

The dual role of ERK signaling in the apoptosis of neurons

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1. ABSTRACT

The extracellular signal-regulated kinase (ERK) signaling pathway participates in various cell responses, such as proliferation, migration, differentiation and death. In neuronal apoptosis, the ERK pathway has been shown to have a dual role. Although the majority of studies have demonstrated the ERK pathway to have an anti-apoptotic role in neurons, pro-apoptosis induced by ERK signaling, has also been observed. The different effects of the ERK pathway may be due to the different kinds of neurons used in these studies, stimulus, interplay with other MAPK pathways and maybe other as yet unclear factors. In this review, we will summarize the role of the ERK signaling pathway in the apoptosis of neurons.

2. INTRODUCTION

Extracellular signal-regulated kinase (ERK) is a protein kinase intracellular signaling molecule and is a member of the mitogen-activated protein kinase (MAPK) family, which also includes p38MAPKs, c-Jun N-terminal kinases (JNKs) and ERK5. These enzymes are activated through a sequential phosphorylation cascade that amplifies and transduces signals from the cell membrane to the nucleus. ERK is a crucial participant in the regulation of cell growth and differentiation that regulates meiosis, mitosis, and post mitosis (1). The ERK pathway is stimulated by growth factors, cytokines, virus infection, ligands for heterotrimeric G protein-coupled receptors, transforming agents or carcinogens. Phosphorylation of

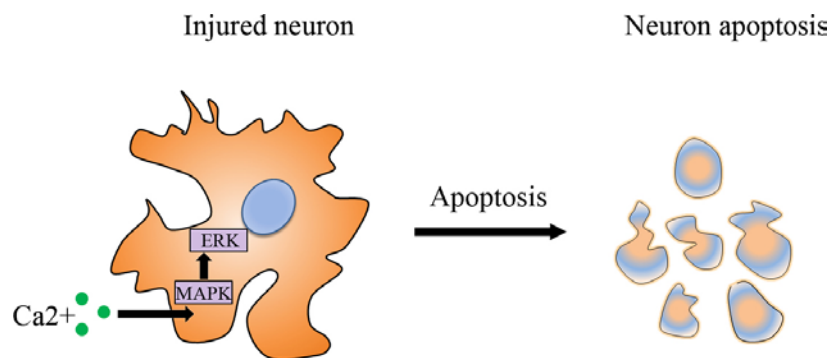


Figure 1. Calcium ion (Ca^{2+}) triggers MAPK/ERK signaling in neurons apoptosis. During the injury-associated apoptosis of neurons, Ca^{2+} is a key trigger in the activation of MAPK/ERK cascade in both peripheral neurons and central neurons, resulting in the apoptosis.

ERKs causes the activation of ERK1 and ERK2, which are two isoforms of ERK. ERK1 and ERK2 are two protein kinases with 85% sequence identity (2).

During development of the nervous system, many neurons undergo apoptosis (3). The initial overproduction of neurons, followed by the death of some, is thought to be an adaptive process that provides enough neurons to form nerve cell circuits that are precisely matched to their functional specifications (4). The apoptosis of neurons can be triggered during development of the nervous system and possibly in neurodegenerative disorders (3,5,6). The triggers of apoptosis are complex, and involve the excitatory neurotransmitter glutamate, calcium influx, increased oxidative stress, and so on (7-10). Abnormal apoptosis, or death of neurons, leads to diseases or injury. For example, death of hippocampal and cortical neurons results in the symptoms of Alzheimer's disease (AD); death of midbrain neurons occurs in Parkinson's disease, in which there is a defect in the use of the neurotransmitter dopamine; Huntington's disease is associated with the death of neurons in the striatum, which controls body movements; and death of lower motor neurons manifests as amyotrophic lateral sclerosis. Excessive apoptosis occurs in neurologic disorders including AD, stroke and Parkinson's disease (11). The ERK pathway regulates whether neurons live or die. In chick retinal neurons, the ERK-dependent pathway maintains high levels of survival proteins (12). In hippocampal neurons, apoptosis is regulated via the ERK survival pathway (13). In this review, we will summarize the role of the ERK signaling pathway in the apoptosis of neurons.

