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Review

The role of glutamate and its receptors in mesocorticolimbic dopaminergic regions in opioid addiction

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ABSTRACT

Accumulating evidence suggests that glutamate, as one of the most important excitatory neurotransmitters in the brain, plays a key role in drug addiction including opioid addiction. There is substantial evidence for glutamatergic projections into mesocorticolimbic dopaminergic neurons, which are associated with opioid psychological dependence and are also the key regions of enhancement effect. Glutamate may be involved in the process of opioid addiction not only by acting on its ionotropic and metabotropic glutamate receptors that activate several signal transduction pathways, but also by interacting with other neurotransmitters or neuropeptides such as opioids, dopamine, γ -aminobutyric acid and substance P in the mesocorticolimbic dopaminergic regions. Studies on the role of glutamate and its receptors in opioid addiction will provide a new strategy for the exploitation of drugs for the treatment of opioid addiction.

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1. Introduction

Drug addiction is a kind of chronic relapsing brain disease characterized by the loss of control over drug intake, repeated unsuccessful attempts at quitting or reducing drug use, continued drug use despite negative consequences, reduction in engagement in social, occupational and recreational activities in lieu of drug-seeking or self-administration behavior, and the emergence of symptoms of tolerance or withdrawal (American Psychiatric Association, 1994; Koob and Nestler, 1997; Koob et al., 1998, 2004; Gass and Olive, 2008). Some addictive drugs such as opioid, cocaine, cannabinoids, heroin, amphetamine and nicotine can produce physical and psychological dependence (Dackis and Gold, 1985; Koob, 1992; Di Chiara, 1995; Wise, 1996; Manzanares et al., 1999). Although opioids are useful analgesics for clinical use, major problems associated with the chronic use of opioids are tolerance and dependence. In addition, long-term use of opioids can lead to serious physical and psychological dependence, limiting the usage of opioids and causing an adverse impact on the society (Ree et al., 1999). Therefore, research on the neurobiological mechanism and treatments of opioid dependence have been vigorous.

Since all addictive drugs facilitate dopamine (DA) transmission, determining the role of DA has been the predominant focus of biomedical research in addiction for the past 20 years (Kalivas, 2004). Recently, accumulating evidence indicates that glutamate plays an important role in drug addiction especially in latest 5 years (Tzschentke and Schmidt, 2003; Gass and Olive, 2008). Glutamate is one of the most abundant excitatory neurotransmitters in the brain, mediating as much as 70% of the synaptic transmission within the central nervous system (Fonnum, 1984; Cotman et al., 1987; Headley and Grillner, 1990; Gass and Olive, 2008). There are glutamatergic projections and/or neurons expressing glutamate receptors in some regions of the brain, including the mesocorticolimbic dopaminergic regions (Heimer et al., 1997; Wolf, 1998; Groenewegen et al., 1999; Geisler et al., 2007; Kalivas and O'Brien, 2008), which provide an anatomical basis for the role of glutamate in addiction.

Drug addiction is a complex process. Interaction of many brain nuclei with neurotransmitters or neuropeptides constitutes a neural network, which affects the intracellular signal transduction and is involved in drug addiction including opioid addiction (De Vries and Shippenberg, 2002; Kalivas, 2004; Wang et al., 2005). Many brain regions are involved in the opioid addiction including locus ceruleus, periaqueductal gray, medial thalamus, hypothalamus, amygdala (AMY), globus pallidus, nucleus raphe magnus, gigantocellular reticular nucleus, ventral tegmental area (VTA), nucleus accumbens (NAc) and substantia nigra (Temple and Zukin, 1987; Nestler and Aghajanian, 1997; Ivanov and Aston-Jones, 2001; Koob, 2003). Among these brain regions, the VTA and NAc, important components of mesocorticolimbic dopaminergic regions, are prominent regions to opioid psychological dependence and also thought to serve as key regions for mediating reinforcement processes (Harris and Aston-Jones, 1994; Grant et al., 1996; De Vries and Shippenberg, 2002; Spanagel and Weiss, 2002). This review will summarize recent research progress on the role and mechanism of glutamate and its receptors in the mesocorticolimbic dopaminergic regions in opioid addiction.

2. Anatomy of mesocorticolimbic dopaminergic regions

Mesocorticolimbic dopaminergic pathway is composed of VTA dopaminergic neurons and its projections, the NAc, AMY and the medial prefrontal cortex (mPFC), in which the VTA and NAc are the important nuclei involved in a variety of reward effects (Kalivas, 1993; White, 1996; Bjorklund and Dunnett, 2007). When the VTA, NAc and central or lateral nucleus of amygdala were lesioned with

a DC current, morphine-induced conditioned place preference (CPP) can be inhibited (Wang et al., 2002). Morphological study showed that the both volume and number of neurons in the VTA and NAc in morphine withdrawal rats decreased (Spiga et al., 2003). There are also evidence that indicates drug-seeking in morphine-dependent rats and heroin-induced self-administration are related to the electrical activities of DA neurons in the VTA and NAc (Chang et al., 1997; Kiyatkin and Rebee, 2001). The DA level in the VTA and NAc decreased in morphine withdrawal rats, while increased in morphine-dependent rats during drug-seeking (Acquas and Di Chiara, 1992; Herz et al., 1992; Shaham et al., 1996). These results indicate that the mesocorticolimbic dopaminergic regions play important roles in the development of morphine dependence and during withdrawal.

