be homeostatic, whereas continuous c-Fos expression may disrupt synaptic activity and lead to neuronal death. From a clinical perspective, detecting c-Fos immunoreactivity in AD brains using sensitive imaging techniques may represent an early marker of neurodegeneration.[71,114]

c-Fos expression in glial cells of AD subjects

In addition to neurons, which show expression of c-Fos in the presence of hyperactivation, neuroinflammation in AD, and glutamate toxicity, c-Fos rapidly increase in astrocytes as well.[1,36] Cytokine elevation in AD also induces glial expression of IEGs, which regulate complement factor H and lead to neuronal loss in AD,[33] as evidenced by LPS-induced c-Fos expression in astrocytes of the spinal cord in AD.[64] Therefore, c-Fos expression in glial cells contributes to neuroinflammation and neuronal loss in AD.

Possible mechanisms of c-Fos in AD

The role of c-Fos in the pathophysiology of AD has not yet been fully understood, and whether c-Fos activation is causative or compensatory requires further investigation. There is no doubt that possible factors initiating AD, including inflammation, oxidative stress, Ca^{2+} toxicity, glutamate dysregulation, epigenetic alterations, brain metabolic disturbances, and imbalance in neural activity are likely to occur years before symptoms appear, or a diagnosis is made. Therefore, glutamate toxicity,[67] elevation in intracellular calcium levels, and reactive oxygen species (ROS) not only independently of c-Fos, initiate neural apoptosis, but also may contribute to synaptic and neural loss through c-Fos.[51,70,73] According to evidence, overexpression of c-Fos in the hippocampal neurons may contribute to neurodegeneration, highlighting its potential role in the disease's progression.[72–74]

As we reviewed above, in AD which is a chronic condition, neural hyperactivation causes expression without habituation, in contrast to healthy conditions. How can c-Fos differentiate these distinct physiological and pathological situations? One possible explanation might be, the variety of novel upstream extrinsic and intrinsic stimuli in the microenvironment of affected cells in AD, including neurochemical, electrical, metabolic, oxidative stress, calcium, and abnormal protein products of organelles, which cumulatively intensify c-Fos expression. Regrettably, some of these factors contribute to a vicious cycle in AD progression and exacerbate the disease pathology. For example, increased Ca^{2+} influx into neurons through different pathways,[75,116–118] and binding with calmodulin, activates CaMKII, CREB, and MAPK.[76,118–120] These regulatory elements bind to the promoter of the c-Fos gene and synthesize Fos protein,[75,121] which returns to the nucleus and acts on target genes like Aβ, increasing its expression.[21] Then Aβ causes a rapid increase in intracellular hydrogen peroxide in neurons, which may be the signal for c-Fos activation.[71] Finally, Fos dimerizes with c-Jun and acts as a transcriptional regulator at the AP-1 binding site of DNA,[22] contributing to programmed cell death.[65,77]

Another explanation for c-Fos elevation in AD is the dysregulation of c-Fos O-GlcNAcylation,[23,122–124] which reduces the interaction between OGA and c-Fos,[125] resulting in higher transcriptional activity of the c-Fos/c-Jun complex, to downregulate genes including CREB and brain-derived neurotrophic factor (BDNF); two proteins highly involved in memory formation under physiological conditions.[126,127] Moreover, c-Fos might act as an epigenetic regulator, modifying chromatin accessibility around a subset of its binding sites across the genome in amyloid neurotoxicity in rats and AD-related hyperactivity.[12,67,68,128] For example, ΔFosB binding to c-Fos promoter triggers histone deacetylation,[12] and inhibits memory formation (Fig. 1).[129] Moreover FOS dimerization with Jun exerts positive modulation, binding with activation transcription factor 3 (ATF3) leads in neural loss.[1] It should be noted that the effect of some c-Fos upstream molecules, such as CREB, depends on the level and duration of activation.[130] In fact, constitutive CREB activation causes chronic c-Fos expression and leads to memory deficits,[131] cognitive decline,[132] memory retrieval deficits,[131] and neurodegeneration.[133] Some of the upstream signaling pathways underlying c-Fos expression in AD have been summarized in Table 1.

