Published in final edited form as:

Prog Mol Biol Transl Sci. 2016 ; 137: 1–40. doi:10.1016/bs.pmbts.2015.10.017.

Molecular mechanism: ERK signaling, drug addiction and behavioral effects

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Abstract

Addiction to psychostimulants has been considered as a chronic psychiatric disorder, characterized by craving and compulsive drug seeking and use. Over the past two decades, accumulating evidence has demonstrated that repeated drug exposure causes long-lasting neurochemical and cellular changes that results in enduring neuroadaptation in brain circuitry and underlie compulsive drug consumption and relapse. Through intercellular signaling cascades, drugs of abuse induce remodeling in the rewarding circuitry that contributes to the neuroplasticity of learning and memory associated with addiction. Here, we review the role of the extracellular signal-regulated kinase (ERK), a member of the mitogen-activated protein kinase, and its related intracellular signaling pathways in drug-induced neuroadaptive changes that are associated with drug-mediated psychomotor activity, rewarding properties and relapse of drug seeking behaviors. We also discuss the neurobiological and behavioral effects of pharmacological and genetic interferences with ERK-associated molecular cascades in response to abused substances. Understanding the dynamic modulation of ERK signaling in response to drugs may provide novel molecular targets for therapeutic strategies to drug addiction.

Keywords

ERK; drug addiction; dopamine receptor; glutamate receptor; immediate early gene

1. Introduction

Drug addiction is a chronic brain disease characterized by high relapse rates and compulsive drug use despite negative consequences. To date, there is no effective treatment for drug addiction. Understanding the neurobiological aspects underlying substance abuse provides a basis for developing potential therapeutic strategies targeting to drug addiction. Accumulating evidence demonstrates that drugs of abuse alter dopamine (DA) and glutamate (Glu) neurotransmission in the mesocorticolimbic system to exert their molecular and behavioral effects[1–3]. DA neurons in the ventral tegmental area (VTA) and their descending projections to the nucleus accumbens, prefrontal cortex (PFC) and other limbic

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regions, including the hippocampus (HIPP) and amygdala (Amy), comprise the mesocorticolimbic system[4], which is crucial for reward and reinforcement processing, motivation, and goal-directed behavior[5,6]. The NAc and VTA also receive Glu output from the PFC. In addition, a reciprocal Glu connection is found between the PFC and Amy. The nigrostriatal pathway containing the DA projection from the substantia nigra to the caudate putamen (CPu/dorsal striatum) has also been implicated in molecular events, rewarding effects and habitual behavior of drug addiction[7,8].

The extracellular signal-regulated kinases (ERK) cascade, one of isoforms of mitogen-activated protein kinases (MAPK), is associated with the pathology of diseases due to its role in cell proliferation, differentiation, survival, and death[9,10]. ERK contains two isoforms, ERK1 and ERK2, which are indicated as “ERK” throughout the current review. Otherwise, individual subtype of ERK is specified as ERK1 or ERK2. In 1996, the activation of ERK was first identified in the VTA after chronic morphine or cocaine administration[11]. Thereafter, several lines of studies have focused ERK-mediated molecular signaling in response to various drugs of abuse during the last two decades. Herein, we review the alterations of ERK signaling induced by abused substances including cocaine, amphetamine, methamphetamine, marijuana, nicotine, and alcohol. In addition, most of these drugs have been shown to induce psychomotor changes, the ERK-associated molecular changes underlying drug-induced behaviors is also discussed. Further, due to the critical role of ERK on the neuroplasticity of learning and memory associated with addiction[12], its influence on the reinforcing, rewarding, and relapse/reinstatement of drug addiction is also described.

2. ERK signaling pathway

Initially, intracellular ERK signaling has been characterized to respond to extracellular stimuli and regulate cell proliferation and differentiation[13]. For example, once activated by growth factors or neurotrophins, the tyrosine kinase receptors recruit Ras family G-proteins and lead to sequential activation of Raf (MAPK kinase kinase), MEK (MAPK kinase), and ERK. Once ERK is activated, the phosphorylated (p)ERK protein can translocate to the nucleus[14], where they phosphorylate the ternary complex factor Elk-1[15,16]. The activated Elk-1 and other ternary complex factors associate with serum response factor, bind to the serum response element site, and promote immediate early gene (IEG) transcription related to neuroadaptation[17–19]. In addition to Elk-1, through phosphorylating ribosomal S6 kinases and mitogen- and stress-activated protein kinases (pRSKs and pMSKs, respectively), ERK has been shown to indirectly result in cAMP response element-binding protein phosphorylation (pCREB), a transcription factor that has been shown to regulate gene expression[20–24]. Increasing evidence shows a glutamate linkage to ERK signaling in neurons both *in vivo* and *in vitro.* For instance, through the elevation of intracellular calcium (Ca^{2+})/calmodulin (CaM)/CaM kinases (CaMK), the activation of the Glu N-methyl-D-aspartate receptor (NMDA-R) can increase the phosphorylation of MEK (pMEK)/ERK/Elk-1 in hippocampal slices, neuronal culture[25–27], cortical cultured neurons[28], and striatal cultured neurons[29–31]. Inhibition of ERK activation attenuates Glu-mediated pElk-1 in the striatal slice[32], striatum including the CPu[33–35] (wrong article for ref 35; should be Sgambato V. et al., J. Neurosci. 1998 18(21):8814–8825), and the HIPP[17]. Alternatively, in PC12 cells, Ca^{2+} may increase the intracellular cAMP through Ca^{2+}/CaM-sensitive adenylyl cyclase (AC)

leading to the activation of PKA. Increase of cAMP and PKA induces pMEK via the activation of Rap1/Raf[36,37]. Consistent with these studies, pharmacological activation of DA D1 receptor (D1-R) or the AC markedly stimulates ERK activity and its phosphorylation in various neuronal cells[33,38–41]. In addition, activation of group 1 metabotropic Glu receptors (mGluR1/5) has been shown to increase the intracellular Ca^{2+} and activate ERK signaling[42–45]. Although the activation of DA D2 receptor (D2-R) inhibits PKA activity, D2-R stimulation also increases ERK signaling through PKC activation[46].

There are several families of ERK-related protein phosphatases (PPs). Among them, PP2A and striatal-enriched protein tyrosine phosphatase (STEP) are the best characterized. PP2A is a major serine/threonine phosphatase containing two regulatory subunits and one catalytic subunit. PP2A mediates a rapid inactivation of pERK *in vitro.* STEP is another phosphatase that regulates ERK activation. Although it is enriched in the CPu and NAc, STEP is expressed abundantly in the mesocorticolimbic system[47,48]. Through direct interaction of a kinase-interacting motif, STEP and its non-neuronal homologues have been shown to dephosphorylate pERK and prevent its nuclear translocation[49,50]. Phosphorylation of STEP (pSTEP) reduces its activity and its capacity to inhibit pERK[49]. STEP is regulated through D1-R/PKA/DARPP-32 signaling[51]. *In vitro*, D1-R activation has been shown to activate pThr34 and inhibit pThr75 DARPP-32 via PKA-activated PP2A[52], respectively. The activation of pThr34 DARPP-32 subsequently inhibits PP1 and thereby increasing pSTEP[53]. In addition, stimulation of NMDA-R has been reported to induce Ca^{2+}-activated PP2A and PP2B which inhibit DARPP-32 signaling[52,54,55] and indirectly modulate ERK activity. Therefore, the PPs of pERK are regulated by DA- and Glu-mediated transmission. Further, dual specificity MAPK phophatases 1 and 3 (MKP-1/3) are also implicated in pERK de-activation. Both *in vitro* and *in vivo* studies indicated that MKP-1/3 expression and activation is dependent on ERK signaling. Once induced and activated, MKP-1/3 reduces the ERK activation as an inhibitory feedback loop[34,56–61]. Furthermore, there is evidence demonstrating that MKP-1 is phosphorylated (pMKP-1) by pERK leading to MKP-1 protein stabilization without altering its ability to dephosphorylate pERK[62].

3. ERK signaling and drug addiction

ERK signaling is responsive to various abused drugs in the mesocorticolimbic system. Both acute and chronic exposure to drugs results in alteration of ERK-mediated signaling in specific brain regions underlying neuronal plasticity and drug-induced behavioral changes. Therefore, we focus on the effects of most prevalent abused substances on ERK signaling and its relationship of drug-mediated behavioral changes across different paradigms including locomotor activity/sensitization, conditioned place preference (CPP), and self-administration (SA), if applicable. Since pharmacological and genetic approaches have been used to interfere with the ERK signaling cascade, their effects on abused drug-mediated behaviors were summarized in Table 1 and Table 2, respectively.

3.1 Cocaine

Numerous studies have demonstrated that acute cocaine administration increases pERK in the CPu, NAc, PFC, central and basolateral Amy (CeA and BLA, respectively), HIPP, and

bed nucleus of the striatal terminals (BNST)[63–77]. The increased pERK and its downstream targets including pMSK-1, pElk-1, pCREB, phosphorylation of GluN2B (pGluN2B) and IEGs by acute cocaine are dependent on the activation of MEK, D1-R/DARPP-32, and NMDA-R[51,63,66,67,70,71,74,76,78–80]. In addition to pMSK-1 induction, the pRSKs in the CPu are also increased by acute cocaine leading to the indirect activation of CREB by pERK[77,79]. In terms of PPs of pERK, acute cocaine has been shown to result in an increase of MKP-1 mRNA in the CPu and cortex[81]. In addition, depending on D1- and NMDA-Rs, the phosphorylation of MKP-1 was also enhanced in the CPu and NAc 45–60 min after acute cocaine, contributing to the transient pERK induction[76]. Further, the pSTEP was also downregulated after acute cocaine in the CPu with corresponding pERK induction[77]. Together, in a time dependent manner, the activation and inactivation of PPs is critical for controlling the acute cocaine-augmented pERK. Behaviorally, the acute cocaine-induced locomotor activity was not affected by the MEK inhibitor, SL327 (30 or 40mg/kg), but partially inhibited or not altered with a higher dose injection (50mg/kg) which has non-specific sedative effect on basal locomotion[51,78,80,82,83]. Similar to acute cocaine, MEK/ERK activation is necessary for the chronic cocaine-induced IEG expression in the CPu, NAc and Amy in a time-dependent manner[66,67]. In cocaine-sensitized animals, 7–21 days but not 1 day withdrawal resulted in increased Glu aminomethyl phosphonic acid receptor (AMPA-R) subunit surface insertion and NDMA-R subunit expression with paralleled pERK induction in the NAc[84–87] (also see[88]). AMPA-R expression in the NAc after prolonged withdrawal from repeated cocaine injection is dependent on the activation of both GluN2B and pERK, which contributes to the development of behavioral sensitization[86]. This conclusion is further supported by a study demonstrating that D1-R/Src kinase-mediated pGluN2B is necessary for the pERK induction in response to repeated cocaine administration[70]. In addition, cocaine challenge after withdrawal from repeated cocaine administration also resulted in sensitized pERK in the CPu and NAc compared to the acute cocaine effect[72,89,90]. The cocaine behavioral sensitization-induced pERK and pCERB in the NAc is dependent on ERK activation[91]. Further, the induction and expression of cocaine behavioral sensitization can be inhibited by systemic SL327 injection or intra-NAc MEK inhibitor infusion[80,92,93]. Similarly through MEK activation, the pERK induction in the VTA is required for the development of behavioral sensitization to cocaine[11,94]. Lastly, studies have indicated that, in response to D1- and NMDA-Rs activation, pERK induced by cocaine is responsible for the chronic cocaine-enhanced dendritic spine density and dendritic length in the CPu and NAc[95,96] providing the morphological evidence mediated by ERK signaling after repeated cocaine administration. Repeated pairing a specific environment with drug administration leads to a memory association between contextual cues and the drug rewarding effect. Subsequently, the context itself directly motivates drug-seeking behavior as a measurement of the reinforcing effect of the drug[97,98], which is associated with ERK signaling. For example, the acquisition of cocaine-CPP is accompanied by pERK induction in the NAc and PFC in a D1-R dependent manner[99]. Systemic pre-administration of SL327 (50mg/kg) and a GluN2B antagonist prevented the development of cocaine-CPP[70,78], indicating the requirement of NMDA-R-mediated ERK activation in the formation of context-drug association memory. ERK activation in the VTA is necessary for the development of cocaine-CPP[100]. Cocaine challenge in the drug-paired environment resulted in pERK and pCREB induction in the subset of neurons of the NAc[101]. In animals with

repeated cocaine administration, the saline challenge enhanced pERK induction in the D1-positive neurons in NAc and CPu indicating context conditioning-induced ERK activity[72]. Similarly, after the establishment of CPP, CPP testing or re-exposure to the cocaine-associated context induced pERK, pCREB and/or ΔFosB in the CPu, HIPP, VTA and NAc as well as in D1-R containing neurons of the NAc[100,102–106]. The CPP test-induced pERK expression in the VTA is dependent on mGluR1 activation and protein synthesis[106]. Further, Miller and Marshall demonstrated that CPP test-elevated pERK and drug-seeking behavior were blocked by intra-NAc core infusion of U0126 (2μg/side) [107]. In the cocaine SA paradigm, context-induced relapse is also associated with enhanced pERK in the NAc core and CPu[108]. Altogether, these results imply that, through ERK signaling, the NAc core and VTA are important for the memory formation of context-drug association. pERK in the NAc core and CPu also involve the retrieval of CPP memory and a general motor activation driven by drug-associated context, respectively.

Memory reconsolidation occurs when well-established drug-associated memories are recalled by re-exposure to drug associated context, cues, or the drug itself during which memories can be destabilized by adding new information or subjected to manipulation[109–111]. The ability to disrupt drug-related memories provides an opportunity to promote treatment outcome and prevent relapse. The general procedure to test the memory reconsolidation on drug seeking behavior contains two phases: re-exposing animals to drug-associated context (phase 1) followed by testing drug seeking behavior after withdrawal (phase 2). A previous study demonstrated that, before or immediately after phase 1, intra-NAc core MEK inhibition through U0126 (1μg/side) or PD98059 (2μg/side) reduced cocaine-CPP during the phase 2. The expression of pERK, pCREB, pElk-1 and c-Fos induced by phase 2 is also attenuated with inhibiting ERK during phase 1[107]. Systemic SL327 injection after phase 1 also decreased subsequent context-induced CPP in animals conditioned by escalating doses of cocaine[112]. Similar to reactivation of CPP memory by context, the memory reconsolidation in response to cocaine is also accompanied by ERK activation in the PFC, NAc, and CPu. With or without cocaine priming, the systemic SL327 (20mg/kg) pre-treatment before phase 1 blocks the subsequent drug seeking behavior[82]. However, the effect of ERK on cocaine-induced memory reconsolidation is still dependent on the presence of context. Thus, the contribution of cocaine itself on memory reconsolidation is still ambiguous. After the establishment of cocaine SA, U0126 (1μg/side) infusion into the BLA immediately after phase 1 prevented context-induced reinstatement and the pERK induction after phase 2[113]. Taken together, these studies indicate that ERK signaling activated during memory reconsolidation is necessary for cocaine seeking behavior. However, a critical time window, 6 hr after the reactivation of memories, has been documented during which the memory is susceptible to alteration in the fear conditioning paradigm[114]. The pre-treatment before phase 1 may influence the memory retrieval instead of reconsolidation. If the ERK signaling actually involves in drug-related memory reconsolidation, the difference should be found when treatment is conducted within and beyond the critical time window in terms of both behavioral and molecular aspects.

