

## Review Article

# Update in the neurobiology of addiction

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**Received:** 23 July 2016

**Accepted:** 10 August 2016

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### ABSTRACT

Addiction is a major global health concern. Up to date, underlying the possible mechanisms of addiction have begun to yield fundamentally important insights to discover the novel therapeutics as there are very few effective treatments for addiction. This review article is designed to outline the underlying mechanisms of addiction.

**Keywords:** Addiction, Mechanism, Synaptic plasticity, BDNF, MicroRNA

## INTRODUCTION

Drug addiction is a chronic relapsing brain disease. Addiction causes long-lasting neuroadaptations. It is characterized by craving for the substances and, in some cases, involvement in risky behaviors that can cause death and high rates of relapse even after long periods of abstinence.<sup>1,2</sup>

"Addiction is caused, in part, by powerful and long-lasting memories of the drug experience. Relapse caused by exposure to cues associated with the drug experience is a major clinical problem that contributes to the persistence of addiction".<sup>3</sup>

### Possible mechanisms underlying addiction

#### Neural circuitry

Addictive drugs have a common neural pathway as they target the mesocorticolimbic dopamine system. This system originates in the ventral tegmental area (VTA) and projects mainly to the nucleus accumbens (NAc) and prefrontal cortex (PFC).<sup>4</sup>

#### Ventral tegmental area (VTA)

Research studies showed that the acquisition and expression of many drug-dependent behaviours involves VTA, a midbrain structure contained dopamine, GABA, and glutamate neurons. Abuse of drugs alters the excitatory and inhibitory synaptic input onto VTA dopamine neurons, suggesting a crucial role for VTA afferents in mediating the effects of drugs.<sup>5</sup> The neural circuitry executing any behaviour is complicated; although wide-ranging research over the past few decades clarifies that the VTA is critically involved with both rewarding and aversive drug-dependent behaviors.<sup>6</sup>

#### Nucleus accumbens (NAc)

GABA neurons in the NAc project to the VTA and are supposed to mediate a "long-loop" inhibitory feedback to regulate dopamine neuron activity.<sup>7</sup>

#### Prefrontal cortex (PFC)

The medial PFC performs a diversity of cognitive and executive functions and is involved in the reinstatement of drug-seeking behavior.<sup>8,9</sup>

### **MicroRNAs in addiction**

Drugs of abuse promotes long-term changes in brain gene and protein expression, which may contribute to the brain alteration accompanied by abuse and dependence.<sup>3</sup>

Addictive drugs provoke long-lasting adaptations in corticostriatal and mesolimbic brain reward circuitry due to long-term alterations in gene expression. MicroRNAs, a class of non-coding RNAs, are potent regulators of gene expression that bind to target mRNAs, thereby inhibiting their translation causing degradation. MicroRNAs are increasingly involved in gene expression changes underlying physiological and pathological conditions as addiction.<sup>10</sup>

The neuronal enhancement and various expression of non-coding RNAs and miRNAs is thought to share in the complexity of cell types and functions within the mammalian central nervous system.<sup>11,12</sup>

### **Role of neurotrophic factors**

Neurotrophic factors (NTFs) are well-recognized for their actions on neuronal survival and differentiation. Likewise, NTFs have been shown to be involved in synaptic plasticity in the brain. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are the most studied NTFs. The relation between drugs of abuse and NTFs seems to be a mutual process; abused drugs can affect the expression of NTFs, and NTFs can affect the outcome of drugs and modify the drug-induced behaviour. Additionally, BDNF is proved to be a promoter of methylation in association with drug addiction. In fact, how GDNF or BDNF affect the drug-seeking behaviour depends on the drug type, addiction phase, and the timing of GDNF/BDNF treatment in relation to drug administration.<sup>1,13</sup> In support of this notion, addictive substances have been revealed to increase the BDNF protein levels in multiple brain regions.<sup>14-16</sup> Enhanced BDNF levels are found in the hippocampus of methamphetamine self-administering rats and the plasma of human methamphetamine users.<sup>17,18</sup> Remarkably, primary results suggest that the BDNF Val (66) Met genotype, which has been associated with neurobehavioral deficits, may promote drug seeking phenotypes in methamphetamine and heroin-dependent individuals.<sup>19-21</sup>

### **Synaptic plasticity**

Synaptic plasticity is considered the basis for most models of learning, memory and development in neural circuits.<sup>22</sup> Drug abuse can elicit neural maladaptation leading to drug addiction.<sup>23</sup> Currently, the role of synaptic plasticity in addiction has begun to yield vitally important insights into mechanisms that underlie the addiction.<sup>24</sup>

Drugs of abuse alter (either increasing or decreasing) the strength of excitatory synapses by tapping into traditional mechanisms of plasticity, including long-term potentiation (LTP) and long-term depression (LTD).<sup>25</sup> Synaptic plasticity is controlled pre-synaptically via the regulation of glutamate release and post-synaptically via the adding or removal of AMPA or NMDA glutamate receptors and addictive drugs interfere with these processes.<sup>26-28</sup>

### **Multiple memory systems/stress approach**

Multiple memory systems approach possibly contributes exclusive components to the learned behaviour supporting drug addiction and relapse. Particularly, the change from recreational drug use to compulsive drug abuse may mirror a neuroanatomical shift from cognitive control of behaviour performed by the hippocampus/dorsomedial striatum toward habitual control of behaviour mediated by the dorsolateral striatum (DLS). Additionally, stress/anxiety may establish a cofactor that facilitates DLS-dependent memory, and this may act as a neurobehavioral mechanism underlying the increased drug use and relapse in humans following stressful event.<sup>29</sup>

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Nafea OE. Update in the neurobiology of addiction. *Int J Sci Rep* 2016;2(9):212-4.