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Mini Review

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, PIK3-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 is 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 PIK3-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.

References

1. Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, et al. (2001) Neural activity related to drug craving in cocaine addiction. Arch Gen Psychiatry 58(4): 334-341.
2. Robinson TE, Berridge KC (2000) The psychology and neurobiology of addiction: An incentive-sensitization view. Addiction 95 Suppl 2: 91-117.
3. Stewart J, de Wit H, Eikelboom R (1984) Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol Rev 91 (2): 251-268.
4. Torregrossa MM, Corlett PR, Taylor JR (2011) Aberrant learning and memory in addiction. Neurobiol Learn Mem 96 (4): 609-623.
5. Bender BN, Torregrossa MM (2020) Molecular and circuit mechanisms regulating cocaine memory. Cell Mol Life Sci 77(19): 3745-3768.
6. Wells AM, Arguello AA, Xie X, Blanton MA, Lasseter HC, et al. (2013) Extracellular signal-regulated kinase in the basolateral amygdala, but not the nucleus accumbens core, is critical for context-response-cocaine memory reconsolidation in rats. Neuropsychopharmacology 38(5): 753-762.
7. Robinson MJ, Franklin KB (2007) Central but not peripheral beta-adrenergic antagonism blocks reconsolidation for a morphine place preference. Behav Brain Res 182(1): 129-134.
8. Miller CA, Marshall JF (2005) Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. Neuron 47(6): 873-884.
9. Minatohara K, Akiyoshi M, Okuno H (2015) Role of Immediate-Early Genes in Synaptic Plasticity and Neuronal Ensembles Underlying the Memory Trace. Front Mol Neurosci 8: 78.
10. Hearing MC, See RE, McGinty JF (2008) Relapse to cocaine-seeking increases activity-regulated gene expression differentially in the striatum and cerebral cortex of rats following short or long periods of abstinence. Brain Struct Funct 213(1-2): 215-227.
11. Strekalova T, Zorner B, Zacher C, Sadovska G, Herdegen T, et al. (2003) Memory retrieval after contextual fear conditioning induces c-Fos and JunB expression in CA1 hippocampus. Genes Brain Behav 2(1): 3-10.
12. Sabatini DM, Erdjument Bromage H, Lui M, Tempst P, Snyder SH (1994) RAFT1: A mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. Cell 78(1): 35-43.
13. Schmelzle T, Hall MN (2000) TOR, a central controller of cell growth. Cell 103(2): 253-262.
14. Laplante M, Sabatini DM (2012) mTOR signaling in growth control and disease. Cell 149(2): 274-293.
15. Lenz G, Avruch J (2005) Glutamatergic regulation of the p70S6 kinase in primary mouse neurons. J Biol Chem 280(46): 38121-38124.
16. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden C, et al. (2018) Metabolic Induction of Trained Immunity through the Mevalonate Pathway. Cell 72(1-2): 135-146.
17. Crosby P, Hamnett R, Putker M, Hoyle NP, Reed M, et al. (2019) Insulin/IGF-1 Drives PERIOD Synthesis to Entrain Circadian Rhythms with Feeding Time. Cell 177(4): 896-909.
18. Kandel ES, Hay N (1999) The regulation and activities of the multifunctional serine/threonine kinase Akt/PKB. Exp Cell Res 253(1): 210-229.
19. Gingras AC, Kennedy SG, O'Leary MA, Sonenberg N, Hay N (1998) 4E-BP1, a repressor of mRNA translation, is phosphorylated and inactivated by the Akt(PKB) signaling pathway. Genes Dev 12(4): 502-513.
20. Peterson RT, Desai BN, Hardwick JS, Schreiber SL (1999) Protein phosphatase 2A interacts with the 70-kDa S6 kinase and is activated by inhibition of FKBP12-rapamycinassociated protein. PNAS 96(8): 4438-4442.
21. Desai BN, Myers BR, Schreiber SL (2002) FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. PNAS A 99(7): 4319-4324.
22. Proud CG (2007) Signalling to translation: How signal transduction pathways control the protein synthetic machinery. Biochem J 403(2): 217-234.

23. Wang X, Li W, Williams M, Terada N, Alessi DR, et al. (2001) Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase. EMBO J 20(16): 4370-4379.

24. Holz MK, Ballif BA, Gygi SP, Blenis J (2005) mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell 123 (4): 569-580.

25. Steward O, Schuman EM (2003) Compartmentalized synthesis and degradation of proteins in neurons. Neuron 40(2): 347-359.

26. Takei N, Kawamura M, Hara K, Yonezawa K, Nawa H (2001) Brain-derived neurotrophic factor enhances neuronal translation by activating multiple initiation processes: Comparison with the effects of insulin. J Biol Chem 276(46): 42818-42825.

27. Dash PK, Orsi SA, Moore AN (2006) Spatial memory formation and memory-enhancing effect of glucose involves activation of the tuberous sclerosis complex-Mammalian target of rapamycin pathway. J Neurosci 26 (31): 8048-8056.

28. Parsons RG, Gafford GM, Helmstetter FJ (2006) Translational control via the mammalian target of rapamycin pathway is critical for the formation and stability of long-term fear memory in amygdala neurons. J Neurosci 26(50): 12977-12983.

29. Wang X, Luo YX, He YY, Li FQ, Shi HS, et al. (2010) Nucleus accumbens core mammalian target of rapamycin signaling pathway is critical for cue-induced reinstatement of cocaine seeking in rats. J Neurosci 30 (38): 12632-12641.

30. Lin J, Liu L, Wen Q, Zheng C, Gao Y, et al. (2014) Rapamycin prevents drug seeking via disrupting reconsolidation of reward memory in rats. Int J Neuropsychopharmacol 17(1): 127-136.

31. Barak S, Liu F, Ben Hamida S, Yowell QV, Neasta J, et al. (2013) Disruption of alcohol-related memories by mTORC1 inhibition prevents relapse. Nat Neurosci 16(8): 1111-1117.

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