Undoing cocaine's consequences on behavior and brain

Barry Setlow[1]

Department of Psychology and Faculty of Neuroscience, Texas A&M University, College Station, TX 77843-4235

A large body of animal research within the field of drug abuse has established that environmental variables can significantly modulate a range of addiction-related behaviors. Stressful and aversive conditions can enhance sensitization to the locomotor stimulant effects of drugs as well as drug-seeking and drug intake (1, 2). Stress-reducing manipulations and nondrug rewards may have the opposite effect, in that they can reduce such behaviors (2, 3). Some of this latter work has shown that the acquisition of addiction-related behaviors such as sensitization and drug self-administration is attenuated in animals housed in "enriched" environments (containing novel toys, food, and conspecifics with which to interact) compared with those housed in standard laboratory conditions (4, 5), but such findings do not present a practical guide to treating drug-addicted humans, who present for treatment only after drug use is acquired. However, in this issue of PNAS, Solinas *et al.* (6) suggest that environmental enrichment can still exert its beneficial effects on addiction-related behaviors even after they are established.

Effects of Enrichment

In the first experiment in this article, mice were subjected to a cocaine sensitization paradigm in which a series of repeated cocaine injections enhanced the locomotor response to a subsequent challenge injection of cocaine (7). This sensitized locomotor response is thought to reflect drug-induced alterations in the neural mechanisms that mediate drug reward and addictive behavior (8). As is typical, mice housed in standard laboratory conditions maintained a sensitized locomotor response to a cocaine challenge for as long as 30 days. However, mice that were moved to enriched housing conditions after the repeated cocaine injections showed no evidence of a sensitized response to cocaine, suggesting that enriched housing either attenuated, prevented the development of, or compensated for the neural adaptations underlying locomotor sensitization. Additional behavioral experiments showed that enriched housing attenuated preference for a cocaine-paired environment (conditioned place preference), as well as the ability of an acute cocaine injection to reinstate a previously extinguished preference for a cocaine-paired environment. A final experiment examined brain activity (using the immediate early gene product c-fos) in response to the reinstatement procedure, and found that the enriched mice showed attenuated activation in limbic-striatal brain regions linked to reinstatement of cocaine-seeking behavior.

Environmental manipulations that reduce established drug-related behaviors are often framed as "alternatives," which render drugs of abuse relatively less attractive in choice situations and thus reduce drug intake. Indeed, such nondrug alternatives (such as highly palatable food or exercise opportunities in animal subjects and money or token equivalents in humans) are effective at reducing drug intake (3, 9, 10). However, the enriched housing environment used by Solinas *et al.* (6) cannot easily be conceptualized as an "alternative" to any of the drug-related behaviors examined in their mice, suggesting that enriched housing exerted its effects in other ways. One likely possibility that is suggested by the authors is through effects on stress. Enriched housing reduces both basal and stress-induced levels of stress hormones and other markers of the stress response (11). Because stress (including that induced by social isolation) can enhance locomotor sensitization and promote relapse to cocaine-seeking (1, 2, 6), stress reduction via enriched housing would be expected to have opposite effects. In addition (and/or possibly through interactions with stress systems), enriched housing causes changes in dopaminergic signaling that would be expected to counteract the behavioral and neural consequences of cocaine administration (5, 12). Notably, some of these changes occur in the same brain regions in which enriched housing attenuated reinstatement-induced c-fos activation in the current work by Solinas *et al.*, suggesting potential neural substrates for the beneficial effects of enrichment on addiction-related behaviors. However, in weighing the clinical implications of these findings, it will be important to take into consideration whether "standard" laboratory housing is comparable to the environmental conditions in which drug-addicted individuals typically live (and thus that "enrichment" would represent an improvement over standard living conditions), or whether it more accurately reflects a severely impoverished environment (and thus that the effects of "enrichment" better represent a rescue from conditions in which few humans would find themselves).

Enriched housing reduces both basal and stress-induced levels of stress hormones.

Remaining Questions and Implications

The findings of Solinas *et al.* (6) are important in that they provide some of the first evidence in an animal model for successful behavioral treatment of addiction-related behaviors. However, several questions remain. First, what are the parameters of the effects of enriched housing on drug-related behaviors? Solinas *et al.* found that enriched housing begun immediately after cocaine administration had no effects on locomotor sensitization or preference for a cocaine-paired environment after 1 day, but eliminated these behaviors after 30 days. However, it is unclear whether the beneficial effects of enriched housing after 30 days were due to the longer duration of enrichment, changes in the neural substrates of these behaviors after 30 days that renders them more susceptible to the effects of enriched housing (13), or some interaction between these factors. Similarly, it is as yet unknown whether the beneficial effects of enriched housing outlast the period of enrichment, or whether enriched housing is effective when begun later during the withdrawal period.

Second, does enriched housing attenuate other addiction-related aspects of behavior? There have recently been considerable strides in developing rodent models of drug (particularly cocaine) self-administration that mimic many of the fundamental features of addiction, including escalation of drug intake, compulsive drug-seeking, and drug-seeking in the face of adverse consequences (14). It will be of partic-

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[1]E-mail: bsetlow@tamu.edu.

ular interest to see whether enriched housing attenuates drug-seeking in these models, especially in subpopulations of animals that exhibit this full range of addictive behaviors and appear most similar to drug-addicted humans (14). In addition, emerging evidence shows that drugs of abuse may cause long-lasting prefrontal cortex-associated cognitive deficits that are similar to those observed in the drug-addicted human population (15, 16). Because these deficits may be dissociable from the drug-induced enhancements in motivation-related behaviors examined by Solinas *et al.* (6), it will be of interest to determine whether enriched housing is beneficial for these consequences of drug administration as well.

Despite the remaining questions, the findings of Solinas *et al.* represent an important advance in modeling treatments for addiction, because there are relatively few treatments (environmental or otherwise) that appear to reverse (as opposed to block) established drug-related behavior (17, 18). These findings may also have implications for social policy decisions surrounding addiction [for example, providing support for the use of "drug courts," which offer drug-addicted criminal offenders community-based treatment options unavailable to individuals in the general court system (19)]. Finally, these findings join a growing body of work suggesting beneficial effects of environmental enrichment in animal models of other neuropsychiatric conditions, including depression and Huntington and Alzheimer diseases (20). Such findings highlight the importance of the role of environmental conditions in disease phenotype, both in animal models and in the clinic.

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