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RESEARCH HIGHLIGHT

Whole brain metabolic mapping—another chapter in a great book on the effects of cocaine in monkeys

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The combined labs of Linda Porrino and Mike Nader have once again made an important contribution toward understanding the systems neurobiology of the acute and chronic effects of cocaine. Over the last 25 years, they have used the ^{14}C-2-deoxyglucose (2-DG) method to map regional changes in brain metabolism associated with non-contingent cocaine exposure and cocaine self-administration in monkeys. This line of research is important, because the neurobiology of psychostimulant effects in rodents and nonhuman primates often differ, and when they do, drug effects in nonhuman primates more closely parallel those in humans. This applies to effects such as sensitization, which, unlike in rodents, does not appear to happen in primates. Even more relevant in regard to 2-DG studies of cerebral metabolism, the direct metabolic effects of psychostimulants in rodents (increased cerebral metabolic activity) are opposite to those in nonhuman and human primates [1].

It is the range of conditions in which the approach of Porrino and Nader has consistently been applied over the years that makes this body of work so valuable. Initial studies examined the effects of acute, non-contingent cocaine exposure. Decreased metabolic activity in both medial prefrontal and orbitofrontal networks was observed, in addition to decreases in ventral striatum and anterior nuclear group of the thalamus.

Because cocaine is not consumed non-contingently, the next condition Porrino and Nader examined was that of self-administered cocaine, with initial studies focused on a model of early stages of drug use, prior to the development of neuroadaptations seen with chronic use [2]. In contrast to non-contingent cocaine effects, Porrino, Nader, and colleagues observed increased metabolic activity in dorsomedial and dorsolateral prefrontal cortex, as well as in thalamic regions, while in dorsal and ventral striatum decreases in activity were seen. When monkeys had a longer history of self-administration (daily sessions for three months), acute cocaine produced more extensive metabolic changes. The striatal territory affected by cocaine spread rostrally and dorsally to include almost the entire extent of dorsal striatum rostral to the anterior commissure [2].

A separate comparison of low and high cocaine dose exposure over 100 self-administration sessions was also made. Here, cocaine self-administration dose-dependently reduced glucose utilization throughout the striatum and prefrontal cortex similar to the initial stages of self-administration. In addition, decreases in glucose utilization were observed (in a dose-independent manner) in large portions of the temporal lobe, including amygdala, hippocampus, and surrounding neocortex. Thus, we see a dynamic progression of the effects of cocaine administration depending on whether monkeys are naive, newly self-administering, or chronically self-administering.

It has been of keen interest to determine the effects of environmental cues associated with cocaine availability in order to ascertain how they might be leading to craving and relapse. Thus, the next critical contribution from the Porrino and Nader labs evaluated the effects of cues without the cocaine (or food in controls) they would normally predict [3]. Rhesus monkeys self-administered 0.3 mg/kg/injection cocaine (30 injections/session) for 100 sessions, while control monkeys had identical schedules of food reinforcement. Sessions were then discontinued for 30 days, after which time, monkeys were exposed to cocaine- or food-paired cues for the 2-DG comparison of food vs cocaine cues. Strikingly, now with cues only, increases in metabolic activity were seen throughout pre-commissural dorsal and ventral striatum and putamen, medial prefrontal cortex, rostral temporal cortex, and limbic thalamus. The 30-day drug-free period modeled relapse after abstinence, which is often seen clinically. Having carefully mapped out the effects of acute cocaine across the contexts of contingency, acute, and chronic exposure, as well as the effects of cues only, the authors now are making yet another novel contribution.

In the present report [4], the authors examined the long-term effects of cocaine on regional metabolism under conditions of zero-order contingency, which renders an environment to be neither a positive, nor a negative discriminative stimulus (i.e., a neutral environment). This was established by placing the monkeys twice a week in behavioral chambers used for the 2-DG studies which were distinct from those used for food or cocaine self-administration. The chambers were fitted with a screen on which videos were presented. The monkeys were exposed to these neutral chambers either before or after a cocaine self-administration session.

The results of this 2-DG experiment reveal the effects of short- and medium-term cessation of chronic cocaine self-administration, uncontaminated by expectation effects. The authors reported significant reductions in metabolic activity in orbitofrontal and dorsolateral prefrontal cortex, entorhinal, inferior parietal, and posterior cingulate in the 30-day, but not 1-day abstinent group, relative to the food controls. Similarly, decreased activity was seen in dorsal and medial portions of striatum, with no changes in ventral striatum, in the 30-day abstinent group. Reductions in activity at both the 1-day and 30-day timepoints were seen in

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several regions of the thalamus. Effects in cortex and striatum were significant after prolonged abstinence, but not during early abstinence from cocaine self-administration, suggesting that these deficits intensify over time. The relevance to clinical observations is that cues that elicit EEG signatures of motivated attention to drug cues are reported to increase or incubate between short (2 day) and medium (1 month) term abstinence [5], similar to the present time-dependent changes in metabolic activity.

Overall, this influential line of research reinforces the dynamic picture of the effects of cocaine self-administration and associated environmental cues on regional metabolic activity. Effects are primarily localized in brain regions associated with decision-making, reward evaluation, and execution of motivated behavior, and the effects of cues can be in direct opposition to those of the drug itself. This new contribution is relevant to an important window of time when there are high rates of relapse and will hopefully provide a basis for future clinical and preclinical studies into how interventions, either cognitive/behavioral or pharmacological, can prevent relapse to cocaine use.

REFERENCES

1. Lyons D, Friedman DP, Nader MA, Porrino LJ. Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. J Neurosci. 1996;16:1230–8.
2. Porrino LJ, Lyons D, Miller MD, Smith HR, Friedman DP, Daunais JB, et al. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. J Neurosci. 2002;22:7687–94.
3. Porrino LJ, Beveridge TJ, Smith HR, Nader MA. Functional consequences of cocaine expectation: findings in a non-human primate model of cocaine self-administration. Addict Biol. 2016;21:519–29.
4. Porrino LJ, Smith HR, Beveridge TJR, Miller MD, Nader SH, Nader MA. Residual deficits in functional brain activity after chronic cocaine self-administration in rhesus monkeys. Neuropsychopharmacology 2021; https://doi.org/10.1038/s41386-021-01136-w.
5. Parvaz MA, Moeller SJ, Goldstein RZ. Incubation of cue-induced craving in adults addicted to cocaine measured by electroencephalography. JAMA Psychiatry. 2016;73:1127–34.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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