DA neurons are abundant in the VTA (A10), receiving afferent fiber projections from the cortex, thalamus, striatum, limbic system and the brain stem. They also project widely to NAc, mPFC, piriform cortex, hippocampus, entorhinal cortex, amygdala, nucleus accumbens and brain stem (including locus coeruleus, parabrachial nucleus and nuclei of median raphe), etc. Not only dopaminergic neurons (Fallon and Moore, 1978; Swanson, 1982; Margolis et al., 2006) but also GABAergic and glutamatergic neurons are cytochemically identified in the VTA (Van Bockstaele and Pickel, 1995; Carr and Sesack, 2000; Margolis et al., 2006; Yamaguchi et al., 2007). It has also been shown that glutamate can be released by some VTA neurons (Chuhma et al., 2004; Lavin et al., 2005; Fields et al., 2007).

The NAc contains three functionally distinct subcompartments, termed as the shell, core and rostral column based on anatomical and biochemical differences (Jongen-Relo et al., 1993, 1994; Voorn et al., 1994; Meredith et al., 1996). The shell region of NAc mainly received dopaminergic projections from the VTA, while the core region of NAc mainly received excitatory glutamatergic projections from amygdala and hippocampus (Kelley et al., 1982; Swanson, 1982; Phillipson and Griffiths, 1985; Groenewegen et al., 1987). Most of the neurons in NAc are GABAergic (O'Donnell and Grace, 1993; Pennartz et al., 1994). Within the NAc, the core subcompartment has the strongest association with drug-seeking (Di Ciano et al., 2001; Everitt et al., 2001). There are two categories of adaptation in glutamate transmission in the NAc: one of which promotes presynaptic glutamate release and the other alters postsynaptic responsiveness to released glutamate. It is proposed that the glutamatergic projection from the mPFC to the NAc is a final common pathway for eliciting drug-seeking behaviors (Kalivas and Volkow, 2007).

The major dopaminergic, glutamatergic and GABAergic efferent and afferent projections in mesocorticolimbic dopaminergic pathway including VTA, NAc, mPFC and AMY are shown in Fig. 1.

3. Types of glutamate receptors

Glutamate is one of the most abundant excitatory neurotransmitters in the central nervous system. Once released into the synaptic cleft, glutamate can bind to its receptors and exert its effect. According to pharmacological and molecular biological classification, glutamate receptors can be divided into two categories, ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs).

3.1. Ionotropic glutamate receptors

Ionotropic glutamate receptors are ligand-gated ion channels and are divided into three subtypes: *N*-methyl-D-aspartic acid (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainic acid (KA). The latter two are also referred

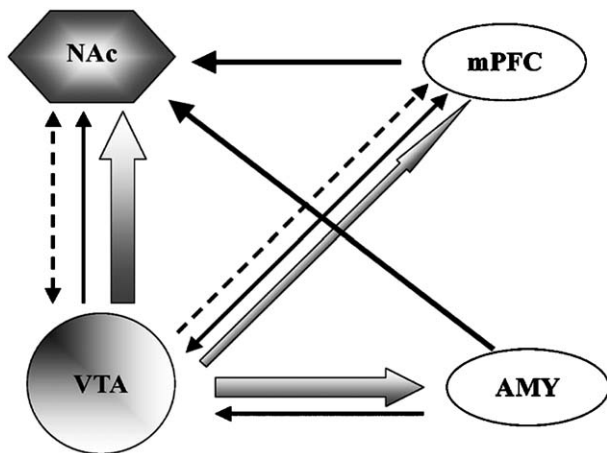


Fig. 1. Major nuclei and efferent and afferent projections in mesocorticolimbic dopaminergic pathway. Dopaminergic efferent and afferent are shown in hollow arrow; glutamatergic efferent and afferent are shown in black arrow; GABAergic efferent and afferent are shown in arrow with dash line. Circle means the neurons in VTA are mainly identified as dopaminergic neurons and the hexagon means the neurons in NAc are mainly identified as GABAergic and some peptidergic neurons. VTA: ventral tegmental area; NAc: nucleus accumbens; AMY: amygdala; mPFC: medial prefrontal cortex.

to non-NMDA receptors (Monaghan et al., 1989; Young and Fagg, 1990; Seeburg, 1993).

