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The ERK Pathway: Molecular Mechanisms and Treatment of Depression

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Abstract

Major depressive disorder is a chronic debilitating mental illness. Its pathophysiology at cellular and molecular levels is incompletely understood. Increasing evidence supports a pivotal role of the mitogen-activated protein kinase (MAPK), in particular the extracellular signal-regulated kinase (ERK) subclass of MAPKs, in the pathogenesis, symptomatology, and treatment of depression. In humans and various chronic animal models of depression, the ERK signaling was significantly downregulated in the prefrontal cortex and hippocampus, two core areas implicated in depression. Inhibiting the ERK pathway in these areas caused depression-like behavior. A variety of antidepressants produced their behavioral effects in part via normalizing the downregulated ERK activity. In addition to ERK, the brain-derived neurotrophic factor (BDNF), an immediate upstream regulator of ERK, the cAMP response element-binding protein (CREB), a transcription factor downstream to ERK, and the MAPK phosphatase (MKP) are equally vulnerable to depression. While BDNF and CREB were reduced in their activity in the prefrontal cortex and hippocampus of depressed animals, MKP activity was enhanced in parallel. Chronic antidepressant treatment readily reversed these neurochemical changes. Thus, ERK signaling in the depression-implicated brain regions was disrupted during the development of depression, which contributes to the long-lasting and transcription-dependent neuroadaptations critical for enduring depression-like behavior and the therapeutic effect of antidepressants.

Keywords Depression · Antidepressant · ERK · MAPK phosphatase · BDNF · CREB · Frontal cortex · Hippocampus

Introduction

Major depressive disorder is one of the most common neuropsychiatric illnesses. As a chronic debilitating disorder, depression affects millions of people worldwide yearly and represents a major economic and medical burden. Despite its high prevalence, brain mechanisms underlying the development of depression-like behavior are far from clear. Accumulating evidence from extensive studies on humans and experimental animals indicates that adaptations of distinctive signaling pathways in neurons of brain regions implicated in depression occur during the progression of depression. These long-lasting adaptive changes in the signaling pathways participate in the remodeling of different forms of neuronal and synaptic plasticity critical for enduring depression-like behavior.

An essential family of serine/threonine protein kinases is the mitogen-activated protein kinase (MAPK). These kinases function to regulate cellular growth, differentiation, and survival in proliferative cells [1]. In addition, MAPKs are expressed in postmitotic neurons of the adult mammalian brain, where MAPKs respond to changing synaptic input and regulate neuronal activity and synaptic plasticity via a transcription-dependent or transcription-independent manner [2]. Activation of the MAPK cascade requires four sequential events involving small GTPases (Ras and Rac proto-oncogenes), MAPK kinase kinases (Raf or MEKK), MAPK kinases (MEK), and MAPKs. After activation, MAPKs become a highly efficient signaling pathway linking a variety of extracellular signals to cytoplasmic, intranuclear, or synaptic responses [2–4].

A prototypic subfamily of MAPKs is the extracellular signal-regulated kinase (ERK) [1]. The Ras-Raf-MEK1/2 pathway is responsible for activating ERK via the dual function MEK-mediated threonine and tyrosine phosphorylation of ERK, whereas the dual-specificity MAPK phosphatase (MKP) and the serine/threonine protein phosphatase (PP) such as PP1 and PP2A dephosphorylate and thereby deactivate

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ERK [5–7]. Among several ERK isoforms (ERK1/2/3/4/5/7), ERK1/2 have been most thoroughly investigated and characterized in the central nervous system [8]. The available data show that ERK1/2 play a pivotal role in various neuropsychiatric disorders, including depression.

Increasing evidence shows that the ERK pathway in the brain regions implicated in major depression is vulnerable to chronic stressors. ERK activity in the prefrontal cortex and hippocampus was reduced in suicide subjects. Various chronic stressors caused a reduction of the cortical and hippocampal ERK signaling in experimental rodents. The MEK inhibitors induced depression-like behavior and blocked the effect of antidepressants. Various antidepressants reversed the hypoactivity of ERK and alleviated depression-like behavior. Altogether, these data support a model that the ERK pathway is downregulated in the cortex and hippocampus of depressed humans and animals, which contributes to the development of depression and serves as a substrate of antidepressants. In addition, brain-derived neurotrophic factor (BDNF), an immediate upstream regulator of ERK, and cAMP response element-binding protein (CREB), a transcription factor downstream to ERK, were downregulated in parallel and play a similar role as ERK in depression. This review, by focusing on recent data, discusses the sensitivity and responsiveness of forebrain ERK to depression and roles of ERK in the pathogenesis of depression and antidepressant action.

