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HOT TOPICS

Swell1 channel-mediated tonic GABA release from astrocytes modulates cocaine reward

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Drug addiction is a chronic brain disorder, characterized by compulsive drug-seeking and -using behavior and high rate of relapse, leading to serious harmful effects and even death. The past two decades have witnessed significant advances in our understanding of how addictive drugs affect the brain to drive addictive behaviors. Indeed, all drugs of abuse, despite their initial effects on distinct molecular targets, exert a series of shared functional effects on the mesolimbic dopaminergic system to increase dopaminergic signaling among the reward circuitry, especially from midbrain ventral tegmental area (VTA) to nucleus accumbens (NAc) in the ventral striatum, [1]. Astrocytes are the most abundant of glial cells in the brain, which have traditionally been considered support cells by maintaining extracellular ion homeostasis and providing trophic support to neurons. Accumulating evidence indicates that astrocytes also play active roles in brain physiology by interacting with pre- and postsynaptic neuronal substrates to regulate synaptic transmission and plasticity [2]. However, the role of astrocytes in mediating the effect of drugs is not well understood. Particularly, whether and how astrocytes regulate the neuronal activity in VTA after drug exposure is largely unknown.

Recently, we revealed a previously unappreciated role for astrocytes in mediating the action of addictive drugs by demonstrating that cocaine impacts VTA neuronal firing by potentiating tonic astrocytic release of GABA [3]. Specifically, we found that chronic cocaine exposure induces tonic GABA release from VTA astrocytes in mice via volume-regulated anion channels (VRACs) with Swell1 as the essential subunit. Interestingly, Swell1-mediated tonic GABA release selectively activates extrasynaptic δ subunit-containing $GABA_A$ receptors (δ-$GABA_A$Rs) on VTA GABA neurons to increase the tonic inhibition currents, thereby downregulating their activity. Since VTA GABA neurons provide strong inhibition directly onto local dopamine (DA) neurons, the enhanced tonic inhibition on VTA GABA neurons after cocaine exposure leads to the disinhibition of VTA DA neurons, excessive DA release in the NAc, and addiction-related behaviors [3]. Importantly, attenuation of tonic inhibition by either deleting Swell1 in VTA astrocytes or disrupting δ-$GABA_A$Rs in VTA GABA neurons reduces cocaine-evoked changes in neuron activity and addiction-related behaviors. Moreover, we performed high-throughput screenings and identified an FDA-approved drug Dicumarol as a novel and potent Swell1 channel inhibitor [4]. It will be exciting to test whether targeting Swell1 channel by Dicumarol can reduce relapse vulnerability associated with cocaine use disorder. Together, we identify a novel mechanism for cocaine reward involving a critical role for astrocytes and reveal a potential therapeutic strategy of targeting astrocytic Swell1 channels to alleviate addictive behaviors.

In addition to our new study, several other works have revealed that astrocytes exhibit alterations upon exposure to addictive drugs, contributing to the development of addiction. For example, repeated self-administration of addictive drugs including cocaine cause a long-lasting adaptation in NAc astrocytes, including down-regulation of the glutamate transporter and process retraction from synapses, resulting in glutamatergic transmission dysfunction that promotes cue-induced reinstatement of drug seeking [5, 6]. Future studies that focus on the interaction between addictive drugs and astrocytes may help discover underlying mechanisms and develop novel therapeutic treatments for addiction.

REFERENCES

1. Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci. 2005;8:1445–9.
2. Haydon PG, Carmignoto G. Astrocyte control of synaptic transmission and neurovascular coupling. Physiol Rev. 2006;86:1009–31.
3. Yang J, Chen J, Liu Y, Chen KH, Baraban JM, Qiu Z. Ventral tegmental area astrocytes modulate cocaine reward by tonically releasing GABA. Neuron. 2023;111:1104–17.e6.
4. Chu J, Yang J, Zhou Y, Chen J, Chen KH, Zhang C, et al. ATP-releasing SWELL1 channel in spinal microglia contributes to neuropathic pain. Sci Adv. 2023;9:eade9931.
5. Scofield MD, Li H, Siemsen BM, Healey KL, Tran PK, Woronoff N, et al. Cocaine self-administration and extinction leads to reduced glial fibrillary acidic protein expression and morphometric features of astrocytes in the nucleus accumbens core. Biol Psychiatry. 2016;80:207–15.
6. Wang J, Holt LM, Huang HH, Sesack SR, Nestler EJ, Dong Y. Astrocytes in cocaine addiction and beyond. Mol Psychiatry. 2022;27:652–68.

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JY and ZQ wrote the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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