NMDA receptors are heterotetrameric protein complexes that form ligand-gated ion channels composed of at least one basic subunit NR1 and regulating subunits NR2 (Dingledine et al., 1999; Stephenson, 2006; Paoletti and Neyton, 2007). NR1 subunit is the common subunit while NR2 subunit determines the pharmacological specificity of the NMDA receptor. There are four types of NR2 subunits named as NR2A, NR2B, NR2C and NR2D (Monyer et al., 1992; Nakanishi, 1992). Recently, two new members of gene families that code NMDA receptor subunits were cloned and named as NR3A and NR3B. They may be involved in the composition of NMDA receptors (Sucher et al., 1996; Myers et al., 1999; Madden, 2002). NMDA receptors are coupled with ion channels including sodium ions, potassium ions and calcium ions. These receptors induce excitatory postsynaptic potential (EPSP). Endogenous agonists of the NMDA receptors are glutamate, aspartate and quinaldonic acid. The activity of NMDA receptors is regulated not only by the endogenous and exogenous agonists but also by the binding position of ions and molecules such as Mg^{2+} , Zn^{2+} , H^+ , glycine and polyamine.

AMPA receptors are heterotetrameric protein complexes that form ligand-gated ion channels composed of various subunits termed as GluR1–4 (also termed as GluRA–D) and GluR δ 1 and 2 (Dingledine et al., 1999). Kainic acid (kainate, KA) receptors are tetrameric protein complexes that form ligand-gated ion channels composed of various subunits. These subunits are termed as GluR5–7 and KA1 and 2 (Kenny and Markou, 2004). Like NMDA receptors, AMPA and KA receptors are permeable to Na^+ and K^+ ions and are able to trigger EPSP.

3.2. Metabotropic glutamate receptors

The mGluRs are G-protein-coupled receptors. Besides having the same sequence characteristics of seven transmembrane regions, these receptors have no homology with other G-protein-coupled receptors. According to sequence similarities, priorities of agonists and the intracellular signal transduction pathway, eight kinds of mGluRs can be divided into three groups (I, II and III; Schoepp et al., 1990; Conn and Desai, 1991; Miller, 1994; Pin and Duvoisin, 1995; Conn and Pin, 1997). Group I mGluRs

(mGluR1 and 5) are predominately located postsynaptically and couple to Gq proteins. They mainly hydrolyze inositol phosphate (PI) into intracellular second messengers diacylglycerol and 1,4,5-inositol trisphosphate (IP_3) through the activation of phospholipase C (Conn and Pin, 1997; Hermans and Challiss, 2001; Coutinho and Knopfel, 2002). Group I mGluRs also can couple to intracellular Homer proteins, possibly through a Homer-phosphatidylinositol 3-kinase (PI3K) enhancer adaptor complex (Xiao et al., 2000; Rong et al., 2003). Group II mGluRs (mGlu2 and 3) are found both pre- and postsynaptically and group III mGluRs (mGlu4, 6, 7 and 8) are predominately located presynaptically. Both of them couple to Gi/o proteins to negatively regulate the activity of adenylyl cyclase (AC) and decrease the content of cAMP (Schoepp, 2001; Mudo et al., 2007; Gass and Olive, 2008). The mGluRs can also promote cGMP production, activation of phospholipase D and the release of arachidonic acid (Conn and Pin, 1997; Madden, 2002; Pin and Acher, 2002; Jingami et al., 2003).

4. The role of glutamate and its receptor in opioid addiction

It is known that certain glutamatergic projection could be impacted by addictive drugs. Data indicate that the activation of glutamatergic efferent fibers from the amygdala and prefrontal cortex is critical in the expression of addictive behaviors (Pierce and Kalivas, 1997; Goldstein and Volkow, 2002; McLaughlin and See, 2003; See et al., 2003; Kalivas, 2004; Kalivas et al., 2009). The alteration of glutamate-mediated transmission, especially the increase of glutamatergic transmission in the NAc may promote the seeking and relapse from abused drugs (Zhu et al., 1998; Watanabe et al., 2002; Kenny and Markou, 2004; Paul and Athina, 2004). Suaud-Chagny et al. (1992) reported that microinjection of glutamate into the VTA can increase exploratory motor behaviors and the release of DA in NAc and mPFC. These results suggest that glutamate plays an important role in opioids dependence.

