2011

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Neuropharmacology 61 (2011) 1088–1096

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

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ARTICLE INFO

Article history:
Received 9 September 2010
Received in revised form
7 January 2011
Accepted 17 January 2011

Keywords:
Synaptic plasticity
LTP
LTD
Opiates
Addiction
Dopamine

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.

This article is part of a Special Issue entitled 'Synaptic Plasticity and Addiction'.

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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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0028-3908/$ – see front matter Published by Elsevier Ltd.
doi:10.1016/j.neuropharm.2011.01.028

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

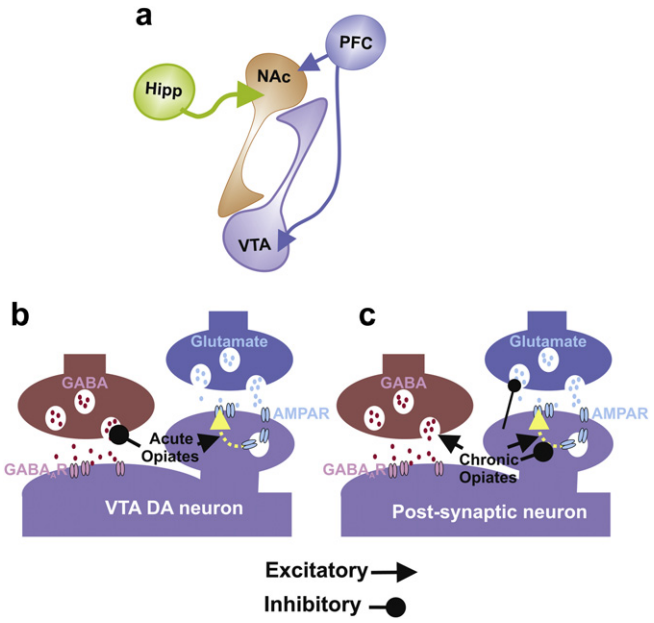

Fig. 1. Neural substrates of opiate addiction and opiate-associated plasticity. (a) demonstrates the mesolimbic DA system consisting of the VTA, NAc, PFC and hippocampus (Hipp) which plays an important role in opiate addiction. (b) and (c) summarizes some of the identified forms of synaptic plasticity associated with acute and chronic *in vivo* exposures to opiates. (b), acute opiates can trigger LTP of excitatory synapses and block NO-mediated LTP at GABAergic synapses in the VTA DA neurons. (c), on the other hand, based on the brain region, chronic opiates may trigger postsynaptic LTP (increased insertion of AMPARs), postsynaptic LTD (decreased surface expression of AMPARs) and/or presynaptic LTD (decreased presyanptic glutamate release). The widespread GABAergic plasticity associated with chronic opiates is the cAMP-dependent LTP (increased presynaptic GABA release).

including opiates on this form of plasticity in these areas have not been further investigated. Therefore, in this section we will only focus on what is known about acute opiate exposure and VTA synaptic plasticity. Although an acute drug use by itself is not necessarily addictive, this manipulation has provided valid models for examining drug-induced alterations of synapses in drug-sensitive neurons that may contribute to the processes involved in over-learning of the incentive value of drugs and/drug-related cues.

