Stress and Addiction

Substance abusers make many bad decisions for the short-term satisfaction of a "high," at the cost of various undesirable longer-term consequences—withdrawal symptoms; physical and mental abuse and their associated medical and psychiatric complications; loss of family, friends, money, and employment; legal prosecution and incarceration; and sometimes death. Their ability to make better decisions is further impaired by a triad of relapse precipitants: drug-related cues, small amounts of the drug itself (called priming), and various types of stress. These precipitants are readily modeled in animals and have been precisely quantified and understood through elegant neurobiological experiments (1, 2). The neurobiological framework for understanding animal reinstatement models for human relapse to addiction has explicated mechanisms ranging from neuroanatomical pathways to neurotransmitters to second-, third-, and fourth-level intraneuronal messengers and the associated gene activations induced by acute and chronic drug self-administration (3). Insights generated from this extensive neurobiology, which has been developing over the past 40 years, are driving translational studies that advance our knowledge further still. The new translational studies are taking our clinical observations about protracted withdrawal and providing them with a biological basis that can have direct pharmacotherapeutic applications in preventing relapse to addiction after the acute withdrawal syndromes have been treated and have abated (4, 5). Like the best of transformative clinical research in psychiatry, these studies link biological probes with behavioral outcomes and interventions.

"Stress unmasked a latent vulnerability, which was associated with β-adrenergic stimulation."

An article by Zhang et al. (6) in this issue of the *Journal* provides an excellent example of translational research on addiction. This study from the Chinese National Institute on Drug Dependence examined the effects of stress on deficits in decision making among formerly dependent heroin addicts. These patients were examined for their ability to make the standardized decisions embedded in the Iowa Gambling Task after a period of abstinence ranging from 15 days to 2 years. Notably, the impairment in decision making observed in this study population was not associated with deficits in general cognitive intelligence or impairments in attention. Furthermore, although this sample's decision making apparently matched that of healthy comparison subjects after 2 years of abstinence, stress was able to disrupt decision making, just as it did in more recently detoxified former addicts. Thus, stress unmasked a latent vulnerability, which was associated with β-adrenergic stimulation. As the authors indicate, similar deficiencies in decisional ability have been shown with other addictions, such as alcohol and nicotine, after considerably shorter periods of abstinence.

The long duration of follow-up is critical to the insights of this study, because we have had clinical information since the 1940s that opiates produced a protracted withdrawal lasting at least 18 months—far longer than the 7 days of acute opiate withdrawal (4). The abnormalities associated with this protracted state were known to include disrupted circadian variation in cortisol levels, cardiovascular disruptions indicative of noradrenergic overdrive, subjective complaints such as anxiety, and observed sleep disruptions. However, a neurobiology of protracted withdrawal was not possible to formulate 60 years ago. Related clinical epidemiology observations over the intervening decades

complemented these small human laboratory studies in showing that relapse to opiates was much less likely in patients who had been abstinent from illicit opiates for 2 years compared to those with shorter durations of abstinence (7). However, a critical mechanistic connection had not been made between the disrupted biology and the epidemiological association of markedly reduced relapse after 2 years of abstinence. The study by Zhang et al. provides some connection between these clinical and epidemiological findings, namely that deficient decision making in former addicts can be normalized after 2 years of opiate abstinence. However, vulnerability to stress persists, since the modest social stress of giving a prepared speech for a few minutes in front of others had a significant effect on these patients' decisional ability after almost 2 years of abstinence. Decision making did not become completely normalized, but decision making under stress could be normalized using a beta-blocker to reduce noradrenergic activation.

Typical modern addiction treatments are structured as relatively nonstressful situations, rather than using the old-style stereotyped confrontations that are sometimes portrayed in the popular media. Treatment is designed to engage and retain the patient, not drive him or her out of treatment with confrontation and high levels of stress. Thus, getting an accurate assessment of the patient's ability to make appropriate decisions that will avoid relapse to addiction when under the stress of the real world is not simple for either the therapist or the patient. The therapeutic insight offered in the Zhang et al. article is that decisional ability can be improved with pharmacotherapy long after the acute withdrawal symptoms have abated. Propranolol is a relatively inexpensive medication with few side effects at the doses used in this study, and newer noradrenergic blockers are longer lasting and have better penetration into the brain, where these antistress effects are presumed to occur. This study's insight may open other therapeutic avenues as well.

While dopamine neurotransmission has been an important focus of addiction research because of its role as a common final pathway in reinforcement and euphoria, other brain neurotransmitter systems are of at least equal importance for relapse after abstinence. The noradrenergic system has become a prime target for pharmacotherapies to prevent stress-induced relapse because of the established animal work of Stewart, Shaham, and others (1, 2). Rather than using postsynaptic noradrenergic blockers like propranolol, larger ongoing clinical trials examining the prevention of stress-induced relapse are using α_2-noradrenergic agonists such as lofexidine or guanfacine in cocaine- as well as opiate-dependent patients (8). These agonists act presynaptically to reduce noradrenergic neurotransmission through feedback inhibition at the level of the locus ceruleus, the largest brainstem source of noradrenergic activity (5).

Zhang et al. applied findings from animal work to the clinical setting for the significant duration of 2 years of abstinence, because 2 years corresponds well with findings from over 60 years of human laboratory and clinical epidemiology research on protracted withdrawal and relapse in opiate addiction. We in the addictions field look forward to further translational and clinical contributions like those of Zhang and colleagues.

References

1. Stewart J: Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. J Psychiatry Neurosci 2000; 25:125–136
2. Shaham Y, Erb S, Stewart J: Stress-induced relapse to heroin and cocaine seeking in rats: a review. Brain Res Brain Res Rev 2000; 33:13–33
3. Nestler EJ: Review: transcriptional mechanisms of addiction: role of DeltaFosB. Philos Trans R Soc Lond B Biol Sci 2008; 363:3245–3255
4. Satel SL, Kosten TR, Schuckit MA, Fischman MW: Should protracted withdrawal from drugs be included in DSM-IV? Am J Psychiatry 1993; 150:695–704
5. Kosten TR, O'Connor PG: Management of drug and alcohol withdrawal. N Engl J Med 2003; 348:1786–1795
6. Zhang X-L, Shi J, Zhao L-Y, Sun L-L, Wang J, Wang G-B, Epstein DH, Lu L: Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. Am J Psychiatry 2011; 168:610–616

7. O'Donnell J, Ball J: Narcotic Addiction. New York, Harper & Row, 1966
8. Sinha R, Kimmerling A, Doebrick C, Kosten TR: Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. Psychopharmacology (Berl) 2007; 190:569–574

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