3. ERK SIGNALING: AN ANTI-APOPTOTIC ROLE

The activation of ERK occurs through a cascade of upstream kinases: firstly, a MAPK kinase kinase (MAPKKK) phosphorylates a dual-specificity protein kinase MAPK kinase (MAPKK), which in turn phosphorylates MAPK and activates the MAPK/ERK signaling cascade. With injury-associated apoptosis in neurons, the MAPK/ERK signaling cascade is up-regulated by calcium (Ca^{2+}). Lallemand and colleagues (14), found

that during the process of cell death of spiral ganglion neurons (SGNs), the MAPK/ERK pathway was activated by protein kinase-C (PKC)- Ca^{2+} signaling, resulting in survival of neurons. Moreover, a study with human astrocytoma cells and rat brain striatum found that by up-regulating the nuclear factor-kappaB (NF-kappaB)/ Ca^{2+} -calmodulin/ERK signaling pathway, inflammatory cytokines such as interleukin-1 beta (IL-1beta) can protect neurons from traumatic injury-associated apoptosis (15). These findings suggest that during the injury-associated apoptosis of neurons, Ca^{2+} is a key trigger in the activation of the MAPK/ERK cascade, in both peripheral neurons and central neurons, resulting in apoptosis (Figure 1).

Furthermore, in the apoptosis of hippocampal neurons, intracellular Ca^{2+} leads to ERK phosphorylation, which is differentially regulated by estrogen receptor alpha and beta subunits (16). The hippocampus is a major component of the human brain and belongs to the limbic system, which is involved in the consolidation of information from short-term memory to long-term memory and spatial navigation. When the hippocampus is damaged, AD may occur. AD is characterized by symptoms of memory loss and disorientation, and affected 6.6 million people worldwide in 2006 and will affect 1 in 85 people globally by 2050 (17). Direct evidence for cellular apoptosis in AD is controversial (18), suggesting the mechanism of apoptosis in the hippocampus is complex. An *in vivo* study in rat hippocampal neurons, showed that the MAPK/ERK signaling pathway may be activated in response to excitotoxic injury, resulting in the protection of neurons from damage and death (19). This suggests a key role for the ERK pathway in the apoptosis of hippocampal neurons, which may provide information for the understanding of AD pathogenesis. Dopaminergic neurons can be protected from 6-hydroxydopamine-induced toxicity through the ERK pathway, resulting in the inhibition of apoptosis (20), or they can be protected from rotenone-induced apoptosis by enhancing ERK-dependent mitophagy (21). The neuroprotective effect of noradrenaline on dopaminergic neurons can be improved by activation of the mitogen-activated protein kinase (ERK1/2) signaling pathway (22).

The findings mentioned above suggest a neuroprotective role of ERK1/2 pathway activation. In addition to dopaminergic neurons, activation of the ERK1/2 signaling pathway may have a neuroprotective role in the cerebral cortex. ERK1/2, activated by ERK kinase MEK1/2, can promote neuronal survival after hypoxic neuronal injury in a mouse model (23). This has been confirmed in rat cortical neurons with an oxidative injury (24). A similar role of the MEK/ERK pathway has been reported in rat cortical neurons, which can be protected from apoptosis caused by mechanical trauma injury through this pathway (25). Thus, the MEK/ERK pathway plays a key role in the apoptosis of cortical neurons. The same role has also been reported in cerebellar granule neurons (26). However, in sympathetic neurons, the phosphorylation of Erk1/2 has a protective role and promotes rat axonal survival (27). This could be due to the negative regulation of the MEK/ERK pathway in the expression of the protein Bim through the three prime untranslated region (3'-UTR) in sympathetic neurons, which is independent of PI3K/Akt and JNK/c-Jun signaling (28).