3.1. LTP and LTD at excitatory synapses

DA released from the VTA DA neurons in a VTA target (especially in the NAc) codes for reward, reward prediction, and also drug-induced reward (Di Chiara and Imperato, 1988; Schultz, 1997). The balance of excitatory (glutamatergic) and inhibitory (GABAergic) inputs onto DA neurons is one of the determinants of DA release (Johnson and North, 1992b). Therefore, it is apparent that LTP and LTD of these excitatory and inhibitory synapses can critically affect DA cell firing and transmitter release. An innovative approach of AMPA/NMDA receptor ratio measurements was taken to determine whether a single *in vivo* treatment with addictive drugs could trigger synaptic plasticity at excitatory synapses (Ungless et al., 2001). A significant increase in AMPA receptor-mediated currents without any change in NMDA receptor mediated-currents results in an increase in AMPA/NMDA receptor ratio which is inferred as glutamatergic LTP. Interestingly, 24 h after a single *in vivo* exposure to multiple drugs of abuse including morphine, glutamatergic synapses in VTA DA neurons are potentiated (seen as increased AMPA/NMDA receptor ratios in slices from drug-treated rats compared to those in slices from saline-treated rats: drug-induced glutamatergic LTP, Fig. 1b) (Saal et al., 2003; Ungless et al., 2001). Cocaine-induced LTP in the VTA had been well characterized; it is dependent on dopamine D_5 receptor activation of NMDA receptors, protein synthesis, insertion of GluR1-containing AMPA receptors and orexin A (Argilli et al., 2008; Borgland et al., 2004, 2006; Dong et al., 2004; Saal et al., 2003; Schilstrom et al., 2006; Ungless et al., 2001). Intriguingly, the magnitude and durability of cocaine-induced LTP was independent of the number of cocaine exposure (acute or chronic intraperitoneal experimenter-administration). However, only self administration of cocaine resulted in a persistent LTP (lasting for three months of abstinence) in contrast to the transient LTP in response to passive cocaine infusions or food/sucrose self administration (Chen et al., 2008). These remarkable results suggest that the process of natural reward-related learning employs transient glutamatergic plasticity in the VTA. On the contrary, active (operant) associative learning processes involved in voluntary intake of drugs are necessary to produce cocaine-induced long-lasting plasticity in the VTA DA neurons (Chen et al., 2008). Unfortunately, data regarding the time course and mechanisms underlying morphine-induced LTP at excitatory synapses in the VTA are not yet available. Because of the similarity between cocaine and heroin-seeking behaviors, it is tempting to assume that the cellular mechanisms underlying cocaine-induced plasticity could be extended to opiates. However, we should also bear in mind that there are drug-specific and even opposite changes in neural systems across these drugs (Bossert et al., 2005; Brown and Lawrence, 2009; De Vries and Shippenberg, 2002; Russo et al., 2010).

Several forms of glutamatergic LTD (metabotropic glutamate receptor (mGluR)-mediated LTD, cAMP-protein kinase A (PKA) dependent LTD and eCB-mediated LTD) have been described in the VTA (Bellone and Luscher, 2005, 2006; Gutlerner et al., 2002; Haj-Dahmane and Shen, 2010; Jones et al., 2000; Thomas et al., 2000). These forms of LTD could also be targeted by opiates. For example, it is possible that synaptic depression induced by opiate exposure could inhibit the induction of glutamatergic LTD in the VTA by reducing glutamate release needed for the induction process. It is yet to be determined how opiates would interact with these different forms of glutamatergic LTD.

3.2. LTP and LTD at inhibitory synapses

Most completed studies to date have focused on the role of glutamatergic excitatory plasticity in the VTA, but emerging evidence suggests the potential role for GABAergic inhibitory plasticity in drug addiction (Nugent and Kauer, 2008). VTA DA neurons have a widely accepted role in reward-motivated behaviors and drug reward. However VTA GABA neurons also respond to rewarding stimuli and drugs of abuse suggesting a DA-independent mechanism for processing reward and drug-induced reward (Laviolette et al., 2004; Laviolette and van der Kooy, 2001; Liu et al., 2005; Melis et al., 2002; Steffensen et al., 2001, 2006; Williams et al., 2001; Xi and Stein, 2002). Interestingly, the DA-dependent mechanism of opiate-reward also involves GABA neurons. Opiates inhibit GABA neurons, and therefore disinhibit DA neurons, resulting in increased DA release in the VTA projection sites as well as an increase in dendrodendritic DA release in the VTA (Beckstead et al., 2007; Johnson and North, 1992a). Interestingly, manipulation of GABA inhibition has been found to modify abuse-related effects of addictive drugs suggesting that inhibitory GABAergic signaling serves as a promising target for treatment of drug addiction (Barrett et al., 2005; Brebner et al., 2002; Brodie et al., 2003; Stromberg et al., 2001). Because of the importance of morphine-induced LTP at excitatory synapses in sensitization (Saal et al., 2003), and given the impact of GABA inhibition on DA cell activity, it is important to determine if GABAergic synapses onto DA neurons can exhibit

plasticity and be modulated by drugs of abuse. Looking beyond glutamatergic plasticity, it is obvious that the plastic capabilities of inhibitory GABAergic synapses could provide natural mechanisms to prevent (through LTP) or promote (through LTD) excitability of DA neurons, therefore modulating DA release.

