The extracellular signal-regulated kinase 1/2 pathway in neurological diseases: A potential therapeutic target (Review)

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Abstract. Signaling pathways are critical modulators of a variety of physiological and pathological processes, and the abnormal activation of some signaling pathways can contribute to disease progression in various conditions. As a result, signaling pathways have emerged as an important tool through which the occurrence and development of diseases can be studied, which may then lead to the development of novel drugs. Accumulating evidence supports a key role for extracellular signal-regulated kinase 1/2 (ERK1/2) signaling in the embryonic development of the central nervous system (CNS) and in the regulation of adult brain function. ERK1/2, one of the most well characterized members of the mitogen-activated protein kinase family, regulates a range of processes, from metabolism, motility and inflammation, to cell death and survival. In the nervous system, ERK1/2 regulates synaptic plasticity, brain development and repair as well as memory formation. ERK1/2 is also a potent effector of neuronal death and neuroinflammation in many CNS diseases. This review summarizes recent findings in neurobiological ERK1/2 research, with a special emphasis on findings that clarify our understanding of the processes that regulate the plethora of isoform-specific ERK functions under physiological and pathological conditions. Finally, we suggest some potential therapeutic strategies associated with agents acting on the ERK1/2 signaling to prevent or treat neurological diseases.

Contents

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1. Introduction

Over the past several years, intracellular signaling targets have been intensely studied as a measure of the cellular processes that occur following specific conditions. Extracellular signal-regulated kinase 1/2 (ERK1/2) ligands interact with their receptor and/or corrector in the cell and subsequently activate the intracellular ERK1/2 signaling pathway. In vertebrates, ERK1/2 signaling begins during development and acts to regulate cell proliferation, differentiation and fate decisions in the mature individual. Dysfunction of ERK1/2 signaling is associated with several human diseases, such as cancer, asthma, stroke and Alzheimer's disease (AD) (1-4). Due to the importance of ERK1/2 in a wide range of biological processes in central nervous system (CNS) disease, better understanding of the precise mechanisms of ERK1/2 signaling may provide fundamental insight into its role in disease development as well as help identify novel targets for therapeutic applications.

2. ERK1/2 pathway

ERK1/2, like other protein kinases, contains unique N- and C-terminal extensions that provide signaling specificity. Human ERK1 consist of 378 amino acid residues while ERK2 consists of 360 amino acid residues. ERK1 and 2 differ from one anther among various species. Gene ablation studies have provided evidence that ERK1 and 2 are not entirely functionally identical. A study showed that the erk1 gene is dispensable for the development of mice, whereas ablation of the erk2 gene is embryonic lethal (5). However, ERK1 was found to play an essential role in thymocyte development in a ERK1-knockout (KO) mouse study (6). Whether functions exist that are unique or preferred to ERK1 or 2 is unknown. Maybe at one time or another during the development of an animal, ERK1 or 2 performs functions unique to that isoform. Even so, ERK1 and 2 have a high degree of similarity, with >95% amino acid identity among humans, mice and rats (7). These two kinases share many physiological and biological functions and are commonly referred to together as ERK1/2. All known cellular stimulants of the ERK1/2 pathway lead to parallel activation of ERK1 and 2 (8). The ERK1/2

activation ratio in cells corresponds with their expression ratio, indicating that the isoforms are activated in parallel (9).

ERK1/2 cascade. A wide variety of extracellular stimuli are capable of activating the ERK1/2 cascade. Mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK)1 and 2 are the immediate upstream kinases that phosphorylate and activate ERK1/2. MEK1 and 2 are dual-specificity protein kinases that mediate the phosphorylation of tyrosine and threonine residues. The activity of MEK1/2 is also regulated by phosphorylation, as MEK1 and 2 are phosphorylated by mitogen-activated protein kinase kinase kinases (MAP3Ks). The most extensively studied MAP3Ks are the Raf proteins, including A-Raf, B-Raf, C-Raf and Raf-1 (10). They are activated by MAP4K proteins, such as Rap1, Ras, PKA and Rho (Fig. 1). ERK1/2 is a ubiquitously expressed hydrophilic non-receptor protein that participates in the Ras-Raf-MEK-ERK signal transduction cascade, which is involved in various diseases, including cancer, cardiac hypertrophy, pain and neuroinflammation (11-14). Therefore, this cascade is an interesting target for basic and translational research, including the development of drugs for therapeutic purposes.