4.1. The role of iGluRs in opioid addiction

Gudehithlu et al. (1994) first reported the change of NMDA receptors in rat brain following long-term treatment with morphine. Then it was shown that the expression of NMDA receptors was upregulated in morphine-dependent rat brains (Koyuncuoglu et al., 1999). Recently, more studies showed that glutamatergic signal transduction can regulate drug effects, resulting in drug tolerance and dependence, including the tolerance and dependence of opioids. Glutamatergic afferents play a key role in regulating the firing of the VTA neurons. Activation of glutamatergic afferents and the VTA infusion of glutamate receptor agonists increase the firing rates of dopaminergic neurons and induce burst firing *in vivo* (Grace and Bunney, 1984; Chergui et al., 1993; Murase et al., 1993). It was also demonstrated that MK801, an NMDA receptor antagonist, completely blocked the withdrawal symptoms induced by glutamate and naloxone (Tokuyama et al., 1996, 2001). MK-801 can also decrease morphine dependence, which may be related to the downregulation of NMDA receptors (Gudehithlu et al., 1994; Koyuncuoglu et al., 1999). Western blot and microdialysis results showed that chronic intermittent use of morphine, cocaine and other addictive drugs can increase the level of glutamate in the VTA, upregulating the expression of AMPA receptor subtypes GluR1 and NMDAR1 in the VTA (Fitzgerald et al., 1996; Kalivas and Duffy, 1998). Co-application of opioids and NMDA receptor competitive or non-competitive antagonists can block the pain tolerance and physical dependence of opioid and the drug-seeking behaviors (Nestler et al., 2001). Bisaga et al. (2001) indicated that glutamatergic signal transduction mediated by NMDA receptors was involved in the formation and maintenance of morphine

dependence in human. It was also reported that MK-801 injected into the VTA reduced the morphine-induced CPP, which suggested that ionotropic glutamate receptors in the VTA were involved in the psychological dependence of opioids (Popik and Kolasiewicz, 1999). Our recent studies found that microinjection of NMDA receptor antagonist MK-801 or non-NMDA receptor antagonist DNQX into the VTA partly attenuated morphine withdrawal symptoms induced by naloxone, suggesting that the NMDA and non-NMDA receptors in the VTA are involved in morphine withdrawal process (H.L. Wang et al., 2004). Moreover, systemic and intracerebroventricular injections of NMDA receptor antagonists (MK-801, memantine and dextromethorphan, etc.) and non-NMDA receptor antagonists (DNQX, CNQX, LY293558 and LY215490) prevented some morphine withdrawal symptoms in rats (Fundytus and Coderre, 1994; Rasmussen, 1995; Manning et al., 1996; Bristow et al., 1997; Popik et al., 1998). Microinjection of ionotropic glutamate receptor antagonists MK-801 or DNQX into the VTA attenuated the reinforcement effect in heroin addiction (Xi and Stein, 2002b). Chronic intermittent injection of escalating doses of morphine is accompanied by ultrastructural plasticity of GluR1 in neurons that are responsive to glutamate, activation of DA-induced D1 dopamine receptor in the NAc shell, and activation of neurons capable of responding to glutamate but not to D1 dopamine receptor stimulation in the NAc core (Glass et al., 2008). These results indicate that glutamate released in the central nervous system plays an important role in opioid withdrawal behaviors and that the iGluRs are involved in the process.

4.2. The role of mGluRs in opioid addiction

Metabotropic glutamate receptors, which mediate slow glutamate neurotransmission, are located throughout the limbic and cortical brain regions implicated in drug addiction. There is significant pharmacological and behavioral evidence that group I mGluRs are widely distributed in the projection neurons and intermediate neurons in the shell and core of NAc, providing the morphological evidence for their regulation and therapeutic effects in reward-related behaviors and drug addiction (Mitrano and Smith, 2007; Mitrano et al., 2008). Palucha et al. (2004) found that 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl] pyridine (MTEP), an mGluR5 antagonist, dose-dependently inhibited morphine withdrawal symptoms induced by naloxone. DA and glutamate play critical roles in the induction of LTP in the NAc through the activation of D1 dopamine receptors and group I mGluRs (Schotanus and Chergui, 2008). It was reported that the number and function of group II mGluRs upregulated the formation of opioids withdrawal. Group II mGluRs (mGluR2 and mGluR3) were involved in the negative regulation in the brain reward circuit and the formation of conditional offensive responses in drug dependence and withdrawal. LY379268, the group II mGluRs agonist, reduced seeking behaviors induced by cocaine (Weiss and Baptista, 2003; Peters and Kalivas, 2006). Agonists of mGlu2/3 receptor prevent the reinstatement of drug-seeking and drug-taking behaviors after a period of abstinence (Markou, 2007). Agonists of group II mGluRs inhibited morphine withdrawal behaviors in 7-, 14- and 21-day-old rats (Zhu and Barr, 2004). The mGlu2/3 receptors in the NAc increased at days 1, 3, and 14 of morphine withdrawal (Modafferi et al., 2008). However, there were some conflicting reports. For instance, chronic application of cocaine decreased the function of group II mGluRs in the NAc (Robbe, 2002). Thus, the role of group II mGluRs in drug dependence was more complicated than previously thought (Kenny and Markou, 2004). Recently, it was reported that group III mGluR7 was implicated in many neurological and psychiatric diseases, including drug addiction. Systemic or intra-NAc administration of the mGluR7 allosteric agonist AMN082 dose-dependently lowered NAc extracellular

GABA and increased extracellular glutamate, and such effects were blocked by (R,S)-alpha-methylserine-O-phosphate (MSOP), a group III mGluR antagonist (Li et al., 2008). The mGluR8 mRNA levels were increased in the caudate putamen and NAc 1 day after the discontinuation of amphetamine treatments and sustained up to 21 days of withdrawal (Parekar and Wang, 2008). However, the role of group III mGluRs in drug dependence is still not well investigated. Further investigation is required to fully understand the role of mGluRs in the pathological process of drug addiction.

