Int J Physiol Pathophysiol Pharmacol 2019;11(6):318-320
www.ijppp.org /ISSN:1944-8171/IJPPP0104669

Commentary

Nicotinamide phosphoribosyltransferase contributes to cocaine addiction through sirtuin 1

Som Singh, Matthew William, Xiang-Ping Chu

Department of Biomedical Sciences, University of Missouri-Kansas City School of Medicine, Kansas, Missouri, USA

Received November 8, 2019; Accepted December 3, 2019; Epub December 15, 2019; Published December 30, 2019

Abstract: Drug addiction is a persistent mental illness and there is no effective treatment. The precise mechanisms underlying addictive responses have not been completely understood, although ion channels, neurotransmitters as well as their receptors, and intracellular endogenous molecules in the brain have been shown to play important roles in cocaine addiction. Nicotinamide phosphoribosyltransferase (NAMPT) is an important rate-limiting enzyme found throughout the body that converts the intracellular pool of nicotinamide adenine dinucleotide (NAD) into nicotinamide mononucleotide (NMN). It reveals a critical role in physiological and pathophysiological conditions such as NAD biosynthesis, aging, inflammation, obesity, diabetes, stroke, motor dysfunction, and cancer. A recent study published in Experimental Neurology by Cen group demonstrated that NAMPT contributes to cocaine reward through sirtuin 1 (SIRT1) signaling in the brain ventral tegmental area. Thus, targeting NAMPT/SIRT1 signaling pathway may provide a promising therapeutic strategy against cocaine addiction.

Keywords: NAMPT, cocaine addiction, dopamine, ventral tegmental area

Introduction

Drug addiction is a major precursor to leading causes of death such as suicide and overdose [1, 2]. Researches on epigenetic and environmental factors that contribute to drug addiction have grown exponentially over the past decade, specifically over the brain reward system in drug addiction [3, 4]. Cocaine is a notorious addictive substance that manipulates this reward pathway through an accelerated build-up of dopamine and other neurotransmitters which lead to feelings of euphoria and eventual craving [5, 6]. Nicotinamide phosphoribosyltransferase (NAMPT) is a rate-limiting enzyme in mammalian nicotinamide adenine dinucleotide (NAD) biosynthesis and regulates various NAD converting enzymes such as sirtuins (SIRT) [7, 8]. NAMPT is found throughout the body; imbalances and dysfunction of NAMPT were well-associated with disorders such as cancer, diabetes, and stroke [9-11]. Although, NAMPT plays a critical role in stroke as well as motor dysfunction in the brain and spinal cord [12, 13], whether it also contributes to psychological diseases such as drug addiction in the brain remains uncertain.

Upregulation of NAPMT in cocaine reward

A recent study reported in *Experimental Neurology* by Kong et al., suggested that NAMPT regulates the dopaminergic stimulation of cocaine through sirtuin 1 (SIRT1) [14]. The study showed that the protein level of NAMPT was significantly upregulated in the ventral tegmental area (VTA) and nucleus accumbens (NAc) of cocaine conditioned mice as compared to saline-conditioned mice. Other brain areas were also tested but not found to have a significant upregulation in NAMPT including the prefrontal cortex, hippocampus, and striatum, which are also involved in the cocaine addiction. Genetic manipulation of NAMPT was studied to further examine NAMPT upregulation when overexpression of NMAPT during cocaine-conditioning. This was done through a bilateral injection in the VTA of mice by lentivirus vectors (LV) with either NAMPT or green fluorescent protein. Ultimately, LV-NAMPT-treated mice had a