ERK1/2 substrates. Once activated, p-ERK1/2 can translocate into the nucleus to activate a wide array of transcription factors or can simply remain in the cytoplasm, where it regulates other subcellular functions (Fig. 1). ERK1 and 2 have more than 175 documented cytoplasmic and nuclear substrates (15). ERK1/2 nuclear targets include the ternary complex factor family of transcription factors. These proteins mediate the expression of immediate early genes, whose products contribute to cell survival, division and motility (16,17). Elk1 is one of the most thoroughly studied targets of the ERK1/2 MAPK kinase cascade, and Elk1 activation leads to increased transcriptional activity (15). Members of the ERK1/2 family of protein kinases participate in a wide variety of cellular processes. To date, more than 50 cytoplasmic substrates have been identified, including the ribosomal S6 kinase (RSK) family of protein kinases, apoptotic proteins and cytoskeletal proteins. The RSK family consists of four human RSK isoforms (RSK1-4), mitogen- and stress-activated kinase (MSK)1 and 2, which are directly activated by ERK1/2 in response to stimuli. RSK1-4 are key components downstream of the Raf-MEK-ERK signaling cascade. The RSK family regulates transcription by mediating the phosphorylation of various types of transcription factors, including nuclear factor-κB (NF-κB), serum response factor (SRF) and transcription initiation factor (TIF), in cells (18).

ERK1/2 scaffolds. Scaffolds are proteins that bind to multiple components of signaling modules. Scaffolds regulate and integrate overall signal transduction and play a pivotal role in the spatial and temporal regulation of the ERK1/2 signaling cascade. In response to stimulus exposure, ERK1/2 binds to a variety of cytoplasmic scaffold and anchor proteins, including the suppressor of Ras (KSR1/2), MEK partner 1 (MP1), IQ motif-containing GTPase activating protein 1 (IQGAP1) and MAP/ERK kinase kinase 1 (MEKK1) (19,20). MP1, which is also known as MAP kinase scaffold protein 1 and LAMTOR3, was identified as a scaffold protein that potentiates MAPK signaling by binding to MEK1 and ERK1. MP1 is localized to endomembrane compartments as part of larger signaling complexes and modulates the Raf-MKK1/2-ERK1/2 pathway together with its partner, p14 (21,22). In fact, IQGAP1 is a well-known regulator of signaling events involved in the MAPK pathway. The interaction between IQGAP1 and ERK1/2 plays a critical role in tumor formation, as competition for ERK1/2 binding between IQGAP1 and a peptide that encompasses the WW domain inhibits Ras and Raf-driven tumorigenesis (23). MEKK1, a MAP3 kinase, catalyzes the phosphorylation of MEK1 and 2, which are components of the ERK pathway. Xu *et al* (24) and Karandikar *et al* (25) both showed that MEKK1 binds to C-Raf, MEK1 and ERK2 of the ERK1/2 MAPK signaling module. Recent studies have suggested that KSR1 and 2 possess catalytic activity and that KSR2 participates in the assembly of a MEK1/KSR2/B-Raf ternary complex that is responsible for promoting rabbit MEK1 phosphorylation by mouse B-Raf (26,27).

3. ERK1/2 as effectors of physiological brain functions

ERK1/2 is abundant in the adult brain, and its activation can play multiple roles in the activity-dependent regulation of neuronal function. Mounting evidence indicates that ERK1/2 signaling plays an essential role in the development of the CNS (28). ERK1 and 2 are also involved in neuroinflammation, neural death, learning and memory formation and the regulation of synaptic plasticity in the adult nervous system.

Synaptic plasticity. Synaptic plasticity is thought to be crucial for information processing in the brain and to underlie many complex behaviours. The best studied forms of synaptic plasticity in the CNS are long-term potentiation (LTP) and long-term depression (LTD). The regulation of protein phosphorylation has an important role in the process of LTP and LTD.