5. The signal transduction pathways of glutamate receptor in opioid addiction

5.1. Activation of NMDA-Ca²⁺-NO-cGMP signal transduction pathway

It was reported that the NMDA-Ca²⁺-NO-cGMP pathway is involved in maintaining the excitability of neurons and plays an important role in opioid addiction and withdrawal (Elliot et al., 1995; Lizasoain et al., 1996; Noda et al., 1996; Vaupel et al., 1997). Nitric oxide synthase (NOS) inhibitor L-NAME as well as the soluble guanylate cyclase inhibitor methylene blue was found to significantly attenuate the naloxone-induced withdrawal contracture in guinea pig ileum. In addition, nitric oxide (NO) precursor and NO donors were able to reverse the effect of L-NAME. This effect also demonstrated that the competitive NMDA receptor antagonist AP-5 potently reduced the amplitude of naloxone-induced contracture in the same model, an effect that was reversed by co-administration of the excitatory amino acid L-glutamate (Gabra et al., 2005). In this pathway, Ca²⁺ is the bridge between NMDA receptor and NO. Repeated application of opioid can activate NMDA receptors, subsequently activating the phosphatidylinositol pathway and increasing the release of Ca²⁺. Ca²⁺ and calmodulin (CaM) combine to activate the Ca²⁺/CaM complex and NOS, resulting in the increase of NO. NO, which acts as a reverse regulator, can increase the concentration of second messenger cGMP by activating soluble guanylate cyclase. cGMP, an important intracellular second messenger, can directly regulate ion channels, affect the cGMP-dependent protein kinase, or change the cAMP content through phosphodiesterase, leading to withdrawal symptoms (Bredt and Snyder, 1992; Buccafusco et al., 1995; Kotecha and MacDonald, 2003). In addition, NO increases the release of glutamate by facilitating the presynaptic NMDA receptors to form a positive feedback loop, contributing to opioid dependence and withdrawal.

5.2. Translocation of protein kinase C

Some studies suggest that NMDA enhances Ca²⁺ influx through receptor-operated Ca²⁺ channels, increasing intracellular calcium concentration and thereby inducing the translocation of protein kinase C (PKC) in guinea pig cerebral synaptoneurosome and immature rat hippocampal slices (Etoh et al., 1991a,b). PKC translocated to cell membrane in superficial layer of spinal cord during morphine tolerance (Mayer et al., 1995). In addition, the development of morphine tolerance was related to the subunit of PKC, the subunits' concentration which was positively correlated to the development of morphine tolerance, and intrathecal injection of MK-801 that blocked the process (Mao et al., 1995). This evidence suggests that NMDA receptors were involved in the upregulation of PKC (Narita et al., 1995). Another study found that the activation of NMDA receptors inhibited the activity of opioid receptors and that the blockage of NMDA receptors inhibited the desensitization of opioid receptors (Cai et al., 1997). When activated by NMDA receptors, the transcription factor PKC translocated into cell nucleus, subsequently promoting the

transcription of PKC and phosphorylate G-protein gene family. Opioid receptor desensitization occurs as a result (Fan et al., 1998).

5.3. Activation of AC–cAMP–CREB pathway

Some studies on the mechanism of morphine addiction suggested that repeated application of morphine induced change in cAMP system played important roles in morphine addiction (Noda et al., 2001). Chronic application of morphine increased the concentration of cAMP, cAMP-dependent protein kinase and cAMP response element binding (CREB) protein, thereby activating transcription and causing dependence and withdrawal symptoms (Nestler and Aghajanian, 1997). CREB is one of the members of CREB/ATF families and is also an important nuclear factor mediating the cAMP pathway and regulating gene transcription. Several studies showed that G-protein–cAMP–CREB pathway is the common mechanism of physical and psychological dependence. Guitart et al. (1992) found that acute application of morphine into locus coeruleus induced the decrease of CREB phosphorylation. On the other hand, long-term application of morphine induced the gradual increase of CREB and triggered a larger increase in the level of phosphorylation during naloxone-induced withdrawal (Hayward et al., 1990). Opioid-induced reinforcement and dependence of drugs by opioid receptors, and opioids receptors changed the cAMP signal transduction system by exciting G-protein or inhibiting AC. In addition, opioids could activate Ca²⁺/CaM-dependent protein kinase (CaMK) and phosphorylate CREB. And the activation may be involved in the dependence triggered by the Ca²⁺–CaM–CaMK–CREB pathway (Wang et al., 1999). Glutamate receptors, especially NMDA receptors, can induce synaptic plasticity change of neurons by activating the AC–cAMP–CREB pathway, and are therefore involved in opioid dependence and withdrawal (Wang et al., 1999, 2007).