Changes in the ERK Pathway in Response to Depression

Among initial attempts toward understanding the possible roles of ERK in depression, Dwivedi et al. assayed changes in expression and catalytic activity of ERK1/2 and expression of MKP-2 in various postmortem brain regions of suicide subjects with major depression as compared with non-psychiatric control subjects [9]. They found that ERK1/2 expressions at both mRNA and protein levels and kinase activity of ERK1/2 were reduced in the prefrontal cortex and hippocampus, two major brain regions implicated in depression [10], but not in the cerebellum. In parallel, MKP-2 that dephosphorylates and deactivates ERK1/2 was enhanced in its expression in the prefrontal cortex and hippocampus. Similarly, the upstream activator of the ERK pathway, i.e., a Raf kinase, was altered by depression. Among the three Raf kinases, i.e., A-Raf, B-Raf, and C-Raf (Raf-1), B-Raf but not Raf-1 was selectively reduced in its catalytic activity and protein expression in the prefrontal cortex and hippocampus of suicide subjects [11]. In addition to Raf kinases, MEK1, an immediate upstream activator of ERK1/2, was downregulated in its catalytic activity and phosphorylation and in its interactions with B-Raf [12]. These results from a series of human studies demonstrate the abnormality of the ERK pathway in defined brain regions of subjects with major depression.

In preclinical animal studies, the responsiveness of the ERK pathway to depression was also investigated mainly in the frontal cortex and hippocampus. ERK phosphorylation and expression in the hippocampus were not significantly altered in an acute animal model of depression (acute restraint stress) [13]. In different studies, a single acute session of restraint stress or other stressors increased ERK phosphorylation in the frontal cortex and hippocampus [14, 15]. In contrast to the acute model, ERK activity in the hippocampus was inhibited in a chronic animal model of depression [16]. A large number of subsequent studies reported the similar downregulation of ERK in various chronic models of depression. For instance, ERK2 phosphorylation was reduced in the prefrontal cortex and hippocampus of rats showing depression-like behavior following chronic forced swim stress [17, 18]. A downregulated level of ERK phosphorylation and expression occurred in the frontal cortex and hippocampus of adult rats that have received neonatal treatment with clomipramine, a chronic model of depression persisting throughout adulthood [19]. These neurochemical changes in the ERK system correlated well with depression-like sexual behavior [19]. Many other stressors that consistently induced depression-like behavior reduced ERK1/2 phosphorylation in the frontal cortex and/or hippocampus [14, 20–34]. These data support a notion that the ERK pathway was downregulated in the prefrontal cortex and hippocampus following chronic stress. In further support of this notion, MKP-1 expression was elevated in the hippocampus of depressed mice [23]. Intrahippocampal infusion of the MKP-1 inhibitor prevented depression-like behavior and normalized local MKP-1 expression and ERK phosphorylation. However, while prenatal restraint stress induced depression-like behavior and reduced ERK2 expression in the prefrontal cortex and hippocampus of 1-month offspring rats [35], ERK phosphorylation and expression in the frontal cortex and hippocampus remained unchanged at 3 months of age following the prenatal stress [36]. There were two other subclasses of MAPKs, the Jun N-terminal kinase (JNK) and p38 kinase, which exhibited a decrease in their phosphorylation in the frontal cortex or hippocampus. Generally, MAPK subclasses may differentially respond to depression, depending upon the specific model of depression, the developmental stage of depression, and other experimental conditions.

In addition to the prefrontal cortex and hippocampus, the lateral septum is a central site implicated in depression. As a major target of monoaminergic projections, the lateral septum receives the strongest noradrenergic and serotonergic input [37, 38]. Early evidence indicates the association of deficiencies in monoaminergic transmission with depression. Antidepressant treatment markedly altered serotonin release and serotonin receptor signaling in the lateral septum in different animal paradigms of depression [39, 40]. As a common signaling pathway downstream to serotonin receptors, ERK in the serotonin receptor-enriched lateral septum is reasoned to

be vulnerable to depression. In fact, in a rat model of depression, ERK phosphorylation was reduced in the lateral septum [13]. This indicates that inhibition of ERK in the lateral septum is also implicated in the development of depression.