Several recent studies have implicated the ERK1/2 pathway in the control of synaptic plasticity in the adult nervous system (29,30). English and Sweatt (31) investigated the role of MAPKs in regulating synaptic plasticity in adult rat neurons, with a particular focus on the modulatory role of ERK1/2 in hippocampal LTP. They provided the first demonstration of *N*-methyl-D-aspartate (NMDA)-receptor dependent activation of ERK2 in rat hippocampal area CA1 in response to LTP-inducing high-frequency stimulation and suggested a crucial regulatory role of ERK2 in synaptic plasticity. Kanterewicz *et al* (32) further confirmed the role of ERK1/2 in NMDA receptor-independent LTP in the hippocampus. Over the past few years, a number of studies have demonstrated that ERK1/2 activity is required for several forms of synaptic plasticity in the amygdala which is associated with fear-dependent learning (33,34). Ratto and Pizzorusso (35) offered evidence, both *in vivo* and *in vitro*, that ERK1/2 plays a crucial role in controlling synaptic plasticity in the visual cortex. Inhibition of ERK1/2 can prevent the induction of various forms of LTP and LTD in the hippocampus and amygdala (33,36). These studies indicated that a requirement for ERK1/2 activation is common to many forms of synaptic plasticity but that the precise targets of ERK1/2 may differ between different types of plasticity.

Brain and development. Evidence has shown that total ERK1/2 activity controls the proliferation of certain late-born progenitor

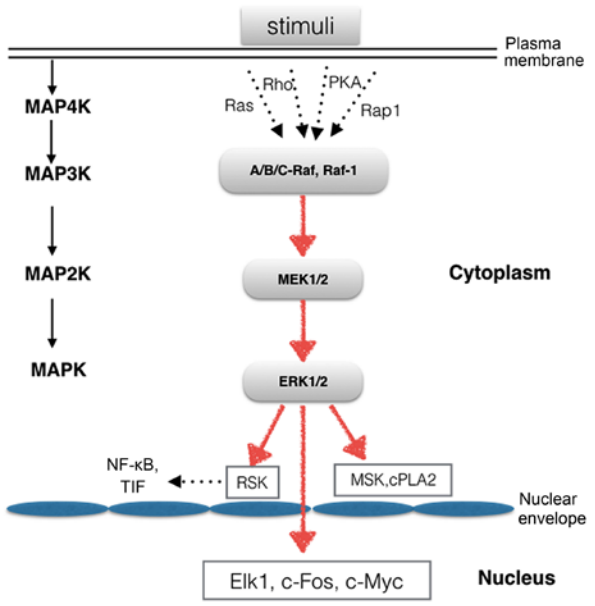

Figure 1. Extracellular signal-regulated kinase 1/2 (ERK1/2) mitogen-activated protein (MAP) kinase cascade. The ERK1/2 MAP kinase, which occur in the cytoplasm and can be translated into the nucleus, catalyze the phosphorylation of many cytosolic proteins and nuclear transcription factors.

cells and the differentiation of neurons and glia during fetal brain development and that the two may compensate for each other during this process, at least in part, due to their overlapping functions (37,38). Samuels *et al* (39,40) also found that mutations that increase ERK1/2 activity can result in macrocephaly, while mutations that decrease ERK1/2 activity can result in microcephaly, suggesting that the ERK1/2 pathway is involved in the expansion of human neural progenitor cells. Furthermore, evidence indicates that ERK1/2 also takes part in regulating the proliferation and differentiation of astrocytes in the developing brain. Li *et al* (41) found that MEK/ERK signaling regulated the generation of glia from radial progenitors in the developing cortex, leading to a major increase in the number of astrocytes in the brain. This finding provides insight into the mechanisms involved in ERK1/2-mediated regulation of normal and abnormal astrocyte function during brain development. Recent evidence has consistently demonstrated that the ERK1/2 pathway is one of the dominant intracellular pathways for the regulation of oligodendroglial development, myelination and remyelination (38,42-44).

Neuronal cell death. Although ERK1/2 activation has generally been associated with brain cell differentiation and proliferation, a number of studies have shown that the activation of ERK1/2 can mediate cell death in several neuronal systems (45,46). The different effects of ERK1/2 on brain cells may be owing to the various stimuli and cell types involved. The activation of ERK1/2 was observed in glutamate- and heme-induced neuronal cell death and the neuronal injury (47,48) and loss of function (49,50) were reduced when suppressing ERK1/2 activation. ERK1/2 was found to play a caspase-independent role in promoting neuronal cell death in several other models. Okadaic acid has been shown to induce pyramidal cell death in hippocampal area CA3 in a manner dependent on ERK1/2 activation but not consistent with apoptosis (51). These findings may help us design strategies that can specifically attenuate ERK1/2-promoted neuronal pathologies.