3.2.1. Opiates block LTP_{GABA}

Our previous work by one of the authors, performed in the laboratory of Dr. Julie Kauer provided the first compelling evidence that a single *in vivo* exposure to opiate drugs (e.g., morphine) blocks a form of an inhibitory LTP (LTP_{GABA}) in VTA DA neurons (Niehaus et al., 2010; Nugent et al., 2009, 2007). LTP_{GABA} is a form of inhibitory GABAergic plasticity which is induced in response to a patterned afferent stimulation and results in long-lasting increase in GABAergic synaptic transmission in the VTA. LTP_{GABA} is heterosynaptic, induced postsynaptically but expressed presynaptically. LTP_{GABA} requires activation of NMDARs in postsynaptic DA neurons which subsequently produces the retrograde messenger, nitric oxide (NO). NO diffuses back to GABAergic terminals to activate a guanylate cyclase (GC)-cGMP-protein kinase G (PKG) pathway, resulting in an increased GABA release from these terminals (LTP_{GABA}). A single injection of morphine *in vivo* is sufficient to block LTP_{GABA} within 2 h and 24 h after exposure to morphine, but not after 5 days (see Fig. 1b) (Niehaus et al., 2010; Nugent et al., 2007). Morphine-induced blockade of LTP_{GABA} specifically affects the NO-cGMP-PKG pathway, presumably at the level of GC (Nugent et al., 2007). Interestingly, activation of GC with a GC activator in slices from morphine-treated rats is also able to induce LTP_{GABA}, providing indirect evidence for the presence of adequate levels of GC in morphine-treated slices to produce enough cGMP and thus mimic LTP_{GABA} (Niehaus et al., 2010). Whether morphine directly or indirectly interacts with GC to disrupt LTP_{GABA} is still not known and merits further investigation. Additionally, transient activation of the cAMP-PKA pathway may persistently increase GABA release at these synapses and interact with LTP_{GABA} suggesting a convergence between PKG and PKA pathways (Nugent et al., 2009). The nature of presynaptic receptors located on the VTA GABAergic interneurons that can activate the cAMP-PKA pathway is not known, nor is the converging mechanism for PKA and PKG. Similar to drug-induced LTP at excitatory synapses in the VTA, blockade of LTP at GABAergic synapses seems to be induced by several addictive drugs (opiates, ethanol, nicotine, and cocaine), and may also occur in response to stress (Guan and Ye, 2010; Niehaus et al., 2010). Intriguingly, the ethanol-induced blockade of LTP_{GABA} involves μORs confirming the role of endogenous opioids in VTA inhibitory plasticity and also in neuroplasticity associated with ethanol (Guan and Ye, 2010).

3.2.2. LTD at GABAergic synapses in the VTA

Most synapses are capable of exhibiting bidirectional plasticity (i.e., expression of LTD in addition to LTP). Recently, we have been able to induce a novel form of non-eCB- mediated LTD at GABAergic synapses onto VTA DA neurons (LTD_{GABA}: a long-lasting decrease in GABAergic transmission) in response to synaptic stimulation that can also be modulated by morphine *in vivo* (Dacher and Nugent, 2010). The induction of LTD at these synapses not only reduces the inhibition of DA neurons, but may also promote the induction of LTP at excitatory synapses (metaplasticity), thereby resulting in increased activity of DA neurons and increased DA release in VTA projection areas, potentially coding or enhancing coding for salience and reward. The control of bidirectional GABAergic plasticity by morphine in the VTA may be a neural correlate of some of the addictive features of morphine action in the VTA.

Taken together, data from Sections 3.1 and 3.2 convincingly support the idea that opioids and opiates are potent intrinsic modulators of synaptic strength in the VTA and even their short-term action may produce long-lasting changes in the brain circuitry. Moreover, recent data support the idea that drug-associated neuroplasticity in the VTA may be a likely common theme for all drugs of abuse in initiation of drug-induced aberrant forms of synaptic plasticity and consequently the establishment of addictive behaviors.

