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Review

Contributions of ERK signaling in the striatum to instrumental learning and performance

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ABSTRACT

The striatum is critical for learning and decision making; however, the molecular mechanisms that govern striatum function are not fully understood. The extracellular signal regulated kinase (ERK) cascade is an important signaling pathway that underlies synaptic plasticity, cellular excitability, learning and arousal. This review focuses on the role of ERK signaling in striatum function. ERK is activated in the striatum by coordinated dopamine and glutamate receptor signaling, where it underlies corticostriatal synaptic plasticity and influences striatal cell excitability. ERK activation in the dorsal striatum is necessary for action-outcome learning and performance of goal-directed actions. In the ventral striatum, ERK is necessary for the motivating effects of reward-associated stimuli on instrumental performance. Dysregulation of ERK signaling in the striatum by repeated drug exposure contributes to the development of addictive behavior. These results highlight the importance of ERK signaling in the striatum as a critical substrate for learning and as a regulator of ongoing behavior. Furthermore, they suggest that ERK may be a suitable target for therapeutics to treat disorders of learning and decision making that arise from compromised striatum function.

Contents

1. Introduction

The striatum, the largest of the basal ganglia nuclei, is a critical substrate for learning and decision making. Impairments in learning and decision making accompany a range of disorders that affect the striatum, including substance abuse disorder, obsessive-compulsive disorder, and Parkinson's disease [1–3]. Furthermore, the application of sophisticated procedures derived from instrumental conditioning in animals has identified parallel corticostriatal circuits that mediate distinct learning and action control processes [4–8]. Nevertheless, the molecular mechanisms that underlie learning and decision making in the striatum are not fully understood. One important regulator of neuronal function is the extracellular signal regulated kinase (ERK) pathway. ERK is a member of mitogen activated protein kinase (MAPK) family, and is critical for nervous system development and plasticity in the adult

Abbreviations: ERK, extracellular signal regulated kinase; LTP, long-term potentiation; LTD, long-term depression; PIT, Pavlovian-instrumental transfer; pDMS, posterior dorsomedial striatum; DLS, dorsolateral striatum; NAc, nucleus accumbens.

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nervous system [9,10]. ERK signaling in the nervous system has a critical role in memory formation, affect and arousal. Furthermore, the efficacy of a number of psychoactive substances, such as mood stabilizers and addictive drugs, depend, in part, on their ability to activate ERK in the nervous system.

In the following review, we highlight the role of ERK signaling in the striatum in learning and decision making. We begin with a brief overview of ERK signaling in the nervous system and its role in learning and behavior regulation. This is followed by a discussion of the role of ERK signaling in striatal-based learning and decision-making tasks. We conclude with a description of the role of ERK signaling in substance abuse, in which we discuss how alterations in ERK signaling by repeated drug exposure may compromise striatum function and produce features of addictive behavior.

2. The ERK signaling pathway

Like other MAPK signaling pathways, the ERK cascade consists of three kinases: ERK, of which there are two isoforms, ERK1 and ERK2, and their upstream kinases MEK and raf (see [11,12] for review). ERK activation occurs in response to a variety of extracellular stimuli and forms an essential pathway for cells to generate adaptive responses to changing environments. These cellular responses include regulation of gene expression and synthesis of new proteins, alteration in cellular structure or metabolism, cellular growth, differentiation and apoptosis. ERK is activated when dual-phosphorylated by MEK at its serine and threonine residues. Raf, which phosphorylates MEK, consists of a family of kinases, and is activated when bound by the GTP-binding protein ras. Ras-ERK activity increases in response to a range of stimuli, including activation of G protein coupled receptors, tyrosine kinase receptors, and Ca^{2+} influx [9,13]. Scaffolding proteins and phosphatases regulate ERK activity, thus providing an additional level of control over ERK function [11]. Upon activation, ERK has many cellular targets and influences a wide range of cellular functions [12]. ERK influences gene expression through its interaction with transcriptional regulators, such as ribosomal s6 kinase (RSK), mitogen- and stress-activated protein kinase-1 (MSK1) as well as the transcription factor elk-1. ERK also influences translation and new protein synthesis [14]. These and many other cellular operations under ERK's regulation enable the cell to produce a coordinated response to extracellular stimuli.