Neuroinflammation. ERK1/2 is expressed in microglia, astrocytes and oligodendrocytes. Microglial cells are the primary immune cells in the CNS and promote host defense by destroying invading pathogens (52). Intra-glial signaling, including ERK1/2 pathway cascades, controls the regulation of inflammatory cytokine production and iNOS expression in activated microglia. Many *in vitro* experiments have demonstrated that the ERK1/2 signaling pathway contributes to the inflammatory response in microglia that is induced upon stimulation with radiation, thrombin or LPS (53-55). ERK1/2 is also involved in the inflammatory response in astrocytes (56,57). Furthermore, accumulating evidence indicates that many of the pharmaceutical-based therapies used to reduce neuroinflammation in stroke, neurodegenerative disorders, intracranial infections and other diseases act by suppressing the ERK1/2 pathway (58-61).

Learning and memory. ERK1/2 is localized in the soma and dendritic trees of neurons in the neocortex, hippocampus, striatum and cerebellum (62). An increase in ERK1/2 activation, as measured as the ratio of phosphorylated to total (phosphorylated and non-phosphorylated) ERK1/2, is necessary for learning and the formation of memory as well as for affect and arousal. In a seminal paper, Atkins *et al* (63) were the first to show that ERK1/2 is involved in memory processing in rat after fear conditioning. Later studies showed that activation of the ERK1/2 pathway is also required for the development of short-term memory and long-term memory consolidation (64,65). Treatment with ERK1/2 inhibition can impair long-term memory retention and prevents the formation of lasting memories of an event or association, including object recognition memory (66,67). Spatial learning and fear conditioning are the types of long-term memory in which the involvement of ERK1/2 has been best characterized (68). Studies of ERK1/2 KO mice demonstrated that ERK1/2 is involved in various aspects of learning and memory formation (69). ERK1 KO mice at first appear to be neurologically normal, whereas ERK2 KO is embryonic lethal; ERK2 KO mice die at embryonic day 6.5 (5,70,71). Selcher *et al* (70) showed that the ERK1 isoform is not required for associative learning in mice; instead, they found that the ERK2 isoform plays a predominant role in the synaptic plasticity that underlies learning and memory. Short-term memory is retained in ERK1-KO mice, but a marked enhancement of long-term memory was found in a one-trial inhibitory avoidance task (72). The results of a re-consolidation study also support the pivotal role of ERK2 in memory process (73). These results suggest that ERK1/2 may be a target for therapeutics to treat disorders of learning and memory.

4. ERK1/2 as effectors of stroke, neurodegeneration and drug addiction

Consistent with its critical role in key cellular activities, including cell proliferation, differentiation, survival and death, the ERK1/2 signaling pathway has been implicated in the

Table I. Brief overview of recent studies concerning the involvement of the ERK1/2 pathway in neurological disease.

