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Invited review

Opiates and plasticity

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ABSTRACT

Opiates are among the most powerful analgesics and pain-relieving agents. However, they are potentially extremely addictive thereby limiting their medical use, making them exceedingly susceptible to abuse and adding to the global drug problem. It is believed that positive memories associated with the pleasurable effects of opiates and negative memories associated with dysphoria during opiate withdrawal contribute to compulsive opiate-seeking behavior characterizing addiction. There is a vast amount of available data regarding the neuroadaptations in response to opiates during opiate tolerance, dependence and withdrawal that contribute to opiate addiction, yet it is still a major challenge to identify the neurobiological adaptations that underlie the hallmarks of opiate addiction such as compulsive drug use, and relapse to drug seeking. Since the discovery of synaptic plasticity as the cellular correlate of learning and memory, strong overlaps between neural and cellular substrates of learning and addiction have been recognized. Consequently, the current notion of addiction supports the idea that aberrant forms of drug-induced synaptic plasticity and learning in the brain drive addictive behaviors. Here we discuss current progress on some of the recently identified forms of synaptic plasticity at excitatory and inhibitory synapses in opioid-sensitive areas of the brain that are targeted by opiates and other addictive drugs. The neuroadaptations involved in opiate tolerance, dependence and withdrawal will be re-visited since they share many features with synaptic learning mechanisms.

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1. Introduction

Opiates are among the most powerful analgesics and pain-relieving agents though extremely addictive. Unfortunately in addition to illicit opiate use, the nonmedical use and abuse of prescription opiates are troublingly on the rise (Rawson et al., 2007) adding to the global drug problem. The phenomena of opiate tolerance, dependence and withdrawal in the context of opiate addiction have been extensively investigated (Christie, 2008; De Vries and Shippenberg, 2002; Frenois et al., 2005; Williams et al., 2001) but it is still a major challenge to identify the neurobiological adaptations that underlie the hallmarks of addiction including compulsive drug use and relapse to drug seeking.

The initial intense sensation of euphoria ("rush") after intravenous heroin use lasts for periods of a few minutes and yet the memories of this experience linger for a lifetime for some people. While this may trigger drug taking, additional factors associated with tolerance, withdrawal and allostasis also substantially contribute to the process of addiction. Based on the allostatic concept of addiction, as the addict develops the compulsion of addiction, the motivation and drive for drug taking behavior transitions from positive reinforcement related to the euphoric effects of drugs to negative reinforcement in which the removal of the aversive states of withdrawal obliges the subject to seek and take the drug and sets the tone for craving and relapse (Aston-Jones and Harris, 2004; Koob and Le Moal, 2001). Additionally, the sensitization theory of addiction favors the idea that drug-induced sensitization (the increase of drug's effect with repeated use of a drug manifested as an increased locomotor activity in sensitized animal models) leads to the enhanced motivational value of the drug, "compulsive wanting", and this incentive salience of drug or of drug-associated stimuli underlies drug craving and vulnerability to relapse (Robinson and Berridge, 2008). Thus, the sensitized behavior of an animal in response to drugs of abuse is interpreted as the compulsive drug seeking and drug taking behaviors of a drug addict.

Abbreviations: LTP, Long-term potentiation; LTD, long-term depression; VTA, ventral tegmental area; NAc, nucleus accumbens; PFC, prefrontal cortex; mPFC, medial PFC; DA, dopamine; eCB, endocannabinoids; PKA, protein kinase A; PKG, protein kinase G; GC, guanylate cyclase; μOR, μ opioid receptor; BDNF, brain-derived neurotrophic factor.

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Whereas discrete brain regions mediate different aspects of addictive behaviors, the dopaminergic pathways originating from the ventral tegmental area (VTA) dopamine (DA) neurons seem to be critically involved in the early key neuroadaptations underlying addiction. The increased release of DA in the VTA projection areas is triggered in response to acute exposure to all classes of major addictive drugs including opiates and also to cues associated with drugs. This enhanced DA release is proposed to mediate positive reinforcing effects of drugs and may also highlight the motivational value of drugs which then promotes drug taking, craving and relapse (Di Chiara and Imperato, 1988; Robinson and Berridge, 1993). The neural substrates for acute drug withdrawal seem to also engage the same neural systems implicated in the positive reinforcing effects of drug of abuse. Therefore, dysphoria and aversion associated with acute drug withdrawal involves a decrease in VTA DA cell activity and consequently low levels of dopamine (Koob, 1992). Along with the VTA dopaminergic system, other critical areas involved in motivation and goal-directed behaviors to include the striatum (ventral and dorsal striatum), prefrontal cortex (PFC), hippocampus, and amygdala all of which play a key role in addiction. Subjective self-reports of reward (pleasure, high, and euphoria), withdrawal (dysphoria, anxiety, depression and loss of motivation for natural reward/anhedonia) and drug craving (wanting drugs, urge to use drugs) in response to drugs, and drug-related stimuli in combination with human brain imaging studies have also highlighted the same neural circuits as the key elements of drug craving and relapse (Sell et al., 1999, 2000; Volkow et al., 2004; Zijlstra et al., 2009). For example, recent work demonstrated the association of the PFC with subjectively reported anhedonia in response to natural rewarding stimuli and also the critical role of the VTA in subjectively reported increases in opiate craving after exposure to heroin-associated cues in opioid-dependent patients (Zijlstra et al., 2009). For a more comprehensive discussion of the neurocircuitry associated with the addiction cycle, see the following reviews (Koob and Volkow, 2009; Volkow et al., 2004).