Unlike pERK sensitization in cocaine-induced behavioral sensitization, immediately after the cessation of cocaine SA, there is an a dissociation between pERK induction and cocaine intake indicating the failure of developing pERK sensitization or tolerance, although with

enhanced pERK expression in several brain regions[115]. However, ERK activation has been implicated in relapse after withdrawal. For example, the extinction test (conditioned cues + context) significantly increased pERK in the CeA and cocaine seeking behavior after 30 days withdrawal. Both enhanced pERK and relapse are dependent on MEK and NMDA-R activation[116]. Similarly, the pERK induction in the ventromedial PFC has been shown to mediate extinction test-induced cocaine seeking behavior after 1 or 30 days withdrawal from cocaine SA[117]. Through ERK activation, direct intra-VTA glial cell line-derived neurotrophic factor (GNDF) or brain derived-neurotrophic factor (BDNF) infusion immediately after the last session of cocaine SA induced robust drug seeking behavior after 3 or 10 days withdrawal[118,119]. These results demonstrated that the potentiated ERK signaling underlies relapse behavior after cocaine SA. In contrast to augmented pERK induction in the PFC after 1 day abstinence of cocaine SA[117], 2 hr after the last cocaine SA session, we have demonstrated a transient reduction of pERK in the PFC[120–122]. The reduction of pERK is associated with an increase of STEP but not PP2A activity accompanied by decreased total GluN2B protein expression and phosphorylation, suggesting the inhibitory effect of STEP on pERK and NMDA-R[123]. Through MEK activation and normalization of pERK in the PFC, direct BDNF infusion into the dorsomedial PFC immediately after the end of the last cocaine SA session resulted in a long-term inhibition on context-, cue- or cocaine-induced relapse[121]. Thus, it indicated that rescuing the ERK signaling or hypofunction in the PFC during early withdrawal might provide a potential therapeutic strategy for preventing cocaine relapse.

Several animal models have been used to dissect the ERK signaling cascade in cocaine-induced behavioral changes. For example, double knockout (KO) type 1 and type 8 Ca^{2+}-stimulated AC resulted in a reduction of basal pERK in medium spiny neurons in the CPu with blunted acute cocaine-induced pERK, pMSK-1 and pCREB. Behaviorally, these double KO AC mice are supersensitive to low dose acute cocaine-induced locomotion and fail to develop behavioral sensitization in response to repeated cocaine administration[124]. Ras-guanine nucleotide-releasing factors 1 (Ras-GRF1), the upstream activator of Ras, can increase ERK signaling. In the CPu and NAc, the protein expression of Ras-GRF-1 is increased by acute psychostimulants including cocaine[125,126]. D1-R agonist and Glu-induced pERK is attenuated in the striatal slice of Ras-GRF-1 KO mice. The acute cocaine-induced pERK is downregulated and upregulated in Ras-GRF-1 KO and overexpressing (OE) mice, respectively. In addition, the development of cocaine behavioral sensitization and cocaine-CPP are attenuated in Ras-GRF-1 KO mice accompanied by a reduction of FosB/ΔFosB in the CPu and NAc. An opposite facilitation on behavior and FosB/ΔFosB was observed in Ras-GRF-1 OE mice in response to repeated cocaine[127]. ERK1 KO mice exhibit higher responsibility to morphine[128]. Similarly, in response to chronic cocaine exposure, ERK1 KO mice display enhanced behavioral sensitization and cocaine-CPP as well as *c-fos* mRNA induction in the CPu[34]. This suggests that ERK1 acts as an inhibitor on ERK2 activation and a heightened stimulus- or cocaine-induced ERK2 signaling after ERK1 KO[129]. In addition, selective ERK2 OE in the VTA resulted in an increase of sensitivity of cocaine-CPP and the repeated cocaine-mediated behavioral sensitization[130]. In contrast, inhibition of ERK2 activity in the VTA attenuated the cocaine-CPP and the development and expression of cocaine-induced locomotor sensitization. Through activating MSKs, ERK

leads to the increase of CREB activity. The acute cocaine-induced pCREB and IEGs as well as histone H3 phosphorylation were attenuated in the CPu and/or NAc of MSK-1 KO mice, indicating the role of MSK-1 in chromatin remodeling in response to cocaine. Although showing higher sensitivity to low dose cocaine-CPP, MSK-1 KO mice have reduced behavioral sensitization in response to repeated cocaine administration[79]. Finally, systemic injection of the peptide inhibiting pElK-1 significantly inhibited acute cocaine-activated pElk-1, pElk-1 nuclear translocation, and histone H3 phosphorylation, as well as IEGs protein and mRNA expression in the CPu and NAc[74,131]. Further, the inhibition of pElk-1 also resulted in an attenuation of repeated cocaine-induced dendritic plasticity in the NAc shell and prevented repeated cocaine-induced behavioral sensitization and CPP[74]. Together, these studies demonstrated that ERK-associated signaling is important for the long-term cocaine-mediated behavioral alterations, rewarding effects and neuronal plasticity. Interestingly, the acute cocaine-mediated locomotor activity was not altered in animal models with manipulation of ERK1 or downstream molecular targets of ERK (e.g. MSK-1, ElK-1), further supporting that ERK signaling is not required for the acute cocaine-induced psychomotor effect.

Since both NMDA- and D1-Rs are implicated in cocaine-induced pERK, the direct protein-protein interaction between both receptors may underlie their effects on ERK activation[132–135]. Previously, we have demonstrated the protein-protein interaction between D1-R and GluN1 of NMDA-R in the CPu. The D1-R/GluN1 complex is disrupted after acute cocaine administration which may underlie transient pERK induction by cocaine[136]. The assumption is supported by a recent finding indicating that interference of D1-R/GluN1 association *in vitro* decreases D1 agonist- and NMDA-induced pERK induction. In addition, disrupting the protein-protein interaction in the NAc also attenuates acute cocaine-induced pERK induction and repeated cocaine-induced behavioral sensitization in the two injection protocol[137]. Further, the receptor complex of sigma-1, histamine H_3, and D1-Rs has been found in the striatum. Through binding to sigma-1-R, cocaine results in a disinhibitory effect of histamine H_3 receptor on D1-Rs leading to pERK activation after either acute cocaine injection or cocaine SA[138]. However, the impact of these receptor-receptor interactions on cocaine-induced behavioral alteration is still unknown.

3.2 Amphetamine

Acute amphetamine (AMPH) has been shown to increase pERK in the CPu, NAc, PFC, and VTA[51,80,92,139–143]. Multiple upstream receptors and molecular activators have been implicated in acute AMPH-induced ERK signaling in a brain region specific manner. For instance, acute AMPH-induced pMEK and pERK in the striatum is regulated by D1-R/DARPP-32 and NMDA-R activation[51]. In contrast, pERK induction in the PFC by acute AMPH is dependent on NMDA-R, adrenoceptors and serotonin receptors but not D1- or D2-Rs[144]. Blockade of mGluR1/5 or mGluR5 specifically in the CPu attenuated acute AMPH-induced pERK, pElk-1, pCREB, and Fos immunoreactivity[145–147]. The activation of Ca^{2+}/calmodulin-dependent protein kinases II (CaMK II) in the CPu is also necessary for acute AMPH-augmented pERK, pElk-1, and pCREB[145]. Direct MEK inhibition via systemic SL327 (20–100 mg/kg) administration or intra-CPu U0216 (2μg/side) infusion attenuated acute AMPH-elevated pERK and pCREB protein expression in the CPu and NAc, and IEGs

including *preproenkephalin*, *preprodynorphin,* and *c-fos* mRNA in the CPu[80,140,141,148]. However, the differential pERK induction profile in the CPu in response to acute psychostimulants is determined by the environment: acute AMPH and cocaine induced pERK expression mainly in D1-R-expressing neurons[51,72,149], whereas, in a novel environment, AMPH dominantly increases pERK in D2-R-containing neurons of the striatum[148]. In line with cocaine, PPs have been shown to be induced by acute AMPH administration which may control ERK activity after AMPH stimulation. For example, in the CPu, acute AMPH significantly increases pSTEP in a DARPP-32 dependent manner[51]. In addition, acute AMPH increases the gene encoding PP2B in the striatum including the CPu and NAc[150] relevant to *MKP-1* mRNA expression and DARPP-32/STEP activity[53,151].

Behaviorally, similar to their enhanced response to rewarding properties of morphine and cocaine, ERK1 KO mice exhibit higher hyperlocomotion after acute AMPH injection[34,128,152]. ERK1 KO mice display increased basal locomotor activity accompanied by a reduction of pRSK expression in the PFC and striatum[128,152,153], indicating a blunted ERK-mediated signaling after ERK1 ablation. The increased basal and acute AMPH-induced locomotion as well as the reduction of pRSK can be replicated by chronic and continuous infusion of MEK inhibitor, PD98059 (50μM), and selective knockdown of ERK1 in the PFC[154]. Although the predominant hypothesis indicates that enhanced stimuli-activated ERK2 signaling in the CPu and NAc in ERK1 KO mice is responsible for increased behavioral responses to abused drugs[34,128], the reduction of ERK-mediated molecular cascade, at least in the PFC, may also contribute to both basal and drug-induced behavioral phenotype due to a general inhibition of ERK1 and ERK2 activity by MEK inhibitor. The latter assumption is supported by our recent finding demonstrating that rats raised in enriched environment have an augmented basal pERK induction in the PFC associated with lower basal and repeated nicotine-induced locomotion compared to control animals[155]. The acute AMPH-induced hyperactivity was not altered by SL327 (30–40 mg/kg) but attenuated by high doses of SL327 (50–100 mg/kg) with a potentially inhibitory effect on basal locomotion[80,92,140,141,156]. Although inhibiting acute AMPH-induced locomotor activity, acute systemic MEK inhibition by SL327 (50 mg/kg) resulted an enhancement to the basal locomotion[157]. The discrepancy may be accounted for experimental procedure, since a potentiated acute AMPH-activated locomotor activity was documented after pERK suppression in the CPu of rats without habituating to the behavioral apparatus[147].

In a D1- and D2-Rs dependent manner, AMPH challenge after withdrawal from repeated AMPH exposure resulted in behavioral sensitization which is associated with pERK and pCREB sensitization in the CPu[158,159]. The chronic AMPH-augmented pERK and pCREB induction is attenuated by D1- but not D2-Rs antagonist. Thus, although antagonism of both D1- and D2-Rs can inhibit the expression of behavioral sensitization, only D1-R-mediated ERK and CREB activation is critical for the expression of behavioral sensitization of the AMPH challenge. In contrast to the CPu, the expression of AMPH-induced behavioral sensitization is required for ERK's inhibitory effect on CREB activity modulated by Ca^{2+} voltage-gated channels in the NAc[80]. However, in the VTA, withdrawal from repeated AMPH exposure results in elevated MKP-1 and PP2B protein expression to downregulate the AMPH-mediated pERK induction[143]. Systemic administration of SL327 (30 or 40

mg/kg) dose-dependently prevents the development and expression of behavioral sensitization as well as the acquisition of conditioned locomotor response to AMPH administration[80,92]. A previous study demonstrated that intra-NAc AMPH infusion led to pERK and the establishment of CPP[160]. The AMPH-CPP was prevented by direct intra-NAc PD98059 (2.5 μg/side) infusion either before or after each conditioning session, suggesting the role of ERK on memory acquisition and consolidation of association of contextual rewarding effect of AMPH. However, the enhanced locomotor response by intra-NAc AMPH infusion is not affected by MEK inhibition. Altogether, it seems that ERK plays an important role in chronic AMPH-induced behavioral alterations ranging from behavioral sensitization, conditioned locomotor response to CPP. However, dynamic molecular mechanisms underlying behaviors including ERK-mediated downstream targets and the modulatory effect of ERK-related protein phosphatases should be further elucidated in specific brain regions associated to AMPH.

3.3 Methamphetamine

Methamphetamine (METH) is a highly addictive psychostimulant causing a serious and growing worldwide problem associated with medical, socioeconomic, and legal domains[161,162]. Although accumulating evidence has implicated the Glu and DA neurotransmission in METH-induced behavioral changes[163–167], a direct exploration of their downstream target, ERK signaling, is limited. Acute METH (3 mg/kg) injection significantly increases pERK in the striatum which is attenuated in serine racemase KO mice[168]. Serine racemase is an enzyme synthesizing D-serine, an endogenous co-agonist of NMDA-R, thereby, partially supporting the requirement of NMDA-R for acute METH-induced pERK. In contrast, a recent study demonstrated that acute METH (2 mg/kg) did not affect pERK in either CPu or NAc[169]. The dose of METH, routes of administration, or the timing of collecting tissue may contribute to the discrepancy.

METH challenge after withdrawal from repeated METH exposure has been shown to induce behavioral sensitization related to pERK induction in both CPu and NAc as well as ΔFosB expression in the CPu[122,169,170]. The development and expression of METH behavioral sensitization and challenge-augmented pERK induction were inhibited by levo-tetrahydropalmatine, an antagonist of D1- and D2-Rs[169,171,172], suggesting the involvement of DA receptors in chronic METH-induced pERK and behavioral sensitization. However, the METH challenge-elevated pERK is associated to the consequences of acute stimulation, since the pERK protein expression in the NAc is transiently increased during early withdrawal or not altered after long-term abstinence[122,173]. In agreement with the increase of pERK induction in the NAc shell after 1 day withdrawal from METH sensitization[122], 2 hr withdrawal from METH SA resulted in elevated D1-R, pCREB, and ΔFosB protein expression as well as transcriptional regulating genes including CREB, Elk-1, and Fos family in the CPu[174,175]. Genes associated with dual-specificity phosphatases 12 and protein tyrosine phosphatase were also upregulated, implying an inhibitory mechanism to dampen ERK signaling during the early phase of withdrawal from METH SA[175–177]. In both D1- and NMDA-Rs dependent manners, acute or chronic METH administration results in increases of *MKP-1* and *MKP-3* mRNA in several brain regions including the PFC, orbital cortex, CPu, NAc, and HIPP[178,179]. Therefore, the ERK-driven MKPs expression and other

phosphatases represent a positive feedback to gate the transient ERK activation in response to acute or chronic METH exposure.

The increase of pERK, pElk-1, pCREB, and/or ΔFosB protein expression in the CPu, NAc or PFC is related to METH-induced CPP[180,181]. Specifically, the acquisition of CPP and pERK induction in the NAc by METH-CPP require D1-R but not NMDA-R activation. Intra-NAc infusion of MEK inhibitor, PD98059 (2 μg/side), also prevents the expression of METH-CPP and pERK induction[180]. Therefore, this demonstrates the importance of the activation of D1-R/MEK/ERK/pElk-1 in the NAc on the development and expression of METH-CPP. In contrast, the METH-CPP testing reduced pERK and pCREB in the NAc after a single pairing session with 2 days withdrawal[182], suggesting either a compensatory reduction in response to overactivation of ERK signaling during conditioning and withdrawal or other molecular cascades are required for the initial acquisition of METH-CPP. Both assumptions should be further deciphered to identify molecular mechanisms underlying the difference between single and multiple condition session-mediated METH-CPP.