Disease	Model	Effect	Inhibitor	Outcome	References
Stroke	MCAO model	Regulates the expression of TNF-β, IL-1β, IL-6 and iNOS	U0126	Reduces infarct size and improves neurological scores	(82)
Stroke	MCAO model	Regulates the expression of MMP-9 and TIMP-1 in the vessel	U0126	Reduces infarct volume and improves neurological function	(109)
Stroke	MCAO; organ culture of cerebral arteries	Regulates the expression of vascular endothelin type B receptor	U0126	Attenuates cerebral vasoconstriction and improves long-term neurologic outcome	(110)
Stroke	MCAO model; organ culture of isolated cerebral arteries	Regulates the level of IL-1β, TNF-α, iNOS, IL-6, cxcl2, MMP9 and MMP13	U0126	Attenuates the expression of inflammatory and extracellular matrix-related genes in the smooth muscle cells of cerebral arteries	(111)
Stroke	MCAO model; organ culture of isolated cerebral arteries	Regulates the expression of TNF-α and TNF-α receptor 1 and 2	U0126	Reduces the expression of TNF-α, TNF-R1 and TNF-R2 in the wall of cerebral arteries	(112)
Stroke	Thrombin injection-induced brain injury	Involved in thrombin-induced striatal neuronal death	PD98059	Reduces the size of the injured area	(79)
Stroke	ICH model	Involved in ICH-induced neuronal injury	PD98059	Blocks striatal tissue injury	(81)
Stroke	Cultured human cerebral arteries	Regulates the expression of vascular contractile receptors	SB386023; SB590885	Decreases vasoconstriction	(76)
Stroke	SAH model	Regulates cerebrocascular inflammatory mediators IL-1β, IL-6, iNOS, MMP-9 and TIMP-1	SB386023-b	Prevents the reduction in cerebral blood flow	(80)
Stroke	SAH model	Regulates cerebrovascular expression of pro-inflammatory mediators IL-1β, IL-6, TNF-α and MMP-9	U0126	Improves neurological function	(83)
Stroke	SAH model	Regulates the expression of cerebrovascular smooth muscle cell receptors	SB386023-b	Prevents reductions in regional cerebral blood flow and neurological scores	(84)
Stroke	SAH model	Regulates the phosphorylation of ERK1/2 and NF-κB activation as well as the level of IL-1β, IL-6, COX-2, MMP-9	BAY 43-9006	Reduces vasospasm, cerebral edema and blood brain barrier permeability	(113)
Stroke	SAH model	Regulates endothelium B and 5-hydroxytryptamine 1B receptors	SB386023-b	Prevents cerebral blood flow reduction	(114)
PD	PC12 cells culture	Regulates ERK1/2 phosphorylation and apoptosis in PC12 cells	GW5074; U0126	Ameliorates cell toxicity induced by 6-hydroxydopamine	(115)
AD	AD model	Regulates the time exploring a novel object	PD98059	Reverses memory impairment	(78)
AD	Culture of lymphoblasts from AD patients	Control cell survival or death decision under trophic factor withdrawal	PD98059	Prevents cell death induced by serum starvation	(116)

Table I. Continued.

Disease	Model	Effect	Inhibitor	Outcome	References
AD	Metabolically competent rat brain slice	Regulates the phosphorylation of tau at Ser198/Ser199/Ser202, Ser262/Ser356 and Ser422	U0126	A lesser extend of tau hyperphophorylation in OA-treated rat brain slice	(117)
AD	Hippocampal slice culture	Regulates the activation of caspase-3 and tau cleavage	U0126	Attenuates the neurotoxic effects of soluble Aβ oligomer in the hippocampus	(118)
AD	Rat brain synaptosome fraction	Regulates the activation of cPLA2 and arachidomic acid release	U0126	Reduces the amyloid beta peptide fragment beta A(25-35)-induced formation of reactive oxygen species	(119)
Drug addiction	Cocaine-treated rat	Mediates cocaine-induced reduction of GABAergic inhibition and facility of LTP induction	U0126; SL327	Reduces the level of D2 receptor (U0126) and blocks cocaine-induced faciliation of LTP induction (SL327) and I-LTD (U0126 and SL327)	(120)
Drug addiction	Ethanol-treated mice	Regulates binge-like alcohol consumption	SL327	Increases ethanol bing-like consumption and home-cage alcohol consumption	(97)
ALS	Microglia culture	Regulates AP-1 activity, COX-2 expression and PGE2 production	U0126	Inhibition of COX-2 expression and PGE2 production by celecoxib reduces the neurotoxicity triggered by TDP-43-deficient microglia	(61)

ERK1/2, extracellular signal-regulated kinase 1/2; AD, Alzheimer's disease; PD, Parkinson's disease; IL, interleukin; TNF, tumor necrosis factor; ALS, amyotrophic lateral sclerosis; MCAO model, middle cerebral artery occlusion model; ICH model, intracerebral hemorrhage; SAH model, subarachnoid hemorrhage.

pathogenesis of many CNS diseases, including stroke, AD, and Parkinson's disease (PD), among others (74-78). The activation of ERK1/2 cascades contributes to disease progression through the regulation of neuronal apoptosis, neuroinflammation and synaptic plasticity.