4. Chronic opiates and synaptic plasticity

The neuroadaptations associated with chronic morphine and the neural correlates of opiate-seeking and relapse have been the subject of several reviews (Aston-Jones and Harris, 2004; Bossert et al., 2005; Brown and Lawrence, 2009; Christie, 2008; De Vries and Shippenberg, 2002; Martini and Whistler, 2007; von Zastrow, 2010; Williams et al., 2001). The emerging view of drug addiction as abnormalities in neuroplasticity of reward learning (Hyman et al., 2006) makes it possible to integrate some of the vast existing data on opiate tolerance, dependence, withdrawal and addiction into a single synaptic model that could explain different aspects of opiate addiction. Opioids and opiates interact and change a variety of signaling pathways that are also involved in synaptic plasticity. In the next section, we will review the most recent progress on synaptic modifications and plasticity associated with chronic opiates in some of opioid-sensitive areas of the brain (see Fig. 1c).

4.1. The VTA

Opiate-induced plasticity at excitatory and inhibitory synapses after a single exposure in the VTA provides potential mechanisms involved in mediating the rewarding effects of opiate drugs and sensitization to such rewarding effects (see previous section). Now the important and challenging question is whether repeated exposure to opiates would induce and stabilize such plasticity at both excitatory and inhibitory synapses.

Gultamatergic neurotransmission and plasticity in the VTA can also be altered in response to chronic opiates. Fitzgerald et al. (1996) showed increased levels of AMPA glutamate receptor subunit (GluR1) levels in the VTA after chronic exposure to morphine, cocaine and stress (which could reflect a postsynaptic excitatory LTP). The authors suggest that excessive excitation of VTA DA neurons, followed by depolarization blockade in response to chronic morphine, would suppress the activity of DA neurons and reduce DA release thus underpinning aversive withdrawal. In contrast, Manzoni and Williams (1999) more recently showed a mGluR II-mediated presynaptic reduction of glutamate release onto VTA DA neurons (reminiscent of presynaptic mGluR2/3-dependent LTD in the NAc, refer to Section 4.2) during withdrawal from chronic opiate exposure. This withdrawal-induced decrease in glutamatergic signaling, in concert with withdrawal-induced increase in GABAergic inhibition (see below), could inhibit DA neurons and subsequently diminish DA release. One may wonder whether the decreased glutamate release would result in a compensatory over-expression of AMPARs as observed in Fitzgerald et al.'s study. Obviously, it is most likely that different forms of glutamatergic plasticity in the VTA DA neurons could be differentially and/simultaneously modulated by opiates, since opiates can interact with and affect a number of signaling mechanisms involved in plasticity. Consistently, chronic morphine induces a structural plasticity in VTA DA neurons (i.e., reduction in the size of DA neurons by 25%) mediated by the insulin receptor substrate 2-thymoma viral proto-oncogen (Akt) signaling that can be observed up to two weeks after withdrawal from morphine. This structural plasticity can be prevented by intra-VTA infusion of

brain-derived neurotrophic factor (BDNF) suggesting that the disruption of BDNF signaling by chronic morphine may be responsible for the structural changes in the VTA (Russo et al., 2007; Sklair-Tavron et al., 1996).

There is a consistency in the literature that continuous opiate exposure triggers a set of homeostatic compensations that is observed during withdrawal as an overshoot of these compensatory mechanisms (Williams et al., 2001). One of the widespread plasticities associated with chronic opiates is increased presynaptic GABA release due to the upregulation of the cAMP-PKA pathway (which may represent a cAMP-PKA- dependent inhibitory LTP) and is recognized as a necessary neural correlate of opiate tolerance, dependence and withdrawal. Interestingly, this inhibitory plasticity is found to be expressed in several areas of the brain to include the VTA, NAc, locus ceruleus, and periaqueductal gray (Christie, 2008; Williams et al., 2001).

Recently, Madhavan et al. (2010) showed the importance of μOR receptor trafficking (a mechanism proposed for opiate tolerance) in a PKA-dependent opiate-induced form of GABAergic plasticity in VTA DA neurons (at $GABA_A$ synapses originating from local VTA GABA neurons in the VTA). This phenomenon was firstly described by Williams' team in the VTA after opiate withdrawal (Bonci and Williams, 1997). There is a general consensus that unlike the majority of opioids and opiates, morphine fails to induce internalization and endocytosis of μORs, thereby resulting in a sustained activity of μORs and upregulation of downstream transduction pathways such as cAMP-PKA (Williams et al., 2001). Madhavan et al. used knock-in mice with a genetic modification in which unlike normal conditions, μORs were capable of undergoing morphine-induced receptor endocytosis and desensitization (i.e., recycling μOR) exclusively in GABA interneurons of the VTA. The cAMP-PKA dependent LTP was absent in recycling μOR knock-in mice suggesting a critical role of receptor trafficking in GABAergic plasticity of the VTA during withdrawal (Madhavan et al., 2010). This increased GABAergic inhibition in the VTA DA neurons could underlie the decreased DA release seen after opiate withdrawal which is thought to be associated with negative motivational states of withdrawal (dysphoria and anhedonia) promoting opiate-seeking and relapse (Koob and Le Moal, 2005).

