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Synaptic and intrinsic plasticity in the ventral tegmental area after chronic cocaine

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Cocaine exposure induces persistent changes in synaptic transmission and intrinsic properties of ventral tegmental area (VTA) dopamine neurons. Despite significant progress in understanding cocaine-induced plasticity, an effective treatment of cocaine addiction is lacking. Chronic cocaine potentiates excitatory and alters inhibitory transmission to dopamine neurons, induces dopamine neuron hyperexcitability, and reduces dopamine release in projection areas. Understanding how intrinsic and synaptic plasticity interact to control dopamine neuron firing and dopamine release could prove useful in the development of new therapeutics. In this review, we examine recent literature discussing cocaine-induced plasticity in the VTA and highlight potential therapeutic interventions.

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Introduction

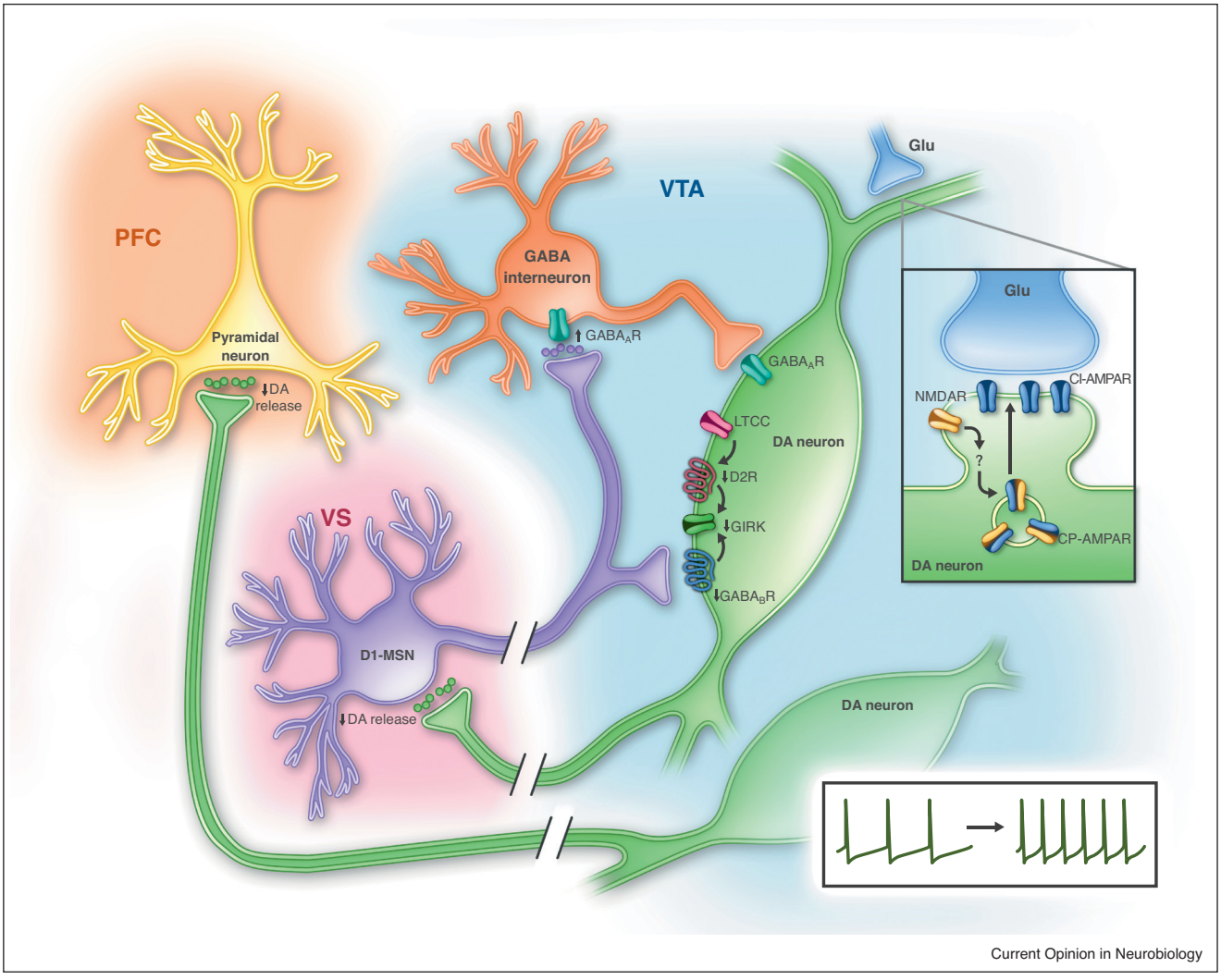
Despite an ever-increasing body of literature on brain mechanisms contributing to cocaine addiction, therapeutic treatments remain limited. Treating cocaine addiction is complex due to distinct and persistent changes — *plasticity* — in multiple brain regions, including the ventral tegmental area (VTA), prefrontal cortex (PFC), and ventral striatum [1]. Improving the odds of treating cocaine addiction lies in a greater understanding of cocaine-induced plasticity.

