Neuropsychopharmacology www.nature.com/npp

RESEARCH HIGHLIGHT

Sugar now or cocaine later?

Anne-Noël Samaha [1,2]

Neuropsychopharmacology (2021) 46:271–272; https://doi.org/10.1038/s41386-020-00836-z

A few years ago, I was teaching a graduate course on drugs of abuse and addiction. We were on the topic of preclinical choice studies, where laboratory rats must make a mutually exclusive choice between self-administering cocaine or an alternative reward (e.g., sweetened water, appetitive foods, or another rat to interact with). These studies consistently show that most rats prefer the nondrug reward over cocaine [1] (and over heroin or methamphetamine [2–5]). After I had reviewed these studies in my class, a student asked, '*Does this mean that sugar is more addictive than cocaine?*'. This question summed up the problem. Across species, drugs like cocaine are thought to have rewarding effects that greatly surpass those of other, nondrug rewards. So, shouldn't most rats choose cocaine? Yet, most rats choose the other, nondrug reward instead. This is true for both sexes, and even for rats with rather extensive drug using histories.

Addiction neuroscientists like me have pondered over this with consternation. Do rats truly find many nondrug rewards more rewarding than cocaine? The data certainly suggested it was so. But this interpretation was troublesome. First, it is incompatible with a very influential theory in addiction, the dopamine hypothesis. With years of empirical support, this hypothesis proposes that cocaine is a very rewarding and potentially addictive drug in part because it evokes a uniquely large dopamine response in the ventral striatum [6–8]. This should make cocaine much more wanted than nondrug rewards. Second, if most rats do indeed prefer a variety of different nondrug rewards over cocaine, could this mean that most rats do not find cocaine that rewarding after all? If this is so, then how useful is it to use rats to study the neurobiological, psychological or behavioural mechanisms of drug reward? Finally, if even rats with significant cocaine-taking histories readily forego the drug for sugar or a playmate, does this mean that rats cannot develop a robust, reliable addiction-like phenotype? Despite these thorny questions, there remained no other convincing explanations for why most rats seem to prefer nondrug rewards over cocaine.

In this issue of *Neuropsychopharmacology*, Canchy et al. [9] investigated this apparent paradox. They propose that if rats in cocaine choice studies choose the alternative reward so often, it is likely because the delay to cocaine reward is longer than it is for the nondrug reward (sweetened water here). In other words, perhaps cocaine is not chosen because its rewarding effects are comparatively delayed, and not necessarily because sweet water reward is larger in magnitude than cocaine reward is. Canchy et al. [9] first analysed the literature to compare the respective delays of action of intravenous cocaine versus food reward on dopamine parameters in rat ventral striatum. This analysis showed that intravenous cocaine exerts effects on dopamine uptake inhibition and extracellular dopamine concentrations within an average delay of ~15 s for 10% of peak effect, ~35 s for 50% of peak effect, and ~60 s for peak effect. In contrast, food rewards (pellets, sucrose, or saccharin) evoke an almost immediate dopaminergic effect (~0.25 s for 10% of peak effect, ~1 s for 50% of peak effect, and ~2 s for peak effect). Thus, cocaine has delayed effects on dopamine kinetics compared to food reward, even when cocaine is administered by the rapid intravenous route.

Next, Canchy et al. [9] determined how soon cocaine-experienced male rats respond when cocaine is omitted during a self-administration session. If during self-administration sessions rats learn that cocaine reward comes after a certain delay, then their response time after a drug omission should approximate that delay. Indeed, after cocaine omission, the rats waited on average ~40–45 s before responding again. When an additional delay was programmed between the operant response and the cocaine infusion during self-administration, rats now waited even longer before responding in drug omission tests. Together, these findings indicate that the omission response time indeed reflects the learned delay to cocaine reward.

Finally, in a clever and decisive experiment, the authors added programmed delays to both the cocaine reward and the alternative, sweet water reward. If rats normally choose the alternative reward over cocaine because the delay to cocaine reward is longer (a pharmacokinetic account of choice behaviour), then with a sufficiently long delay, rats should shift their choice from sweet water to cocaine. If sweetened water is actually more rewarding than cocaine (a pharmacodynamic account), then the rats should continue to choose the sweetened water over the drug, regardless of the programmed delay. In support of the pharmacokinetic explanation, the delay attenuated the rats' normal preference for the nondrug reward. First, rats became slower to make a choice, and while they respond faster for sweetened water than for cocaine when there is no added delay, they now responded most slowly for the sweetened water. Second, rats now chose cocaine over sweetened water more often, and most rats actually shifted their preference to cocaine (Fig. 1). Thus, when there was no programmed delay, rats preferred the sweetened water, choosing cocaine on average only 20% of the time. When there was a 30-s programmed delay, rats showed no preference, choosing cocaine on average 50% of the time. When the programmed delay was increased to 60 s, the rats preferred cocaine, selecting it ~65% of the time. These findings suggest that, in choice studies, rats normally choose the alternative reward over cocaine likely because the delay to cocaine reward is longer.