Considering the myriad signaling pathways mediating opiates' actions, it is logical to expect that other signaling molecules could also be upregulated or altered in parallel with the cAMP-PKA pathway in opioid-sensitive neurons. For example, the NO-cGMP-PKG mediated LTP_{GABA} shown in the VTA (Nugent et al., 2007) may also be triggered in parallel with the cAMP-PKA withdrawal LTP and participate in the withdrawal-induced GABAergic plasticity in the VTA and also in other addiction-related brain regions. In fact, several reports provided strong independent support for a role of the NO-cGMP-PKG pathway in opiate dependence and withdrawal (Adams et al., 1993; Hall et al., 1996; Herman et al., 1995; Kimes et al., 1993; Tayfun Uzbay and Oglesby, 2001).

Taken together these results confirm that chronic opiates potently modulate both glutamatergic, GABAergic, and structural plasticity in the VTA possibly through complicated and interconnected processes with the final outcome of decreased excitability of DA neurons.

4.2. The NAc

Similar to the VTA, chronic exposure to opiates could affect NAc glutamatergic plasticity. The general observation in cocaine-induced plasticity in the NAc is enhanced cell surface expression of AMPAR GluR1 type subunits after chronic cocaine exposure and during withdrawal (Chen et al., 2010). In contrast to stimulants, chronic morphine exposure results in decreased levels of surface expression of AMPARs in the NAc (Glass et al., 2008) which is consistent with the reducing effects of chronic morphine on NAc dendritic spine density (Robinson et al., 2002). On the other hand, it has been shown that presynaptic mGluR2/3-dependent LTD at glutamatergic synapses in the NAc is absent in slices from morphine-withdrawn mice (Robbe et al., 2002). This in fact could result in increased inhibitory NAc-VTA feedback and may explain why activation of mGluR2/3 has been found to attenuate heroin-seeking behaviors in animal models of opiate relapse (maybe through restoration of mGluR2/3 LTD)(Bossert et al., 2006). This could be true if LTD is blocked by morphine withdrawal, however it is also possible that withdrawal from morphine would induce mGluR2/3 LTD, thereby occluding further induction of LTD in response to a mGluR2/3 agonist. As mentioned earlier (Section 4.1) similar to the VTA a form of GABAergic plasticity (i.e. the cAMP-dependent withdrawal LTP) at $GABA_A$ synapses onto medium spiny neurons in the NAc has also been reported after opiate withdrawal which could result in suppression of activity of these neurons during withdrawal (Chieng and Williams, 1998).

Different forms of plasticity are reported in the striatum including NAc; e.g., expression of eCB-mediated LTD seems to be a widespread property of both excitatory and inhibitory synapses in the brain including this area and the VTA (Heifets and Castillo, 2009; Lovinger, 2008). Yet the modulation of this plasticity and other forms of plasticity in response to morphine and other drugs of abuse is still a major question warranting future investigation (although more is known about cocaine-induced plasticity).

