Current Status of Substance Abuse in East Asia and Therapeutic Prospects

Q Ren, M Ma, K Hashimoto

Abstract

The abuse of drugs, including opioids and stimulants, is a major public health problem worldwide, including in East Asia. Nonetheless, there are no pharmacological treatments for many psychiatric or neurological symptoms associated with that abuse. Abused drugs exert several detrimental effects on structural plasticity in brain regions associated with reward circuits. Understanding the molecular mechanisms that underlie this structural plasticity in brain neurons will aid in the development of novel therapeutic drugs for substance abuse. In this review, we discuss recent topics in substance abuse in East Asia and the therapeutic drugs available. Finally, we discuss potential therapeutic signalling pathways involved in long-term changes to structural plasticity in the brain after repeated administration of opioids and stimulants.

Key words: Analgesics, opioid; Central nervous system stimulants; Neuronal plasticity; Nucleus accumbens; Reward

Introduction

Abuse of substances such as cannabis, opioids, cocaine, and amphetamine-type stimulants (ATS) is a major global public health problem. It has been estimated that about 5.2% of the world population aged 15 to 64 years used an illicit drug at least once in the previous year.1 Notably, the abuse of opioids and ATS, including amphetamine, methamphetamine (METH), and 3,4-methylenedioxymethamphetamine (MDMA; ecstasy), is a serious and growing problem in Asia.1-5 In China, the most prevalent illicit drugs are heroin and ATS, and the number of registered drug abusers is increasing by about 122% per year.6,7 Heroin and ATS are also commonly used illicit drugs in Hong Kong and Taiwan.5,8,9 In Hong Kong, the proportion of abusers who consume psychotropic substances, including ketamine, and METH, increased to 59% in 2012.8 Lee et al9 reported that from 1999 to 2011, the distribution percentage of METH identified in urine and non-urine samples in Taiwan was over 47% and 25%, respectively. In Japan, METH is the most popular drug of abuse in adults.10 Amphetamine-type stimulants account for a high proportion of drugs of abuse in South Korea.11 In other Asian countries, including Indonesia, the Philippines and Thailand, heroin, ATS, and cannabis are abused more than other illicit drugs5 (Table 1).

Table 2 shows the short- and long-term effects of heroin, METH, and ketamine. Heroin is converted to morphine in the brain and binds to opioid receptors.12,13 Short-term effects of heroin include rush, respiratory depression, clouded mental functioning, nausea and vomiting, suppression of pain, and spontaneous abortion. Repeated use of heroin is associated with addiction, viral infections (e.g. human immunodeficiency virus infection and hepatitis), collapsed veins, bacterial infections, abscesses, infection of the heart lining and valves, rheumatological problems, and liver and kidney disease.12 As a powerful stimulant, METH in small doses can cause increased physical activity and wakefulness, decreased fatigue and appetite, hyperthermia, increased blood pressure, and irregular heartbeat. Long-term METH use results in addiction, altered brain structure and function, deficits in thinking and motor skills, increased distractibility, memory loss, aggressive or violent behaviour, mood disturbances, dental problems, and weight loss.4,14 Ketamine is a classic dissociative drug. Low and moderate doses of ketamine produce numbness, disorientation, dizziness, and sensory perception changes in humans. High doses of ketamine cause several effects such as hallucinations, memory loss, and physical distress.15 Chronic use of ketamine is associated with psychosis and/or depression.16,17 It also produces conceptual disorganisation and disrupted delayed recall.18

Despite the severe health consequences of substance abuse, we still face a serious situation of abuse of illicit
drugs. The precise molecular mechanisms of action of abused drugs in the brain are currently unknown. There is no pharmacological treatment for the wide range of symptoms associated with opioids and ATS.\textsuperscript{19,20} In this review, we will discuss recent findings with regard to the molecular mechanisms and potential pharmacotherapeutic drugs for opioid and ATS abusers.

### Current Therapeutic Approaches to Drug Abuse

The development of therapeutic drugs for heroin addiction is mainly focused on opioid receptors: (1) Opioid receptor agonists or partial agonists that are used to replace addictive drugs that act via opioid receptors and are safer and less likely to produce addiction; (2) opioid receptor antagonists that block receptors and affect the rewarding effects of opioids.\textsuperscript{12,19,20}

Methadone, a slow-acting opioid receptor agonist, is an excellent drug to alleviate opioid addiction, and this has been permitted for treatment of outpatients.\textsuperscript{12} Methadone suppresses the “high” and prevents the withdrawal symptoms of opioid abuse. Nonetheless, methadone also has shortcomings in tolerability, compliance, and effectiveness.\textsuperscript{19,20} Buprenorphine, a partial opioid receptor agonist, represents another milestone in the history of