5.4. Activation of MAPK pathway

The subfamilies of mitogen-activated protein kinases (MAPKs) include extracellular signal-regulated kinases (ERK1 and ERK2), c-Jun N-terminal kinases (JNK1, JNK2 and JNK3), p38 MAPKs (p38 α , p38 β , p38 γ and p38 δ), ERK3/4, and ERK5 (Davis, 2000; Chen et al., 2001; Chang and Karin, 2001; Johnson and Lapadat, 2002; Roux and Blenis, 2004). In recent years, the understanding of the role of the MAPK pathway in opioid-induced effects has evolved rapidly (Li and Chang, 1996; Chuang et al., 1997; Whistler and von Zastrow, 1999). Increasing evidence shows that cocaine or amphetamine and other substances of abuse can strongly activate the ERK pathway in the striatum or other forebrain structures through signaling mechanisms initiated by the activation of either DA or glutamate receptors or both (Berhow et al., 1996; Valjent et al., 2000, 2005; Freeman et al., 2001; Choe et al., 2002; Zhang et al., 2004; Jenab et al., 2005; Lu et al., 2005; Shi and McGinty, 2006; Tonini et al., 2006). All three subtypes of iGluRs and the three subgroups of mGluRs seem to consistently modulate the MAPK pathway in a stimulatory fashion (Wang et al., 2007). The iGluRs, particularly the NMDA receptor, may also activate the MAPK pathway through the Ca²⁺-sensitive Ras guanine nucleotide releasing factor, Ca²⁺-sensitive CaMKII and PI3K. Activation of the Ca²⁺-permeable NMDA receptors results in an increase in Ca²⁺ influx. The Ca²⁺ signals then activate several Ca²⁺-dependent kinases to increase ERK phosphorylation. After activation, ERK translocates to the nucleus and phosphorylate Elk-1 and CREB to facilitate gene expression (Valjent et al., 2000; Choe et al., 2002; Radwanska et al., 2005; Shi and McGinty, 2006). The alterations in the ERK-dependent transcriptional activity are then translated into molecular mechanisms underlying several types of persistent behavioral plasticity, such as rewarding response and behavioral

sensitization induced by single or repeated psychostimulant administration. Blockage of the ERK pathway therefore abolishes these behavioral responses (Pierce et al., 1999; Valjent et al., 2000, 2005, 2006; Gerdjikov et al., 2004; Lu et al., 2005). AMPA receptors positively regulate MAPK/ERK phosphorylation (J.Q. Wang et al., 2004), and Ca²⁺-sensitive CaMKII and PI3K are the major kinases that form a pathway between AMPA receptors and ERK (Perkinton et al., 1999). Activation of KA receptors increased ERK phosphorylation in striatal neurons (Mao et al., 2004). This increase is also dependent on extracellular Ca²⁺ ions, but it is currently unclear whether other factors are involved in the process. The mGluRs can also activate MAPK pathway, mainly by the activation of tyrosine kinase receptor through Ca²⁺ non-sensitive channels (Wang et al., 2007).

6. The interaction of glutamate and other neurotransmitters in opioid dependence

6.1. Glutamate and endogenous opioid peptide

Endogenous opioid peptide is one of the most important neurotransmitters that are involved in opioid dependence. It has been demonstrated that μ -opioid receptor is widely distributed in the VTA and the NAc. Opioids bind to endogenous μ -opioid receptor in these regions, activate the reward circuit and induce the reward effect (McLean et al., 1986; Mansour et al., 1987; Johnson and North, 1992). It was reported that MK-801, a non-competitive NMDA receptor antagonist, inhibited the analgesic tolerance induced by chronic morphine treatment. Pretreatment with MK-801 can eliminate the withdrawal symptoms in morphine-dependent mice (Trujillo and Akil, 1991). Studies have indicated that high concentration of opioid receptor agonists or antagonists can directly bind to NMDA receptors and share some characteristics of non-competitive agonists or antagonists of glutamate receptors (Yamakura et al., 1999). Enkephalin released by some neurons in the NAc can act on the μ - and δ - receptor and regulate the release of glutamate. MK-801 also can inhibit the downregulation of μ -receptor in morphine-dependent rats (Koyuncuoglu et al., 1999). In addition, studies about the regulation of glutamate receptor on the opioid receptor have been reported. Competitive as well as non-competitive NMDA receptor antagonists enhance morphine's antinociceptive effect and prevent the development of morphine tolerance (Wong et al., 1996). All these studies suggest that there exists the interaction between glutamate receptors and opioid receptors which jointly participate in opiate dependence. The mechanism underlying the interaction is regarded to be postsynaptic. The glutamate receptor and opioid receptor can be co-expressed in the same neurons. Opioids can act on its receptor and induce the disinhibition of interneurons, which causes the release of glutamate and the activation of glutamate receptors. It is also presumed that opioids can act on their receptors, decrease the concentration of cAMP by inhibiting AC through Gi and Gs, and induce the activation of PKC. The activation of PKC can remove the blockage of Mg²⁺ on NMDA receptors and subsequently activates them (Tingley et al., 1997).

