Rapid dopamine changes in the nucleus accumbens during cocaine self-administration

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Abstract

Electrophysiological studies have demonstrated activation of dopaminergic neurons on presentation of natural reinforcers or of cues predicting them. The conclusion of these studies is that rapid, transient changes in extracellular dopamine may provide a learning signal for reward. To test this hypothesis for cocaine reinforcement, we made direct measurements of extracellular dopamine with subsecond time resolution during cocaine self-administration.

Male rats (n = 6) were implanted with chronic jugular catheters and trained to press a lever for intravenous cocaine (0.33 mg/infusion; 2 hr). Once stable self-administration behavior was observed, animals were surgically prepared for voltammetry. During subsequent self-administration sessions, extracellular dopamine in the core of the nucleus accumbens was monitored at 100 ms intervals using fast-scan cyclic voltammetry.

Phasic increases in extracellular dopamine (89.4 ± 12.8 nM) were observed within 0.6 ± 0.2 s of every lever-press for cocaine (116 responses). When cocaine-related cues were randomly presented during the session (without cocaine), dopamine transients of a similar magnitude (84.9 ± 12.9 nM) were also observed (16 trials). Changes in extracellular dopamine were not detected for the same cues in rats that had no prior experience of their pairing with cocaine-delivery.

These rapid dopamine changes may represent a learning signal for cocaine that is central to acquisition, cue-related craving and relapse of drug-taking behavior.

Acknowledgements

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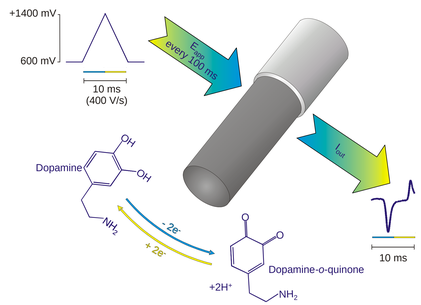
Detection of dopamine

Dopamine was monitored using fast-scan cyclic voltammetry at carbon fiber microelectrodes.

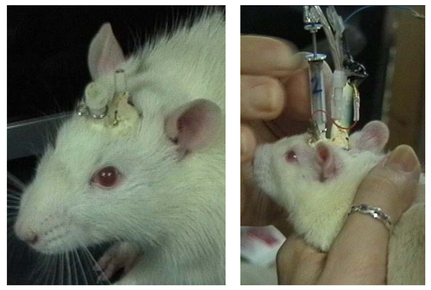
A triangular waveform (E_{app}) was applied to the electrode every 100 ms.

In the presence of dopamine, the output current (I_{out}) consists of a negative (oxidation) peak followed by a positive (reduction) peak.

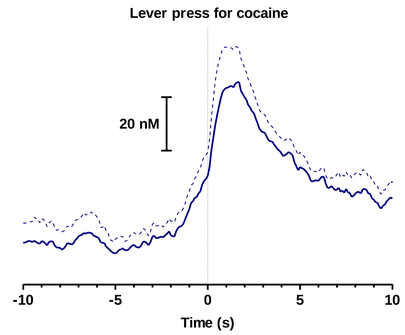


When this is plotted against the input potential, a cyclic voltammogram is produced, which allows chemical identification.

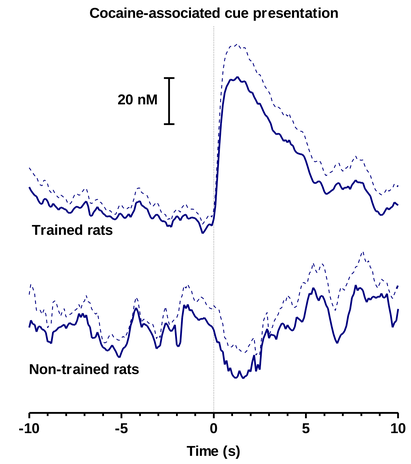
Temporal changes in extracellular dopamine concentration are quantified from the current at the potential where the peak oxidation reaction occurred (~0.6 V vs Ag/AgCl), normalized to an *in vitro* electrode calibration.



Dopamine increases during responding for cocaine

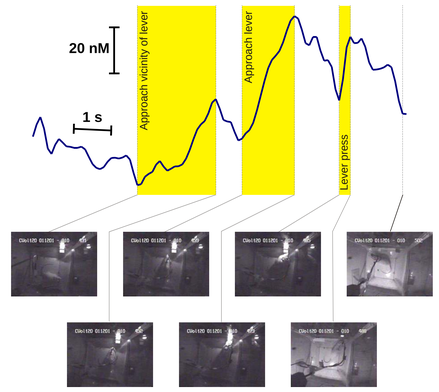


Dopamine release is evoked by cues with learned salience

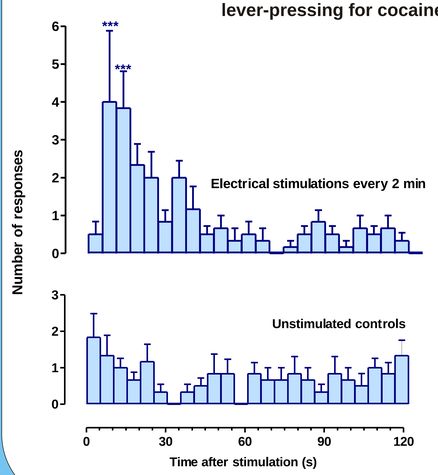


Rapid increases in dopamine promote drug-seeking behaviors

Increases in dopamine temporally coincide with drug-seeking behaviors



Electrically-evoked dopamine release promotes lever-pressing for cocaine



Selectivity

Anatomical: Postmortem histological verification confirmed that all the recording sites were in the core of the nucleus accumbens.

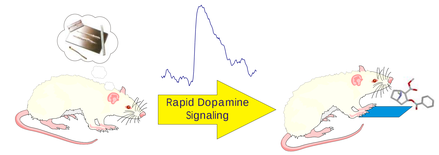
Physiological: Stimulating dopaminergic cell bodies before and after behavioral sessions and detecting dopamine demonstrated that recording sites could support rapid dopamine release.

Pharmacological: In the presence of the monoamine oxidase inhibitor, pargyline (75 mg/kg, intraperotoneal), signals were not attenuated.

Chemical: Cyclic voltammograms of signals during behavioral session were compared to those from electrical stimulations at the same recording site and those from *in vitro* calibration of the electrode. In addition to oxidizable species, both movement artifacts and ionic changes in the extracellular space (especially pH) produce current at the electrode. These can be identified using the cyclic voltammogram and eliminated from dopamine signals with differential measurements.

Conclusions

In cocaine addiction, the dopaminergic system samples sensory information on a millisecond timescale for salience with respect to this drug. Such stimuli cause rapid dopamine signaling that promotes initiation of drug-seeking behaviors.



Such a functional role for rapid dopamine signaling could generalize to other reinforcers and may have evolved to improve acquisition of natural reinforcement.