### Table 1. Main illegal drugs abused in countries of East Asia.

<table>
<thead>
<tr>
<th>Country / region</th>
<th>Major abused substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>China\textsuperscript{6-7}</td>
<td>Heroin, amphetamine, METH, MDMA</td>
</tr>
<tr>
<td>Hong Kong\textsuperscript{5,8}</td>
<td>Heroin, ketamine, METH</td>
</tr>
<tr>
<td>Taiwan\textsuperscript{9}</td>
<td>Heroin, METH, ketamine, MDMA</td>
</tr>
<tr>
<td>Japan\textsuperscript{10}</td>
<td>METH</td>
</tr>
<tr>
<td>South Korea\textsuperscript{11}</td>
<td>ATS</td>
</tr>
<tr>
<td>Indonesia\textsuperscript{5}</td>
<td>ATS, heroin, cannabis</td>
</tr>
<tr>
<td>Philippines\textsuperscript{5}</td>
<td>ATS, cannabis</td>
</tr>
<tr>
<td>Thailand\textsuperscript{5}</td>
<td>ATS, cannabis</td>
</tr>
</tbody>
</table>

Abbreviations: ATS = amphetamine-type stimulants; MDMA = 3,4-methylenedioxymethamphetamine; METH = methamphetamine.

### Table 2. Short-term and long-term effects of heroin, methamphetamine, and ketamine in humans.\textsuperscript{4,12-18}

<table>
<thead>
<tr>
<th>Heroin</th>
<th>Methamphetamine</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term</strong></td>
<td><strong>Long-term</strong></td>
<td><strong>Short-term</strong></td>
</tr>
<tr>
<td>Rush</td>
<td>Extreme addiction</td>
<td>Increased attention and decreased fatigue</td>
</tr>
<tr>
<td>Depressed respiration</td>
<td>Infectious disease</td>
<td>Increased activity and wakefulness</td>
</tr>
<tr>
<td>Clouded mental functioning</td>
<td>Collapsed veins</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Bacterial infections</td>
<td>Euphoria and rush</td>
</tr>
<tr>
<td>Suppression of pain</td>
<td>Abscesses</td>
<td>Increased respiration</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>Infection of heart lining and valves</td>
<td>Rapid irregular heartbeat</td>
</tr>
<tr>
<td>Rheumatic problems</td>
<td>Hyperthermia</td>
<td>Mood disturbances</td>
</tr>
<tr>
<td>Liver and kidney disease</td>
<td>Weight loss</td>
<td>Psychological distress</td>
</tr>
</tbody>
</table>
treatment of opioid addiction and also alleviates drug craving without harmful side-effects. Although buprenorphine shows a favourable safety profile, it retains abuse potential and cautious regulation and prescription distribution must be maintained.12,19 Ultimately in the treatment of opioid addiction, a disadvantage of both methadone and buprenorphine is that they merely substitute one addictive drug for another.20 On the contrary, the opioid antagonist, naltrexone, can block the action of opioids and incur no addiction or physical dependence. Naltrexone has been reasonably effective in sustaining drug abstinence. Although naltrexone can be administered as a depot formulation, its high price makes it suitable only for the most severely affected patients.20

In contrast to opioid addiction, the development of therapeutic drugs for ATS addiction involves multiple systems, including the dopaminergic, serotonergic, and cholinergic systems; γ-aminobutyric acid (GABA) receptors, opioid receptors, and immune system.4 Methamphetamine increases striatal dopamine (DA) levels and inhibits the DA transporter (DAT).4,21,22 Dopamine is well known to play an important role in the regulation of motor function, reward, and pleasure in the brain. Both DA D1 and D2 receptor antagonists block METH-induced behavioural abnormalities in rodents.23,24 The antipsychotic drug risperidone, a DA D2 receptor and 5-hydroxytryptamine2A (5-HT2A) receptor antagonist, blocked the development of behavioural abnormality induced in rodents by METH.25 An open-labelled pilot study showed that risperidone has a significant effect on decreased METH use and improved motor function.26 Another atypical antipsychotic aripiprazole, a DA D2 and 5-HT1A receptor partial agonist, had beneficial effects on METH-induced behavioural sensitisation and self-administration of METH in rats.27,28 Although aripiprazole has a potential therapeutic effect on METH dependence, it cannot attenuate the craving for METH in patients. Moreover, aripiprazole treatment is associated with amphetamine-like effects because of its DA partial agonism and thus has limited use for treatment of METH dependence.29 In contrast, DA receptor agonists such as modafinil, dextroamphetamine, and methylphenidate reduce METH use and METH-induced DA release in rodents. Nonetheless, therapeutic effects of these drugs in METH-addicted humans are limited.5