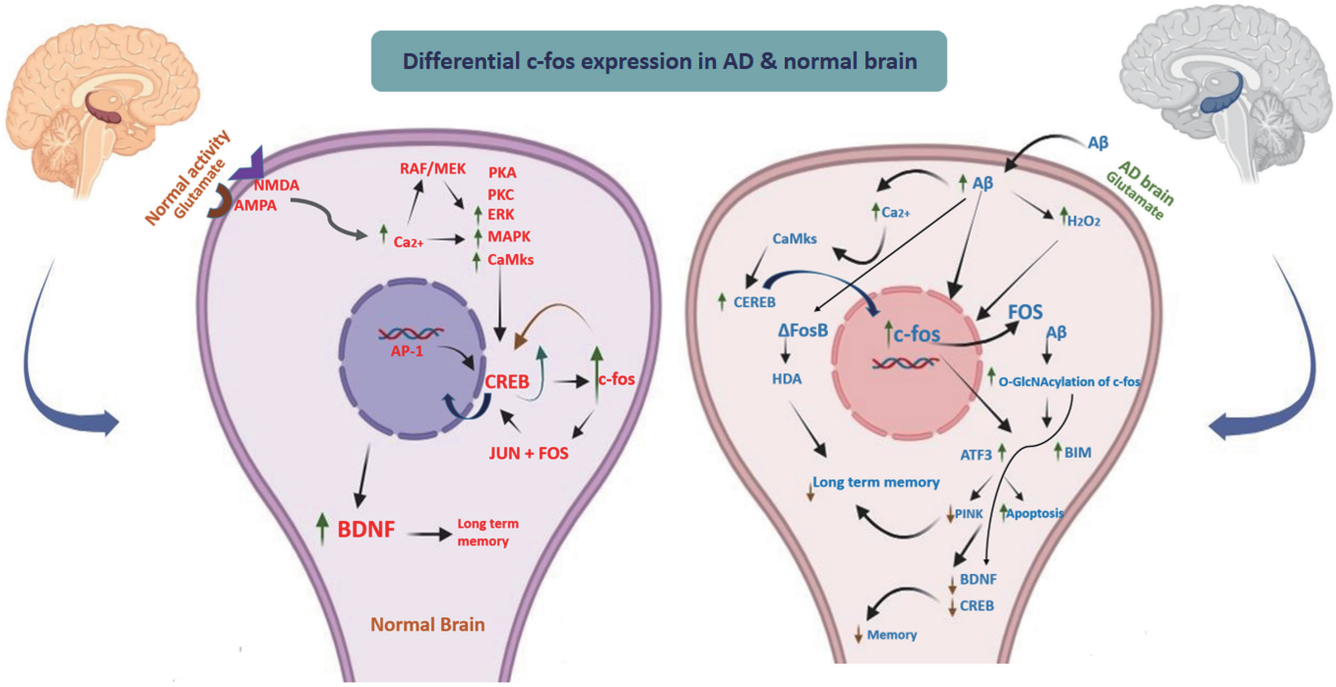

Fig. 1. Proposed mechanisms by which c-Fos contribute to neuroprotection or neurodegeneration outcome in hippocampus. Neural activity in healthy brain releases glutamate which binds to synaptic receptors and activates Ca^{++} influx and further signaling pathways of CAM/ERK/MAPK/CREB in neurons. CREB elevation leads in memory improvement via expression of c-Fos, and BDNF. Then the FOS protein is returns to the nucleus and acts together with c-Jun by binding and forming the activator protein-1 (AP-1) heterodimer, and leads in long term memory. On the other hand, hyper activation of extra synaptic NMDA receptors elevates ROS and Aβ toxicity, and increase transcription of c-Fos. The expressed c-Fos protein is additionally stabilized by Aβ42-induced O-GlcNAcylation, and the glycosylated c-Fos binds with c-Jun stimulates neuronal cell death by activating the apoptotic factor Bim, ATF3 and cytochrome c, besides, it downregulates CREB and BDNF which leads in memory impairment. AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AP-1, activator protein-1; ATF, activation transcription factor; Aβ, amyloid beta; BDNF, brain derived neurotrophic factor; BIM, B-cell lymphoma 2 interacting mediator of cell death; CREB, cAMP response element binding; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NMDA, N-methyl-D-aspartate; PKA, protein kinase A; PKC, protein kinase C; RAF, rapidly accelerated fibrosarcoma kinase.