4.3. The hippocampus

The role of endogenous opioids and opioid receptors in induction and/modulation of hippocampal plasticity has been well documented (Bramham, 1992; Drake et al., 2007; Harrison et al., 2002; Simmons and Chavkin, 1996; Wagner et al., 2001; Weisskopf et al., 1993). The hippocampus has traditionally been recognized for its role in learning and memory but recent evidence also supports its key action in the rewarding and aversive central actions of drugs of abuse including opiates. Several lines of evidence suggest that changes in plasticity and its molecular mechanisms in the hippocampus are associated with the formation of drug-induced contextual positive and negative memories, promoting relapse to drug seeking in addicts (Frenois et al., 2005; Hou et al., 2009; Robbins and Everitt, 2002; Taubenfeld et al., 2010; Wise, 1989). In other words, the strong link between environmental cues and drug use could take place through drug-induced signaling and plasticity in the hippocampus. Opiate dependence/withdrawal has been shown to affect hippocampal plasticity with the general observation of inhibition of LTP (Bao et al., 2007; Lu et al., 2010; Pu et al., 2002; Salmanzadeh et al., 2003). Interestingly, the effects of acute opiates on hippocampal circuitry are exclusively mediated through inhibitory GABAergic interneurons (resulting in excitation of pyramidal neurons through disinhibition) (Robinson and Deadwyler, 1980) which could in fact facilitate LTP. So is it possible that the blockade or reduction of hippocampal LTP after chronic opiate treatment is due to the fact that chronic opiates induce LTP thereby occluding further induction of LTP in response to synaptic stimulation. Given the powerful inhibitory impact of GABAergic interneurons in the hippocampus, and the fact that hippocampal GABAergic synapses are also capable of expressing plasticity (Gibson et al., 2008; McMahon and Kauer, 1997), it will be critical to assess how hippocampal plasticity involving hippocampal GABAergic interneurons might be altered after chronic opiates. It should also be noted that chronic opiate treatment upregulates the cAMP-adenosine cascade, a regulator of transmitter release at most synapses, through which they could

alter presynaptic transmitter release (Williams et al., 2001). Recent evidence also confirmed that the disruption of hippocampal LTP at excitatory synapses onto CA1 neurons is linked to the enhanced adenosine-adenosine A1 receptor signaling in the hippocampus after chronic morphine (Lu et al., 2010). On the other hand, Billa et al. (2010) demonstrated the effects of chronic morphine treatment on AMPAR expression, its subunit composition and LTD. Like the VTA (Section 4.1), the expression of AMPAR GluR1 subunit was increased after chronic morphine treatment at hippocampal synapses. Furthermore, chronic morphine increased the expression of the GluR3 subunit and resulted in a switch in the subunit composition of AMPARs (replacement of GluR2-containing receptors for GluR2-lacking receptors, similar to cocaine-induced plasticity in the NAc, Conrad et al., 2008). Because of this switch chronic morphine reduced the magnitude of LTD in the hippocampus. These changes in glutamatergic signaling in the hippocampus in response to chronic morphine are also proposed to underlie the extinction of morphine-induced conditional place preference (Billa et al., 2009). Altogether these studies suggest that morphine-induced modulation of hippocamal plasticity may provide the neural basis for memory deficits seen in opiate addicts. Furthermore, the relapse caused by drug-associated environmental cues could be linked to drug-induced plasticity in the hippocampus which is tightly interconnected with other opioid-sensitive areas such as the reward mesolimbic pathway (see Fig. 1a).

4.4. The prefrontal cortex

The prefrontal cortex (PFC), a crucial part of the reward pathway, plays an important role in the initiation of motivated behaviors and is critically involved in opiate addiction. Specifically, relapse in response to drug-associated cues could involve this region (De Vries and Shippenberg, 2002). New studies have shown that relapse to heroin-seeking is associated with plasticity in both glutamatergic and GABAergic synapses in the PFC specifically in the medial part (mPFC). For example, using an animal model of heroin self administration, Van den Oever et al. (2008) elegantly demonstrate that re-exposure of heroin self-trained animals to heroin-associated cues produces an LTD (reduced AMPAR- but not NMDAR-mediated currents) in the mPFC pyramidal neurons which is dependent on clathrin-mediated endocytosis of GluR2 AMPARs. Prevention of AMPAR endocytosis significantly attenuated cue-evoked relapse to heroin-seeking suggesting that glutamatergic plasticity and AMPAR endocytosis in the PFC are critical targets for opiates in reinstatement of heroin-seeking behaviors. Recently, the same group provided evidence for heroin-induced GABAergic plasticity in the mPFC. Interestingly, re-exposure to heroin-cues in animals self-administering heroin also strengthened GABAergic transmission, thereby enhancing the inhibition of mPFC pyramidal neurons. Given that both the VTA and NAc are the main recipients of the PFC inputs, the reduced excitatory inputs from the PFC could critically affect the activity of its target neurons and contribute to drug-induced plasticity in these areas (see Fig. 1a).

