Does Stress Contribute to the Incubation of Craving?

To the Editor:

The concept of incubation of craving in humans was first noted over 25 years ago in cocaine addicts who experienced increased drug craving and drug seeking in response to drug cues that persisted even after long periods of abstinence (1). This phenomenon has since been observed using the extinction/reinstatement paradigm in rodents. Animals have shown time-dependent increases in drug seeking after withdrawal from cocaine (2), alcohol (3), heroin (4), and methamphetamine (5). Dovetailing this work, Bedi et al. (6) found that cue-induced craving in abstinent human smokers increases with time, even as baseline levels of craving and withdrawal decrease. Taken together, this evidence has clear implications for treatment and relapse prevention. However, mechanisms underlying incubation of craving are not well understood, and it is unclear whether drug cues alone precipitate incubation of craving and relapse or whether another confounding factor, such as stress, may be the causal agent. Stress is known to be a significant risk factor that predisposes individuals to develop substance use disorders and puts recovering addicts at risk for relapse (7). By looking at the role of stress using parallel animal and human models, we can perhaps gain a new perspective on the issue of incubation of craving.

The allostatic model proposed by Koob (8) views addiction as a persistent state of stress, involving increased reward set-points and activation of hormonal stress responses. In this model, baseline levels of stress are so high that environmental cues are more likely to lead to drug seeking in an effort to relieve this constant stress (9). These dysregulated stress and reward circuits persist into abstinence, increasing craving and vulnerability to relapse. Thus, stress can be viewed as the underlying contributor to incubation of craving within this framework. For example, in animal models, the presentation of a drug cue that is not followed by drug reward is likely to be stressful for the animal. Failure to receive an expected reward is known to cause a depression in firing of dopamine neurons below basal firing rate (10), which may contribute to a negative, stressful state for the animal. Thus, the presence of stress during drug cue presentation may confound the interpretation of previous animal studies regarding incubation of cue-induced craving and drug seeking. Measuring the stress response (i.e., corticosterone levels) in animals presented with drug cues without subsequent reward and testing the extent to which this stress response is associated with incubation of craving and drug seeking could shed some light on this hypothesis.

It is also important to note that a major difference between human and animal models is that animals are not motivated by psychosocial factors to become abstinent. In contrast, among abstinent human smokers, a cigarette cue may be anxiety provoking, as it not only activates conditioned psychophysiological responses but also may elicit fear about “falling off the wagon.” For this reason, the drug-seeking response to a cue may be partially related to stress or anxiety that arises when abstinent substance users are presented with cues that threaten their ability to remain abstinent. Cocaine-dependent subjects showed overall higher mean cortisol levels throughout a cocaine-cue task compared with control subjects (11). Although these subjects were not tested after periods of protracted abstinence, the above findings suggest that cocaine cues are stressful for cocaine users, and this phenomenon could be further examined during abstinence periods. It is possible then that humans may be particularly susceptible to the effects of stress on incubation of craving, given that for humans there may be both a biological stress (e.g., suppression of dopamine neuron firing after the presentation of a cue without the actual reward and increases in cortisol in response to cues) and a psychosocial stress, as noted above.

The current gap in our understanding of incubation of craving can be addressed in both human and animal research, keeping in mind that current animal models fail to capture the stressful psychosocial experience of trying to quit and remain abstinent from an addictive substance. Future studies need to test an alternative interpretation that suggests that it is the stress associated with a drug cue, rather than the incentive value of the cue alone, that causes increased craving or drug seeking. As researchers progress toward an understanding of the incubation of craving phenomenon that incorporates both stress and drug cues into its causal framework, the potential to prevent relapse in individuals suffering from a wide array of addictive disorders may be significantly improved.

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