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HPA axis function and drug addictive behaviors: insights from studies with Lewis and Fischer 344 inbred rats

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Abstract

Much research supports a link between stress and its concomitant hypothalamic–pituitary–adrenal (HPA) axis responses with behavioral sensitivity to psychoactive drugs. Our research demonstrates that Lewis inbred rats more readily acquire drug self-administration than Fischer 344 (F344) inbred rats and, compared to this strain, Lewis rats have hyporesponsive HPA axis responses to stress exposure. This association appears to conflict with investigations using outbred rats and suggests that the relationship between drug sensitivity and HPA axis responsiveness is more complicated than originally thought. It is essential to better understand this relationship because of its relevance to vulnerability and relapse to drug abuse. Thus, this paper reviews the literature in which these two inbred strains have been compared. We discuss strain differences in HPA axis function, in characteristics of the mesolimbic dopamine system, and in behaviors thought to reflect emotionality. Strain differences in unconditioned and conditioned effects of psychoactive drugs are then reviewed. Next, we discuss the possible role of sex and gonadal hormones on responsiveness to psychoactive drugs in these strains. Finally, a comparison of results obtained from these strains to three other comparator groups (e.g., high and low responders) suggests that a non-monotonic relationship between behavioral sensitivity to drugs and HPA axis responsiveness can explain much of the discrepancies in the literature.

Keywords: Cocaine; Opiates; Dopamine; Corticosterone; Vulnerability; Rat

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1. Introduction

Drug addiction is a serious problem today with over 6 million deaths in 1998 attributed to this disease worldwide (WHO, 1999). In addition to causing mortality, drug addiction exerts emotional and economic strains on the individual, their family, and on society. Problems associated with drug addiction include crime, job loss, disruption of family life, and health concerns, including HIV and AIDS. Opiate abuse is treated with one of three approved medications in the United States, alcohol abuse with one of two medications, but there are no effective treatments for cocaine or other psychostimulant addictions (Kosten, 2001). Even in cases that have approved treatment approaches, recidivism remains high reflecting the chronic relapsing nature of addiction. This underscores the necessity of instituting more effective drug abuse prevention programs. The most cost-effective approach would be to target such programs to individuals with high risk of developing these disorders. The challenge has been to determine how to identify such individuals.

Drug addiction is influenced by environmental and genetic factors and may cluster with other behavioral or neurohormonal characteristics. The search for markers that predict drug abuse has led many to examine temperament or personality factors (Cloninger, 1987; Zuckerman, 1979). Such variables include arousal, sensation-seeking, and emotional reactivity all of which are associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis. Thus, the purpose of this paper is to examine the research investigating the relationship between HPA axis function and behavioral responses thought to predict drug addiction. We focus our review on studies of Lewis and Fischer 344 (F344) inbred rat strains for three reasons: 1) each of us have researched these strains for many years with one of us examining the effects of cocaine and the other examining the effects of morphine, 2) this approach provides a unique insight into this complex behavioral and neurohormonal relationship, and 3) the comparison of results from this line of investigation to those of other approaches allows a more rich understanding of behavioral responsiveness to psychoactive drugs that can ultimately suggest more effective drug abuse prevention and treatment strategies.

This paper will present an overview of strain differences in HPA axis function, neurochemical characteristics of the mesolimbic DA system, and the behavioral effects of psychoactive drugs. How stress and psychoactive drugs affect HPA axis function and mesolimbic DA activity will be reviewed. Next, we discuss results of behavioral studies including assessments of measures thought to reflect fear, anxiety, or emotional reactivity as well as the behavioral responses to psychoactive drugs. Then, because most studies of HPA axis function and stress utilized female rats whereas most studies of mesolimbic DA function and behavioral responses to drugs utilized male rats, we discuss how sex or ovarian hormones may interact with these systems. To shed light on the relationships between HPA axis activity, mesolimbic DA activity, emotional reactivity, and responsiveness to psychoactive drugs, we compare results from studies of Lewis and F344 rats to results obtained from three other comparison groups that differ by either or both genetic and environmental influences. These include inbred mouse strains, rats with early life stress, and rats categorized as high vs. low responders (HR vs. LR). Finally, we propose that many of the dis-