Methamphetamine-induced behavioural responses are associated with long-term changes in serotonin (5-HT) systems.2,3,30,31 Selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, paroxetine, and ondansetron (a 5-HT1 receptor antagonist), have potential as therapeutic drugs for METH addiction. Several studies have shown that SSRI attenuate METH-induced development of behavioural sensitisation, hyperactivity, and stereotypy in rodents.5,32,33 Preliminary clinical studies, however, have shown that SSRI are unlikely to be efficacious for the treatment of METH addiction. A similar situation has arisen in studies of therapeutic drugs in the cholinergic system: GABA receptor agonists and opioid receptor antagonists. Despite their effectiveness in the treatment of METH dependence in animal models, their use in clinical studies is limited.4

**Anti-inflammatory Drug Minocycline as a Therapeutic Drug**

Microglia are the resident antigen-presenting cells in the brain. When activated by inflammation, damage, or disease, these immune-like cells can migrate to sites of injury. Activation of microglia, a common feature of most neurodegenerative diseases, causes the release of proinflammatory mediators and other injury response factors that ultimately compromise neuronal and oligodendroglial viability.34 Bowyer et al35 reported that METH resulted in the activation of microglia in the rat striatum and that microglia were activated in response to nerve terminal damage. Several lines of evidence suggest that METH-induced neurotoxicity is associated with microglial activation.36,37

Minocycline is a second-generation tetracycline that readily crosses the blood-brain barrier and has powerful anti-inflammatory and neuroprotective properties.38,39 Zhang et al38 reported the effects of minocycline on behavioural changes and neurotoxicity in the dopaminergic neurons induced by the administration of METH. Pretreatment with minocycline attenuated hyperlocomotion in mice after a single administration of METH. The development of behavioural sensitisation after repeated administration of METH was attenuated by pretreatment with minocycline. A reduction in DA and DAT levels in the striatum after repeated administration of METH was attenuated by pretreatment with and subsequent administration of minocycline. Minocycline attenuated the increased microglial activation in the striatum after repeated administration of METH, and attenuated METH-induced rewarding effects in mice.39

In a recent study, daily bilateral intra-accumbal injection of minocycline during the extinction period blocked the persistence of the METH rewarding effect, suggesting that minocycline should be considered as a promising therapeutic drug to prevent relapse in METH-dependent patients.40 Administration of minocycline during the extinction period could facilitate extinction and abolish the ability of drug-associated cues to evoke reinstatement. These findings suggest that minocycline can ameliorate behavioural changes as well as neurotoxicity in dopaminergic terminals after administration of METH.38,41 Zhang et al41 reported that minocycline ameliorated neurotoxicity in the serotonergic neurons after repeated administration of MDMA. Using a conscious-monkey positron emission tomography study, Hashimoto et al42 showed that pretreatment and subsequent administration of minocycline markedly attenuated the reduction of DAT density in the monkey striatum after administration of METH. Post-treatment and subsequent administration of minocycline also attenuated the reduction of DAT in the monkey brain after administration of METH.

A double-blind, placebo-controlled, crossover study showed that minocycline attenuates subjective rewarding
effects of dextroamphetamine in healthy subjects. In addition, Tanibuchi et al. reported that psychotic symptoms in a female patient with METH-use disorder were successfully improved by minocycline. A randomised, double-blind, placebo-controlled study of minocycline in patients with METH-use disorders is needed.

**Vaccines as Novel Pharmacotherapeutic Treatments for Drug Abuse**

Vaccines are also being developed as therapy in substance abuse. These vaccines act as blockers and can theoretically be developed to be active against any drug of abuse. Vaccines act pharmacokinetically, but not pharmacodynamically, via 2 processes. First, they provoke production of antibodies against the drug. Second, the antibodies bind to the drug and prevent it from leaving the bloodstream and entering the brain and other organs. In clinical trials, cocaine vaccine attenuated the subjective experience and euphoria derived from smoked cocaine. A few subjects showed mild, but not serious adverse effects that included mild tachycardia, elevated temperature, and hypertension. A successful vaccination programme requires several months and the patient must be brought to a treatment site for the series of vaccinations. Continued drug abuse during this period may increase the risk of failure to appear for follow-up visits. The full clinical registration path for the U.S. Food and Drug Administration (FDA) approval will require more comprehensive clinical trials. Vaccines for METH and opioids are still at the preclinical stage of development. A conjugate vaccine against METH has been shown to attenuate METH-induced hypolocomotion and activity levels in mice. Active vaccination inhibited the acquisition of METH self-administration in mice. Opioid vaccines have some difficulties in obtaining FDA approval, including the need for opioid replacement. Although such vaccines appear safer than naltrexone, they face an additional challenge. The current epidemic of prescription opioid abuse involves at least 5 different chemical entities, including morphine, codeine, thebaine, methadone, and buprenorphine, and each may require a separately developed vaccine.