more significant cocaine conditioned place preference (CPP) than saline-treated mice. FK866, a well-known NAMPT inhibitor, was micro-injected into the VTA and it showed a significant downregulation of protein level of NAD and nicotinamide mononucleotide (NMN) in the VTA of cocaine-conditioned mice. The authors also bilaterally injected NMN into the VTA of mice 30 minutes after the NAMPT inhibitor FK866 was infused. They found that NMN supplementation clearly decreased the inhibitory effect of FK866 on cocaine reward, suggesting the feedback role of NMN in NAMPT. Therefore, they hypothesized that NAMPT may participate in cocaine reward through the NAD/SIRT1 signaling pathway. Consistent with this finding, they further altered NAMPT expression or function in the VTA through the aforementioned processes (i.e. NMN supplementation, FK866 introduction, etc.) and then measured SIRT1 expression. As a result, intraperitoneal injection of FK866 and intra-VTA injection of FK866 were found to have a significant downregulation of SIRT1 expression, whereas NMN supplementation and LV-NAMPT treatment upregulated SIRT1 expression. Furthermore, VTA-specific inhibition of NAMPT significantly attenuated cocaine-induced CPP in wild-type (WT) mice, but this effect was almost completely abolished in SIRT1 VTA-knock-out (KO) mice. Moreover, LV-NAMPT-treated WT mice developed a more robust cocaine-induced CPP compared to SIRT1 VTA-KO mice. Collectively, this data suggest that NAMPT may participate in cocaine reward through the upregulation of NAMPT/NAD/STRT1 signaling pathway [14]. Thus, targeting this pathway may provide a novel strategy for combating cocaine addiction.

Perspective

Although there is a growing body of studies related to NAMPT as one of the key factor for therapeutic target against stroke and cancer [9-11], present study by Kong et al., uniquely links NAMPT and SIRT1 pathway to cocaine addiction, and opens a new avenue for understanding of mechanism of cocaine addiction and drug discovery for treatment of drug addiction. In the present studies, the authors mainly focused on the VTA, which dopamine cells are widely expressed in this region. Further studies may need to explore another important brain region, NAc, in cocaine addiction and investigate the role of NAc in NAMPT/NAD/SIRT1 signaling pathway in cocaine-conditioned mice. Because both the VTA and NAc are the two critical structures to receive afferent input from multiple brain regions which may affect dopaminergic circuits [15, 16]. For example, dopamine receptors on medium spiny neuron of NAc have been demonstrated to be responsible for cocaine reward and aversion [17, 18]. Further, the behavioral measurement of CPP was used to monitor cocaine reward in the present study, however, self-administration model of cocaine addiction will be another important measure for drug addiction and reinforcement. Moreover, whether drug withdraw symptom also links to brain NAMPT needs to be determined in the future study.

In addiction to brain region and behavioral model conducted in the present studies, specific inhibitor of NAMPT was also applied. Present studies focused on FK866 inhibition of NAMPT to test their hypothesis. FK866 is highly specific noncompetitive inhibitor of NAMPT [19], which is currently under phase II clinical trials. This study opens the door to understanding the NAMPT/SIRT1 pathway in cocaine reward with other NAMPT inhibitors such as CHS-828 which is also in clinical trials [20]. It is necessary to test the role of CHS-828 in cocaine-treated mice in the future. Furthermore, a recent discovery of a similar NAMPT inhibitor called trans-3-(pyridin-3-yl) acrylamide-derived sulfamide [21] could potentially be used as a target to see if the NAMPT/SIRT1 pathway responds in a similar fashion in cocaine addiction as what was seen with FK866 in the present study.

Acknowledgements

SS received Sarah Morrison Research Award from the University of Missouri-Kansas City School of Medicine, Missouri, USA. X-PC received the research support from American Heart Association (19AIREA34470007).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiang-Ping Chu, Department of Biomedical Sciences, University of Missouri-Kansas City School of Medicine, 2411 Holmes Street, Kansas, Missouri 64108, USA. Tel: 816-235-2248; E-mail: chux@umkc.edu

References

[1] McClelland KI and Davies TH. Understanding links among opioid use, overdose, and suicide. N Engl J Med 2019; 380: 1379-1380.

[2] Maxwell JC. Is cocaine coming back? A commentary. Subst Use Misuse 2019; 1-4.

[3] Browne CJ, Godino A, Salery M and Nestler EJ. Epigenetic mechanisms of opioid addiction. Biol Psychiatry 2020; 87: 22-33.

[4] Koob GF. Neurobiology of opioid addiction: opponent process, hyperkatifeia, and negative reinforcement. Biol Psychiatry 2020; 87: 44-53.

[5] Borroto-Escuela DO, Wydra K, Filip M and Fuxe K. A2AR-D2R heteroreceptor complexes in cocaine reward and addiction. Trends Pharmacol Sci 2018; 39: 1008-1020.