Chronic METH use causes cognitive deficits associated with altered neurotransmission[183–186]. In animal studies, repeated METH administration leads to spatial learning and memory impairment, which is associated with reduced total ERK in the PFC[187]. In addition, deficits in spatial working memory and novel object recognition (NOR) are accompanied by an inability of pERK induction in the HIPP and PFC by the learning process or stimuli[188–191]. Interestingly, intra-PFC infusion of PD98509 (2 μg/side) mimics the METH-induced cognitive impairment in NOR[188], indicating that a reduced pERK signaling is responsible for the cognitive dysfunction after long term METH exposure. Several drugs have been demonstrated to ameliorate the cognitive deficit by METH through ERK signaling. For example, depending on nicotinic acetylcholine receptors (nAChRs), D1-R and MEK activation, galantamine, a drug used to treat Alzheimer's disease by inhibiting acetylcholinesterase and allosterically modulating nAChRs, alleviates NOR impairment through pERK induction in the PFC[190]. Similarly, modafinil, a cognitive enhancer with a weak DA transporter inhibiting effect, also activates pERK in the PFC to rescue the NOR deficit[191,192] probably through increasing extracellular DA levels. Finally, clozapine, an atypical antipsychotic medication, reverses dysfunctional pERK signaling in the HIPP with an attenuating effect on spatial working memory impairment induced by chronic METH[189]. Taken together, these results demonstrate that the cognitive impairment induced by chronic METH is attributed to the downregulation of ERK signaling during learning and memory-a potential therapeutic molecular biomarker for future drug development.

3.4 Marijuana

Δ9-tetrahydrocannabinol (THC) is the main psychoactive component of marijuana which is one of the most used illicit drugs[193]. Cannabinoid receptors 1 and 2 (CB1-R and CB2-R) have been identified and located mainly in neuronal and peripheral tissues, respectively. Activation of the CB1-R leads to the closing of Ca^{2+} and the opening of potassium channel, subsequently inhibiting AC and activating protein kinase including ERK[194]. Acute low dose THC injection (1 mg/kg) has been demonstrated to increase pERK expression in the

mesocorticolimbic system[63,195]. Specifically, in the CPu and NAc, the THC-activated pERK is mediated by CB1-, D1-, D2- and NMDA-Rs indicating a synergistic action among cannabinoid, DA and Glu neurotransmission. Acute THC-induced ERK downstream targets, pElk-1 and *zif268* mRNA, were inhibited by D1-R antagonist and the MEK inhibitor, SL327 (100 mg/kg). Further, in response to repeated low dose of THC injection, the development of THC-CPP was attenuated by SL327 (50 mg/kg), suggesting that ERK-regulated signaling is involved in THC rewarding effect[196]. Similarly, acute THC- (1 mg/kg) induced transient pERK induction in the HIPP was dependent on the activation of CB1- and NMDA-Rs. SL327 (100 mg/kg) pre-treatment also inhibited the acute THC-induced IEG expression (c-Fos protein, *Zif268* and *BDNF* mRNAs) in the HIPP[197]. However, the relevance between acute THC-induced behavioral changes and ERK signaling should be further elucidated, since there is no significant locomotor activity alteration by low dose THC[198].

In contrast to the low dose of THC, high dose of THC (≥10 mg/kg) acutely resulted in hypolocomotor activity in the CPu and cerebellum with pERK, pCREB, and *c-fos* induction depending on CB1-R and Ras-GRF1[195,199,200]. Although the ERK signaling in both brain regions is distinct from the acute THC-induced hypolocomotor, it is necessary for the development of behavioral tolerance, a gradually behavioral recovery from the initial hypolocomotor by acute THC, after repeated THC injection[199–201]. In an ERK dependent manner, the behavioral tolerance is mediated by recruiting G protein-coupled receptor kinases and β-arrestins to desensitize and internalize CB1-R in the CPu and cerebellum. The chronic THC-mediated cerebellar synaptic transmission and plasticity as well as reduced sensitivity of CB1-R activation were also prevented in Ras-GRF1 KO mice[202]. In addition, chronic THC exposure-induced pCREB and FosB protein expression in the PFC and HIPP is inhibited by either SL327 (50 mg/kg) or in Ras-GRF1 null mice[201]. Taken together, the results demonstrated that, in response to a high dose of THC, the activation of pERK-mediated signaling in the CPu and cerebellum is critical for the development of behavioral tolerance. In the PFC and HIPP, the ERK-associated molecular cascade may underlie the addicted state for THC. However, the latter assumption needs to be examined due to a similar analgesic tolerance effect after a chronic high dose of THC. Since THC-induced behavioral sensitization and self-administration have been documented[203–205], it will be worthwhile to determine the role of ERK on reinforcing/rewarding effects of THC in specific brain region(s).

In addition to the THC action on CB1-R, dopamine agonist and psychostimulants have been shown to increase endocannabinoid release[206–208]. A previous study has indicated that acute cocaine-induced pERK, and c-Fos in the CPu and NAc was inhibited by CB1-R antagonist pretreatment, and mice with CB1-R KO or conditional deletion in the forebrain neurons[68]. In addition, the elevated pERK protein expression-induced by chronic cocaine in the VTA is dependent on CB1-R activation. The development of cocaine-CPP and underlying pERK induction were also inhibited by intra-VTA CB1-R antagonist infusion[100], implicating the role of CB1-R and endocannabinoids in regulating the rewarding effect of cocaine mediated by ERK signaling activation.

3.5 Nicotine

Cigarette smoking is the largest preventable cause of death and diseases worldwide with an estimated 6 million deaths each year[209]. It has been shown that nicotine, through activation of the DA- and Glu-related signaling in the mesocorticolimbic system, exerts its reinforcing effects[210–212]. Several *in vitro* studies have demonstrated that activation of ERK and CREB by acute and chronic administration of nicotine depends on nAChRs, CaMKs, PKA, and MEK activity[213–217]. A genome-wide expression analysis revealed acute nicotine exposure, through activation of ERK signaling, induced alterations of gene expression[218]. Similarly, acute nicotine induced transient ERK activation through nAChRs, Ca^{2+} voltage-gated channels, CaMKs, and MEK in primary cortical and hippocampal neurons[219,220]; however, only PKA is required for pERK induction by nicotine in the hippocampal neurons, suggesting differential upstream activators for ERK activity in distinct neuronal types. Chronic nicotine exposure in mesencephalic dopaminergic neuronal culture resulted in increases of dendritic length and soma size through nAChRs- and D3-R-recrutied ERK signaling[221], demonstrating that ERK involves nicotine-mediated structural neuronal plasticity. *In vivo*, acute nicotine administration increases pERK levels in the NAc, CPu, PFC, Amy, and BNST[51,63] (also see[222,223]). In both the CPu and NAc, acute nicotine-induced pERK is mediated by D1-R/PKA/DARPP-32 signaling pathways[63,64], indicating the relevance of dopaminergic neurotransmission in response to nicotine. After chronic oral consumption of nicotine, the levels of pERK and pCREB were increased in the PFC, but pCREB was decreased in the NAc[222], suggesting an increase of PFC excitatory output into the NAc. Indeed, pERK was increased in the NAc of nicotine-induced CPP animals[223], supporting the role of PFC-NAc projection in the conditioned rewarding effect of nicotine. Interestingly, a direct protein-protein interaction between α7nAChR and GluN2A has been identified in the HIPP, which can be upregulated by chronic nicotine exposure[224]. After nicotine self-administration, disruption of the α7nAChR-NMDA-R complex decreased ERK activity and blocked cue-induced reinstatement of nicotine seeking behavior[224]. Taken together, these results demonstrate that the ERK signaling pathway is a key integrator of the DA/D1-R and Glu/NMDA-R signaling that induces long-term cellular alterations and behavioral adaptation in response to nicotine exposure. However, a direct manipulation on ERK is warranted to examine its effect on nicotine-induced behavioral changes.

Environment is an important factor affecting the vulnerability for drug abuse[225–227]. Exposure to an environmental enrichment paradigm results in neurobiological adaptations, particularly in the PFC of the mesocorticolimbic dopaminergic system[155,228–230]. Our recent study has demonstrated that the basal level of pERK was higher in animals housing in an enriched environment condition compared with animals housing in an impoverished condition, which was negatively correlated with their respective baseline locomotor activities[155]. After nicotine sensitization or nicotine SA, the pERK induction was significantly increased in the PFC of rats raised in either impoverished or standard condition. In contrast, due to their higher basal ERK activity in the PFC, nicotine did not alter pERK protein levels in animals raised in an enriched environment condition with a decreased sensitivity in response to chronic nicotine[155]. Regardless of raising conditions, the pERK induction is positively correlated to the amount of nicotine intake during nicotine SA. Thus, these results suggest that pERK induction in the PFC may underlie the rewarding effect of

nicotine which is consistent with a previous study demonstrating a preference for ERK-mediated signaling pathway activation in the PFC after nicotine SA[231].

3.6 Alcohol (ethanol)

In a time dependent manner, acute injection with higher doses of ethanol (EtOH, 2.5–4.7g/kg) reduced pERK and pCREB in the PFC, NAc, CPu, Amy, HIPP, cerebellum, and BNST in various ages of rodents[232–235]. In contrast, acute administration of a lower dose of EtOH (1g/kg) significantly increased pERK in various regions including the NAc, and CeA in the D1-R and neuropeptide S receptor dependent manner[236,237]. The acute EtOH-induced *c-fos* induction in the medial Amy was inhibited by the MEK inhibitor, U0126[238]. Similarly, acute acetaldehyde (ACD), the first and main metabolite of EtOH, enhanced pERK in the NAc, CeA and BNST through activation of D1-R and opioid receptors[239,240]. Behaviorally, the low dose of acute EtOH (1mg/kg) is associated an anxiolytic response accompanied by the rapid increase of spine density in the CeA and medial Amy (MeA) through the BDNF-mediated TrkB phosphorylation and pERK/pElk-1/pCREB and *Arc* induction[241]. In addition to the acute EtOH-mediated pERK signaling, its intrinsic activation state may contribute to the alcohol intake or preference. For example, despite the mixing results of acute EtOH-mediated pERK level in alcohol preferring animals, they have higher basal pERK level in the PFC and NAc as well as *Ras-GRF2* expression, the upstream activator of MEK, in the brain compared to their alcohol non-preferring counterparts[242–245]. The Ras-GRF2 KO mice exhibited lower EtOH intake associated with an aberrant DA transmission in the VTA-NAc projection mediated by ERK activation[242], revealing a functional role of ERK on acute EtOH-mediated DA signaling underlying the preference of alcohol.

The effect of chronic EtOH exposure on pERK is heavily dependent on administering paradigms, time of withdrawal and brain regions. Immediate cessation of repeated EtOH oral consumption and vaporized EtOH exposure has been demonstrated to decrease pERK in the PFC, NAc, CPu, Amy, and HIPP, although with an enhanced pERK induction after 7–11 hr withdrawal[235,246,247]. In contrast, the chronic EtOH-attenuated neuronal plasticity during early withdrawal (e.g. within 1 day withdrawal) is associated with the downregulation of pERK and the inability of pERK induction in response to stimulus in the HIPP[248]. Similarly, a desensitization/tolerance of pERK or *c-fos* expression in response to EtOH re-exposure or challenge after withdrawal from repeated EtOH has been found in the PFC and HIPP[238,247]. Further, a paralleled attenuated phosphorylation of GluN1 and CaMKII is also documented immediately after chronic EtOH exposure[235,247]. Taken together, these results demonstrate that a reduction of Glu receptor-mediated ERK activity during early withdrawal leads to the desensitization of subsequent EtOH-induced pERK signaling. In contrast, Pandey and colleagues demonstrated that 24hr withdrawal from repeated EtOH consumption produced anxiety-like behavior followed by blunted BDNF/TrkB/pERK/pElk-1 and Arc protein expression with reduced spine density in the CeA and MeA[241]. Intra-CeA BDNF infusion restored the early withdrawal-induced ERK signaling dysfunction and inhibited the anxiety-like behavior. Similarly, knockdown of the BDNF-mediated ERK signaling in the CeA and MeA induces anxiety and promotes EtOH intake[249]. This suggests that withdrawal syndrome after chronic EtOH consumption accompanied by physical signs and negative emotional state (e.g. anxiety, depression and irritability[250,251]) may precipitate the relapse of

EtOH intake. In addition, withdrawal from repeated EtOH has been demonstrated to result in an enhancement of fear conditioning depending on pERK activation in the BLA by NMDA-R and MEK activation[252]. Thus, the ERK signaling in the Amy complex is important for the development and further acquisition of the negative affective state underlying the vulnerability for subsequent alcohol seeking behavior after withdrawal.

The role of ERK signaling pathway in EtOH-mediated rewarding effect has been documented. In the CPP model, the alcohol metabolite ACD-CPP is dependent on D1-R activation and the development of ACD-CPP can be attenuated by the MEK inhibitor, PD98059[253]. In contrast, a previous study has indicated that the systemic SL327 administration in the ERK-independent learning mechanism in EtOH-CPP did not affect the acquisition, expression and extinction of EtOH-CPP (2g/kg) as well as pERK after acute EtOH administration (2.5g/kg)[254]. However, EtOH-CPP has been shown to be established by the lower dose of EtOH (1g/kg) in D1-R dependent manner[253], which is sufficient to induce pERK induction as described above. Based on the D1-R-activated pERK and significant pERK induction after acute EtOH, it is required to further test the effect of D1-R/ERK signaling on EtOH-CPP by the lower dose of EtOH. The ERK signaling is also implicated in the operant rewarding effect of EtOH. For instance, systemic MEK inhibition resulted in an increase of EtOH SA[255], indicating the antagonism of acute pharmacological effect of alcohol promoting the drug taking behavior. After abstinence form EtOH SA, re-exposure to conditioned cues induced alcohol seeking behavior accompanied by pERK and c-Fos expression in the BLA[256]. The ERK signaling is also critical for the Glu transmission-mediated alcohol seeking. After extinction from EtOH SA, systemic mGluR5 inhibition attenuated cue-induced reinstatement and the cue-induced pERK expression in the BLA and NAc shell in alcohol-preferring rats[257]. Probably through restoring the Glu transmission, L-cysteine prevents EtOH SA and EtOH-primed-induced drug seeking[258]. In addition, the reinstatement-induced pERK in the NAc shell is also inhibited by the L-cystine pre-treatment. Finally, ERK activation in the VTA has been demonstrated to mediate the inhibitory effect of GDNF in preventing EtOH intake and reacquisition of EtOH SA after extinction[259].

