Editorial Focus: A central role for the periphery in the rapid action of cocaine on brain neurons: focus on “Rapid EEG desynchronization and EMG activation induced by intravenous cocaine in freely moving rats: a peripheral, nondopamine neural triggering”

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BACK IN THE DAY WHEN research in neuropharmacology was done almost exclusively on peripheral tissue, limited technology prevented sophisticated assessments of drug-induced changes in brain function. As technology improved, so did the scope of investigation, and researchers today study the brain directly to assess how drugs alter gene and protein expression, second-messenger cascades, synaptic activity, and other key events. Current views of how drugs shape behavior come from these modern lines of investigation. Drug effects on peripheral tissue, however, should not be ignored. When drugs are administered systemically, they act on cardiovascular and other aspects of internal physiology even before they reach the brain, and these peripheral changes make an important contribution to the drug experience. This point is emphasized in the report by Kiyatkin and Smirnov (7) who show that intravenous (IV) cocaine acts as a peripheral somato-sensory stimulus that rapidly activates the brain and thus can play an important role in the learning that underlies the development of addiction.

Drug addiction is closely tied to activity in the brain’s motive circuit, a network of predominately forebrain structures that drive goal-directed behavior (9). Operation of this circuit is critically dependent on dopamine input. An increase in dopamine transmission has been implicated in the motivation to obtain naturally occurring rewards such as food, sex, and access to novelty (2, 15). Dopamine release also occurs in response to electrical stimulation of the medial forebrain bundle, which has reinforcing effects on behavior (4). Thus, when drugs of abuse were found to increase motive-circuit dopamine, it seemed reasonable to conclude that this mechanism was responsible for the euphoria that these drugs produce (14).

Cocaine increases dopamine by blocking its removal or uptake from the synapse (11). Linking this mechanism to drug-induced euphoria, however, is not as straightforward as it may appear. Not only does dopamine receptor blockade fail to prevent the euphoric effect of cocaine (3), but the timing of the euphoric effect is difficult to explain. A cocaine high, for example, occurs almost immediately after IV injection even though additional time is required for the drug to reach the brain, diffuse through brain tissue, and interfere with the uptake mechanism. In rats that receive a dose of IV cocaine, known to have reinforcing effects, several minutes are required to achieve effective blockade of dopamine uptake in the nucleus accumbens, a key region of the motive circuit (6). In contrast, cocaine also acts directly on ion channels that control neuronal excitability (10), and these channels are abundantly expressed on the terminals of sensory nerves that innervate blood vessels and other visceral organs (8). By acting on sensory nerve terminals, cocaine could quickly alter the flow of sensory information to the brain and thus produce a rapid activation of the key brain circuits that ultimately drive the response to take more drug.

Kiyatkin and Smirnov (7) take an important step toward testing this hypothesis by examining the effects of IV cocaine on rapid changes in the electroencephalogram (EEG) and electromyogram (EMG) of freely behaving rats. If the somato-sensory action of cocaine is critical for driving brain circuits, then drug-induced changes in the EEG and EMG should resemble those produced by a peripheral stimulus and should be blocked by general anesthesia. This is exactly what was found. Both IV cocaine and an auditory stimulus (clap) produced a rapid EEG desynchronization and EMG activation. In fact, the effects of cocaine appeared within 2–6 s after the onset of a 10-s injection. Urethane anesthesia, moreover, blocked the rapid electrophysiological changes produced by either cocaine or the clap. Interestingly, however, urethane failed to block the prolonged EEG desynchronization that emerged as late as 60 s after a cocaine injection, suggesting that this slower onset response reflects an action of the drug directly on brain tissue. Consistent with this suggestion, blockade of dopamine receptors did not alter the rapid changes in EEG and EMG induced by cocaine, but did attenuate the EEG desynchronization that occurred several minutes after cocaine injection. Thus, the cortical activation that occurs within seconds after IV cocaine can be explained by a peripheral, non-dopamine mechanism.

This idea was confirmed in a separate group of rats treated with an equimolar dose of cocaine methiodide, a peripherally acting analog of cocaine that does not penetrate the blood-brain barrier. Cocaine methiodide mimicked the rapid EEG desynchronization and EMG activation produced by cocaine itself, but subsequent electrophysiological changes were significantly shorter as would be expected for a peripherally acting drug. The notion of a peripheral signal contributing to the drug experience is supported by evidence that procaine, a drug structurally similar to cocaine but with little or no effect on dopamine uptake, can elicit strong sensory effects and mimic the acute euphoria of cocaine in experienced cocaine users without being addictive itself (1). It appears, therefore, that the peripheral somato-sensory effects of cocaine are an integral part of the addiction process; they may not
be sufficient to elicit drug craving, but they appear to be necessary.

Several decades of brain research have shown that the mechanisms underlying drug addiction are complex. Not only has the perceived role of dopamine release changed over the years from a simple association with reward to just one step in the processing of drugs and drug-related stimuli as salient events that drive the motivation for more drug regardless of its rewarding effects (13), there also is the realization that other transmitters are likely to be even more critical for the long-term craving that defines addiction. Glutamate, for example, appears to be responsible for the neuroadaptations that drive drug-seeking strategies (5), making drugs that modulate glutamate transmission potential therapeutic targets (12). Into this search for the substrates of addiction must be added the peripheral nerve fibers that convey critical information about drug-induced changes in the internal state. The challenge now is to identify the mechanisms by which peripheral drug effects activate the brain circuits underlying drug addiction.

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DISCLOSURES

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REFERENCES