

The impact of stress on addictive behavior

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Scientists have been aware of the existence of a complex relationship between stress and the subsequent activation of the hypothalamo-pituitary-adrenal (HPA) axis and the endocrine and neurobehavioral effects of cocaine for many years now. Our research program has focused on the involvement of HPA axis activation in cocaine reinforcement using the intravenous self-administration model. Uncontrollable electric footshock shifts the ascending limb of the acquisition dose-response curve upwards and to the left, demonstrating an increased sensitivity to cocaine. Sensitivity to low doses of cocaine falling on the ascending limb of the acquisition dose-response curve can also be augmented by increasing circulating levels of corticosterone with exogenous injections of the hormone, but similar treatments do not affect responding maintained by higher doses. Since corticosterone secretion ultimately results from the actions of corticotropin-releasing hormone (CRH), our results indirectly suggest a role for CRH in the acquisition of cocaine self-administration. In a similar vein, ongoing, low-dose cocaine self-administration is decreased by drugs affecting the synthesis and/or secretion of corticosterone. The corticosterone synthesis inhibitor ketoconazole reduces low dose cocaine self-administration, as do the benzodiazepines chlordiazepoxide, alprazolam and oxazepam, but these effects can be overcome by increasing the unit dose of cocaine. On the other hand, the self-administration of doses falling on both the ascending and descending limbs of the cocaine dose-response curve can be attenuated by drugs that block central CRH receptors, which further demonstrates the role for CRH in cocaine reward. Finally, CRH is also critical for the cue-induced reinstatement of extinguished cocaine-seeking behavior, which illustrates the involvement of CRH and the HPA axis in the relapse to cocaine use. Continued investigations into how stress, CRH secretion and the subsequent activation of the HPA axis affect cocaine self-administration will likely result in the identification of more effective and efficient treatment for cocaine addiction.

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