The findings of Canchy et al. [9] are remarkable and thought-provoking, because they suggest that in cocaine choice studies, and perhaps in choice studies with other drugs of abuse as well, rats could be choosing not only between drug and nondrug reward, but

[1]Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Montreal, QC, Canada and [2]Groupe de recherche sur le système nerveux central, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada
Correspondence: Anne-Noël Samaha (Anna.samaha@umontreal.ca)

Received: 17 August 2020 Accepted: 20 August 2020
Published online: 1 September 2020

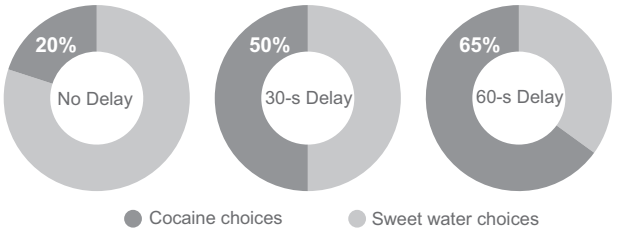

Fig. 1 When rats must choose between cocaine and an alternative, nondrug reward (sweet water), adding a programmed delay to both options causes rats to shift their preference to cocaine. In this issue of *Neuropsychopharmacology*, Canchy et al. [9] tested the hypothesis that rats in cocaine choice studies choose the alternative reward more often than they choose the drug because the delay to cocaine reward is longer than it is for the nondrug option. To test this hypothesis, they allowed male rats to make a mutually exclusive choice between cocaine and sweet water, during tests where a delay was added to both options. When there was no delay (0 s), rats chose cocaine over sweet water on average only 20% of the time. With a 30-s delay, rats increased their cocaine choice, opting for the drug on average 50% of the time. Finally, with a 60-s delay, rats shifted their preference from sweet water to cocaine, choosing the drug on average 65% of the time.

between reward now and reward later. This might explain why rats choose the alternative, nondrug reward so often. Thus, cocaine choice studies are not incompatible with the notion that drugs like cocaine have supranormal rewarding effects, or the notion that addiction-relevant changes in brain, psychology, and behaviour can be modelled in laboratory animals. And finally, these new findings suggest that the conflict between data from choice studies and the dopamine hypothesis of addiction could be more apparent than real.

FUNDING AND DISCLOSURE

I am supported by a salary grant from the Fonds de Recherche du Québec—Santé (grant number 28988). I declare no competing interests.

ACKNOWLEDGEMENTS

I thank Mister Patrick Castell for kind assistance in generating Fig. 1. I also thank Dr. Yavin Shaham for comments on an early version of this text.

REFERENCES

1. Lenoir M, et al. Intense sweetness surpasses cocaine reward. PLoS ONE. 2007;2: e698.
2. Tunstall BJ, Riley AL, Kearns DN. Drug specificity in drug versus food choice in male rats. Exp Clin Psychopharmacol. 2014;22:364–72.
3. Lenoir M, et al. Extended heroin access increases heroin choices over a potent nondrug alternative. Neuropsychopharmacology. 2013;38:1209–20.
4. Schwartz LP, et al. Heroin and saccharin demand and preference in rats. Drug Alcohol Depend. 2017;178:87–93.
5. Venniro M, et al. Incubation of methamphetamine but not heroin craving after voluntary abstinence in male and female rats. Neuropsychopharmacology. 2017;42:1126–35.
6. Di Chiara G. Drug addiction as dopamine-dependent associative learning disorder. Eur J Pharmacol. 1999;375:13–30.
7. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004;5:483–94.
8. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18:247–91.
9. Canchy, L, et al., Pharmacokinetics trumps pharmacodynamics during cocaine choice: a reconciliation with the dopamine hypothesis of addiction. Neuropsychopharmacology. 2020. Epub ahead of print.