4. Conclusion and future direction

Drug addiction is a significant public health problem and has been considered as a chronic psychiatric disorder, characterized by craving and compulsive drug seeking and use. The main obstacle in drug addiction treatment is the cycle of relapse/reinstatement from drugs of abuse. This review summarizes the current understanding on the role of ERK signaling and its associated intracellular signaling pathways in drug-induced neuroadaptive changes underlying the rewarding and reinforcing mechanisms in response to abused drugs. Despite the differential regulatory pathways in which all drugs of abuse can affect ERK signaling, one evolving theme in all cases is the regulation of the ERK molecules at the phosphorylation level. It is therefore important to understand the precise mechanisms that underlie the regulation of ERK phosphorylation by different drugs of abuse. The ERK signaling pathway may play a critical role in the early intervention during withdrawal from chronic drug administration. For example, our recent studies demonstrated that normalizing the prefrontal ERK signaling pathway during the early withdrawal from repeated cocaine

exposure leads to a long-term inhibitory effect on cocaine relapse[120,121] and restores the extracellular glutamate dysregulation in the NAc[260]. In contrast, after prolonged withdrawal from cocaine, an increase of PKA-mediated signaling is dominant in the PFC and NAc responsible for cocaine seeking[85,121,261–263], implicating that ERK activity in the PFC-NAc projection is dynamically regulated by multiple intracellular pathways. Future studies will evaluate the ability of novel therapeutic interventions to restore normal ERK signaling activity in the brain for inhibiting addictive drug-seeking behavior. On the other hand, environmental factors can also influence vulnerability to drug addiction. We demonstrated that environmental enrichment induces compensatory alterations of D1-R/DARPP-32 and ERK signaling pathways in the PFC, which may contribute to environmental enrichment-dependent reduction of susceptibility to nicotine[155,264]. Although current knowledge of multiple factors regulating ERK activity has greatly expanded, many aspects of this regulation remain to be elucidated. For example, overexpression of microRNA-221 attenuates nicotine-induced pERK (unpublished data), whereas activation of ERK can regulate microRNA-221 expression[265]. Furthermore, ERK signaling has been associated with epigenetic mechanisms including chromatin remodeling through histone methylation and DNA methylation associated with drug addiction[266–268], which are critical for the regulation of gene expression, neuronal plasticity, and drug-induced behavioral alteration. In summary, several molecular signaling pathways are involved in the complexity of drug addiction; with ERK being the most highly characterized during the past two decades. Herein, we provide the general role of ERK-mediated molecular cascade in response to various abused drugs, but it is by no means exhaustive. Future studies are warranted to dissect the ERK signaling pathway providing a better understanding for the development of feasible and potential therapeutic strategies for drug addiction and related disorders.

Acknowledgments

This research was supported by a grant from the National Institute on Drug Abuse to Jun Zhu (DA035714). We acknowledge Dr. Jacqueline F. McGinty (Medical University of South Carolina, Charleston, SC) for commenting on the manuscript.

Abbreviations

AMPH	amphetamine
DA	dopamine
Glu	glutamate
VTA	ventral tegmental area
PFC	prefrontal cortex
HIPP	hippocampus
Amy	amygdala
CPu	caudate putamen
NAc	nucleus accumbens

ERK	extracellular signal-regulated kinase
MAPK	mitogen-activated protein kinase
MEK	MAPK kinase
CB1-R	Cannabinoid receptor 1
CB2-R	Cannabinoid receptor 2
pERK	phosphorylated ERK
IEG	immediate early gene
RSK	ribosomal S6 kinase
MSK	mitogen and stress-activated protein kinase
CREB	cAMP response element-binding protein
pCREB	phosphorylated CREB
Ca^{2+}	calcium
CaM	calcium/calmodulin
CaMK	CaM kinase
pMEK	phosphorylation of MEK
AC	adenylyl cyclase
mGluR1/5	metabotropic glutamate receptor-1/5
D1-R	dopamine D1 receptor
METH	methamphetamine
D2-R	dopamine D2-R
PKA	Protein Kinase A
PKC	Protein Kinase C
PP2A	Protein phosphatase 2A
PP2B	proteinphosphatase 2B
STEP	striatal-enriched protein tyrosine phosphatase
pSTEP	phosphorylation of STEP
DARPP-32	dopamine and cAMP regulated phosphoprotein-32
pThr75 DARPP-32	phosphorylation of DARPP-32 at Threonine 75
MKP-1/3	MAPK phosphatases 1 and 3

CPP	conditioned place preference
SA	self-administration
BNST	bed nucleus of the striatal terminals
pGluN2B	phosphorylation of glutamate receptor, ionotropic, N-methyl D-aspartate 2B
BDNF	brain derived-neurotrophic factor
Ras-GRF-1	Ras-guanine nucleotide-releasing factors 1
nAChRs	nicotinic acetylcholine receptors
THC	Δ9-tetrahydrocannabinol

References

1. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci. 2001; 2(2):119–128. [PubMed: 11252991]
2. Kalivas PW. Glutamate systems in cocaine addiction. Curr Opin Pharmacol. 2004; 4(1):23–29. [PubMed: 15018835]
3. Feltenstein MW, See RE. The neurocircuitry of addiction: an overview. Br J Pharmacol. 2008; 154(2):261–274. [PubMed: 18311189]
4. Swanson LW. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull. 1982; 9(1–6):321–353. [PubMed: 6816390]
5. Schultz W. Predictive reward signal of dopamine neurons. Journal of neurophysiology. 1998; 80(1): 1–27. [PubMed: 9658025]
6. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004; 5(6):483–494. [PubMed: 15152198]
7. Canales JJ. Stimulant-induced adaptations in neostriatal matrix and striosome systems: transiting from instrumental responding to habitual behavior in drug addiction. Neurobiology of learning and memory. 2005; 83(2):93–103. [PubMed: 15721792]
8. Wise RA. Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. Trends Neurosci. 2009; 32(10):517–524. [PubMed: 19758714]
9. Kyosseva SV. Mitogen-activated protein kinase signaling. International review of neurobiology. 2004; 59:201–220. [PubMed: 15006489]
10. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. Biochim Biophys Acta. 2010; 1802(4):396–405. [PubMed: 20079433]
11. Berhow MT, Hiroi N, Nestler EJ. Regulation of ERK (extracellular signal regulated kinase), part of the neurotrophin signal transduction cascade, in the rat mesolimbic dopamine system by chronic exposure to morphine or cocaine. J Neurosci. 1996; 16(15):4707–4715. [PubMed: 8764658]
12. Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. The MAPK cascade is required for mammalian associative learning. Nature neuroscience. 1998; 1(7):602–609. [PubMed: 10196568]
13. Seger R, Krebs EG. The MAPK signaling cascade. FASEB J. 1995; 9(9):726–735. [PubMed: 7601337]
14. Chen RH, Sarnecki C, Blenis J. Nuclear localization and regulation of erk- and rsk-encoded protein kinases. Mol Cell Biol. 1992; 12(3):915–927. [PubMed: 1545823]
15. Gille H, Strahl T, Shaw PE. Activation of ternary complex factor Elk-1 by stress-activated protein kinases. Curr Biol. 1995; 5(10):1191–1200. [PubMed: 8548291]

16. Gille H, Sharrocks AD, Shaw PE. Phosphorylation of transcription factor p62TCF by MAP kinase stimulates ternary complex formation at c-fos promoter. Nature. 1992; 358(6385):414–417. [PubMed: 1322499]
17. Davis S, Vanhoutte P, Pages C, Caboche J, Laroche S. The MAPK/ERK cascade targets both Elk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus in vivo. J Neurosci. 2000; 20(12):4563–4572. [PubMed: 10844026]
18. Hill CS, Marais R, John S, Wynne J, Dalton S, Treisman R. Functional analysis of a growth factor-responsive transcription factor complex. Cell. 1993; 73(2):395–406. [PubMed: 8477450]
19. Treisman R. Regulation of transcription by MAP kinase cascades. Current opinion in cell biology. 1996; 8(2):205–215. [PubMed: 8791420]
20. Pende M, Fisher TL, Simpson PB, Russell JT, Blenis J, Gallo V. Neurotransmitter- and growth factor-induced cAMP response element binding protein phosphorylation in glial cell progenitors: role of calcium ions, protein kinase C, and mitogen-activated protein kinase/ribosomal S6 kinase pathway. J Neurosci. 1997; 17(4):1291–1301. [PubMed: 9006973]
21. Frodin M, Gammeltoft S. Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. Molecular and cellular endocrinology. 1999; 151(1–2):65–77. [PubMed: 10411321]
22. Xing J, Kornhauser JM, Xia Z, Thiele EA, Greenberg ME. Nerve growth factor activates extracellular signal-regulated kinase and p38 mitogen-activated protein kinase pathways to stimulate CREB serine 133 phosphorylation. Mol Cell Biol. 1998; 18(4):1946–1955. [PubMed: 9528766]
23. Merienne K, Pannetier S, Harel-Bellan A, Sassone-Corsi P. Mitogen-regulated RSK2-CBP interaction controls their kinase and acetylase activities. Mol Cell Biol. 2001; 21(20):7089–7096. [PubMed: 11564891]
24. Arthur JS, Cohen P. MSK1 is required for CREB phosphorylation in response to mitogens in mouse embryonic stem cells. FEBS Lett. 2000; 482(1–2):44–48. [PubMed: 11018520]
25. Kurino M, Fukunaga K, Ushio Y, Miyamoto E. Activation of mitogen-activated protein kinase in cultured rat hippocampal neurons by stimulation of glutamate receptors. J Neurochem. 1995; 65(3):1282–1289. [PubMed: 7643105]
26. Robinson TE, Kolb B. Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. Eur J Neurosci. 1999; 11(5):1598–1604. [PubMed: 10215912]
27. Chandler LJ, Sutton G, Dorairaj NR, Norwood D. N-methyl D-aspartate receptor-mediated bidirectional control of extracellular signal-regulated kinase activity in cortical neuronal cultures. J Biol Chem. 2001; 276(4):2627–2636. [PubMed: 11062237]
28. Xia Z, Dudek H, Miranti CK, Greenberg ME. Calcium influx via the NMDA receptor induces immediate early gene transcription by a MAP kinase/ERK-dependent mechanism. J Neurosci. 1996; 16(17):5425–5436. [PubMed: 8757255]
29. Mao L, Tang Q, Samdani S, Liu Z, Wang JQ. Regulation of MAPK/ERK phosphorylation via ionotropic glutamate receptors in cultured rat striatal neurons. Eur J Neurosci. 2004; 19(5):1207–1216. [PubMed: 15016079]
30. Perkinton MS, Ip JK, Wood GL, Crossthwaite AJ, Williams RJ. Phosphatidylinositol 3-kinase is a central mediator of NMDA receptor signalling to MAP kinase (Erk1/2), Akt/PKB and CREB in striatal neurones. J Neurochem. 2002; 80(2):239–254. [PubMed: 11902114]
31. Vincent SR, Sebben M, Dumuis A, Bockaert J. Neurotransmitter regulation of MAP kinase signaling in striatal neurons in primary culture. Synapse. 1998; 29(1):29–36. [PubMed: 9552173]
32. Vanhoutte P, Barnier JV, Guibert B, et al. Glutamate induces phosphorylation of Elk-1 and CREB, along with c-fos activation, via an extracellular signal-regulated kinase-dependent pathway in brain slices. Mol Cell Biol. 1999; 19(1):136–146. [PubMed: 9858538]
33. Choe ES, McGinty JF. Cyclic AMP and mitogen-activated protein kinases are required for glutamate-dependent cyclic AMP response element binding protein and Elk-1 phosphorylation in the dorsal striatum in vivo. J Neurochem. 2001; 76(2):401–412. [PubMed: 11208903]

34. Ferguson SM, Fasano S, Yang P, Brambilla R, Robinson TE. Knockout of ERK1 enhances cocaine-evoked immediate early gene expression and behavioral plasticity. Neuropsychopharmacology. 2006; 31(12):2660–2668. [PubMed: 16407894]
35. Seyler CE. Nonlinear 3-D evolution of bounded kinetic Alfven waves due to shear flow and collisionless tearing instability. Geophysical Research Letters. 1998; 15(8):756.
36. Grewal SS, Horgan AM, York RD, Withers GS, Banker GA, Stork PJ. Neuronal calcium activates a Rap1 and B-Raf signaling pathway via the cyclic adenosine monophosphate-dependent protein kinase. J Biol Chem. 2000; 275(5):3722–3728. [PubMed: 10652372]
37. Vossler MR, Yao H, York RD, Pan MG, Rim CS, Stork PJ. cAMP activates MAP kinase and Elk-1 through a B-Raf- and Rap1-dependent pathway. Cell. 1997; 89(1):73–82. [PubMed: 9094716]
38. Gerfen CR, Miyachi S, Paletzki R, Brown P. D1 dopamine receptor supersensitivity in the dopamine-depleted striatum results from a switch in the regulation of ERK1/2/MAP kinase. J Neurosci. 2002; 22(12):5042–5054. [PubMed: 12077200]
39. Impey S, Obrietan K, Wong ST, et al. Cross talk between ERK and PKA is required for Ca2+ stimulation of CREB-dependent transcription and ERK nuclear translocation. Neuron. 1998; 21(4):869–883. [PubMed: 9808472]
40. Roberson ED, English JD, Adams JP, Selcher JC, Kondratick C, Sweatt JD. The mitogen-activated protein kinase cascade couples PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus. J Neurosci. 1999; 19(11):4337–4348. [PubMed: 10341237]
41. Zanassi P, Paolillo M, Feliciello A, Avvedimento EV, Gallo V, Schinelli S. cAMP-dependent protein kinase induces cAMP-response element-binding protein phosphorylation via an intracellular calcium release/ERK-dependent pathway in striatal neurons. J Biol Chem. 2001; 276(15):11487–11495. [PubMed: 11139572]
42. Dale LB, Babwah AV, Bhattacharya M, Kelvin DJ, Ferguson SS. Spatial-temporal patterning of metabotropic glutamate receptor-mediated inositol 1,4,5-triphosphate, calcium, and protein kinase C oscillations: protein kinase C-dependent receptor phosphorylation is not required. J Biol Chem. 2001; 276(38):35900–35908. [PubMed: 11461909]
43. Kawabata S, Kohara A, Tsutsumi R, et al. Diversity of calcium signaling by metabotropic glutamate receptors. J Biol Chem. 1998; 273(28):17381–17385. [PubMed: 9651322]
44. Schnabel R, Palmer MJ, Kilpatrick IC, Collingridge GL. A CaMKII inhibitor, KN-62, facilitates DHPG-induced LTD in the CA1 region of the hippocampus. Neuropharmacology. 1999; 38(4): 605–608. [PubMed: 10221764]
45. Choe ES, Wang JQ. Group I metabotropic glutamate receptor activation increases phosphorylation of cAMP response element-binding protein, Elk-1, and extracellular signal-regulated kinases in rat dorsal striatum. Brain Res Mol Brain Res. 2001; 94(1–2):75–84. [PubMed: 11597767]
46. Yan Z, Feng J, Fienberg AA, Greengard P. D(2) dopamine receptors induce mitogen-activated protein kinase and cAMP response element-binding protein phosphorylation in neurons. Proc Natl Acad Sci U S A. 1999; 96(20):11607–11612. [PubMed: 10500224]
47. Boulanger LM, Lombroso PJ, Raghunathan A, During MJ, Wahle P, Naegele JR. Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. J Neurosci. 1995; 15(2):1532–1544. [PubMed: 7869116]
48. Lombroso PJ, Naegele JR, Sharma E, Lerner M. A protein tyrosine phosphatase expressed within dopaminoceptive neurons of the basal ganglia and related structures. J Neurosci. 1993; 13(7): 3064–3074. [PubMed: 8331384]
49. Nika K, Hyunh H, Williams S, et al. Haematopoietic protein tyrosine phosphatase (HePTP) phosphorylation by cAMP-dependent protein kinase in T-cells: dynamics and subcellular location. Biochem J. 2004; 378(Pt 2):335–342. [PubMed: 14613483]
50. Zuniga A, Torres J, Ubeda J, Pulido R. Interaction of mitogen-activated protein kinases with the kinase interaction motif of the tyrosine phosphatase PTP-SL provides substrate specificity and retains ERK2 in the cytoplasm. J Biol Chem. 1999; 274(31):21900–21907. [PubMed: 10419510]
51. Valjent E, Pascoli V, Svenningsson P, et al. Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. Proc Natl Acad Sci U S A. 2005; 102(2):491–496. [PubMed: 15608059]