Exposure to cocaine results in two forms of changes: *synaptic plasticity* defined as changes in synaptic transmission and *intrinsic plasticity* defined as changes in the intrinsic electrical properties of neurons. Interplay between synaptic inputs and intrinsic properties control the ultimate outputs of the neuron, action potential (AP) firing and neurotransmitter release. In this review, we discuss recent animal model studies of cocaine-induced synaptic and intrinsic plasticity in the VTA, highlighting the findings thought to contribute to the vulnerability to relapse (Figure 1). We then illustrate the translational potential of some of these findings into the clinic.

Synaptic plasticity

It has been nearly two decades from our first report of cocaine-induced synaptic plasticity in the VTA. A single injection of cocaine causes an *N*-methyl-D-aspartate (NMDA) receptor (R)-dependent potentiation of glutamatergic synaptic transmission (i.e. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-R-dependent) onto VTA dopamine neurons for at least five days [2]. This long-term potentiation (LTP) of glutamatergic (AMPA)-R-dependent transmission arises 3–5 hours after cocaine exposure, following a transient dopamine D1/D5 receptor-dependent strengthening of NMDA-R-dependent transmission [3,4]. Following chronic cocaine self-administration (>14 days), LTP of glutamatergic transmission persists for at least 3 months [5]. Expression of LTP coincides with greater insertion of Ca^{2+}-permeable (CP) AMPA-Rs without a change in the total number of AMPA-Rs [6]. The higher conductance of these receptors contributes to the potentiation of excitatory transmission, and their Ca^{2+} permeability alters synaptic signaling to induce and maintain drug-related plasticity [7]. Positive modulation of metabotropic glutamate receptors (mGluR1s) can target and prevent this plasticity in the VTA and other brain regions [6,8•,9], providing a potential therapeutic target for cocaine addiction. Additionally, VTA NMDA-R signaling, which is required for excitatory LTP in the VTA [4], is also required for cocaine-induced ventral striatal plasticity and cocaine seeking [8•], suggesting VTA dopamine neuron LTP, CP-AMPA-Rs, and

Figure 1



Cocaine-induced plasticity in VTA dopamine neurons. Cocaine enhances $GABA_A$-R currents at the synapses between ventral striatal (VS) D1-MSNs and VTA GABA interneurons, while reducing inhibitory $GABA_B$-R- and D2-R-activated GIRK conductance on VTA dopamine (DA) neurons. Calcium entry through L-type calcium channels (LTCC) regulates D2-R GIRK conductance and is an important player in cocaine-mediated behavior. Chronic cocaine induces LTP at the glutamatergic (Glu) synapses on VTA dopamine neurons (insert). This LTP is facilitated by activation of NMDA-Rs which drives CP-AMPA-R insertion into the synaptic membrane. These changes in GABAergic and glutamatergic synaptic transmission contribute to hyperexcitability of dopamine neurons. Cocaine decreases dopamine release on VS and prefrontal cortex (PFC) neurons.

downstream adaptations are necessary for reinstatement. However, a direct link between cocaine-induced CP-AMPA-R insertion and NMDA-R signaling has not been shown and methods to examine this phenomenon have proven difficult [10]. Moreover, VTA CP-AMPAR plasticity requires insertion of the Ca^{2+}-impermeable GluN3A NMDA-R subunit [11], suggesting an NMDA-R-independent source of Ca^{2+} is required for potentiation. Additional studies are necessary to fully describe the complex interaction between CP-AMPA-Rs and NMDA-Rs. Overall, cocaine potentiates glutamatergic transmission onto dopamine neurons first by causing a transient potentiation of NMDA-R signaling which in turn strengthens AMPA-R-dependent synaptic transmission.

Persistent cocaine-induced synaptic plasticity is not limited to glutamatergic synaptic transmission but also involves gamma-aminobutyric acid (GABA) signaling including both $GABA_A$-Rs and $GABA_B$-Rs. Overall, $GABA_A$-R signaling on dopamine neurons is reduced following cocaine [12] and opposes excitatory input to control dopamine neuron excitability. Methods to decrease excitation/inhibition ratios enhanced by cocaine reduces *in vivo* firing frequency of dopamine neurons [13,14] and enhances dopamine release in the ventral