5. Synaptic plasticity contributes to addictive behaviors

So far we have discussed the recent literature on opiates and synaptic plasticity in several main opiate-sensitive areas of the brain but the challenging question arises as to how these effects of opiates on synaptic transmission and plasticity contribute to specific aspects of addictive behaviors? Based on the current theories of addiction, at least three major contributors to relapse and compulsive drug use are increased cravings, negative motivational states of withdrawal and diminished inhibitory control (Koob and Volkow, 2009). Here, we will briefly start making the connections between abnormalities of synaptic plasticity induced by opiates in each region to different aspects of opiate-addictive behaviors based on the individual role of each brain region and neuronal pathway in drug-related behaviors. Insights from human imaging studies have tremendously contributed in revealing the roles of different brain regions and neuronal pathways that are activated in response to natural reinforcers, drugs and drug-related stimuli (Volkow et al., 2004). For more details on the correlation between synaptic plasticity and drug-related behaviors, refer to the following excellent reviews (Hyman et al., 2006; Koob and Le Moal, 2001; Volkow et al., 2004; Wolf, 2002).

Many of the behavioral models of addiction such as behavioral sensitization, conditioned place preference, drug- self administration paradigms and human self-reports are context-dependent and require activation of learning mechanisms (involvement of synaptic plasticity) (Sell et al., 1999; Taubenfeld et al., 2010; Valjent et al., 2010, 2006). For example, blockade of NMDA receptors in the VTA prevents the induction of behavioral sensitization (Kalivas and Alesdatter, 1993) as well as glutamatergic LTP in the VTA DA neurons (Ungless et al., 2001). Therefore, it was proposed that LTP at glutamatergic synapses onto the VTA DA neurons leads to sensitization which may underlie altered learning and motivation in response to drugs and drug-related cues contributing to compulsive drug wanting and craving. Acute opiates induce this form of glutamatergic LTP and also block LTP_{GABA} in the VTA which could promote DA cell excitability and result in increased DA release in the NAc and PFC. The increased activity of the meso-corticolimbic DA pathway and consequently prolonged DA release in VTA targets could change synaptic plasticity in these dopaminoceptive areas as dopamine is a modulator of synaptic plasticity. As a result the saliency value of drugs and drug-associated cues could be exaggerated. In fact, it has been shown that cocaine-induced plasticity in the VTA may trigger enduring forms of cocaine-induced synaptic plasticity in the NAc. The authors elegantly showed that local interference with mGluRs in the VTA DA neurons triggered early and long-lasting forms of cocaine-evoked plasticity in the NAc whereas local ablation of NMDARs in DA neurons prevented cocaine-evoked plasticity in the NAc (Mameli et al., 2009). Their data provided the first evidence for a hierarchical link of cocaine-evoked plasticity between the VTA and NAc and demonstrated the critical role for drug-induced plasticity in the VTA and NAc in cue-induced cocaine seeking behaviors. We assume that acute opiate-induced abnormalities of LTP and LTD in the VTA and NAc may also account for positive reinforcement of opiate-taking behaviors and opiate craving.

Opposite to the acute effects of opiates, chronic opiates are associated with decreased DA release as a result of a marked reduction in DA cell activity which could contribute to anhedonia (less sensitivity to natural reinforcing and salient stimuli), dysphoria and loss of inhibitory control observed in addicts (Volkow et al., 2004). We assume that low- tonic level of DA activity could also be shifted transiently to high-phasic DA activity in response to drugs and drug-related cues promoting craving and relapse. In the next paragraphs we will discuss how opiate-induced plasticity in different brain regions may be involved in low- tonic and high-phasic DA activity and its shift after chronic opiate use and during withdrawal.

The effects of opiates on glutamatergic plasticity in the VTA are complicated. Whereas chronic opiates have been shown to increase the expression of GluR1 subunits in the VTA (induction of LTP), however withdrawal from chronic opiates also results in decreased glutamate release in the VTA (induction of LTD). Moreover, the increased GABAergic inhibition (inhibitory LTP) in the VTA in addition to the diminished size of DA neurons (structural plasticity) after withdrawal from chronic opiate exposure would result in

