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RESEARCH HIGHLIGHT

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Deviating from the norm: cocaine-induced synaptic plasticity in the nucleus accumbens via σ_1 receptors and endocannabinoid signaling

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The coca plant has thousands of years of history. Once chewed by ancient populations for its stimulating and euphoric effects, the leaves of the coca plant are now processed into a potent powder form of the plant's psychoactive ingredient—cocaine—which has become one of the most abused substances around the world. Despite an extended history, how cocaine affects signaling in the brain is still not fully understood. The dogma is that the psychostimulant effects of cocaine stem from its ability to impair clearance of extracellular monoamines (dopamine, noradrenaline, and serotonin) via transporter blockade, effectively elevating the levels of these chemicals in the brain. However, a growing body of research shows that some effects of cocaine occur through activation of intracellular sigma-1 (σ_1) receptors [1]. In this issue of *Neuropsychopharmacology*, Manz and colleagues [2] performed a thorough series of pharmacological experiments in mouse brain slices to reveal a non-canonical mechanism of cocaine-induced synaptic plasticity in parvalbumin-expressing fast-spiking interneurons (PV-INs) in the nucleus accumbens.

Glutamatergic input from different brain regions excites nucleus accumbens PV-INs, which in turn inhibit medium spiny projection neurons (MSNs) in the local neural circuit. Despite the established role of this circuit in reward- and drug-related behaviors, the neuromodulatory effects of cocaine are incompletely understood. Using mouse brain slices, whole-cell voltage-clamp recordings were made from PV-INs. Electrically stimulating the brain slice evoked glutamate release from nearby glutamatergic axon terminals onto the PV-INs, producing an excitatory postsynaptic current (EPSC). Cocaine, when applied to the brain slice, reduced the size of EPSC. Using the paired-pulse-ratio—an indicator of the probability of vesicle release—the authors showed that cocaine reduced the EPSC by suppressing the release of glutamate.

At other synapses, cocaine increases the activation of presynaptic monoamine receptors indirectly by blocking transporter-dependent reuptake. Surprisingly, the reduction of the EPSC by cocaine was not altered by dopamine, noradrenaline, or serotonin transporter blockade, nor affected by antagonizing their cognate receptors. The action of cocaine was independent of monoamine signaling. Instead, when cannabinoid type-1 (CB_1) receptor signaling was prevented, cocaine failed to reduce the EPSC. Classically, activation of presynaptic CB_1 receptors occurs after the release of endocannabinoids (eCBs) from the postsynaptic neuron which traverse the synaptic cleft retrogradely. In cell lines and midbrain dopamine neurons, cocaine can mobilize endocannabinoids through binding to σ_1 receptors [3]. σ_1 receptors are intracellular receptors enriched in the membrane of the endoplasmic reticulum, which assist in regulating intracellular calcium homeostasis. Here, the authors demonstrated the involvement of σ_1 receptors in cocaine-induced suppression of glutamate release in three ways: (1) in the presence of a σ_1 receptor antagonist, cocaine had no effect, (2) activation of σ_1 receptors by a selective agonist mirrored the effects of cocaine at PV-INs synapses, and (3) in the presence of a σ_1 receptor agonist, cocaine did not reduce the EPSC further. These findings strongly support a model where σ_1 receptor is a postsynaptic effector of cocaine that subsequently initiates retrograde eCB signaling.

Intriguingly, σ_1 receptors may facilitate the mobilization of eCBs in multiple ways. In midbrain dopamine neurons, activation of σ_1 receptors by cocaine mobilizes the secretion of the endocannabinoid 2-AG in extracellular vesicles through a process that likely involves the exchange of GDP for GTP [3]. In contrast, Manz et al. [2] showed that in PV-INs, activation of σ_1 receptors mobilized anandamide, but not 2-AG. The mechanism of anandamide secretion was not completely resolved but involved the release of calcium from intracellular calcium stores. The effect of cocaine on the EPSC was prevented by BAPTA, a fast calcium chelator, in the internal solution. These results indicate that intracellular calcium signaling, specifically in the recorded PV-INs and not the surrounding cells, is necessary for mobilization of anandamide. However, when GTP in the internal solution was replaced with a non-hydrolyzable GDP analog that acts as a competitive antagonist at GTP binding sites, the effect of cocaine persisted, indicating that the release of anandamide may not involve GDP/GTP exchange. Thus, σ_1 receptors may initiate retrograde eCB signaling in distinct ways with some cell-type- or synapse-specificity.