52. Nishi A, Bibb JA, Snyder GL, Higashi H, Nairn AC, Greengard P. Amplification of dopaminergic signaling by a positive feedback loop. Proc Natl Acad Sci U S A. 2000; 97(23):12840–12845. [PubMed: 11050161]
53. Greengard P, Allen PB, Nairn AC. Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. Neuron. 1999; 23(3):435–447. [PubMed: 10433257]
54. Halpain S, Greengard P. Activation of NMDA receptors induces rapid dephosphorylation of the cytoskeletal protein MAP2. Neuron. 1990; 5(3):237–246. [PubMed: 2169265]
55. Nishi A, Bibb JA, Matsuyama S, et al. Regulation of DARPP-32 dephosphorylation at PKA- and Cdk5-sites by NMDA and AMPA receptors: distinct roles of calcineurin and protein phosphatase-2A. J Neurochem. 2002; 81(4):832–841. [PubMed: 12065642]
56. Bokemeyer D, Sorokin A, Yan M, Ahn NG, Templeton DJ, Dunn MJ. Induction of mitogen-activated protein kinase phosphatase 1 by the stress-activated protein kinase signaling pathway but not by extracellular signal-regulated kinase in fibroblasts. J Biol Chem. 1996; 271(2):639–642. [PubMed: 8557667]
57. Brondello JM, Brunet A, Pouyssegur J, McKenzie FR. The dual specificity mitogen-activated protein kinase phosphatase-1 and -2 are induced by the p42/p44MAPK cascade. J Biol Chem. 1997; 272(2):1368–1376. [PubMed: 8995446]
58. Muda M, Theodosiou A, Rodrigues N, et al. The dual specificity phosphatases M3/6 and MKP-3 are highly selective for inactivation of distinct mitogen-activated protein kinases. J Biol Chem. 1996; 271(44):27205–27208. [PubMed: 8910287]
59. Camps M, Nichols A, Gillieron C, et al. Catalytic activation of the phosphatase MKP-3 by ERK2 mitogen-activated protein kinase. Science. 1998; 280(5367):1262–1265. [PubMed: 9596579]
60. Hafen E. Kinases and phosphatases--a marriage is consummated. Science. 1998; 280(5367):1212–1213. [PubMed: 9634402]
61. Zhou B, Wang ZX, Zhao Y, Brautigan DL, Zhang ZY. The specificity of extracellular signal-regulated kinase 2 dephosphorylation by protein phosphatases. J Biol Chem. 2002; 277(35): 31818–31825. [PubMed: 12082107]
62. Brondello JM, Pouyssegur J, McKenzie FR. Reduced MAP kinase phosphatase-1 degradation after p42/p44MAPK-dependent phosphorylation. Science. 1999; 286(5449):2514–2517. [PubMed: 10617468]
63. Valjent E, Pages C, Herve D, Girault JA, Caboche J. Addictive and non-addictive drugs induce distinct and specific patterns of ERK activation in mouse brain. Eur J Neurosci. 2004; 19(7):1826–1836. [PubMed: 15078556]
64. Valjent E, Herve D, Girault JA. Drugs of abuse, protein phosphatases, and ERK pathway. Med Sci (Paris). 2005; 21(5):453–454. [PubMed: 15885186]
65. Valjent E, Bertran-Gonzalez J, Aubier B, Greengard P, Herve D, Girault JA. Mechanisms of locomotor sensitization to drugs of abuse in a two-injection protocol. Neuropsychopharmacology. 2010; 35(2):401–415. [PubMed: 19759531]
66. Radwanska K, Valjent E, Trzaskos J, Caboche J, Kaczmarek L. Regulation of cocaine-induced activator protein 1 transcription factors by the extracellular signal-regulated kinase pathway. Neuroscience. 2006; 137(1):253–264. [PubMed: 16263220]
67. Radwanska K, Caboche J, Kaczmarek L. Extracellular signal-regulated kinases (ERKs) modulate cocaine-induced gene expression in the mouse amygdala. Eur J Neurosci. 2005; 22(4):939–948. [PubMed: 16115217]
68. Corbille AG, Valjent E, Marsicano G, et al. Role of cannabinoid type 1 receptors in locomotor activity and striatal signaling in response to psychostimulants. J Neurosci. 2007; 27(26):6937–6947. [PubMed: 17596442]
69. Zhang L, Lou D, Jiao H, et al. Cocaine-induced intracellular signaling and gene expression are oppositely regulated by the dopamine D1 and D3 receptors. J Neurosci. 2004; 24(13):3344–3354. [PubMed: 15056714]
70. Pascoli V, Besnard A, Herve D, et al. Cyclic adenosine monophosphate-independent tyrosine phosphorylation of NR2B mediates cocaine-induced extracellular signal-regulated kinase activation. Biol Psychiatry. 2011; 69(3):218–227. [PubMed: 21055728]

71. Jiao H, Zhang L, Gao F, Lou D, Zhang J, Xu M. Dopamine D(1) and D(3) receptors oppositely regulate NMDA- and cocaine-induced MAPK signaling via NMDA receptor phosphorylation. J Neurochem. 2007; 103(2):840–848. [PubMed: 17897358]
72. Bertran-Gonzalez J, Bosch C, Maroteaux M, et al. Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. J Neurosci. 2008; 28(22):5671–5685. [PubMed: 18509028]
73. Xu S, Kang UG. Cocaine induces ubiquitination of Egr-1 in the rat dorsal striatum. Neuroreport. 2014; 25(17):1362–1367. [PubMed: 25325348]
74. Besnard A, Bouveyron N, Kappes V, et al. Alterations of molecular and behavioral responses to cocaine by selective inhibition of Elk-1 phosphorylation. J Neurosci. 2011; 31(40):14296–14307. [PubMed: 21976515]
75. Jenab S, Festa ED, Nazarian A, et al. Cocaine induction of ERK proteins in dorsal striatum of Fischer rats. Brain Res Mol Brain Res. 2005; 142(2):134–138. [PubMed: 16271798]
76. Sun WL, Zhou L, Hazim R, Quinones-Jenab V, Jenab S. Effects of dopamine and NMDA receptors on cocaine-induced Fos expression in the striatum of Fischer rats. Brain Res. 2008; 1243:1–9. [PubMed: 18822274]
77. Sun WL, Zhou L, Hazim R, Quinones-Jenab V, Jenab S. Effects of acute cocaine on ERK and DARPP-32 phosphorylation pathways in the caudate-putamen of Fischer rats. Brain Res. 2007; 1178:12–19. [PubMed: 17920048]
78. Valjent E, Corvol JC, Pages C, Besson MJ, Maldonado R, Caboche J. Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. J Neurosci. 2000; 20(23):8701–8709. [PubMed: 11102476]
79. Brami-Cherrier K, Valjent E, Herve D, et al. Parsing molecular and behavioral effects of cocaine in mitogen- and stress-activated protein kinase-1-deficient mice. J Neurosci. 2005; 25(49):11444–11454. [PubMed: 16339038]
80. Giordano TP, Tropea TF, Satpute SS, et al. Molecular switch from L-type Ca v 1.3 to Ca v 1.2 Ca2+ channel signaling underlies long-term psychostimulant-induced behavioral and molecular plasticity. J Neurosci. 2010; 30(50):17051–17062. [PubMed: 21159975]
81. Berke JD, Paletzki RF, Aronson GJ, Hyman SE, Gerfen CR. A complex program of striatal gene expression induced by dopaminergic stimulation. J Neurosci. 1998; 18(14):5301–5310. [PubMed: 9651213]
82. Valjent E, Corbille AG, Bertran-Gonzalez J, Herve D, Girault JA. Inhibition of ERK pathway or protein synthesis during reexposure to drugs of abuse erases previously learned place preference. Proc Natl Acad Sci U S A. 2006; 103(8):2932–2937. [PubMed: 16473939]
83. Pascoli V, Turiault M, Luscher C. Reversal of cocaine-evoked synaptic potentiation resets drug-induced adaptive behaviour. Nature. 2011; 481(7379):71–75. [PubMed: 22158102]
84. Boudreau AC, Reimers JM, Milovanovic M, Wolf ME. Cell surface AMPA receptors in the rat nucleus accumbens increase during cocaine withdrawal but internalize after cocaine challenge in association with altered activation of mitogen-activated protein kinases. J Neurosci. 2007; 27(39):10621–10635. [PubMed: 17898233]
85. Boudreau AC, Ferrario CR, Glucksman MJ, Wolf ME. Signaling pathway adaptations and novel protein kinase A substrates related to behavioral sensitization to cocaine. J Neurochem. 2009; 110(1):363–377. [PubMed: 19457111]
86. Schumann J, Yaka R. Prolonged withdrawal from repeated noncontingent cocaine exposure increases NMDA receptor expression and ERK activity in the nucleus accumbens. J Neurosci. 2009; 29(21):6955–6963. [PubMed: 19474322]
87. Kim S, Kim JH. Time-dependent change of ERK phosphorylation levels in the nucleus accumbens during withdrawals from repeated cocaine. Neurosci Lett. 2008; 436(2):107–110. [PubMed: 18359158]
88. Peng Q, Sun X, Liu Z, Yang J, Oh KW, Hu Z. Microinjection of CART (cocaine- and amphetamine-regulated transcript) peptide into the nucleus accumbens inhibits the cocaine-induced upregulation of dopamine receptors and locomotor sensitization. Neurochem Int. 2014; 75:105–111. [PubMed: 24953280]

89. Yoon HS, Kim S, Park HK, Kim JH. Microinjection of CART peptide 55–102 into the nucleus accumbens blocks both the expression of behavioral sensitization and ERK phosphorylation by cocaine. Neuropharmacology. 2007; 53(2):344–351. [PubMed: 17610912]

90. Janes AC, Kantak KM, Cherry JA. The involvement of type IV phosphodiesterases in cocaine-induced sensitization and subsequent pERK expression in the mouse nucleus accumbens. Psychopharmacology (Berl). 2009; 206(2):177–185. [PubMed: 19588125]

91. Mattson BJ, Bossert JM, Simmons DE, et al. Cocaine-induced CREB phosphorylation in nucleus accumbens of cocaine-sensitized rats is enabled by enhanced activation of extracellular signal-related kinase, but not protein kinase A. J Neurochem. 2005; 95(5):1481–1494. [PubMed: 16219028]

92. Valjent E, Corvol JC, Trzaskos JM, Girault JA, Herve D. Role of the ERK pathway in psychostimulant-induced locomotor sensitization. BMC Neurosci. 2006; 7:20. [PubMed: 16512905]

93. Kim S, Shin JK, Yoon HS, Kim JH. Blockade of ERK Phosphorylation in the Nucleus Accumbens Inhibits the Expression of Cocaine-induced Behavioral Sensitization in Rats. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology. 2011; 15(6):389–395.

94. Pierce RC, Pierce-Bancroft AF, Prasad BM. Neurotrophin-3 contributes to the initiation of behavioral sensitization to cocaine by activating the Ras/Mitogen-activated protein kinase signal transduction cascade. J Neurosci. 1999; 19(19):8685–8695. [PubMed: 10493769]

95. Ren Z, Sun WL, Jiao H, et al. Dopamine D1 and N-methyl-D-aspartate receptors and extracellular signal-regulated kinase mediate neuronal morphological changes induced by repeated cocaine administration. Neuroscience. 2010; 168(1):48–60. [PubMed: 20346392]

96. Zhang L, Li J, Liu N, et al. Signaling via dopamine D1 and D3 receptors oppositely regulates cocaine-induced structural remodeling of dendrites and spines. Neuro-Signals. 2012; 20(1):15–34. [PubMed: 22076064]

97. Cardinal RN, Everitt BJ. Neural and psychological mechanisms underlying appetitive learning: links to drug addiction. Curr Opin Neurobiol. 2004; 14(2):156–162. [PubMed: 15082319]

98. Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron. 2004; 44(1):161–179. [PubMed: 15450168]

99. Chen L, Xu M. Dopamine D1 and D3 receptors are differentially involved in cue-elicited cocaine seeking. J Neurochem. 2010; 114(2):530–541. [PubMed: 20456009]

100. Pan B, Zhong P, Sun D, Liu QS. Extracellular signal-regulated kinase signaling in the ventral tegmental area mediates cocaine-induced synaptic plasticity and rewarding effects. J Neurosci. 2011; 31(31):11244–11255. [PubMed: 21813685]

101. Marin MT, Berkow A, Golden SA, Koya E, Planeta CS, Hope BT. Context-specific modulation of cocaine-induced locomotor sensitization and ERK and CREB phosphorylation in the rat nucleus accumbens. Eur J Neurosci. 2009; 30(10):1931–1940. [PubMed: 19912338]

102. Fricks-Gleason AN, Marshall JF. Role of dopamine D1 receptors in the activation of nucleus accumbens extracellular signal-regulated kinase (ERK) by cocaine-paired contextual cues. Neuropsychopharmacology. 2011; 36(2):434–444. [PubMed: 20944555]

103. Nygard SK, Klambatsen A, Hazim R, et al. Sexually dimorphic intracellular responses after cocaine-induced conditioned place preference expression. Brain Res. 2013; 1520:121–133. [PubMed: 23665060]

104. Tropea TF, Guerriero RM, Willuhn I, et al. Augmented D1 dopamine receptor signaling and immediate-early gene induction in adult striatum after prenatal cocaine. Biol Psychiatry. 2008; 63(11):1066–1074. [PubMed: 18275938]

105. Tropea TF, Kosofsky BE, Rajadhyaksha AM. Enhanced CREB and DARPP-32 phosphorylation in the nucleus accumbens and CREB, ERK, and GluR1 phosphorylation in the dorsal hippocampus is associated with cocaine-conditioned place preference behavior. J Neurochem. 2008; 106(4):1780–1790. [PubMed: 18554320]

106. Yu F, Zhong P, Liu X, Sun D, Gao HQ, Liu QS. Metabotropic glutamate receptor I (mGluR1) antagonism impairs cocaine-induced conditioned place preference via inhibition of protein synthesis. Neuropsychopharmacology. 2013; 38(7):1308–1321. [PubMed: 23348064]