a reduced DA signaling. These alterations in synaptic transmission in the VTA-NAc-PFC pathway after exposure to chronic opiates could contribute to low-tonic DA activity which underlies the aversive and negative motivational states of withdrawal critical for opiate replace (Koob, 1992; Koob et al., 1989). Consistently, chronic opiate-induced plasticity in the PFC (induction of glutamatergic LTD and inhibitory LTP) could result in reduced activity of PFC neurons, thereby decreasing the excitatory actions of PFC on the VTA which may also contribute to low-tonic DA activity and the aversive aspects of opiate withdrawal. A recent human study has also confirmed that the PFC might be involved in anhedonia seen in opiate addicts (Zijlstra et al., 2009). On the other hand, it is possible that exposure to opiates and opiate-related cues triggers glutamatergic LTP and inhibitory LTD_{GABA} while blocks LTP_{GABA} in VTA DA neurons. This could shift the DA activity from low-tonic to high-phasic mode, resulting in an opiate-enhanced phasic DA signaling. If this occurs, the phasic increase in DA release could promote the sensitization to incentive motivational values of opiates and opiate-related cues. In fact, higher activity of VTA is shown in response to heroin-associated cues in abstinent heroin users (Zijlstra et al., 2009). Consistently, the effects of chronic opiates on NAc plasticity (induction of glutamatergic LTD and GABAergic LTP) could lead to a reduced inhibitory feedback onto VTA DA neurons, promoting an increase in activity of DA neurons. Nevertheless, we should consider the possibility that different forms of plasticity in response to drugs may be triggered simultaneously and/or sequentially in different areas of the brain and each circuitry may only be activated in response to specific stimulus/stimuli (for example contextual cues for the hippocampus, see below).

The glutamatergic inputs from PFC, hippocampus and amygdala and the DA inputs from the VTA determine NAc neuronal excitability. The NAc therefore acts like a hub to integrate different signals arising from limbic and cortical areas. The plasticity induced by opiates in each of these areas could influence the net NA activity. For example, the less excitability of NAc and PFC after chronic opiates is proposed to underlie the loss of inhibitory control important in drug addiction as both regions play an important role in execution of goal-directed behaviors as well as drug seeking behaviors (Wolf, 2002). Interestingly, the association between environment and general contexts with the availability of drugs could be shaped through hippocampal plasticity which could enable drug-related contextual cues to elicit craving and relapse (Taubenfeld et al., 2010). While different studies have linked the impairment of hippocampal LTP to memory deficits in addicts, the role of opiate-induced hippocampal plasticity in drug-related contextual memories has been far less studied. Finally, it is worthwhile to mention that an abnormal drug-induced plasticity may be the first step in the cascade leading to the structural brain changes that are necessary for long-lasting modifications in brain function and consequently shaping drug-related behaviors (Robinson and Kolb, 2004; Thomas et al., 2008; Wolf, 2002).

6. Conclusion

Regardless of the vast amount of data on the neuroadaptations induced by opiates, it is a major challenge to pinpoint specific adaptations underlying the hallmark features of opiate addiction, i.e. opiate relapse and compulsive opiate-seeking and opiate-taking. Fortunately, after the discovery of synaptic plasticity as a cellular correlate of learning and memory, it has been recognized that the process of addiction involves synaptic plasticity and consequent pathological over-learning of drug values by the brain. Different forms of plasticity at excitatory and inhibitory synapses are found in opioid-sensitive areas of the brain that are the main targets for opiates and also other addictive drugs. In general acute and chronic opiates mainly induce LTP at excitatory glutamatergic synapses (with some exceptions, e.g., in the NAc and the PFC). On the other hand, the effects of acute and chronic opiates on GABAergic plasticity may be different. Whereas acute opiates block LTP, and may promote LTD at inhibitory GABAergic synapses, chronic opiates mostly induce inhibitory LTP. It will be critical to assess how glutamatergic, GABAergic and structural plasticity in different opioid-sensitive areas work in concert to finally shape opiate-addictive behaviors. The new synaptic concept of addiction has begun to reveal the specific neurobiological processes involved in natural reward as well as drug reward and holds high promise in the discovery of efficient pharmacologic targets for drug craving and relapse in addicts.

Acknowledgements

The opinions and assertions contained herein are the private opinions of the authors and are not to be construed as official or reflecting the views of the Uniformed Services University of the Health Sciences or the Department of Defense or the Government of the United States. This work was supported by a DOD-intramural grant from the Uniformed Services University (USUHS), and the PhRMA Foundation Research Starter Grant to F.S.N. The funding agencies did not contribute to writing this article or deciding to submit it. Thanks to Drs. Brian Cox and Thomas Cote for their helpful and constructive discussions for the present review.

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