Mechanisms Underlying Plastic Changes in the ERK Pathway

How adaptive changes in the ERK pathway in response to depression occur is incompletely studied. The less activation of ERK seen in depressed humans and animals could occur as a result of the concurrent downregulation of upstream elements that are responsible for activating ERK. At the receptor level, ERK is coupled with various neurotransmitter receptors, including serotonin, adrenergic, dopamine, and glutamate receptors [8, 41]. The activation of distinct subtypes of these receptors leads to phosphorylation of ERK. Intracellularly, ERK is subjected to the positive regulation by several common protein kinases, such as protein kinase A (PKA) and protein kinase C (PKC), and generally, PKA and PKC activators activated ERK1/2 in the hippocampus [42]. Thus, the hypoactive state of any receptors or effectors (PKA or PKC) in response to depression may subsequently result in the less activation of ERK. Consistent with this, the activity level of PKA, PKC, and adenylyl cyclase was reduced in the postmortem brain of suicide subjects or patients with major depression [43–46] or in the brain of depressed animals [47, 48]. The PKA activator exhibited the antidepressant activity [49], whereas the PKA and PKC inhibitors blocked the effect of antidepressants [50, 51]. In addition, MEK1 was downregulated in its phosphorylation and catalytic activity in the prefrontal cortex and hippocampus of suicide subjects [12]. MEK1/2 phosphorylation was decreased in the medial orbital cortex and dorsal endopiriform nuclei of the prefrontal cortex of stressed mice [24]. These data indicate that abnormal MEK1/2 activity may be linked to aberrant responses of ERK1/2 to depression.

In addition to the elements catalyzing phosphorylation of ERK, dephosphorylation of ERK could be another layer of mechanisms underlying the downregulation of the ERK pathway. The phosphatases that dephosphorylate and thereby deactivate ERK could undergo adaptive changes in response to depression, which thereby results in corresponding changes in ERK. It has been reported that expression of phosphatases (MKP-1, MKP-2, PP1) was elevated in the prefrontal cortex and hippocampus of depressed humans or animals [9, 19, 23, 52]. Intracranial injection of the MKP-1 inhibitor reversed the reduced hippocampal ERK phosphorylation and reduced behavioral responses to stress [23, 53]. Chronic antidepressant treatment normalized the responses of MKP-1 and behavior to stress, and mice lacking MKP-1 were resilient to stress [52]. Thus, accelerated dephosphorylation of ERK due to hyperactive phosphatases contributes to the inactivation of the ERK pathway during the development of depression. It is likely that both activation and deactivation mechanisms work in concert to accurately control the responsiveness of ERK and depression-like behavior.

Roles of ERK in Depression-Like Behavior and Antidepressant Effects

Plastic changes in the ERK pathway in depressed humans and animals imply a possible role of ERK in the development of depression. It is reasoned that direct inhibition of ERK may induce depression-like behavior if the loss of ERK activity is causally linked to the pathogenesis and symptomatology of depression. Indeed, while the acute behavioral effect of the ERK inhibition was inconsistent [54–58], chronic pharmacological inhibition of the ERK pathway by repeated infusions of U0126, a specific MEK inhibitor, into the dorsal hippocampus induced anhedonia and anxiety-like behavior [59]. U0126 after infusions into the medial prefrontal cortex also produced anhedonia. These results support that the lowered ERK activity in the frontal cortex and hippocampus contributes to mediating depression-like behavior. Consistent with this, while conventional ERK2 knockouts were not viable [60], conditional and region-specific ERK2 knockout in the central nervous system caused deficits in social behavior [61]. Overactivation of ERK2 in ERK1-deficient mice reduced depression-like behavior, which was fully reversed by the MEK inhibitor SL327 [56].

If inducible inhibition of ERK plays a role in mediating depression, restoration of the reduced ERK activity may be of an antidepressant property. In fact, a number of studies reveal that various antidepressants possess the common ability to reverse the loss of ERK activity in the frontal cortex and hippocampus of depressed animals. Antidepressants (amitriptyline and fluoxetine) reversed the inhibition of ERK1/2 phosphorylation in the frontal cortex and hippocampus when they suppressed depression-like behavior [18, 20, 21, although 62]. The antidepressant quetiapine in combination with transcranial magnetic stimulation also reversed the diminished hippocampal ERK1/2 phosphorylation and produced antidepressant effects [63]. Other antidepressants showed similar effects [24, 27, 28, 31, 33, 34, 64–67]. In addition to antidepressants, a selective MKP-1 inhibitor sanguinarine injected into the hippocampus or ventrolateral orbital cortex increased ERK activation and reduced depressive immobility [23, 53]. The effect of several antidepressants was blocked by a systemic, intracerebroventricular, or intrahippocampal injection of an MEK inhibitor U0126, SL327, or PD98059 [58, 68–74]. The MEK inhibitor PD184161 also blocked the antidepressant effect of desipramine and sertraline [55]. These data altogether support the role of ERK in mediating the effect of antidepressants.