6.2. Glutamate and dopamine

It is well known that DA is the key neurotransmitter since most abused drugs increase its levels. Many pharmacotherapies have thus targeted this system (Nutt et al., 2003). The content of DA in the blood of withdrawal rats was significantly higher than that in normal rats. Microdialysis analysis showed that morphine could increase the release of DA (Di Chiara and Imperato, 1998). When drug-taking behaviors were initiated, dopaminergic and glutamatergic neurotransmission in the mesocorticolimbic system was

activated (Tzschentke and Schmidt, 2003). Morphological studies showed that there existed axon–axon synapses of glutamate and DA in mPFC, the ventral striatum and the NAc, providing the morphological evidence for the interaction between glutamate and DA in the mesocorticolimbic dopaminergic pathway (Bouyer et al., 1984; Goldman-Rakic, 1999). Anatomical and electrophysiological evidence indicates that glutamate can be co-released with DA and induce long-term regulation on the plasticity (Lapish et al., 2006). Local application of glutamate can enhance the release of DA in the NAc (Youngren et al., 1993; Svensson et al., 1994). Electrical stimulation of basolateral amygdala (BLA) nucleus can increase the level of DA through its glutamatergic projections into the NAc and this effect can be blocked by perfusing glutamate receptor antagonists into the NAc (Floresco et al., 1998). Activation of iGluRs and mGluRs in the VTA increased the exploring behaviors and the levels of DA in the NAc and the mPFC (Suaud-Chagny et al., 1992; Swanson and Kalivas, 2000). These results suggest that glutamate can facilitate the release of DA by its receptors and can be involved in drug dependence and withdrawal processes. Application of glutamate receptor antagonists attenuated most of the withdrawal symptoms. In the addicted state, different dopaminergic projections may be altered differentially, resulting in an altered DA–glutamate interaction that ultimately leads to aberrant control over behaviors and compulsive drug-taking behaviors (Tzschentke and Schmidt, 2003). DA and glutamate interact in a complex way. Glutamatergic input to the VTA increases the activity of dopaminergic cells and enhances DA release in the NAc (Tzschentke and Schmidt, 2000; Tzschentke, 2001). At the level of the NAc, glutamate also facilitates dopaminergic transmission, presumably by presynaptically influencing DA release (Blaha et al., 1997; Floresco et al., 1998). The DA releasing effect of glutamate in the NAc may be predominantly mediated by AMPA (rather than NMDA) receptors (Youngren et al., 1993). However, some studies found that application of glutamate receptor antagonists increased the movement enhancement in withdrawal rats (Narayanan et al., 1995; Kretschmer, 1999; Ungless et al., 2001). Consistent with the above, studies also found that microinjection of glutamate receptor antagonist MK-801 or DNQX into the VTA attenuated most of the morphine withdrawal symptoms, except the wall-climbing behavior (H.L. Wang et al., 2004; Wang et al., 2005). The reason for these phenomena is that there exist some GABAergic neurons in the VTA and the NAc, which can inhibit the release of DA. Glutamate receptor antagonists can increase the release of DA by inhibiting GABA neurons. DA also affects glutamatergic transmission. For instance, DA modulates glutamatergic signals in the NAc originating from the amygdala and hippocampus in a manner consistent with the concept of a gating mechanism or input selection (Floresco et al., 2001; Tzschentke and Schmidt, 2003).

6.3. Glutamate and γ -aminobutyric acid

GABA is an inhibitory neurotransmitter in the central nervous system. It is involved in opioid dependence and can inhibit withdrawal symptoms induced by naloxone (Zarrindast and Mousa-Ahmadi, 1999). The release of GABA and the amplitude and frequency of inhibitory postsynaptic potentials of GABAergic neurons increased in morphine withdrawal rats. The activation of opioid receptors on VTA interneurons inhibited the activities of GABA neurons and reduced the release of GABA, which caused the disinhibition of the DA neurons in the VTA and the release of DA in the NAc, contributing to opioid withdrawal (Bonci and Williams, 1997). Single or chronic exposure to morphine inhibited the release of GABA in the NAc. This effect persisted even after the stop of morphine. The inhibition of baclofen, a GABA agonist, on morphine withdrawal symptoms suggested the involvement of GABA in