Collectively, in AD, which is a chronic pathological state, one or more stimuli initiate excitotoxic neuronal activation, which then spreads molecular signaling to glial cells, thereby intensifying neuroinflammation. Below, we explain apoptosis as a mechanism of c-Fos-mediated neuronal death in more detail.

c-Fos and apoptosis in AD

Regulated cell death is a cluster of signaling events involving both gene expression and enzyme activity, resulting in neural death, by various mechanisms including apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy-dependent cell death in AD.[97,134] Sajan *et al*.[97] compared the expression of 14 apoptotic genes between normal and AD human hippocampi and noted upregulation in gene expression for c-Fos and BAK in AD patients, suggesting a role for these genes in the apoptotic cascade of AD. Also, Lee *et al*.[135,136] highlighted increased ATF immunoreactivity within the nuclei of hippocampal pyramidal CA1 neurons in early-stage, and CA2 neurons in late-stage AD, compared to age-matched healthy control brains.

c-Fos expression is linked to apoptosis or hippocampal cell death, which is a significant mechanism of neurodegeneration.[69,78,79,137] Fos can increase apoptosis via ATF3, which further inhibits the activity of the PTEN induced kinase 1 (PINK1) promoter and causes cell death.[80,138] It is known that glycosylated c-Fos binds with c-Jun and stimulates neuronal cell death by activating the apoptotic factor Bim,[22,139] which translocates to the mitochondria to form pores that release cytochrome c and promote cell death,[22,140] while inhibition of the ERK/FOS pathway reduces apoptosis.[69,78,112] Finally, the finding of synaptic degeneration preceding neuronal loss and memory impairment in AD patients, may be related to the apoptotic roles of c-Fos via ATF3 or complement factor H (Fig. 1).[33,141–143]

Oxidative stress and c-Fos expression in AD

Exposure of neurons to multiple stresses and divergent cytotoxic mechanisms including elevation in ROS levels, synaptic dysfunction, excitotoxicity, ER stress, inflammation, and mitochondrial dysfunction results in neuronal cell death.[142,144,145] Oxidative stress plays a central role in AD pathogenesis by disrupting cellular homeostasis and triggering multiple signaling cascades that contribute to neurodegeneration.[144]

In AD, oxidative stress is primarily driven by mitochondrial dysfunction, Aβ aggregation, and neuroinflammation, which together activate various redox-sensitive signaling pathways, exacerbating neuronal damage via activation of the nuclear factor erythroid 2-related factor 2 (*NRF2*) signaling pathway.[146] *NRF2* is a key transcription factor that regulates the antioxidant response by inducing the expression of detoxifying enzymes, such as heme oxygenase-1, superoxide dismutase, and glutathione peroxidase.[147,148]

Increased oxidative stress results in the hyperactivation of JNK and ERK, which in turn upregulate c-Fos expression.[81,82] Activation of c-Fos not only leads to programmed cell death,[83] but also disrupts mitochondrial function, which amplifies oxidative damage and neuroinflammation through increased inflammatory cytokines.[1,84–86,149–151]

Collectively, ROS-induced c-Fos contributes to AD progression not only through the production of Aβ at early stages, but also through apoptosis and neuronal death at later stages. Then, neuronal death reduces brain volume and leads to hyperactivation of neurons, which exacerbates the production of Aβ.

Conclusions

In this narrative review, we compiled evidence from cell cultures, animal, and human studies supporting the relevance of c-Fos for learning and memory in neurons and glia. Although, the brains of AD patients, differ in terms of neural network synchrony and epigenetic regulation, which alter the response to stimuli at the levels of c-Fos expression compared with normal conditions. c-Fos contributes to AD progression not only through the production of Aβ at early stages, but also through apoptosis and neuronal death at later stages, through prolonged CREB activation and increasing ATF3, Bim, and cytochrome c. The relationship between c-Fos expression and AD suggests it as a biomarker for disease progression or a possible target for therapeutic intervention. Thus, tracing of c-Fos alterations in both neurons and glia might offer a useful and reliable understanding of physiological or pathological responses to specific stimuli.

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Conflict of interest

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Author contributions

Conception, manuscript writing, reference update (PB), table, figure drawing, drafting of the manuscript (NF), data searching (KE), data bank searching, writing, revision (PB, NF). All authors have made a significant contribution to this study and have approved the final manuscript.

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