The ERK pathway serves as an information superhighway between the surface membrane and the nucleus and effectively links environmental signals to genomic responses. After activation, cytoplasmic ERK translocates to the nucleus where ERK activates specific transcription factors to regulate gene transcription [75]. The transcription factor Elk-1 is a nuclear substrate of ERK [75]. Another transcription factor CREB is also a downstream target of ERK [76]. Several studies reveal a role of the ERK-CREB coupling in depression-like behavior and antidepressant action. Chronic stress induced depression behavior and reduced ERK and CREB phosphorylation (activation) in the rat prefrontal cortex and hippocampus, which was reversed by fluoxetine [18]. Other studies also found that CREB phosphorylation was decreased in the frontal cortex and/or hippocampus of stressed humans and animals, which was usually accompanied by a decrease in ERK activity [30, 34, 65, 77–80]. Antidepressants reversed the reduction of CREB phosphorylation in stressed animals [25, 34, 66, 69, 78] or increased CREB phosphorylation in naive rats [81–84]. Infusion of U0126 into the medial prefrontal cortex or hippocampus induced depression-like behavior and reduced local CREB phosphorylation [59]. These results support a model that the ERK-CREB pathway is downregulated in the prefrontal cortex and hippocampus during the development of depression, which might participate in mediating depression-like behavior. As such, reversal of downregulated CREB could yield an antidepressant effect. Of note, the role of CREB in the nucleus accumbens seems to be different. Prolonged social isolation induced anxiety- and anhedonia-like symptoms in adult rodents [85]. Only the anxiety phenotype and its reversal by an antidepressant were mediated by CREB in the nucleus accumbens shell, while the anhedonia-like symptoms were not.

The BDNF-ERK Pathway in Depression

Neurotrophic factors are critical for the etiology and treatment of depression [86]. The MAPK cascade, including the ERK pathway, is one of the best-characterized signaling transduction pathways downstream to the BDNF-activated TrkB receptor [3]. Since ERK was downregulated in the prefrontal cortex and hippocampus of depressed humans and animals (see above), the BDNF signaling is likely reduced in depression. In fact, BDNF expression or TrkB phosphorylation was reduced in the prefrontal cortex and/or hippocampus of depressed humans and animals [25, 29, 34, 74, 87–91]. The reduction of TrkB phosphorylation occurred along with a decrease in ERK phosphorylation [20, 66]. These results imply that BDNF could serve as a biomarker of depression as reduced BDNF indicates a higher state of vulnerability to depression. Indeed, a higher vulnerability to stress and depression was seen in humans with a decreased release of BDNF due to carrying a BDNF polymorphism (Val66/Met) [92]. A decreased volume of the hippocampus in depressed patients is consistent with the likelihood of a reduced neurotrophic factor support in the brain [93, 94].

Antidepressants normalized the reduction of BDNF expression in the hippocampus of depressed patients and animals [25, 29, 34, 70, 74, 91, 95–97] or upregulated hippocampal BDNF expression [98–102], indicating a role of BDNF in the behavioral response to antidepressants. The role of BDNF is further supported by the following findings. Chronic peripheral administration of BDNF enhanced ERK and CREB phosphorylation in the mouse hippocampus and produced antidepressant effects in cellular and behavioral models of depression [103]. Direct injection of BDNF into the midbrain or hippocampus mimicked the antidepressant effect of BDNF administered systemically [104–106] and increased local ERK phosphorylation [106]. Inhibition of ERK with U0126 blocked the antidepressant effect of BDNF directly infused into the hippocampus [105]. The TrkB inhibitor K252a also caused a loss of effects of antidepressants [28, 66, 70]. In addition, heterozygous BDNF null mice were resistant to antidepressants [107] and displayed a depressive phenotype when combined with a low-dose of the MEK inhibitor or mild stress exposure [55]. Loss of function of BDNF in transgenic mice [108, 109] or depletion of hippocampal BDNF by transfecting lentivirus-derived shBDNF [110] suppressed the behavioral response to antidepressants, indicating that normal BDNF signaling is required for the effect of antidepressants. Collectively, BDNF has a potential to serve as an etiological and therapeutic biomarker for depression. While the precise mechanisms(s) underlying BDNF involvements are unclear, the ERK pathway seems to play a role in linking BDNF to depression as well as to antidepressant properties.