Stroke. ERK1/2 pathway activation is also known to play physiological and pathological roles post-development, and a large body of evidence suggests that ERK1/2 also contributes to the regulation of inflammatory responses, cytokines, cell apoptosis and death in ischemic and hemorrhagic brain injury (78-82). Several pharmacological studies have also demonstrated that suppression of ERK1/2 activation frequently downregulates features of apoptosis and inflammation and reduces neurological damage after stroke (49,81-83). Madami and Edvinsson showed that the elevated microvascular pro-inflammatory cytokine expression observed following focal ischemia in MCAO models also involved the ERK1/2 pathway (82). Moreover, Shioda *et al* (3) found that ERK1/2 signaling plays an important role in neurogenesis following brain ischemia. Substantial evidence has suggested that the ERK1/2 pathway is involved in regulating the changes in inflammation, cytotoxicity and cerebral vasospasm that occur after hemorrhagic stroke (76,84). Recently, Feng *et al* (85) showed that Ras/Raf/ERK signals participate in the neuronal apoptosis observed in the hippocampus in early post-subarachnoid hemorrhage brain injury. Taken together, these results suggest that therapies targeted at suppression of the ERK1/2 pathway may be beneficial in stroke.

PD. PD is the second most prevalent neurodegenerative disease after AD and is characterized by selective dopaminergic neuronal loss in the substantial nigra. The ERK1/2 pathway is known to play a major regulatory role in PD-related cellular processes. Accumulating evidence indicates that microglial cells play a crucial role in the degeneration of dopaminergic neurons in animal models of PD. Recent studies have shown that the oxidative stress response plays a central role in the etiology of PD (86,87). The oxidative stress response that occurs in microglia is mediated by the activation of the ERK1/2 signaling pathway upon stimulation with pro-inflammatory stimuli. Furthermore, ERK1/2 has been shown to participate in L-DOPA-induced dyskinesia through striatal synaptic plasticity (75,88). In addition, in the dopamine-depleted striatum, ERK1/2 plays an important role in the development of L-DOPA-induced dyskinesia in both mouse and non-human primate models of PD (75,89). The inhibition of ERK1/2 attenuated LID and completely inhibited all markers of angiogenesis in rat and mouse models of LID (75,90). Therefore, the modulation of ERK1/2 in response to dopamine in PD patients may be therapeutic for motor complications.

AD. AD is a neurodegenerative disease that is characterized by progressive cognitive decline and memory dysfunction as well as the presence of neurofibrillary tangles (NFTs) and senile plaques composed primarily of β-amyloid. ERK1/2 is one of the kinases known to phosphorylate tau and has been shown to be associated with NFTs and senile plaques (74). Increased levels of activated ERK1/2 have been found in AD

brains, and inhibition of the pathway can reduce β-amyloid neurotoxicity (91-93). Activated ERK1/2 is found specifically in intracytoplasmic punctate structures and intracellular NFTs, primarily in the subpopulation of neurons that exhibits early AD-related protein deposition. As mentioned above, ERK1/2 is known to play a critical role in hippocampus synaptic plasticity and learning and memory. Abnormal ERK1/2 activation in the hippocampus may impair hippocampal function and contribute to memory deficits in AD patients. Therefore, improving regulation of the ERK1/2 pathway may be a central facet for the development of potential treatments for AD.

Drug addiction. Drug addiction is recognized as a type of neuroadaptive disorder. Because the ERK1/2 pathway plays an important role in neuronal plasticity in the adult brain, understanding of the role of this pathway is critical for overall understanding of the molecular mechanisms underlying drug addiction and relapse. Exposure to a variety of substances with abuse potential, including nicotine, alcohol, amphetamine and cocaine, acutely active ERK1/2 in the striatum and other brain areas (94-97). Many of the enduring behavioral effects of acute drug exposure depend on ERK1/2 signaling. Studies have suggested that ERK1/2 is dynamically regulated following repeated drug exposure and withdrawal and that changes in ERK1/2 activation directly affect striatal cell excitability (98,99). These effects may be responsible for the expression of addictive behavior, and alterations of this pathway may contribute to the drug's rewarding effects and to the long-term maladaptation induced by drug abuse. Evidence indicates that ERK1/2 plays a dual role in gene regulation and drug addiction through direct activation of transcription factors, including Elk1 and cAMP response element-binding protein (CREB), and by chromatin remodeling via MSK1 and histone H3 phosphorylation (100,101). Because ERK1/2 activation is a key molecular process in drug self-administration, targeting it may be a potential treatment strategy for drug addiction.