In the adult nervous system, ERK is intimately involved in synaptic plasticity (see [15] for review). ERK inhibition prevents the induction of various forms of long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus and amygdala [16–20]. ERK activation is necessary for a number of physiological processes that underlie synaptic plasticity, including AMPA receptor trafficking and spine restructuring [21–24]. Among the ways ERK influences synaptic plasticity is through its regulation of transcription and translation [14,25,26]. Finally, the effects of various neuromodulators on LTP and LTD induction and maintenance depend on ERK signaling [26–30]. Consistent with its role in synaptic plasticity, ERK has been shown to be necessary for long-term memory formation across a variety of tasks. An increase in ERK activation, measured as the ratio of phosphorylated to total (phosphorylated and non-phosphorylated) ERK, occurs in a number of brain regions during learning. Furthermore, treatments that interfere with ERK signaling such as the MEK/ERK inhibitors SL327, U0126 or PD98059, impair long-term memory retention. ERK inhibition prevents the formation of lasting memories of an event or association, including spatial memory, fear memory, and object recognition memory [31–39]. More recently, genetic approaches have been used to examine ERK function and have yielded similar effects on behavior. ERK2 conditional knockouts show impaired long-term retention in spatial memory and fear conditioning tasks [14,40]. Based on these data, ERK activation is necessary for the establishment of long-lasting changes in behavior, likely by mediating changes in synaptic strength.

In addition to its role in synaptic plasticity, ERK activation in the nervous system is important for plasticity of cellular intrinsic excitability. This form of plasticity involves changes in the electrical properties of the cell membrane that render neurons more or less responsive to synaptic inputs [41]. In particular, *A*-type K^+ channels located in distal dendrites are an important determinant of cellular excitability by limiting dendritic action potential back-propagation and raising action potential thresholds (see [41,42] for review). Recently it has been shown that the inwardly rectifying K^+ channel $K_V4.2$ is regulated by ERK (see [43] for review). ERK phosphorylates the pore-forming unit of the $K_V4.2$ channel, which results in down regulation of this channel's activity [44–46]. The net effect of this modulation is to increase cellular excitability and facilitate LTP induction in neurons with elevated ERK phosphorylation [46,47]. Thus, $K_V4.2$ channel phosphorylation and its effect on membrane electrical properties enable ERK activation to increase cellular excitability and potentially alter cellular information processing and ongoing behavior.

Alterations in cellular excitability have been proposed to have a role in behavior regulation [48,49]. In this context, ERK's regulation of cellular excitability may underlie its increasingly recognized role in regulating emotional arousal and affective states. For example, inhibition of ERK activation with the systemic ERK inhibitor SL327 reduces the amount of time rats swim in the forced swim test, which suggests that ERK inhibition has a depressant effect on behavior [50,51]. Likewise, knockout of ERK1 increases basal ERK2 activation and increases measures of behavioral arousal, an effect that is reversed by ERK inhibition [52,53]. These studies suggest a link between altered levels of basal ERK activation and mood disorders, such as mania and depression. This is supported by findings that chronic exposure to the stress hormone corticosterone produces a depressive phenotype in rats, reduces basal levels of ERK activation in the hippocampus and reduces performance on measures of motivation and arousal. Exposure to anti-depressants reverses the behavioral effects of corticosterone exposure and restores ERK phosphorylation levels in the hippocampus [54,55]. One explanation for these behavioral effects is that ERK activation modulates affect and arousal through its effects on cellular excitability. This would explain why ERK inhibition acutely disrupts behavior on these tasks, since it is unlikely that such rapid effects of ERK inhibition could be mediated by alterations in gene expression. Recent evidence showing that olfactory discrimination learning relies on increased basal ERK phosphorylation and changes in cellular intrinsic excitability in the piriform cortex supports this conclusion [56]. Of course, it is unlikely that such a general behavioral measure as arousal is mediated solely by the excitability of neurons in a single brain region. Additionally, changes in basal ERK activation not only influence intrinsic excitability, but also cause structural changes in neurons that are responsible for phenotypes characteristic of mood disorders such as mania and depression [57]. Nevertheless, these results highlight the importance of basal ERK signaling in regulation of arousal and affective states and its impact on ongoing behavior.

2.1. Summary

ERK is one of the primary cellular signal transduction pathways in the nervous system, and confers adult neurons with plasticity that is crucial for learning and adaptive behavior. ERK enables synaptic plasticity through its regulation of receptor trafficking, transcription and translation, operations that are vital for the formation of lasting memories. ERK enables plasticity of cellular