107. Miller CA, Marshall JF. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. Neuron. 2005; 47(6):873–884. [PubMed: 16157281]
108. Edwards S, Bachtell RK, Guzman D, Whisler KN, Self DW. Emergence of context-associated GluR(1) and ERK phosphorylation in the nucleus accumbens core during withdrawal from cocaine self-administration. Addiction biology. 2011; 16(3):450–457. [PubMed: 21309958]
109. Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci. 2004; 24(20): 4787–4795. [PubMed: 15152039]
110. Reichelt AC, Lee JL. Memory reconsolidation in aversive and appetitive settings. Frontiers in behavioral neuroscience. 2013; 7:118. [PubMed: 24058336]
111. Tronson NC, Taylor JR. Addiction: a drug-induced disorder of memory reconsolidation. Curr Opin Neurobiol. 2013; 23(4):573–580. [PubMed: 23415831]
112. Liddie S, Itzhak Y. Variations in the stimulus salience of cocaine reward influences drug-associated contextual memory. Addiction biology. 2014
113. Wells AM, Arguello AA, Xie X, et al. Extracellular signal-regulated kinase in the basolateral amygdala, but not the nucleus accumbens core, is critical for context-response-cocaine memory reconsolidation in rats. Neuropsychopharmacology. 2013; 38(5):753–762. [PubMed: 23232446]
114. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 2000; 406(6797):722–726. [PubMed: 10963596]
115. Edwards S, Graham DL, Bachtell RK, Self DW. Region-specific tolerance to cocaine-regulated cAMP-dependent protein phosphorylation following chronic self-administration. Eur J Neurosci. 2007; 25(7):2201–2213. [PubMed: 17439498]
116. Lu L, Hope BT, Dempsey J, Liu SY, Bossert JM, Shaham Y. Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. Nat Neurosci. 2005; 8(2):212–219. [PubMed: 15657599]
117. Koya E, Uejima JL, Wihbey KA, Bossert JM, Hope BT, Shaham Y. Role of ventral medial prefrontal cortex in incubation of cocaine craving. Neuropharmacology. 2009; 56(Suppl 1):177–185. [PubMed: 18565549]
118. Lu L, Wang X, Wu P, et al. Role of ventral tegmental area glial cell line-derived neurotrophic factor in incubation of cocaine craving. Biol Psychiatry. 2009; 66(2):137–145. [PubMed: 19345340]
119. Lu L, Dempsey J, Liu SY, Bossert JM, Shaham Y. A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal. J Neurosci. 2004; 24(7):1604–1611. [PubMed: 14973246]
120. Berglind WJ, See RE, Fuchs RA, et al. A BDNF infusion into the medial prefrontal cortex suppresses cocaine seeking in rats. Eur J Neurosci. 2007; 26(3):757–766. [PubMed: 17651427]
121. Whitfield TW Jr, Shi X, Sun WL, McGinty JF. The suppressive effect of an intra-prefrontal cortical infusion of BDNF on cocaine-seeking is Trk receptor and extracellular signal-regulated protein kinase mitogen-activated protein kinase dependent. J Neurosci. 2011; 31(3):834–842. [PubMed: 21248106]
122. Sun LL, Zhang Y, Liu JF, et al. Role of melanin-concentrating hormone in the nucleus accumbens shell in rats behaviourally sensitized to methamphetamine. Int J Neuropsychopharmacol. 2013; 16(8):1767–1780. [PubMed: 23449013]
123. Sun WL, Zelek-Molik A, McGinty JF. Short and long access to cocaine self-administration activates tyrosine phosphatase STEP and attenuates GluN expression but differentially regulates GluA expression in the prefrontal cortex. Psychopharmacology (Berl). 2013; 229(4):603–613. [PubMed: 23624776]
124. DiRocco DP, Scheiner ZS, Sindreu CB, Chan GC, Storm DR. A role for calmodulin-stimulated adenylyl cyclases in cocaine sensitization. J Neurosci. 2009; 29(8):2393–2403. [PubMed: 19244515]
125. Parelkar NK, Jiang Q, Chu XP, Guo ML, Mao LM, Wang JQ. Amphetamine alters Ras-guanine nucleotide-releasing factor expression in the rat striatum in vivo. Eur J Pharmacol. 2009; 619(1–3):50–56. [PubMed: 19686726]

126. Zhang GC, Hoffmann J, Parelkar NK, et al. Cocaine increases Ras-guanine nucleotide-releasing factor 1 protein expression in the rat striatum in vivo. Neurosci Lett. 2007; 427(2):117–121. [PubMed: 17931779]

127. Fasano S, D'Antoni A, Orban PC, et al. Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) controls activation of extracellular signal-regulated kinase (ERK) signaling in the striatum and long-term behavioral responses to cocaine. Biol Psychiatry. 2009; 66(8):758–768. [PubMed: 19446794]

128. Mazzucchelli C, Vantaggiato C, Ciamei A, et al. Knockout of ERK1 MAP kinase enhances synaptic plasticity in the striatum and facilitates striatal-mediated learning and memory. Neuron. 2002; 34(5):807–820. [PubMed: 12062026]

129. Brambilla R. Targeting Ras/ERK signaling in the striatum: will it help? Molecular psychiatry. 2003; 8(4):366–368. [PubMed: 12740591]

130. Iniguez SD, Warren BL, Neve RL, Russo SJ, Nestler EJ, Bolanos-Guzman CA. Viral-mediated expression of extracellular signal-regulated kinase-2 in the ventral tegmental area modulates behavioral responses to cocaine. Behav Brain Res. 2010; 214(2):460–464. [PubMed: 20561901]

131. Lavaur J, Bernard F, Trifilieff P, et al. A TAT-DEF-Elk-1 peptide regulates the cytonuclear trafficking of Elk-1 and controls cytoskeleton dynamics. J Neurosci. 2007; 27(52):14448–14458. [PubMed: 18160653]

132. Fiorentini C, Gardoni F, Spano P, Di Luca M, Missale C. Regulation of dopamine D1 receptor trafficking and desensitization by oligomerization with glutamate N-methyl-D-aspartate receptors. J Biol Chem. 2003; 278(22):20196–20202. [PubMed: 12646556]

133. Lee FJ, Liu F. Direct interactions between NMDA and D1 receptors: a tale of tails. Biochemical Society transactions. 2004; 32(Pt 6):1032–1036. [PubMed: 15506956]

134. Lee FJ, Xue S, Pei L, et al. Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. Cell. 2002; 111(2):219–230. [PubMed: 12408866]

135. Pei L, Lee FJ, Moszczynska A, Vukusic B, Liu F. Regulation of dopamine D1 receptor function by physical interaction with the NMDA receptors. J Neurosci. 2004; 24(5):1149–1158. [PubMed: 14762133]

136. Sun WL, Zhou L, Quinones-Jenab V, Jenab S. Cocaine effects on dopamine and NMDA receptors interactions in the striatum of Fischer rats. Brain Res Bull. 2009; 80(6):377–381. [PubMed: 19716863]

137. Cahill E, Pascoli V, Trifilieff P, et al. D1R/GluN1 complexes in the striatum integrate dopamine and glutamate signalling to control synaptic plasticity and cocaine-induced responses. Molecular psychiatry. 2014; 19(12):1295–1304. [PubMed: 25070539]

138. Moreno E, Moreno-Delgado D, Navarro G, et al. Cocaine disrupts histamine H3 receptor modulation of dopamine D1 receptor signaling: sigma1-D1-H3 receptor complexes as key targets for reducing cocaine's effects. J Neurosci. 2014; 34(10):3545–3558. [PubMed: 24599455]

139. Corvol JC, Valjent E, Pascoli V, et al. Quantitative changes in Galphaolf protein levels, but not D1 receptor, alter specifically acute responses to psychostimulants. Neuropsychopharmacology. 2007; 32(5):1109–1121. [PubMed: 17063155]

140. Beaulieu JM, Sotnikova TD, Gainetdinov RR, Caron MG. Paradoxical striatal cellular signaling responses to psychostimulants in hyperactive mice. J Biol Chem. 2006; 281(43):32072–32080. [PubMed: 16954211]

141. Shi X, McGinty JF. Extracellular signal-regulated mitogen-activated protein kinase inhibitors decrease amphetamine-induced behavior and neuropeptide gene expression in the striatum. Neuroscience. 2006; 138(4):1289–1298. [PubMed: 16459022]

142. Mao LM, Reusch JM, Fibuch EE, Liu Z, Wang JQ. Amphetamine increases phosphorylation of MAPK/ERK at synaptic sites in the rat striatum and medial prefrontal cortex. Brain Res. 2013; 1494:101–108. [PubMed: 23201445]

143. Rajadhyaksha A, Husson I, Satpute SS, et al. L-type Ca2+ channels mediate adaptation of extracellular signal-regulated kinase 1/2 phosphorylation in the ventral tegmental area after chronic amphetamine treatment. J Neurosci. 2004; 24(34):7464–7476. [PubMed: 15329393]

144. Pascoli V, Valjent E, Corbille AG, et al. cAMP and extracellular signal-regulated kinase signaling in response to d-amphetamine and methylphenidate in the prefrontal cortex in vivo: role of beta 1-adrenoceptors. Mol Pharmacol. 2005; 68(2):421–429. [PubMed: 15890841]

145. Choe ES, Wang JQ. CaMKII regulates amphetamine-induced ERK1/2 phosphorylation in striatal neurons. Neuroreport. 2002; 13(8):1013–1016. [PubMed: 12060798]

146. Choe ES, Chung KT, Mao L, Wang JQ. Amphetamine increases phosphorylation of extracellular signal-regulated kinase and transcription factors in the rat striatum via group I metabotropic glutamate receptors. Neuropsychopharmacology. 2002; 27(4):565–575. [PubMed: 12377393]

147. Schwendt M, Sigmon SA, McGinty JF. RGS4 overexpression in the rat dorsal striatum modulates mGluR5- and amphetamine-mediated behavior and signaling. Psychopharmacology (Berl). 2012; 221(4):621–635. [PubMed: 22193724]

148. Ferguson SM, Robinson TE. Amphetamine-evoked gene expression in striatopallidal neurons: regulation by corticostriatal afferents and the ERK/MAPK signaling cascade. J Neurochem. 2004; 91(2):337–348. [PubMed: 15447667]

149. Gerfen CR, Paletzki R, Worley P. Differences between dorsal and ventral striatum in Drd1a dopamine receptor coupling of dopamine- and cAMP-regulated phosphoprotein-32 to activation of extracellular signal-regulated kinase. J Neurosci. 2008; 28(28):7113–7120. [PubMed: 18614680]

150. Wang XB, Uhl GR. Subtracted differential display: genes with amphetamine-altered expression patterns include calcineurin. Brain Res Mol Brain Res. 1998; 53(1–2):344–347. [PubMed: 9473720]

151. Lim HW, New L, Han J, Molkentin JD. Calcineurin enhances MAPK phosphatase-1 expression and p38 MAPK inactivation in cardiac myocytes. J Biol Chem. 2001; 276(19):15913–15919. [PubMed: 11279073]

152. Engel SR, Creson TK, Hao Y, et al. The extracellular signal-regulated kinase pathway contributes to the control of behavioral excitement. Molecular psychiatry. 2009; 14(4):448–461. [PubMed: 18227838]

153. Selcher JC, Nekrasova T, Paylor R, Landreth GE, Sweatt JD. Mice lacking the ERK1 isoform of MAP kinase are unimpaired in emotional learning. Learning & memory. 2001; 8(1):11–19. [PubMed: 11160759]

154. Creson TK, Hao Y, Engel S, et al. The anterior cingulate ERK pathway contributes to regulation of behavioral excitement and hedonic activity. Bipolar disorders. 2009; 11(4):339–350. [PubMed: 19500087]

155. Gomez AM, Sun WL, Midde NM, Harrod SB, Zhu J. Effects of environmental enrichment on ERK1/2 phosphorylation in the rat prefrontal cortex following nicotine-induced sensitization or nicotine self-administration. Eur J Neurosci. 2015; 41(1):109–119. [PubMed: 25328101]

156. Carr KD, de Vaca SC, Sun Y, Chau LS, Pan Y, Dela Cruz J. Effects of the MEK inhibitor, SL-327, on rewarding, motor- and cellular-activating effects of D-amphetamine and SKF-82958, and their augmentation by food restriction in rat. Psychopharmacology (Berl). 2009; 201(4):495–506. [PubMed: 18766328]

157. Einat H, Yuan P, Gould TD, et al. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. J Neurosci. 2003; 23(19):7311–7316. [PubMed: 12917364]

158. Shi X, McGinty JF. Repeated amphetamine treatment increases phosphorylation of extracellular signal-regulated kinase, protein kinase B, and cyclase response element-binding protein in the rat striatum. J Neurochem. 2007; 103(2):706–713. [PubMed: 17635666]

159. Shi X, McGinty JF. D1 and D2 dopamine receptors differentially mediate the activation of phosphoproteins in the striatum of amphetamine-sensitized rats. Psychopharmacology (Berl). 2011; 214(3):653–663. [PubMed: 21057772]

160. Gerdjikov TV, Ross GM, Beninger RJ. Place preference induced by nucleus accumbens amphetamine is impaired by antagonists of ERK or p38 MAP kinases in rats. Behav Neurosci. 2004; 118(4):740–750. [PubMed: 15301601]

161. Gonzales R, Mooney L, Rawson RA. The methamphetamine problem in the United States. Annual review of public health. 2010; 31:385–398.