[6] Kaneda K. Neuroplasticity in cholinergic neurons of the laterodorsal tegmental nucleus contributes to the development of cocaine addiction. Eur J Neurosci 2019; 50: 2239-2246.

[7] Garten A, Schuster S, Penke M, Gorski T, de Giorgis T and Kiess W. Physiological and pathophysiological roles of NAMPT and NAD metabolism. Nat Rev Endocrinol 2015; 11: 535-546.

[8] Imai S and Yoshino J. The importance of NAMPT/NAD/SIRT1 in the systemic regulation of metabolism and ageing. Diabetes Obes Metab 2013; 15 Suppl 3: 26-33.

[9] Zhu Y, Liu J, Park J, Rai P and Zhai RG. Subcellular compartmentalization of NAD^+ and its role in cancer: a sereNADe of metabolic melodies. Pharmacol Ther 2019; 200: 27-41.

[10] Wang SN and Miao CY. Targeting NAMPT as a therapeutic strategy against stroke. Stroke Vasc Neurol 2019; 4: 83-89.

[11] Yoshino J, Baur JA and Imai SI. NAD^+ Intermediates: the biology and therapeutic potential of NMN and NR. Cell Metab 2018; 27: 513-528.

[12] Wang X, Li H and Ding S. Pre-B-cell colony-enhancing factor protects against apoptotic neuronal death and mitochondrial damage in ischemia. Sci Rep 2016; 6: 32416.

[13] Wang X, Zhang Q, Bao R, Zhang N, Wang Y, Polo-Parada L, Tarim A, Alemifar A, Han X, Wilkins HM, Swerdlow RH, Wang X and Ding S. Deletion of Nampt in projection neurons of adult mice leads to motor dysfunction, neurodegeneration, and death. Cell Rep 2017; 20: 2184-2200.

[14] Kong J, Du C, Jiang L, Jiang W, Deng P, Shao X, Zhang B, Li Y, Zhu R, Zhao Q, Fu D, Gu H, Luo L, Long H, Zhao Y and Cen X. Nicotinamide phosphoribosyltransferase regulates cocaine reward through Sirtuin 1. Exp Neurol 2018; 307: 52-61.

[15] Beier KT, Steinberg EE, DeLoach KE, Xie S, Miyamichi K, Schwarz L, Gao XJ, Kremer EJ, Malenka RC and Luo L. Circuit architecture of VTA dopamine neurons revealed by systematic input-output mapping. Cell 2015; 162: 622-634.

[16] Beier KT, Kim CK, Hoerbelt P, Hung LW, Heifets BD, DeLoach KE, Mosca TJ, Neuner S, Deisseroth K, Luo L and Malenka RC. Rabies screen reveals GPe control of cocaine-triggered plasticity. Nature 2017; 549: 345-350.

[17] Soares-Cunha C, de Vasconcelos NAP, Coimbra B, Domingues AV, Silva JM, Loureiro-Campos E, Gaspar R, Sotiropoulos I, Sousa N and Rodrigues AJ. Nucleus accumbens medium spiny neurons subtypes signal both reward and aversion. Mol Psychiatry 2019; [Epub ahead of print].

[18] Coimbra B, Soares-Cunha C, Vasconcelos NAP, Domingues AV, Borges S, Sousa N and Rodrigues AJ. Role of laterodorsal tegmentum projections to nucleus accumbens in reward-related behaviors. Nat Commun 2019; 10: 4138.

[19] Hasmann M and Schemainda I. FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis. Cancer Res 2003; 63: 7436-7442.

[20] Galli U, Travelli C, Massarotti A, Fakhfouri G, Rahimian R, Tron GC and Genazzani AA. Medicinal chemistry of nicotinamide phosphoribosyltransferase (NAMPT) inhibitors. J Med Chem 2013; 56: 6279-6296.

[21] Zhang K, Ni Y, Chen J, Tu Z, Wu X, Chen D, Yao H and Jiang S. Discovery of trans-3-(pyridin-3-yl)acrylamide-derived sulfamides as potent nicotinamide phosphoribosyltransferase (NAMPT) inhibitors for the potential treatment of cancer. Bioorg Med Chem Lett 2019; 29: 1502-1506.