**Plasticity of Synaptic Morphology in Drug Addiction**

The brain reward circuitry is a target for drugs of abuse. This circuitry plays a role in rewarding behaviour closely associated with natural reinforcement, such as elation, food, and sexual behaviour. Within this circuitry, the dopaminergic neurons in the ventral tegmental area (VTA) are projected to the nucleus accumbens (NAC, a part of the ventral striatum), prefrontal cortex (PFC), amygdala, and hippocampus. A general characterisation of structural plasticity in the brain’s reward circuitry describes altered dendrite branching or arborisation and changes in the density or morphometry of dendritic spines.

Drugs of abuse can corrupt or hijack the brain’s reward circuitry. Abuse of opioids and stimulants is associated with diverse morphological changes in the structure of neurons and dendritic processes in different brain regions. Robinson et al. reported that administration of morphine caused decreased spine density in the NAC shell, medial prefrontal cortex (mPFC), parietal cortex (Par1), and hippocampus regions in rat brains (Table 3). Furthermore, the number of dendritic branches was decreased in the NAC shell, mPFC, and Par1 of morphine-treated rat brains. Nonetheless, spine density in the apical and basilar orbital prefrontal cortex (oPFC) was increased in response to morphine. Several studies have shown that

### Table 3. Opioid- and stimulant-induced changes in neuronal morphology

*In several brain regions, opioids reduce spine density and dendritic branches, while stimulants cause the opposite effects.*

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Spine density</th>
<th>Dendritic branches</th>
<th>Stimulants</th>
<th>Spine density</th>
<th>Dendritic branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAc shell</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>NAc core</td>
<td>NA</td>
<td>NA</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>CPu</td>
<td>NA</td>
<td>NA</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>mPFC</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>oPFC</td>
<td>Increased</td>
<td>NA</td>
<td>Decreased</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Par1</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Oc1</td>
<td>Decreased</td>
<td>NA</td>
<td>Decreased</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Decreased</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>VTA</td>
<td>Soma size decreased</td>
<td></td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CPu = caudate putamen; mPFC = medial prefrontal cortex; NA = no data; NAc = nucleus accumbens; Oc1 = occipital cortex; oPFC = orbital prefrontal cortex; Par1 = parietal cortex; VTA = ventral tegmental area.
opiates reduce the overall soma size of VTA dopaminergic neurons.5,35,56,57

In contrast to opiates, stimulants show an opposite effect on structural plasticity in brain reward regions. Amphetamine consistently increased spine density and dendritic branches in the NAc core, NAc shell, mPFC, caudate, and putamen, but decreased spine density in pPFC and Oc1.54,58-60 Cocaine increased dendritic spine density and dendritic branches in the NAc shell, medium spiny neurons, mPFC pyramidal neurons, and VTA dopaminergic neurons (Table 3).55,59,61-64

In summary, opioids and stimulants exert opposite adverse effects on dendritic spines and dendritic branches in different regions of the brain’s reward circuitry. The precise mechanisms that underlie alterations to synaptic plasticity by opioids and stimulants are poorly understood.

Cellular Signalling Pathway in Synaptic Plasticity

Although the precise mechanisms of drug abuse–induced changes to synaptic plasticity are unclear, there is evidence that certain signalling pathways in synaptic plasticity are potential therapeutic targets for drug abuse. Brain-derived neurotrophic factor (BDNF) and its receptor TrkB signalling pathways play a key role in spine formation, maintenance, and remodelling.53,65-69 Accumulating evidence suggests the role of BDNF-TrkB signalling in the plasticity of brain regions after repeated administration of drugs of abuse.5,35,60,70-72

We have reported that the TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) attenuates behavioural abnormalities (such as hyperlocomotion and prepulse inhibition deficits) in mice after administration of METH and that 7,8-DHF attenuates the development of behavioural sensitisation and dopaminergic neurotoxicity in mice after repeated administration of METH.22,73 Zhang et al74 reported that 7,8-DHF and the TrkB antagonist ANA-12 protected against different changes in spine density of NAc, hippocampus, and frontal cortex in depressed mice brains. Shirayama et al75 reported that these substances exerted the same effect in rats with learned helplessness. Taken together, these findings suggest that the BDNF-TrkB signalling pathway is a potential therapeutic target for drug abuse.

Conclusion

Drug abuse is a serious public health problem in East Asia and repeated drug abuse may cause long-lasting damage to structural plasticity in the brain. There is currently no approved therapeutic approach, and the development of pharmacotherapy for drug abuse is still in its infancy. Accumulating evidence reveals that opioids and stimulants show opposite effects on morphological changes in different brain regions. In view of the role of BDNF-TrkB signalling in the synaptic plasticity in the brain, BDNF-TrkB signalling pathways are a potential therapeutic target of substance abuse. Understanding the molecular mechanisms that underlie the roles of these signalling pathways in drug abuse will contribute to the development of novel therapeutic drugs.

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