Among the different MAPK/ERK cascades, the Raf/MEK/ERK complex is activated by extracellular mitogenic or differentiating signals, during the process of which, the Raf family functions as MAPK kinase kinases (MAPKKK). In sympathetic neurons, the Raf/MEK/ERK signaling pathway, but not the Ras/phosphatidylinositol 3-kinase (PI3K)/Akt pathway, plays a crucial role in survival (29). However, a later study reported that activation of both the PI3K/Akt pathway and the ERK pathway are involved in resistance to ceramide-induced apoptosis of cortical neurons (30). A similar role for both the PI3K/Akt and ERK pathways in neuronal survival and proliferation was also found in vomeronasal neurons (31). Although the PI3K/Akt and ERK pathways play a similar role in the survival of neurons, the PI3K pathway also has a different function from the ERK pathway in regulating the early onset of inflammatory pain (32).

Furthermore, after transient middle cerebral artery occlusion, phosphorylated ERK (p-ERK) and cytochrome c are coordinately expressed in rat brain neurons, and they participate in the survival of neurons in different temporal and spatial profiles (33). A study using rat brain neurons showed a similar effect – that the expression of p-ERK and phosphorylated Akt (p-Akt) was coordinated; but they also function independently, in that p-ERK is activated at critical times and p-Akt acts as a maintenance signal for survival at an early stage after reperfusion (34). However, a later study suggested that ERK pathway activation has a different role alongside the Akt pathway. The apoptosis of cerebellar granule neurons has been found to be inhibited by activating Akt and inhibiting endogenously active ERK via preventing the generation of ERK activator reactive oxygen species (35). This suggests a possible pro-apoptotic effect of the ERK pathway, when activated alongside the Akt pathway. The conflicting findings between these studies

may be due to the different kind of neurons used and the methods used for inducing cell death. In the former study, the apoptosis of neurons was induced by ischemia, whereas in the later study, it was induced by low potassium. Although ischemia in cells usually leads to low potassium, other intracellular factors may influence ERK-related apoptosis. These findings also suggest that ERK signaling plays a role in pro-apoptotic pathways, in addition to the prevention of apoptosis, which is due to several factors.

4. ERK SIGNALING: PRO-APOPTOTIC ROLE

As mentioned before, activation of the ERK pathway has a dual role in apoptosis, which is influenced by interaction factors. For instance, aberrant activation of the MEK/ERK signaling pathway, induced by neurotoxic agents such as β -amyloid peptide, promotes the apoptosis of rat embryonic cortical neurons by regulating the entry of neurons into the cell cycle (36).

Although the ERK pathway activated by Ca^{2+} could be anti-apoptotic in hippocampal neurons (15), the neurodegeneration of hippocampal neurons damaged by rotenone, a mitochondrial complex-I inhibitor, occurs when ERK1/2 phosphorylation is activated by the Ras/Raf-1/MEK signaling pathway (37). Agents such as catalpol can prevent neuronal apoptosis in ERK-mediated neurodegenerative disorders (38). The apoptosis of hippocampal neurons can be induced through the Raf/MEK/ERK pathway with depletion of intracellular zinc (39), which is an essential structural and regulatory ion for normal neurological functions including neurogenesis, neuronal migration, and synaptogenesis (40). A further study found that activation of caspase-3 is the down-stream signal of this pathway (41). Thus, intracellular zinc depletion in hippocampal neurons stimulates the Raf/MEK/ERK pathway, and then activates caspase-3, finally resulting in neuronal apoptosis (Figure 2). In addition, these findings may provide a novel view in the understanding of AD pathogenesis.

When ERK signaling is activated alongside JNK activation, apoptosis of the human central nervous system cells is promoted (42). Thus, JNK activation may contribute to the pro-apoptotic role of the ERK pathway. In rat cortical neurons, activation of both the ERK1/2 and JNK pathways is involved in the apoptosis, as well as p38MAPKs (43). From this finding, the p38MAPKs are also involved in neuronal apoptosis. In addition, Willaime and colleagues (44) found that apoptosis of cortical neurons is mediated by an increase in p38 phosphorylation. A later study found that instead of JNK, the apoptosis of cerebellar granule neurons involves p38 MAPK and ERK1/2, which may be the target of Ca^{2+} signaling and reactive oxygen species (45).