morphine dependence and withdrawal (Acquas and Di Chiara, 1992). The reward effect in mice and physical dependence induced by naloxone was attenuated when GABA transporters were over expressed (Schoffelmeer et al., 2001; Hu et al., 2003). Application of GABA_B receptor antagonist 2-OH-saclofen alone significantly increased the extracellular concentration of DA, suggesting that the DA neurons in the VTA were inhibited tonically by endogenous GABA (Xi and Stein, 2002a). Microinjection of baclofen into the VTA activated GABA_B receptors and blocked self-administration behaviors induced by heroin, DA release in the NAc (Xi and Stein, 1998, 1999) and morphine-induced CPP (Tsuji et al., 1996). It can be presumed that GABA_B receptors in the VTA play a key role in opioid dependence. Anatomical studies show that NMDA and non-NMDA receptors are located in the postsynaptic GABAergic projection neurons. Glutamatergic projections from the mPFC connected to the GABAergic spinous neurons with excitatory synapses (Xi and Stein, 2002a). The balance between excitatory amino acid and the inhibitory amino acid determines the state and response of neurons. These results suggest that glutamate activate GABAergic neurons in the NAc by NMDA or AMPA receptor. The activation of GABAergic neurons increases the release of GABA and inhibit the activities of DA in the VTA, and finally contribute to the opioid addiction.

6.4. Glutamate and substance P

Substance P (SP) is an important sensory neuropeptide widely distributed in the central and peripheral nervous system and peripheral tissues. Morphological studies show that nerve fibers containing SP connect to DA neurons with synapses in the VTA. There also exist medium-density bradykinin immune positive fibers in the NAc (Otsuka and Yoshioka, 1993). It has been reported that SP in the NAc binding with NK-1 receptor could indirectly inhibit excitatory synaptic transmission by increasing extracellular level of DA and adenosine (Kombian et al., 2003). Recent studies have shown that knockout of preprotachykinin A (PPT-A) can reduce the number of δ -opioid receptors inserted into the surface. The knockout of this molecule also removed spinal analgesia and the morphine tolerance mediated by δ -opioid receptor, suggesting that there may exist a direct link between tachykinin and opioid system through interacting with tachykinin/ δ -opioid receptors (Guan et al., 2005). Knockout of NK-1 receptors in mice decreased CPP score induced by morphine and influenced reward effects of morphine (Gadd et al., 2003). Behavioral studies have shown that SP (1–7) and SP (1–11) attenuate opioid reward and a variety of physical withdrawal symptoms, and that SP (1–7) can significantly reduce the D2 dopamine receptor transcription in the NAc and mPFC (Zhou et al., 2003). Microperfusion of SP N-terminal fragment into the VTA increased the content of DA and the DA metabolism in the NAc in morphine withdrawal mice, suggesting that N-terminal peptides of SP could attenuate the morphine withdrawal symptoms by increasing DA release and its metabolism in the NAc. This mechanism may be related to glutamatergic transmission (Zhou and Nyberg, 2002). Morphological studies have demonstrated that SP and other neurotransmitters such as Glu and DA are co-localized in mesocorticolimbic dopaminergic pathway, indicating that SP may interact with other neurotransmitters and that it is involved in drug dependence. Some studies have shown that SP can enhance the effects of glutamate in the spinal dorsal horn and induce the wind-up phenomenon, which is regarded as the mechanism underlying the central sensitization (Dougherty et al., 1993). Local injection of SP enhanced the nociceptive behavioral response in spinal cord (Carlton et al., 1998) and increased the discharge of primary afferent fibers induced by glutamate (Zhang et al., 2006). Administration of monosodium glutamate could increase the expression of PPT-A mRNA in cerebral cortex, amygdala, etc. (Xu et al., 2007). All these results

indicate that there exists interaction between glutamate and SP, but their exact roles in opioid dependence has yet to be studied.

7. Conclusion

Opioid addiction is a chronically relapsing disorder and the neural network involved is associated with several brain nuclei and neurotransmitters/neuropeptides. There is evidence that the mesocorticolimbic dopaminergic regions, especially the VTA and NAc, are the key regions of opioid psychological dependence. Historically, research into the neurobiological substances that underlie the drug addiction has focused on the DA system. In the latest 5 years, more attention has focused on the role of glutamate and its receptors in mesocorticolimbic dopaminergic regions in opioid addiction. As a primary excitatory neurotransmitter in the brain, glutamate can be responsible for development of addictive behaviors by binding with its iGluRs and mGluRs and involved in the opioid addiction. The role of iGluRs is well investigated and antagonists of both NMDA and AMPA receptors attenuate the withdrawal syndrome of opioid dependence. The role of mGluRs is still unclear and needs to be further studied. The activations of several signal transduction pathways including NMDA–Ca²⁺–NO–cGMP pathway, AC–cAMP–CREB pathway and MAPK pathway are involved in the plastic changes induced by glutamate. In addition, glutamate receptors and other neurotransmitter/neuropeptide receptors such as opioids, DA, GABA and SP coexisted in the mesocorticolimbic dopaminergic regions and interact with each other in opioid addiction. In summary, glutamate and its receptors are important in opioid addiction, and these findings have increased our understanding of the neuropathological processes associated with opioid addiction and have provided new targets for pharmacological approach to the treatment of opioid addiction.

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