162. Lu L, Wang X. Drug addiction in China. Ann N Y Acad Sci. 2008; 1141:304–317. [PubMed: 18991965]
163. Brennan KA, Carati C, Lea RA, Fitzmaurice PS, Schenk S. Effect of D1-like and D2-like receptor antagonists on methamphetamine and 3,4-methylenedioxymethamphetamine self-administration in rats. Behav Pharmacol. 2009; 20(8):688–694. [PubMed: 19881334]
164. Zhang Y, Loonam TM, Noailles PA, Angulo JA. Comparison of cocaine- and methamphetamine-evoked dopamine and glutamate overflow in somatodendritic and terminal field regions of the rat brain during acute, chronic, and early withdrawal conditions. Ann N Y Acad Sci. 2001; 937:93–120. [PubMed: 11458542]
165. Ohmori T, Abekawa T, Muraki A, Koyama T. Competitive and noncompetitive NMDA antagonists block sensitization to methamphetamine. Pharmacol Biochem Behav. 1994; 48(3): 587–591. [PubMed: 7938110]
166. Kuribara H, Asami T, Ida I, Iijima Y, Tadokoro S. Effects of repeated MK-801 on ambulation in mice and in sensitization following methamphetamine. Psychopharmacology (Berl). 1992; 108(3):271–275. [PubMed: 1523278]
167. Kim HS, Jang CG. MK-801 inhibits methamphetamine-induced conditioned place preference and behavioral sensitization to apomorphine in mice. Brain Res Bull. 1997; 44(3):221–227. [PubMed: 9323434]
168. Horio M, Kohno M, Fujita Y, et al. Role of serine racemase in behavioral sensitization in mice after repeated administration of methamphetamine. PLoS One. 2012; 7(4):e35494. [PubMed: 22530033]
169. Zhao N, Chen Y, Zhu J, et al. Levo-tetrahydropalmatine attenuates the development and expression of methamphetamine-induced locomotor sensitization and the accompanying activation of ERK in the nucleus accumbens and caudate putamen in mice. Neuroscience. 2014; 258:101–110. [PubMed: 24269936]
170. Yan T, Li L, Sun B, et al. Luteolin inhibits behavioral sensitization by blocking methamphetamine-induced MAPK pathway activation in the caudate putamen in mice. PLoS One. 2014; 9(6):e98981. [PubMed: 24901319]
171. Mantsch JR, Li SJ, Risinger R, et al. Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats. Psychopharmacology (Berl). 2007; 192(4):581–591. [PubMed: 17361394]
172. Wang JB, Mantsch JR. l-tetrahydropalamatine: a potential new medication for the treatment of cocaine addiction. Future medicinal chemistry. 2012; 4(2):177–186. [PubMed: 22300097]
173. McDaid J, Graham MP, Napier TC. Methamphetamine-induced sensitization differentially alters pCREB and DeltaFosB throughout the limbic circuit of the mammalian brain. Mol Pharmacol. 2006; 70(6):2064–2074. [PubMed: 16951039]
174. Krasnova IN, Chiflikyan M, Justinova Z, et al. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. Neurobiology of disease. 2013; 58:132–143. [PubMed: 23726845]
175. Cadet JL, Brannock C, Jayanthi S, Krasnova IN. Transcriptional and epigenetic substrates of methamphetamine addiction and withdrawal: evidence from a long-access self-administration model in the rat. Molecular neurobiology. 2015; 51(2):696–717. [PubMed: 24939695]
176. Caunt CJ, Keyse SM. Dual-specificity MAP kinase phosphatases (MKPs): shaping the outcome of MAP kinase signalling. FEBS J. 2013; 280(2):489–504. [PubMed: 22812510]
177. Toledano-Katchalski H, Kraut J, Sines T, et al. Protein tyrosine phosphatase epsilon inhibits signaling by mitogen-activated protein kinases. Molecular cancer research : MCR. 2003; 1(7): 541–550. [PubMed: 12754301]
178. Takaki M, Ujike H, Kodama M, Takehisa Y, Nakata K, Kuroda S. Two kinds of mitogen-activated protein kinase phosphatases, MKP-1 and MKP-3, are differentially activated by acute and chronic methamphetamine treatment in the rat brain. J Neurochem. 2001; 79(3):679–688. [PubMed: 11701771]
179. Ujike H, Takaki M, Kodama M, Kuroda S. Gene expression related to synaptogenesis, neuritogenesis, and MAP kinase in behavioral sensitization to psychostimulants. Ann N Y Acad Sci. 2002; 965:55–67. [PubMed: 12105085]

180. Mizoguchi H, Yamada K, Mizuno M, et al. Regulations of methamphetamine reward by extracellular signal-regulated kinase 1/2/ets-like gene-1 signaling pathway via the activation of dopamine receptors. Mol Pharmacol. 2004; 65(5):1293–1301. [PubMed: 15102958]

181. Son JS, Jeong YC, Kwon YB. Regulatory effect of bee venom on methamphetamine-induced cellular activities in prefrontal cortex and nucleus accumbens in mice. Biological & pharmaceutical bulletin. 2015; 38(1):48–52. [PubMed: 25744457]

182. Herrold AA, Shen F, Graham MP, et al. Mirtazapine treatment after conditioning with methamphetamine alters subsequent expression of place preference. Drug Alcohol Depend. 2009; 99(1–3):231–239. [PubMed: 18945553]

183. Nordahl TE, Salo R, Leamon M. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. J Neuropsychiatry Clin Neurosci. 2003; 15(3):317–325. [PubMed: 12928507]

184. Chang L, Ernst T, Speck O, et al. Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. Psychiatry Res. 2002; 114(2):65–79. [PubMed: 12036507]

185. Sekine Y, Iyo M, Ouchi Y, et al. Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. Am J Psychiatry. 2001; 158(8):1206–1214. [PubMed: 11481152]

186. Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry. 2001; 158(3):377–382. [PubMed: 11229977]

187. Chen YJ, Liu YL, Zhong Q, et al. Tetrahydropalmatine protects against methamphetamine-induced spatial learning and memory impairment in mice. Neuroscience bulletin. 2012; 28(3): 222–232. [PubMed: 22622821]

188. Kamei H, Nagai T, Nakano H, et al. Repeated methamphetamine treatment impairs recognition memory through a failure of novelty-induced ERK1/2 activation in the prefrontal cortex of mice. Biol Psychiatry. 2006; 59(1):75–84. [PubMed: 16139811]

189. Nagai T, Takuma K, Dohniwa M, et al. Repeated methamphetamine treatment impairs spatial working memory in rats: reversal by clozapine but not haloperidol. Psychopharmacology (Berl). 2007; 194(1):21–32. [PubMed: 17514479]

190. Noda Y, Mouri A, Ando Y, et al. Galantamine ameliorates the impairment of recognition memory in mice repeatedly treated with methamphetamine: involvement of allosteric potentiation of nicotinic acetylcholine receptors and dopaminergic-ERK1/2 systems. Int J Neuropsychopharmacol. 2010; 13(10):1343–1354. [PubMed: 20219155]

191. Gonzalez B, Raineri M, Cadet JL, Garcia-Rill E, Urbano FJ, Bisagno V. Modafinil improves methamphetamine-induced object recognition deficits and restores prefrontal cortex ERK signaling in mice. Neuropharmacology. 2014; 87:188–197. [PubMed: 24530829]

192. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. Psychopharmacology (Berl). 2013; 229(3):415–434. [PubMed: 23934211]

193. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. Addiction. 1996; 91(11):1585–1614. [PubMed: 8972919]

194. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002; 54(2):161–202. [PubMed: 12037135]

195. Daigle TL, Wetsel WC, Caron MG. Opposite function of dopamine D1 and N-methyl-D-aspartate receptors in striatal cannabinoid-mediated signaling. Eur J Neurosci. 2011; 34(9):1378–1389. [PubMed: 22034973]

196. Valjent E, Pages C, Rogard M, Besson MJ, Maldonado R, Caboche J. Delta 9-tetrahydrocannabinol-induced MAPK/ERK and Elk-1 activation in vivo depends on dopaminergic transmission. Eur J Neurosci. 2001; 14(2):342–352. [PubMed: 11553284]

197. Derkinderen P, Valjent E, Toutant M, et al. Regulation of extracellular signal-regulated kinase by cannabinoids in hippocampus. J Neurosci. 2003; 23(6):2371–2382. [PubMed: 12657697]

198. Long LE, Chesworth R, Huang XF, McGregor IS, Arnold JC, Karl T. A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. Int J Neuropsychopharmacol. 2010; 13(7):861–876. [PubMed: 19785914]

199. Rubino T, Forlani G, Vigano D, Zippel R, Parolaro D. Modulation of extracellular signal-regulated kinases cascade by chronic delta 9-tetrahydrocannabinol treatment. Mol Cell Neurosci. 2004; 25(3):355–362. [PubMed: 15033164]

200. Rubino T, Forlani G, Vigano D, Zippel R, Parolaro D. Ras/ERK signalling in cannabinoid tolerance: from behaviour to cellular aspects. J Neurochem. 2005; 93(4):984–991. [PubMed: 15857401]

201. Rubino T, Vigano D, Premoli F, et al. Changes in the expression of G protein-coupled receptor kinases and beta-arrestins in mouse brain during cannabinoid tolerance: a role for RAS-ERK cascade. Molecular neurobiology. 2006; 33(3):199–213. [PubMed: 16954596]

202. Tonini R, Ciardo S, Cerovic M, et al. ERK-dependent modulation of cerebellar synaptic plasticity after chronic Delta9-tetrahydrocannabinol exposure. J Neurosci. 2006; 26(21):5810–5818. [PubMed: 16723539]

203. Rubino T, Vigano D, Massi P, Parolaro D. The psychoactive ingredient of marijuana induces behavioural sensitization. Eur J Neurosci. 2001; 14(5):884–886. [PubMed: 11576193]

204. Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci. 2000; 3(11):1073–1074. [PubMed: 11036260]

205. Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G. Behavioural sensitization after repeated exposure to Delta 9-tetrahydrocannabinol and cross-sensitization with morphine. Psychopharmacology (Berl). 2001; 158(3):259–266. [PubMed: 11713615]

206. Giuffrida A, Parsons LH, Kerr TM, Rodriguez de Fonseca F, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nat Neurosci. 1999; 2(4):358–363. [PubMed: 10204543]

207. Patel S, Rademacher DJ, Hillard CJ. Differential regulation of the endocannabinoids anandamide and 2-arachidonylglycerol within the limbic forebrain by dopamine receptor activity. J Pharmacol Exp Ther. 2003; 306(3):880–888. [PubMed: 12808005]

208. Centonze D, Battista N, Rossi S, et al. A critical interaction between dopamine D2 receptors and endocannabinoids mediates the effects of cocaine on striatal gabaergic Transmission. Neuropsychopharmacology. 2004; 29(8):1488–1497. [PubMed: 15100701]

209. Nguyen K, Marshall L, Hu S, Neff L. State-specific prevalence of current cigarette smoking and smokeless tobacco use among adults aged >/=18 years - United States, 2011–2013. MMWR Morb Mortal Wkly Rep. 2015; 64(19):532–536. [PubMed: 25996096]

210. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature. 1996; 382(6588):255–257. [PubMed: 8717040]

211. Dani JA, Jenson D, Broussard JI, De Biasi M. Neurophysiology of Nicotine Addiction. Journal of addiction research & therapy. 2011; S1(1)

212. Lenoir M, Kiyatkin EA. Intravenous nicotine injection induces rapid, experience-dependent sensitization of glutamate release in the ventral tegmental area and nucleus accumbens. J Neurochem. 2013; 127(4):541–551. [PubMed: 24032718]

213. Dajas-Bailador F, Wonnacott S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. Trends Pharmacol Sci. 2004; 25(6):317–324. [PubMed: 15165747]

214. Nakayama H, Shimoke K, Isosaki M, Satoh H, Yoshizumi M, Ikeuchi T. Subtypes of neuronal nicotinic acetylcholine receptors involved in nicotine-induced phosphorylation of extracellular signal-regulated protein kinase in PC12h cells. Neurosci Lett. 2006; 392(1–2):101–104. [PubMed: 16219421]

215. Nakayama H, Numakawa T, Ikeuchi T, Hatanaka H. Nicotine-induced phosphorylation of extracellular signal-regulated protein kinase and CREB in PC12h cells. J Neurochem. 2001; 79(3):489–498. [PubMed: 11701752]

216. Nakayama H, Numakawa T, Ikeuchi T. Nicotine-induced phosphorylation of Akt through epidermal growth factor receptor and Src in PC12h cells. J Neurochem. 2002; 83(6):1372–1379. [PubMed: 12472891]

217. Utsugisawa K, Nagane Y, Obara D, Tohgi H. Over-expression of alpha7 nicotinic acetylcholine receptor induces sustained ERK phosphorylation and N-cadherin expression in PC12 cells. Brain Res Mol Brain Res. 2002; 106(1–2):88–93. [PubMed: 12393268]

218. Wang J, Cui W, Wei J, et al. Genome-wide expression analysis reveals diverse effects of acute nicotine exposure on neuronal function-related genes and pathways. Frontiers in psychiatry. 2011; 2:5. [PubMed: 21556275]

219. Dajas-Bailador FA, Soliakov L, Wonnacott S. Nicotine activates the extracellular signal-regulated kinase 1/2 via the alpha7 nicotinic acetylcholine receptor and protein kinase A, in SH-SY5Y cells and hippocampal neurones. J Neurochem. 2002; 80(3):520–530. [PubMed: 11905997]

220. Steiner RC, Heath CJ, Picciotto MR. Nicotine-induced phosphorylation of ERK in mouse primary cortical neurons: evidence for involvement of glutamatergic signaling and CaMKII. J Neurochem. 2007; 103(2):666–678. [PubMed: 17666046]

221. Collo G, Bono F, Cavalleri L, et al. Nicotine-induced structural plasticity in mesencephalic dopaminergic neurons is mediated by dopamine D3 receptors and Akt-mTORC1 signaling. Mol Pharmacol. 2013; 83(6):1176–1189. [PubMed: 23543412]

222. Brunzell DH, Russell DS, Picciotto MR. In vivo nicotine treatment regulates mesocorticolimbic CREB and ERK signaling in C57Bl/6J mice. J Neurochem. 2003; 84(6):1431–1441. [PubMed: 12614343]

223. Neugebauer NM, Henehan RM, Hales CA, Picciotto MR. Mice lacking the galanin gene show decreased sensitivity to nicotine conditioned place preference. Pharmacol Biochem Behav. 2011; 98(1):87–93. [PubMed: 21172385]

224. Li S, Li Z, Pei L, Le AD, Liu F. The alpha7nACh-NMDA receptor complex is involved in cue-induced reinstatement of nicotine seeking. The Journal of experimental medicine. 2012; 209(12): 2141–2147. [PubMed: 23091164]

225. Leshner AI. Vulnerability to addiction: new research opportunities. Am J Med Genet. 2000; 96(5):590–591. [PubMed: 11054764]

226. Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. Arch Gen Psychiatry. 2003; 60(12):1256–1264. [PubMed: 14662558]

227. Stairs DJ, Bardo MT. Neurobehavioral effects of environmental enrichment and drug abuse vulnerability. Pharmacol Biochem Behav. 2009; 92(3):377–382. [PubMed: 19463254]

228. Bowling SL, Rowlett JK, Bardo MT. The effect of environmental enrichment on amphetamine-stimulated locomotor activity, dopamine synthesis and dopamine release. Neuropharmacology. 1993; 32(9):885–893. [PubMed: 8232791]

229. Zhu J, Green T, Bardo MT, Dwoskin LP. Environmental enrichment enhances sensitization to GBR 12935-induced activity and decreases dopamine transporter function in the medial prefrontal cortex. Behav Brain Res. 2004; 148(1–2):107–117. [PubMed: 14684252]

230. Del Arco A, Mora F, Mohammed AH, Fuxe K. Stimulation of D2 receptors in the prefrontal cortex reduces PCP-induced hyperactivity, acetylcholine release and dopamine metabolism in the nucleus accumbens. J Neural Transm. 2007; 114(2):185–193. [PubMed: 16897609]

231. Konu O, Kane JK, Barrett T, et al. Region-specific transcriptional response to chronic nicotine in rat brain. Brain Res. 2001; 909(1–2):194–203. [PubMed: 11478936]

232. Kalluri HS, Ticku MK. Ethanol-mediated inhibition of mitogen-activated protein kinase phosphorylation in mouse brain. Eur J Pharmacol. 2002; 439(1–3):53–58. [PubMed: 11937092]

233. Chandler LJ, Sutton G. Acute ethanol inhibits extracellular signal-regulated kinase, protein kinase B, and adenosine 3′:5′-cyclic monophosphate response element binding protein activity in an age- and brain region-specific manner. Alcohol Clin Exp Res. 2005; 29(4):672–682. [PubMed: 15834234]