The NMDA subtype of glutamate receptors (NMDARs) is involved in the regulation of multiple processes related to synaptic plasticity. Stimulation of NMDARs can cause ERK phosphorylation (46). A

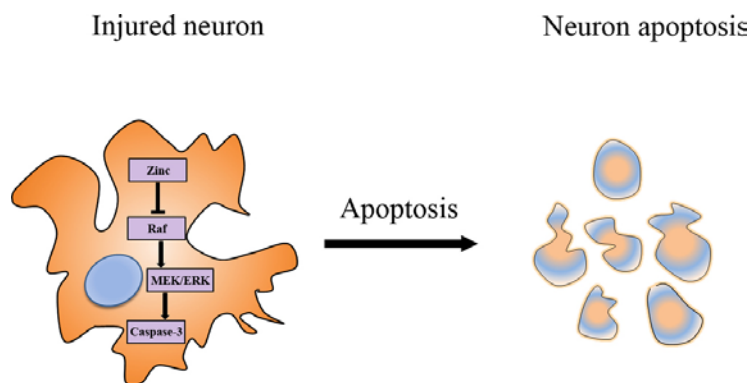


Figure 2. Zinc depletion triggers Raf/MEK/ERK signalling in neurons apoptosis. Intracellular zinc depletion in hippocampal neurons stimulates Raf/MEK/ERK pathway, and then activates caspase-3, finally resulting in neurons apoptosis

further study found that NMDARs, including the NR2B subunit, play a dual role in the regulation of ERK based on their localization, in that synaptic receptors activate ERK, whereas the extrasynaptic NMDARs control ERK deactivation (47). In addition to the localization of NMDARs, the effect of NMDARs on ERK signaling depends on the stage of neuronal development, in that NMDARs activate ERK signaling in young neurons, whereas ERK signaling is inhibited in mature neurons (48). When NMDARs are activated by tumor necrosis factor alpha, the death of mouse cortical neurons is triggered via the ERK signaling pathway (49). Moreover, L-3,4-dihydroxyphenylalanine (L-DOPA), the natural precursor of dopamine, promotes ERK phosphorylation at nontoxic concentrations, whereas at high concentrations, it enhances caspase-3 activity through the JNK and p38 MAPK signaling pathways, and also induces ERK phosphorylation (50). The ERK 1/2 phosphorylation itself can lead to a dual effect on neuronal apoptosis, in that transient ERK1/2 phosphorylation induced by cyclic AMP promotes cell survival, whereas sustained ERK1/2 phosphorylation results in apoptosis (51). Thus, the dual role of ERK signaling in the apoptosis of neurons may be attributable to complex factors.

5. CONCLUSION

The ERK signaling pathway participates in the process of neuronal apoptosis. Although the majority of studies demonstrate an anti-apoptotic role in neurons, a dual role in the apoptosis of neurons has been also found. The different effects of the ERK pathway may be due to the differences in the kinds of neurons in the studies, the stimulus, interplay with other MAPK pathways and maybe other as yet unclear factors. These findings demonstrate a crucial role of the ERK signaling pathway in the apoptosis of neurons, which may provide novel information in the understanding of diseases, such as AD, in which there is abnormal cell death of neurons.

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Abbreviations: ERK, extracellular signal-regulated kinase (); mitogen-activated protein kinase (MAPK) c-Jun N-terminal kinases (JNKs) Alzheimer's disease (AD) spiral ganglion neurons (SGNs) MAPK kinase kinases (MAPKKK) phosphorylated ERK (p-ERK) NMDA subtype of glutamate receptors (NMDARs) L-3,4-dihydroxyphenylalanine (L-DOPA)

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