In a prior study, the authors describe another form of anandamide-dependent synaptic plasticity at glutamatergic synapses onto PV-INs using low-frequency stimulation of the brain slice [4]. This repetitive stimulation procedure produced long-term depression (LTD); a form of synaptic plasticity commonly employed at synapses to dampen an overwhelming response. Since the action of cocaine at these synapses converged

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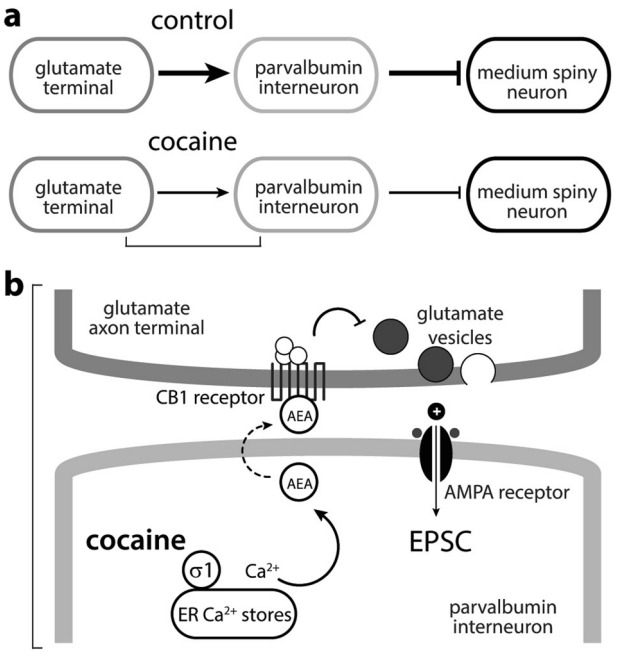

Fig. 1 Cocaine mobilizes endocannabinoids via action on intracellular σ_1 receptors. a In the nucleus accumbens, glutamate axon terminals excite (→) fast-spiking parvalbumin interneurons (PV-INs) which inhibit (⊣) medium spiny projection neurons (MSNs). Manz et al. [2] find that cocaine reduces excitatory drive from glutamate terminals on PV-INs, which may reduce inhibition on MSNs. **b** Cocaine activates σ_1 receptors which through release of calcium from intracellular stores, mobilizes the endocannabinoid, anandamide (AEA) and suppresses glutamate release via activation of presynaptic CB_1 receptors.

mechanistically with LTD, the prediction was that after cocaine exposure, low-frequency stimulation would be ineffective. Indeed, after brain slices were incubated in cocaine for an hour, LTD could no longer be induced with low-frequency stimulation. Cocaine exposure, via activation of σ_1 receptors, occluded other forms of eCB-dependent synaptic plasticity [2]. At the level of the neural circuit, these findings suggest that prior cocaine exposure may alter the way salience is encoded by PV-INs.

Taken together, this article showcases a novel action of cocaine on nucleus accumbens PV-INs in mouse brain slices. In the PV-INs, cocaine binds with intracellular σ_1 receptors, initiating the release of calcium from intracellular stores and mobilizing eCBs. Then, eCBs activate presynaptic CB_1 receptors on glutamatergic axon terminals and suppress glutamate release onto the postsynaptic PV-INs (Fig. 1). The authors' findings add to a growing body of compelling evidence that σ_1 receptors are involved in cocaine-induced adaptations in the nucleus accumbens. Ultimately, cocaine reduces excitatory drive onto the PV-INs, which in the absence of compensatory intrinsic mechanisms, may disinhibit the MSNs (Fig. 1). Whether this disinhibition precedes, or is sufficient to overcome the cocaine-induced, σ_1 receptor-dependent reduction in intrinsic excitability of dopamine D1 receptor-expressing MSNs [5] is unknown. We anticipate a number of future studies to consolidate monoamine-dependent and independent effects of cocaine, ultimately toward extending these findings to in vivo cocaine administration models.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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