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Review

Pharmacological modulation of protein kinases as a new approach to treat addiction to cocaine and opiates

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ABSTRACT

Drug addiction shares brain mechanisms and molecular substrates with learning and memory processes, such as the stimulation of glutamate receptors and their downstream signalling pathways. In the present work we provide an up-to-date review of studies that have demonstrated the implication of the main memory-related calcium-dependent protein kinases in opiate and cocaine addiction. The effects of these drugs of abuse in different animal models of drug reward, dependence and addiction are altered by manipulation of the mitogen-activated protein kinase (MAPK) family, particularly extracellular signal regulated kinase (ERK), calcium/calmodulin-dependent kinase II (CaMKII), the protein kinase C (PKC) family (including PKMζ), cAMP-dependent protein kinase A (PKA), cGMP-dependent protein kinase G (PKG), the phosphatidylinositol 3-kinase (PI3K) pathway and its downstream target mammalian target of Rapamycin (mTOR), cyclin-dependent kinase 5 (Cdk5), heat-shock proteins (Hsp) and other enzymes and proteins. Research suggests that drugs of abuse induce dependence and addiction by modifying the signalling pathways that involve these memory-related protein kinases, and supports the idea that drug addiction is an excessive aberrant learning disorder in which the maladaptive memory of drug-associated cues maintains compulsive drug use and contributes to relapse. Moreover, the studies we review offer new pharmacological strategies to treat opiate and cocaine dependence based on the manipulation of these protein kinases. In particular, disruption of reconsolidation of drug-related memories may have a high therapeutic value in the treatment of drug addiction.

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1. Introduction

Drug addiction and learning and memory processes have brain mechanisms and molecular substrates in common. In fact, the transition from occasional to compulsive drug consumption (loss of control) that characterises the development of drug addiction can be understood in terms of learning-induced neuroplasticity (Belin et al., 2013; Everitt, 2014). Dopaminergic transmission within corticostriatal systems, which normally mediates learning and memory processes in the context of natural rewards, is dramatically altered by drugs of abuse (Arias-Carrión et al., 2014; Everitt, 2014). The brain reward system has evolved to guarantee survival. Natural rewards (food, water, sex, etc.) activate neurons in the ventral tegmental area and provoke the release of dopamine in the nucleus accumbens. DA release induces a positive subjective experience that, through a process of instrumental learning, increases the probability of the subject performing the behaviour in question in the future. The reinforcing effects of drugs of abuse depend on a potent increase in dopamine transmission in the nucleus accumbens, which favours drug intake behaviour through operant and classical (pavlovian) conditioning. Environmental stimuli acquire high motivational significance by becoming associated with a drug's effects, predicting drug availability, evoking drug memories, inducing craving and eliciting and maintaining the instrumental behaviours of drug-seeking and taking. These behaviours become increasingly under the control of the drug-associated stimuli, and are eventually consolidated as a maladaptive stimulus–response habit (Everitt, 2014).

Stimulation of the ionotropic and metabotropic glutamate receptors (NMDA, AMPA, and mGlu) and their downstream signalling pathways, such as production of nitric oxide and activation of calcium-dependent protein kinases are essential to memory formation, consolidation, storage, retrieval, reconsolidation and extinction (Keifer and Zheng, 2010; Morris, 2013; Mukherjee and Manahan-Vaughan, 2013; Rudy, 2014; Shepherd, 2012).

Protein kinases are enzymes that induce the phosphorylation of target proteins, altering their conformation, functioning and interaction with other proteins (Kim et al., 2011). Phosphorylation is one of the most crucial post-translational modifications of proteins because it allows for flexible signalling and facilitates neuronal communication and plasticity. Although at least 260 kinases are expressed in the adult mouse brain, only a small subset of protein kinases are required for neuronal plasticity processes related with learning and memory, including long-lasting strengthening of existing synapses, such as long-term potentiation, synaptogenesis and neurogenesis. The main learning and memory-related kinases are calcium/calmodulin-dependent kinase II (CaMKII), the mitogen-activated protein kinase (MAPK) family - which consists of seven kinases: extracellular signal regulated kinase (ERK) 1, 2, and 5, c-Jun N-terminal kinases (JNKs) 1–3, and p38-, cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA), cGMP-dependent protein kinase G (PKG), the phosphatidylinositol 3-kinase (PI3K) pathway, cyclin-dependent kinase 5 (Cdk5), the protein kinase C (PKC) family (including PKMζ), and the tyrosine kinase fyn. These protein kinases impact on synaptic transmission by altering the properties or density of ion channels, and regulate synaptic structure and synaptogenesis by impacting on gene expression and protein synthesis (Giese and Mizuno, 2013).

Psychostimulants and opiates induce rewarding effects through different mechanisms of action. Cocaine increases dopamine levels through the inhibition of the cell surface dopamine transporter, while opiates activate different Gi/o-coupled protein receptors (mainly mu, delta and kappa opioid receptors). However, both types of drugs of abuse appear to activate some similar downstream signalling events. In particular, the glutamatergic system plays an important role in the development of drug addiction and in the relapse induced by drug-associated cues during abstinence (Kalivas et al., 2009; Peters and De Vries, 2012; Pomierny-Chamioło et al., 2014). Similarly, several proteins involved in memory processing, long-term potentiation and neuroplasticity have been related with drug abuse and maintenance of drug-associated memories, which contributes to the high rate of relapse. In particular, drugs of abuse modify the activity of several signalling pathways that include different protein kinases (e.g. CaMKII, ERK, PKA, PKC, Cdk5) that are highly expressed in the different structures of brain reward system (Lee and Messing, 2008). As a consequence of the action of these protein kinases, several transcription factors (proteins that increase or decrease the transcription of genes), such as the transcription factor cAMP response element-binding protein (CREB) and the transcription factor ΔFosB, are activated within the mesolimbic system, initiating a multitude of molecular pathways that cause genetic, molecular and structural alterations related with the physiological and behavioural changes induced by chronic drug exposure (Nestler, 2013; Ruffle, 2014). In the present review we will update and summarize the knowledge achieved in the last years (2009–2015) about the role of different protein kinases and related molecules in the effects of opiates and cocaine in animal models of reward, dependence and addiction. In the last section we will discuss the pharmacological modulation of intracellular signalling as a promising approach to the treatment of addiction to cocaine and opiates.

2. Protein kinases involved in opiate and cocaine addiction

2.1. Mitogen-activated protein kinase (MAPK) family

Several events associated with the MAPK family seem to contribute to neuroadaptations underlying the addiction process