



mTOR Signaling and Drug Memory

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Introduction

Drug addiction is a chronic, relapsing brain disorder. Pathological neuroplasticity changes in the brain areas involved in cognition, memory and reward lead to intensely psychological dependence on abused drugs in addicts. The key to drug addiction treatment is how to prevent the high relapse rate after withdrawal. Mammalian Target of Rapamycin (mTOR) signaling pathway exists widely *in vivo* and has variously complex physiological function, which can regulate drug memory by affecting synaptic plasticity. This mini-review discussed the role and research progress of the mTOR signaling pathway in drug memory.

Drug memory and relapse

Drug addiction is a chronic and highly relapse brain disorder with the following clinical characteristics, including compulsive drug-taking, drug-seeking and a high rate of relapse to drug resumption [1]. Drug addiction not only harms the physical and mental health of addicts, but also leads to the spread of many diseases and increases the social and economic burden. The pharmacological effect of drug addiction is to reduce the plasticity of the central nervous system by increasing dopamine in the striatum, and eventually lead to dysfunction of self-control, cognitive, learning and memory, and impulse control [2]. Addiction is widely perceived as an aberrant process of learning and memory, in which drug memory usurp the neurobiological mechanisms of normal learning and memory, which is known as the major cause of relapse [3]. Drug memory have some same basic process as normal memories, including acquisition, consolidation and reconsolidation [4]. Memories are in unstable stages that can be intervention after acquisition or reactivation, which are called consolidation and reconsolidation, respectively. Various interventions to block molecular mechanisms or neural circuits in consolidation and reconsolidation can effectively impair drug memory, thereby inhibiting psychological craving and compulsive

drug seeking behavior [5]. Therefore, activating drug memory to into the reconsolidation process by re-exposure to drug-associated cues provides operability for intervention of drug memory [6]. The reconsolidation of drug memory is a protein synthesis dependence and time specificity process and accompanied by a series of changes in molecular and signaling pathways [5,7]. For example, the activity of Extracellular Regulated Protein Kinases (ERK) increases after the activation of cocaine addiction memory in the Nucleus Accumbens Core (NAC core) in the Conditioned Place Preference (CPP) model, and ERK inhibitors can disrupt the reconsolidation process of cocaine addiction memory [8]. Immediate Early Genes (IEGs) are activated by the signal transduction pathway after activation addiction memory, which affects the expression of proteins related to synaptic plasticity in reconsolidation. Some immediate early genes, such as ZIF268, Arc and c-Fos, were significantly upregulated during the reconsolidation process, and knockdown these immediate early genes could disrupt the reconsolidation process of addictive memory [9-11]. Hence, exploring interventions that disturb the reconsolidation of drug memory is a promising strategy for preventing relapse.

mTOR Signaling

The mTOR signaling pathway is well known to exert complex physiological functions *in vivo*, especially, plays a critical role in gene transcription regulation and protein translation initiation via modulating downstream target proteins [12-14]. TSC1/TSC2 heterodimer is an inhibitory regulator upstream of the mTOR signaling pathway, PI3K-PDK-Akt pathway and AMP-activated Protein Kinase (AMPK) are classical upstream regulatory pathways of TSC1/TSC2. Besides, activate glutamate receptors in the central nervous system, such as NMDA receptor, can also increase the phosphorylation level of downstream mTOR [15]. Protein tyrosine kinase (PTK) regulated system is a critical upstream regulatory

mechanism of mTOR signaling pathway [16,17]. Extracellular signals, such as Brain-Derived Neurotrophic Factor (BDNF) and Insulin/Insulin growth factor-1 (IGF-1) act on the PTK receptor in cytomembrane to activate downstream PI3K, then promoting biosynthesis of phosphatidylinositol-3,4,5-triphosphate 3 (PIP3), by which activate the protein kinase Akt signaling pathway and TSC1/TSC2 heterodimer [18,19]. The mTOR signaling pathway plays a critical role in the protein translation process by regulating the downstream translation initiation factor, the eIF4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinases (S6Ks) [20,21]. mTOR regulates the initiation of protein translation via changing the binding state of eIF4E and 4E-BP1 phosphorylation level [22]. mTOR activation increases the phosphorylation level of downstream S6Ks and promotes peptide chain elongation during protein translation [23,24]. Hence, the mTOR signaling pathway regulates protein synthesis via regulating the activity of downstream target proteins 4E-BP1 and S6Ks.

mTOR Signaling and Drug Memory

Transcription regulation and protein translation initiation of mTOR signaling are closely related to synaptic plasticity. It has been reported that rapamycin inhibits mTOR activity to block the formation of long-term facilitation [25]. Rapamycin blocks late Long-Term Potentiation (L-LTP) induced by Brain Derived Neurotrophic Factor (BDNF), which activates mTOR through the PI3K-PDK-Akt signaling pathway, indicating mTOR signaling is involved in BDNF related regulation of synaptic plasticity [26]. mTOR activity is required for memory consolidation and reconsolidation in different memory types, including spatial memory [27], fear memory [28], as well as drug memories [29]. In the Conditioned Place Preference (CPP) model, it is found that inhibition of mTOR signal by rapamycin disrupts reconsolidation of reward memory to prevent drug seeking [30,31]. In summary, the mTOR signaling pathway may regulate the consolidation and reconsolidation of drug memory by affecting the synaptic plasticity.

Conclusion and Future Direction

The mTOR signaling pathway in the central nervous system regulates drug memory via affect synaptic plasticity, suggesting that the mTOR signaling pathway may be a potential target for the treatment of addiction. Therefore, future research should focus on elucidating the underlying mechanisms of drug memory in order to provide effective treatment for addiction.

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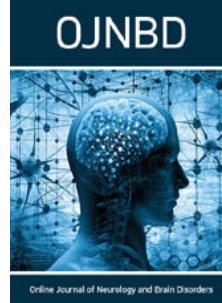
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