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Reduced GABA-B/GIRK-mediated regulation of the VTA following a single exposure to cocaine

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In this paper, Arora and colleagues expand on their previous work on GIRK channels in the ventral tegmental area (VTA) presenting evidence that a single exposure to cocaine reduces inhibitory GABAergic transmission to dopamine (DA) neurons in the ventral tegmental area[1,2]. Mice receiving i.p. injections of cocaine saw a short lived (1-5 days) decrease in GABAb mediated G-protein coupled inwardly-rectifying potassium (GIRK) currents in DA neurons in the VTA. This decrease parallels an NMDA-mediated increase in the frequency of glutamatergic neurotransmission. Chronic cocaine injections had no additional effects beyond those seen with single injections. Though they found no change in mRNA levels for GABAb receptors, GIRK channels, or RGS-2 (a G-protein regulator), immunoelectron microscopy indicated a decrease in levels of GIRK channels in the plasma membrane of the dendrites of VTA DA neurons. The cocaine-mediated decrease in GIRK currents was abolished in the presence of D2/3R antagonist sulpiride, but not in the presence of D1/5 antagonist SCH23390, indicating a link between D2/3 receptor activation and GIRK activity. Interestingly, the addition of quinpirole, a D2/3 agonist, elicited similar GIRK currents, though they were smaller than those mediated by GABAb receptors. Similarly, acute injections of cocaine significantly diminished quinpirole-evoked currents.

The paper supports the literature that shows that acute cocaine exposure can disrupt the balance of excitation and inhibition in VTA dopamine neurons. An imbalance in glutamatergic and GABAergic transmission caused by cocaine exposure is a common theme in addiction research[3], and it is possible that the acute effects seen in the VTA mediate downstream effects in areas such as the prefrontal cortex (PFC) and nucleus accumbens (NAc). However, exactly how short-lived (1-5 days) effects in the VTA translate into long-lived (up to a year or more) changes in the PFC and NAc is currently unknown. One possibility is that transient increases in glutamatergic and dopaminergic VTA activity drives an increase in NMDA activity and cyclic AMP production in the PFC, which in turn activates immediate early genes Arc and c-fos, respectively. It has been demonstrated that VTA DA neurons project to both pyramidal and inhibitory interneurons in the PFC[1], and that a single injection of cocaine can induce Arc activation in the PFC[4]. Systemically blocking D1 signaling in the PFC prevents the activation of fos in response to cocaine-paired cues.

This paper also provides further evidence of cocaine administration resulting in an imbalance in glutamatergic and GABAergic activity. However, the decrease in inhibitory-mediated activity and increase in glutamatergic activity seen here in the VTA is the opposite of what occurs following long term cocaine treatment in the PFC. In the PFC of cocaine addicted humans, MRI data shows decreased basal levels of activity[1] that then increase when the subject was presented with drug-related cues[1]. This data is supported by work demonstrating that injections of NMDA into the VTA cause a decrease in firing

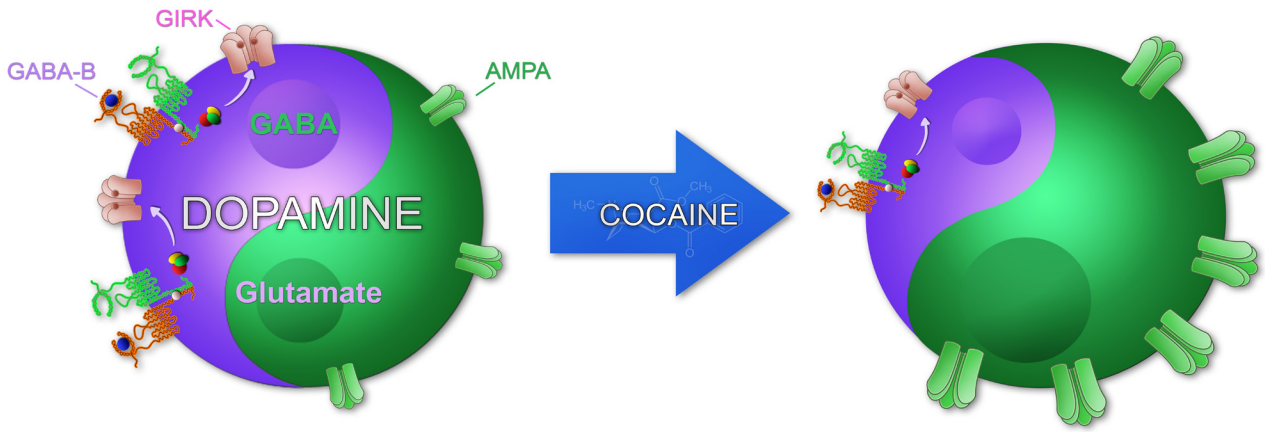

Illustration by Joseph Strine

rates of excitatory pyramidal neurons in the PFC and an increase in firing rates of inhibitory interneurons[1]. Similarly, chronic cocaine injections cause an increase in interneuron activity in the PFC[1] and increases in extracellular GABA[1]. As stated above, it is possible that DA neurons from the VTA synapse on inhibitory interneurons in the PFC, and that the acute increases in glutamatergic activity seen here result in an increase in inhibitory activity in the PFC. Similar alterations in glutamatergic activity occur in the NAc[3].

It should be noted that while a single injection of cocaine acutely alters activity in the VTA, it is still unknown whether this truly drives systemic, long-term plasticity in other regions. The acute plasticity demonstrated here in the VTA recovers between 5 and 10 days, while plasticity in downstream regions such as the PFC and NAc may not occur until 5 or more days of chronic treatment or self-administration[1]. Additionally, papers that focus on acute or chronic cocaine effects must take into account the physiological and behavioral effects of non-contingent drug intake. Animals yoked to self-administering animals demonstrate differences in behavior and levels of glutamate and DA in the Nac[1,5]. Overall the paper shows how brief exposure to cocaine can lead to homeostatic excitatory/inhibitory imbalance within the dopamine system.

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