234. Davis MI, Szarowski D, Turner JN, Morrisett RA, Shain W. In vivo activation and in situ BDNF-stimulated nuclear translocation of mitogen-activated/extracellular signal-regulated protein kinase is inhibited by ethanol in the developing rat hippocampus. Neurosci Lett. 1999; 272(2):95–98. [PubMed: 10507550]

235. Zhu Y, Wang Y, Zhao B, et al. Differential phosphorylation of GluN1-MAPKs in rat brain reward circuits following long-term alcohol exposure. PLoS One. 2013; 8(1):e54930. [PubMed: 23372792]
236. Ibba F, Vinci S, Spiga S, et al. Ethanol-induced extracellular signal regulated kinase: role of dopamine D1 receptors. Alcohol Clin Exp Res. 2009; 33(5):858–867. [PubMed: 19320634]
237. Thorsell A, Tapocik JD, Liu K, et al. A novel brain penetrant NPS receptor antagonist, NCGC00185684, blocks alcohol-induced ERK-phosphorylation in the central amygdala and decreases operant alcohol self-administration in rats. J Neurosci. 2013; 33(24):10132–10142. [PubMed: 23761908]
238. Hansson AC, Rimondini R, Neznanova O, Sommer WH, Heilig M. Neuroplasticity in brain reward circuitry following a history of ethanol dependence. Eur J Neurosci. 2008; 27(8):1912–1922. [PubMed: 18412612]
239. Vinci S, Ibba F, Longoni R, Spina L, Spiga S, Acquas E. Acetaldehyde elicits ERK phosphorylation in the rat nucleus accumbens and extended amygdala. Synapse. 2010; 64(12): 916–927. [PubMed: 20506324]
240. Peana AT, Muggironi G, Fois GR, Zinellu M, Vinci S, Acquas E. Effect of opioid receptor blockade on acetaldehyde self-administration and ERK phosphorylation in the rat nucleus accumbens. Alcohol. 2011; 45(8):773–783. [PubMed: 21803531]
241. Pandey SC, Zhang H, Ugale R, Prakash A, Xu T, Misra K. Effector immediate-early gene arc in the amygdala plays a critical role in alcoholism. J Neurosci. 2008; 28(10):2589–2600. [PubMed: 18322102]
242. Stacey D, Bilbao A, Maroteaux M, et al. RASGRF2 regulates alcohol-induced reinforcement by influencing mesolimbic dopamine neuron activity and dopamine release. Proc Natl Acad Sci U S A. 2012; 109(51):21128–21133. [PubMed: 23223532]
243. Neznanova O, Bjork K, Rimondini R, et al. Acute ethanol challenge inhibits glycogen synthase kinase-3beta in the rat prefrontal cortex. Int J Neuropsychopharmacol. 2009; 12(2):275–280. [PubMed: 19007447]
244. Nuutinen S, Kiianmaa K, Panula P. DARPP-32 and Akt regulation in ethanol-preferring AA and ethanol-avoiding ANA rats. Neurosci Lett. 2011; 503(1):31–36. [PubMed: 21843598]
245. Rosas M, Zaru A, Sabariego M, et al. Differential sensitivity of ethanol-elicited ERK phosphorylation in nucleus accumbens of Sardinian alcohol-preferring and -non preferring rats. Alcohol. 2014; 48(5):471–476. [PubMed: 24877898]
246. Sanna PP, Simpson C, Lutjens R, Koob G. ERK regulation in chronic ethanol exposure and withdrawal. Brain Res. 2002; 948(1–2):186–191. [PubMed: 12383974]
247. Wang Y, Cui H, Wang W, Zhao B, Lai J. The region-specific activation of Ca2+/calmodulin dependent protein kinase II and extracellular signal-regulated kinases in hippocampus following chronic alcohol exposure. Brain Res Bull. 2012; 89(5–6):191–196. [PubMed: 22960015]
248. Roberto M, Nelson TE, Ur CL, Brunelli M, Sanna PP, Gruol DL. The transient depression of hippocampal CA1 LTP induced by chronic intermittent ethanol exposure is associated with an inhibition of the MAP kinase pathway. Eur J Neurosci. 2003; 17(8):1646–1654. [PubMed: 12752382]
249. Pandey SC, Zhang H, Roy A, Misra K. Central and medial amygdaloid brain-derived neurotrophic factor signaling plays a critical role in alcohol-drinking and anxiety-like behaviors. J Neurosci. 2006; 26(32):8320–8331. [PubMed: 16899727]
250. De Witte P, Pinto E, Ansseau M, Verbanck P. Alcohol and withdrawal: from animal research to clinical issues. Neurosci Biobehav Rev. 2003; 27(3):189–197. [PubMed: 12788332]
251. Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology. 1998; 18(3):135–174. [PubMed: 9471114]
252. Bertotto ME, Maldonado NM, Bignante EA, et al. ERK activation in the amygdala and hippocampus induced by fear conditioning in ethanol withdrawn rats: modulation by MK-801. Eur Neuropsychopharmacol. 2011; 21(12):892–904. [PubMed: 21315561]

253. Spina L, Longoni R, Vinci S, et al. Role of dopamine D1 receptors and extracellular signal regulated kinase in the motivational properties of acetaldehyde as assessed by place preference conditioning. Alcohol Clin Exp Res. 2010; 34(4):607–616. [PubMed: 20102564]

254. Groblewski PA, Franken FH, Cunningham CL. Inhibition of extracellular signal-regulated kinase (ERK) activity with SL327 does not prevent acquisition, expression, and extinction of ethanol-seeking behavior in mice. Behav Brain Res. 2011; 217(2):399–407. [PubMed: 21074569]

255. Faccidomo S, Besheer J, Stanford PC, Hodge CW. Increased operant responding for ethanol in male C57BL/6J mice: specific regulation by the ERK1/2, but not JNK, MAP kinase pathway. Psychopharmacology (Berl). 2009; 204(1):135–147. [PubMed: 19125235]

256. Radwanska K, Wrobel E, Korkosz A, et al. Alcohol relapse induced by discrete cues activates components of AP-1 transcription factor and ERK pathway in the rat basolateral and central amygdala. Neuropsychopharmacology. 2008; 33(8):1835–1846. [PubMed: 17851539]

257. Schroeder JP, Spanos M, Stevenson JR, Besheer J, Salling M, Hodge CW. Cue-induced reinstatement of alcohol-seeking behavior is associated with increased ERK1/2 phosphorylation in specific limbic brain regions: blockade by the mGluR5 antagonist MPEP. Neuropharmacology. 2008; 55(4):546–554. [PubMed: 18619984]

258. Peana AT, Giugliano V, Rosas M, Sabariego M, Acquas E. Effects of L-cysteine on reinstatement of ethanol-seeking behavior and on reinstatement-elicited extracellular signal-regulated kinase phosphorylation in the rat nucleus accumbens shell. Alcohol Clin Exp Res. 2013; 37(Suppl 1):E329–337. [PubMed: 22823513]

259. Carnicella S, Kharazia V, Jeanblanc J, Janak PH, Ron D. GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. Proc Natl Acad Sci U S A. 2008; 105(23):8114–8119. [PubMed: 18541917]

260. Berglind WJ, Whitfield TW Jr, LaLumiere RT, Kalivas PW, McGinty JF. A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens. J Neurosci. 2009; 29(12):3715–3719. [PubMed: 19321768]

261. Hope BT, Crombag HS, Jedynak JP, Wise RA. Neuroadaptations of total levels of adenylate cyclase, protein kinase A, tyrosine hydroxylase, cdk5 and neurofilaments in the nucleus accumbens and ventral tegmental area do not correlate with expression of sensitized or tolerant locomotor responses to cocaine. J Neurochem. 2005; 92(3):536–545. [PubMed: 15659224]

262. Lu L, Grimm JW, Shaham Y, Hope BT. Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats. J Neurochem. 2003; 85(6):1604–1613. [PubMed: 12787079]

263. Sun WL, Coleman NT, Zelek-Molik A, Barry SM, Whitfield TW Jr, McGinty JF. Relapse to cocaine-seeking after abstinence is regulated by cAMP-dependent protein kinase A in the prefrontal cortex. Addiction biology. 2014; 19(1):77–86. [PubMed: 23461423]

264. Gomez AM, Midde NM, Mactutus CF, Booze RM, Zhu J. Environmental Enrichment Alters Nicotine-Mediated Locomotor Sensitization and Phosphorylation of DARPP-32 and CREB in Rat Prefrontal Cortex. PLoS One. 2012; 7(8):e44149. [PubMed: 22952905]

265. Terasawa K, Ichimura A, Sato F, Shimizu K, Tsujimoto G. Sustained activation of ERK1/2 by NGF induces microRNA-221 and 222 in PC12 cells. FEBS J. 2009; 276(12):3269–3276. [PubMed: 19438724]

266. Moonat S, Starkman BG, Sakharkar A, Pandey SC. Neuroscience of alcoholism: molecular and cellular mechanisms. Cellular and molecular life sciences : CMLS. 2010; 67(1):73–88. [PubMed: 19756388]

267. Schmidt HD, McGinty JF, West AE, Sadri-Vakili G. Epigenetics and psychostimulant addiction. Cold Spring Harbor perspectives in medicine. 2013; 3(3):a012047. [PubMed: 23359110]

268. Ciccarelli A, Giustetto M. Role of ERK signaling in activity-dependent modifications of histone proteins. Neuropharmacology. 2014; 80:34–44. [PubMed: 24486378]

Prog Mol Biol Transl Sci. Author manuscript; available in PMC 2017 February 28.

Table 1

Effects of MEK inhibitors on drugs-induced behaviors

Drugs	MEK inhibitors (dose, area)	Behavioral effects	References
None	SL327 (50 mg/kg, i.p.)	↑ basal locomotor activity	152
	SL327 (50–100 mg/kg, i.p.)	↓ basal locomotor activity	92,156,254,255
	PD98059 (50 μM, continuous infusion into the PFC)	↑ basal locomotor activity↓	154
Cocaine	SL327 (50 mg/kg, i.p.)	↓ acute cocaine-induced locomotion	78
	SL327 (30 mg/kg, i.p.); PD98059 (10 μM, VTA)	↓ development of locomotor sensitization (inhibitors were injected/infused before each cocaine injection)	92,94
	SL327 (40 mg/kg, i.p.); PD98059 (2 μg) or U0126 (1 μg, NAc)	↓ expression of locomotor sensitization (inhibitors were injected/infused before cocaine challenge)	80,93
	SL327 (30 mg/kg, i.p.)	↓ conditioned locomotor response (inhibitor was injected before each cocaine injection during conditioning)	92
	SL327 (50 mg/kg, i.p.); U0126 (0.1 μg, VTA)	↓ development of CPP (inhibitors injected/infused before each cocaine injection during conditioning)	78,100
	U0126 (1 μg, NAc core)	↓ expression of CPP (inhibitor was infused before CPP test)	107
	SL327 (30 mg/kg, i.p.); PD98059 (2 μg) or U0126 (1 μg, NAc core); U0126 (1 μg, BLA)	↓ context- and cocaine priming-induced expression of CPP and ↓ context-induced reinstatement after SA by impairing memory reconsolidation (inhibitors were injected/infused either before or after reconsolidation phase)	82,107,112,113
	U0126 (1 μg, CeA)	↓ context+cues-induced relapse after abstinence from SA (inhibitor was infused before relapse testing)	116
	U0126 (1 μg, VTA)	↓ BDNF/GDNF-enhanced relapse by context+cues after abstinence from SA (infusions were conducted immediately after the end of the last SA session)	118,119
	U0126 (0.5 μg, dmPFC)	↓ BDNF's inhibitory effect on context-, cues- and cocaine priming-induced drug seeking after abstinence/extinction of SA (infusions were conducted immediately after the end of the last SA session)	121
Amphetamine	SL327 (50–100 mg/kg, i.p.)	↓ acute amphetamine-induced locomotion	78,140,141
	PD98059 (50 μM, continuous infusion into the PFC)	↑ acute amphetamine-induced locomotor activity	154
	SL327 (40 mg/kg, i.p.)	↓ expression of locomotor sensitization (inhibitors were injected/infused before amphetamine challenge)	80
	SL327 (30 mg/kg, i.p.)	↓ conditioned locomotor response (inhibitor was injected before each amphetamine injection during conditioning)	92
	PD98059 (2.5 μg, NAc)	↓ development of intra-NAc amphetamine-induced CPP (inhibitor was infused before or after each intra-NAc amphetamine infusion during conditioning)	160
	PD98059 (2 μg, NAc)	↓ expression of amphetamine-CPP (inhibitor was infused before CPP testing)	180
Marijuana (THC)	SL327 (50 mg/kg, i.p.)	↓ development of THC-induced locomotion tolerance (inhibitor was injected before each THC administration)	200
	SL327 (50 mg/kg, i.p.)	↓ development of THC-CPP (inhibitor was injected before each conditioning session)	196

Drugs	MEK inhibitors (dose, area)	Behavioral effects	References
Alcohol	PD98059 (30 or 90 μg, i.c.v)	↓ development of ACD-CPP (inhibitor was infused before each conditioning session)	253
	SL327 (30 mg/kg, i.p.)	↑ ethanol SA (inhibitor was injected before SA session)	255
	U0216 (0.5 μg, VTA)	↓ GDNF's inhibitory effect on ethanol SA (infusions were conducted before SA session)	259

i.p. = intraperitoneal injection; i.c.v = intracerebroventricular infusion; ↑ = enhancing effect; ↓ = inhibiting effect

Table 2

Effects of interfering ERK signaling-related genes/proteins on drug-induced behaviors

Target genes/proteins	Behavioral effects	References
Ca^{2+}-stimulated AC1/AC8 (KO)	↑ acute cocaine-induced locomotion ↓ development of cocaine locomotor sensitization	124
Ras-GRF-1 (KO)	↓ development and expression of cocaine locomotor sensitization ↓ cocaine-CPP ↓ repeated THC-induced behavioral tolerance	127,199,200
Ras-GRF-1 (OE)	↑ development and expression of cocaine locomotor sensitization ↑ cocaine-CPP	127
Ras-GRF-2 (KO)	↓ ethanol intake and preference (two bottle free choice task)	242
ERK1 (KO)	↑ basal locomotor activity ↑ acute amphetamine-induced locomotion ↑ development of cocaine locomotor sensitization ↑ cocaine-CPP	34,128,152,153
ERK1 (KD in the PFC)	↑ basal locomotor activity ↑ acute amphetamine-induced locomotion	154
ERK2 (OE in the VTA)	↑ development and expression of cocaine locomotor sensitization ↑ cocaine-CPP	130
ERK2 (KD in the VTA)	↓ development and expression of cocaine locomotor sensitization ↓ cocaine-CPP	130
MSK-1 (KO)	↓ development and expression of cocaine locomotor sensitization ↑ cocaine-CPP	79
Inhibition of pElk-1	↓ development and expression of cocaine locomotor sensitization ↓ the establishment of cocaine-CPP	74

KO = knockdown; KD = knockdown; OE = overexpression; ↑ = enhancing effect; ↓ = inhibiting effect