Conclusions

ERK is enriched in postmitotic neurons in brain regions implicated in major depression. Long-lasting adaptive changes in ERK phosphorylation, expression, and function occur in the prefrontal cortex and hippocampus during the course of the development of depression. In addition to ERK, the ERK-linked BDNF and CREB are sensitive to depression and display comparable changes in their expression and function (Fig. 1). In fact, as sequential and coherent events, BDNF may be initially reduced in its expression and function in the prefrontal cortex and hippocampal, which subsequently leads to a decrease in downstream elements, i.e., ERK and CREB. Through the BDNF-ERK-CREB pathway as well as other pathways, extracellular signals are transmitted to the nucleus to regulate a network of the depression-associated genes, which transcriptionally determines the pathogenesis and severity of depression-like behavior [111]. In addition, the BDNF-ERK-CREB cascade is a substrate of antidepressants. Various antidepressants act to

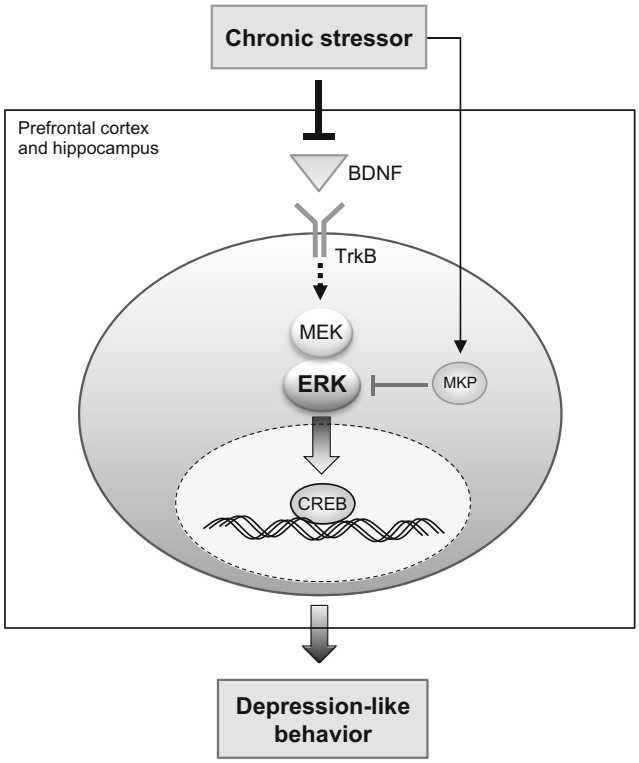

Fig. 1 A schematic diagram illustrating the role of the BDNF-ERK-CREB pathway in the development of depression-like behavior. Chronic stressors that cause depression-like behavior induce a reduction of BDNF expression in the brain regions implicated in the pathogenesis of depression, including the prefrontal cortex and hippocampus. This leads to downregulation of the ERK pathway downstream to TrkB, a receptor which BDNF interacts with. Chronic stressors also induce an increase in MKP activity in the same brain regions, which contributes to the downregulation of the ERK pathway. The downregulated ERK pathway results in a less amount of active ERK translocating from the cytoplasm to the nucleus, leading to hypoactivation of transcription factors such as CREB. Lowered CREB activity causes long-lasting adaptive changes in expression of a discrete set of genes associated with depression and transcriptionally contributes to enduring depression-like behavior

reverse the downregulated BDNF-ERK-CREB pathway to alleviate depression-like behavior. Thus, the BDNF-ERK-CREB system represents a current target for developing new pharmacotherapies for depression.

While a traditional view is that ERK once activated translocates into the nucleus to regulate gene expression and thereby transcriptionally regulate cellular and synaptic activities, a sub-pool of ERK also notably resides in peripheral structures of neurons, such as postsynaptic dendritic spines, in various brain regions surveyed [112–115]. A complete set of all MAPK cascade components are present in the postsynaptic density microdomain [116, 117]. Moreover, synaptic ERK is readily activated in response to changing synaptic input [2]. Functionally, ERK interacts with and regulate a number of synaptic proteins, including scaffold proteins, ion channels, and G protein-coupled receptors, to determine the strength and efficacy of synaptic plasticity [2]. Apparently, ERK resides and functions at synaptic sites in addition to the nuclear location. To date, whether and how synaptic ERK responds to depression and plays a role in the pathophysiology of depression and antidepressant action are unclear. Future studies need to elucidate accurate roles of synaptic ERK in the reshape of excitatory transmission and plasticity critical for the progression of depression.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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