Now the major question is what changes induced by drugs of abuse in these brain areas are critical to promote addictive behaviors, in another words, how does the brain become addicted? The current best hypothesis for how the nervous system stores memories and other forms of experience-dependent plasticity involves changes in synaptic strength between neurons (synaptic plasticity). The two best-studied forms of synaptic plasticity are long-term potentiation (strengthening of synapses, LTP) and long-term depression (weakening of synapses, LTD) (Bliss and Collingridge, 1993). Emerging evidence suggests that the pursuit of rewards and avoidance of harmful stimuli engage synaptic plasticity mechanisms in areas of the brain essential for processing of reward (Chen et al., 2008; Reynolds et al., 2001; Schultz, 2010; Stuber et al., 2008). Therefore, synaptic plasticity could be an ideal neural substrate for reward-based learning and motivated behaviors. With this current perspective of synaptic plasticity in the field of drug addiction, neuroscientists have begun to make exciting new discoveries of the molecular mechanisms underpinning the reinforcing, aversive and addictive properties of drugs of abuse through their interaction with learning mechanisms (Gerdeman et al., 2003; Harnett et al., 2009; Hyman et al., 2006; Kauer and Malenka, 2007; Wolf, 2002). Recent research now suggests that during addiction, the reward pathways are hijacked by addictive drugs in a manner suggesting that drug-associated memories are critical parts of the addiction process (Kauer and Malenka, 2007). Therefore, it appears that the brain may, in fact, be learning to crave drugs. The correlation between synaptic plasticity and drug addiction has also been made in recent work by Piazza and Manzoni's teams (Kasanetz et al., 2010). They show a form of "anaplasticity" (lack of plasticity) associated with cocaine addiction which may also occur during opiate addiction. Their data convincingly suggests that synaptic plasticity is one of the active processes that could allow for control of drug intake, and its selective permanent loss in addiction-prone animals could promote the shift from a controlled drug use to addiction. In this review, we will further elaborate on the topic of synaptic plasticity associated with opiates in areas of the brain important in opiate addiction. An understanding of how neurons integrate and form these cellular memories could conceivably point to a better understanding of neural mechanisms underlying motivated behaviors and also present new directions in pharmacotherapy for drug addiction.

2. Acute *in vitro* opiates and synaptic plasticity

Opiates act through G- protein coupled opioid receptors, though the action of opiates on μ opioid receptors (μOR) is mostly responsible for the major addictive effects of opiates. The best known acute effects of opiates are the activation of potassium channels (specifically the G protein inwardly rectifying K^+ channels/GIRKs), inhibition of calcium channels, inhibition of adenylyl cyclase, and inhibition of transmitter release. These effects are mediated through the GTP-bound form of the α-subunit as well as free β/γ-subunits of G proteins (Williams et al., 2001). Given the widespread expression of opioid receptors in the brain, it is no wonder that opioids and opiates could modulate neurotransmission and regulate synaptic strength (plasticity). Interestingly, it has been shown that an abrupt cessation of a brief exposure to opioids *in vitro* is able to induce an activity-independent form of LTP at excitatory synapses of nociceptive C fibers in the spinal cord that is proposed to underlie opioid-induced hyperalgesia (Drdla et al., 2009; Zhou et al., 2010). Curiously, we have observed a similar plasticity (LTP) at VTA GABAergic synapses after a brief *in vitro* exposure to morphine which may explain the aversive aspect of opioid-induced hyperalgesia at the supra-spinal level (unpublished observations, see below for detailed information on this type of LTP). These data suggest that even an acute *in vitro* exposure to opioids and opiates locally in the spinal cord and the VTA is enough to produce powerful and long-lived synaptic modifications which may provide mechanisms for some of the central reinforcing and aversive effects of acute opiates.

3. Acute *in vivo* opiates and synaptic plasticity in the VTA

Numerous brain regions are identified to be critically involved in opiate addiction (De Vries and Shippenberg, 2002). Among those the VTA and nucleus accumbens (NAc/ventral striatum), critical components of the brain reward circuitry, have been a particular focus of vigorous investigation (Fig. 1a) (Di Chiara and Imperato, 1988; Schultz, 1997; Wise, 1989, 2008). It is a general consensus that synaptic plasticity in the VTA may be a common and initial cellular substrate for all drugs of abuse in the establishment of addictive behaviors (Bellone and Luscher, 2006; Borgland et al., 2004; Dong et al., 2004; Faleiro et al., 2004; Guan and Ye, 2010; Mansvelder and McGehee, 2000; Melis et al., 2002; Nugent et al., 2007; Saal et al., 2003; Ungless et al., 2001).The effects of a single *in vivo* passive administration of drugs of abuse on synaptic plasticity have been mostly evaluated in the VTA because of its critical role in initiation of sensitization, a prominent model of addiction (Kauer and Malenka, 2007). Strikingly, a single *in vivo* exposure to cocaine and tetrahydrocannabinol (THC) also transiently blocks an endocannabinoid (eCB)-mediated LTD at excitatory and inhibitory synapses in the NAc, and the hippocampus (Fourgeaud et al., 2004; Mato et al., 2004), but the acute effects of other addictive drugs