Other neurological diseases. Amyotrophic lateral sclerosis (ALS) is a CNS disease that causes the death of motor neurons and that can be either sporadic or familial origin. Mutant SOD1 is one of the genetic factors that contribute to the etiology of ALS, and mutant SOD1 induces motor neuron vulnerability. Phosphorylated ERK1/2 has been shown to be increased in the hippocampus and cerebellum in SOD1 G93A transgenic models (102). Apolloni *et al* (103) showed that ERK1/2 also participates in P2X7 receptor-induced enhancement of oxidative stress in ALS microglia, together with the NOX2 pathway. A previous study also identified ERK1/2 as a novel player in the pathogenesis of ALS associated with transactive response DNA-binding protein 43 (TDP-43) (77). A recent study also showed that depletion of TDP-43 in microglia strikingly upregulated the production of COX-2 and PGE2 through the activation of ERK1/2 signaling (61).

Huntington's disease (HD), a devastating neurodegenerative disease that is characterized by progressive and severe cognitive, psychiatric and motor dysfunction, is caused by an expanded CAG repeat in the huntingtin (Htt) gene. MAPK signaling, and particularly the Ras-ERK cascade, is among the pathways that have been implicated in HD. In response to mutant huntingtin, ERK1/2 is activated and directs a protective transcriptional response and inhibits apoptotic caspase-3 and -7 activation (104,105). Data from different model systems indicate that ERK1/2 is involved in HD excitotoxicity at both the intercellular and intracellular level (106-108). Pharmacological interventions that promote ERK1/2 activation could suppress the adverse effects of mutant Htt by activating pro-survival mechanisms and suppressing apoptotic responses. Thus, studies in both cells and animal models suggest that the ERK1/2 cascade may be a potential target for therapeutic interventions for currently untreatable disorders.

5. Therapeutic inhibitors of the ERK1/2 signaling cascade

ERK1/2 pathway regulated kinase is a central point in the signaling network and is firmly established as an attractive target for pharmacological intervention in many diseases. Currently, inhibitors of the kinase function of Raf and MEK represent the most studied and advanced approaches for blocking the ERK1/2 pathway, with several inhibitors under evaluation in clinical trials and additional inhibitors in preclinical analyses. Morever, many neurological disease-related studies have investigated the effects of ERK1/2 pathway inhibitors, whose main mechanism of action is to prevent the phosphorylation of ERK1 and 2 by the upstream kinases, MEK1 and 2. A number of highly selective MEK1/2 inhibitors have been development, and many of them have been tested in a clinical setting. PD98059 and U0126 are first-generation small-molecule inhibitors of MEK1/2. In preclinical study, they feature potency and high specificity, with no or little inhibitory effects on other kinase. Most Raf inhibitors target mutant B-Raf and the most extensively studied B-Raf inhibitor in neurological disease is SB386023-b. Both Raf and MEK inhibitors have been widely applied in many experimental studies to better understand this pathway and explore its roles in neurological diseases (Table I). Other selected new and emerging MEK inhibitors have not been well studied in neurological diseases, such as PD0325901, selumetinib, cobimetinib, refametinib and trametinib. The main results obtained to date strongly suggest that the ERK1/2 pathway may represent a valid therapeutic target in neurological disorder conditions. Finally, it has also been proposed that ERK1/2 pathway may be a significant tool through which to study stroke, neurodegenerative disease and drug addiction.

6. Summary and perspectives

In summary, the link between the ERK1/2 signaling pathway and a variety of neurological diseases, including stroke, neurodegenerative diseases and drug addiction, demonstrates the importance of studying the ERK1/2 pathway to human health. More detailed knowledge of the physiological and pathological functions of ERK1/2 in the adult nervous system may not only provide insight for the development of new therapeutic drugs for neurological disorders but also achieve clinical benefits for patients. Over the next several years, additional novel therapeutic strategies that utilize ERK1/2 signaling inhibitors will likely be developed for neurological disease clinical trials.

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