

Short review

Dorsal Raphe Nucleus 5-HT Neurons: A New Target for Rewarding Regulation and Drug Addiction

Bo Fu^{1*}, Xiaoming Wang^{2*}, Ming Huang³, Zeqi Li¹, Chang Lu⁴ and Hui Peng¹

¹Laboratory of Occupational Medicine, Tianjin Institute of Environmental and Occupational medicine, Tianjin, China

²Institute of Environment and Operational Medicine, Academy of Military Medical Sciences, Academy of Military Sciences, Tianjin, China

³School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China

⁴Tianjin University of Traditional Chinese Medicine, Tianjin, China

Abstract

In current paper, we reviewed the functional mechanisms of Dorsal Raphe Nucleus (DRN) 5-HT neurons in rewarding regulation and drug addiction in the level of molecular, neuron and neural circuits. Furtherly, we prospected that the DRN 5-HT neurons might be a new drug target for addiction treatment in future.

Introduction

It has been proposed that reward was divided into two types, including the pleasure brought by the enjoyment of emotion and motivation made by motivating individuals to obtain the reward. According to the classification of reward attributes, it can be divided into natural reward and drug reward. Natural rewards usually refer to water, food, sex and social interaction, while drug rewards usually induced by drugs such as morphine and cocaine. The mechanisms of rewarding effect are still complex and controversial. Traditional

*Corresponding authors: Bo Fu, Laboratory of occupational medicine, Tianjin Institute of Environmental and Occupational medicine, Tianjin, 300050, China, Tel: +86 02284655056; E-mail: faith_fubo@outlook.com

Xiaoming Wang, Institute of environment and operational medicine, Academy of Military Medical Sciences, Academy of Military Sciences, Tianjin, 300050, China, E-mail: sisuo55123@sina.com

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views suggest that the limbic dopamine system is the key to inducing the reward and leading to the addictive behaviors. Take morphine for example. Morphine interacts with m-Opioid Receptors (MORs) expressed in the Ventral Tegmental Area (VTA) γ -Aminobutyric acid (GABAergic) neurons and relieves the local inhibitory tone leading to reduced inhibition of the VTA dopaminergic neurons [1]. This in turn releases Dopamine (DA) in the Nucleus Accumbens (NAc) [2], which is considered a reward center for reward [3].

However, the long-term use of morphine can lead to drug abuse and addiction. Morphine addiction is characterized by negative physical and emotional feelings when the drug is terminated and causes drug-craving in mental functions and drug-seeking in behavioral changes [4]. Conversely, knockout of the dopamine transporter genetically does not inhibit the rewarding properties in the model of self-administration and Conditioned Place Preference (CPP) [5,6]. In addition, morphine addiction is still observed in dopamine-deficient mice [7], indicating that additional mechanisms of morphine addiction existed outside the dopaminergic system.

5-HT and Reward Regulation

5-Hydroxytryptamine (5-HT), is an important inhibitory neurotransmitter in the brain, which is synthesized and secreted by Dorsal Raphe Nucleus (DRN) 5-HT neurons. DRN 5-HT neurons can form synaptic connections with almost whole brain nucleus and project to the forebrain and limbic areas like Medial Prefrontal Cortex (mPFC), NAc, amygdala, lateral habenula nucleus and VTA to form complex neural circuits [8]. Clinical studies have shown that 5-HT reuptake inhibition like fluoxetine and ciproteridran can relieve anhedonia in depression patients, suggesting that 5-HT is closely associated with rewarding effect. Genetically deleted both dopamine and 5-HT transporter in mice inhibited the cocaine CPP [9], indicating that 5-HT might play a role in reward regulation beside dopamine. Recently, several researches have reported that motivational, reinforcement and reward waiting behaviors could be induced by activating of DRN 5-HT neurons optogenetically in mice [10-12]. Our group showed that optogenetically activated 5-HT neurons in the DRN to mediate real-time CPP, suggesting that rewarding effect was led by activation of 5-HT neurons [13]. Other work in our group has shown that long-term fluoxetine use can induce significant conditional place preference (not published). These results suggest that 5-HT plays a more important role in reward regulation.

However, there is some controversy about the reward regulation of DRN 5-HT neurons because of 5-HT can show reward and punishment through different neural projections. This means DR 5-HT neurons can encode reward and aversion [14].

5-HT and Drug Addiction

It is generally believed that the addictive drugs mediated the dysfunction of mesolimbic dopaminergic system are the reasons of addiction. In neuroanatomy, DRN 5-HT neurons interactions with the mesolimbic dopaminergic system and regulate the reward effect of addictive drugs such as morphine [15]. A recently study reported

that the inhibitory pathway of GABAergic neurons in the cephalic region of the VTA project to the DRN 5-HT neurons played an important role in morphine addiction, and optogenetically activated this inhibitory pathway to block the morphine rewarding effect and rescued the mental dependence [15]. By activating this GABAergic inhibitory pathway projected to the DRN, the inhibitory neurotransmitter GABA was released locally in the DRN, and then inhibited the activity of 5-HT neurons. Our study also found that morphine could increase DRN 5-HT neurons firing rate *in vivo*, and inhibited 5-HT neurons after morphine administration by optogenetic blocked morphine-induced CPP [13].

5-HT receptor is closely related to reward regulation and drug addiction. 5-HT receptors can be divided into 7 families according to their function, structure and signal transduction characteristics, including 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇. Except for 5-HT₃ receptor conjugated with cationic channel type receptor, the other receptors were G protein conjugated receptors [16]. Many researched reported that 5-HT₂ receptor family might be a key factor in drug addiction. The selective 5-HT_{2C} receptor agonist Ro60-0175 did not affect methamphetamine-induced impulsive behavior at low doses. However, a higher dose of Ro60-0175 and M100907, a selective antagonist of 5-HT_{2A}, can reduce the impulsive behavior of methamphetamine and cocaine [17]. Injection of 5-HT_{2A} receptor antagonist M100907 into mPFC attenuated cue-induced cocaine seeking behavior, but the same dose of M100907 did not affect cocaine self-administration. These results further confirmed the role of 5-HT_{2A} receptor of mPFC in cue-induced cocaine seeking behavior [18]. Systematic injection of 5-HT_{2C} receptor agonist RO60-0175 reduced self-administration of cocaine [19]. The mPFC administered 5-HT_{2C} receptor agonist MK212 in a dose-dependent manner to reduce cocaine ignition and drug-seeking behavior induced by conditioned cues, which was reversed by selective 5-HT_{2C} receptor antagonist SB242084 [20]. Activation of 5-HT_{2C} receptor in VTA leads to a decrease in dopamine level in NAc. Therefore, 5-HT_{2A/2C} receptor may play its role in reducing drug igniting and cue-induced drug seeking behavior. In summary DRN 5-HT neurons will be a new target for the treatment of drug addiction.

Outlook

The DRN 5-HT neurons is believed sensitive to reward and drug addiction, our group presents evidence that morphine regulates DRN 5-HT neurons to induce a rewarding effect and that the DRN 5-HT system participates in chronic morphine-induced CPP [13]. However, further studies are needed to establish the exact role of the DRN 5-HT system on other addictive drug effects that leads to addiction and withdrawal symptoms. The mechanisms including molecular, receptors, synaptic, neurons and even neural circuits should be investigated in the future, and provided more directions to clinical treatment of drug addiction.

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