Published in final edited form as:

Int J Psychophysiol. 2006 March ; 59(3): 193–194.

The hypothalamic–pituitary–adrenocortical axis in addiction

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Keywords

Hypothalamic-pituitary-adrenal axis; Addictions; Nicotine; Alcohol

1. The hypothalamic–pituitary–adrenocortical axis in addiction

This special issue of the International Journal of Psycho-physiology presents recent psychophysiological work on the hypothalamic–pituitary–adrenocortical axis (HPA) and addiction to alcohol and nicotine. The past 15 years have seen increasing recognition that HPA function is dysregulated in persons who have developed a dependence on alcohol, nicotine, and illicit drugs. Why should this be so? Addictions, by their nature, are a derangement of adaptive behavior (Koob and Le Moal, 1997). The HPA has an essential role in normal physiological processes and in adaptation to stress (Selye, 1936). By extension, altered HPA function in relation to addictions provides us with a window into associated derangements of motivational systems in the brain. In this special issue, workers in the fields of alcohol and nicotine addiction present studies that illustrate how HPA function is altered in relation to these conditions.

The term addiction describes a progressive loss of behavioral control leading to dependence on a drug and inability to stop without adverse consequences (American Psychiatric Association, 1994). All abused substances, including tobacco, alcohol, and illicit drugs tend to foster increasing use, threatening to cause dependence and the penalty of withdrawal in the abuser. This suggests that however they differ, all abused drugs have common properties that both depend on and contribute to altered functioning of the central nervous system. It is therefore important to ask whether persons at high risk for future addiction may also share common vulnerabilities those brain systems that respond to these drugs.

George Koob and colleagues have shown that the brain's reward mechanisms are altered in rat strains that are prone to self-administration of alcohol and other drugs. In addition, these alterations are worsened by prolonged self-administration (Ahmed and Koob, 1998; Koob, 2003; Koob and Bloom, 1988; Koob et al, 1994). In Koob's words, the emotional and motivational apparatus of the brain has been "hijacked" in persons that have become drug dependent (Koob and Le Moal, 1997). Other evidence supports a pervasive set of interactions between altered HPA function and drug exposure, addiction, and stress responsivity (Valdez et al., 2003). The papers in this special issue focus on alcohol and nicotine addictions and how both disorders involve some disruption of the HPA axis.

2. Papers in this special issue

The overview by Lovallo discusses HPA function in relation to the brain's dopamine and opioid systems. These systems influence cortisol production and stress responses. This suggests that HPA function may tell us about individual differences in the regulation of the limbic system and prefrontal cortex. Several studies show that recovering alcoholics have a blunted cortisol

response to a range of stressors. This finding naturally questions whether the response attenuation is due to years of excessive drinking or if it represents a more fundamental alteration in the central nervous systems of these persons.

King and her colleagues addressed this question in a study of cortisol reactivity to alcohol administration in young adults who are heavy social drinkers. After consuming alcohol equivalent to 2 and 4 mixed drinks, the heavy drinkers had almost no HPA response to this pharmacologic stimulus. In contrast, light social drinkers responded to both doses of alcohol. Because these groups have different drinking histories, it is impossible to rule out adaptation to alcohol as a factor in the results. However, it would be of interest to know if these heavy social drinkers have diminished HPA responses to stimuli other than alcohol.

Thayer and his coworkers also examined HPA function in relation to quantity of social drinking. They then looked at these variables in relation to heart rate variability, a useful index of central vagal outflow. They report that persons who have less cortisol output during sleep also have greater vagal control of the heart throughout the day. This inverse pattern may index better health and systems functioning. However, this reciprocal relationship between cortisol and heart rate variability is disrupted in heavier drinkers. It appears that a homeostatic relationship between the HPA activity and vagal control of the heart is disrupted by heavy alcohol intake. Alternatively, those persons who are motivated to drink heavily may have a prior alteration in central regulation of these same processes. It would be of interest to examine the HPA–vagal outflow relationship in heavy drinkers who had abstained for a period of time to see if the usual reciprocal pattern is restored in the absence of alcohol.

Sorocco presents a partial answer to this question of causation by presenting a study on healthy young adults who have a positive family history of alcoholism (FH+) but do not drink heavily. She reports that FH+ tend to have a diminished cortisol response to a public speaking stressor, even though their diurnal secretion pattern matches the FH– controls'. It is noteworthy that the response to this social stressor is most attenuated in those FH+ who are behaviorally disinhibited, based on self-reported impulsiveness, rule violations, and risk taking. These are known risk factors for alcoholism. The results accordingly point to possible dysfunction of brain centers that respond to social stimuli and in turn regulate inputs to the HPA. Because the two FH groups are similar in drinking habits, it is unlikely that their HPA differences are caused by alcohol exposure.

Four of these papers deal with the question of HPA function in relation to smoking and nicotine addiction. The one by al'Absi provides an excellent overview of nicotine use and altered HPA regulation, and it summarizes his and others' work showing that smokers have persistent elevations of cortisol. When smokers attempt to quit, cessation results in an abrupt drop in cortisol, and the size of that decline may predict who will have problems in maintaining abstinence. This work also shows that smokers have an attenuated HPA response to stress. Most importantly, stress hyporesponsiveness predicts a shorter time to relapse during smoking cessation. This finding provides a bridge between the field of alcoholism research and nicotine addiction suggesting that blunted HPA stress reactivity may indicate a greater underlying addiction potential in both cases.

Step toe and Ussher also describe studies on smokers attempting to quit. They report that active smokers secrete more cortisol across the day than nonsmokers, suggesting that nicotine stimulates the HPA. Cessation of smoking was associated with an immediate drop in cortisol secretion and then a gradual increase, suggesting a pharmacologic tolerance followed by a rebound recovery. These investigators also found that a larger decline pointed toward a greater risk of relapse. As Step toe and Ussher point out, it is not currently known if the acute drop in cortisol reflects the person's nicotine exposure, or if it relates to more fundamental biological

differences in smokers. The paper also asks the intriguing question of whether cessation could be maintained more effectively by blocking this drop in cortisol by the use of nicotine patches.

Rohleder and Kirschbaum also present evidence showing that nicotine intake chronically stimulates the HPA. They too show that smokers have an attenuated response to psychosocial stress although they respond normally to a challenge with corticotropin releasing factor. An interesting implication is that the extrahypothalamic structures responsible for acute psychological stress responses may be desensitized in smokers but are capable of response to pharmacologic stimuli. A question that arises from this speculation is whether HPA response to corticotropin releasing factor challenge is normal in those who abuse alcohol and other drugs (Adinoff et al., 2005). These authors also collect evidence showing that nicotine exposure causes widespread elevation of inflammatory responses, with implications for immune system functioning.

Olf and her colleagues investigated smoking and circadian cortisol secretion patterns in persons exposed to an industrial explosion and fire in the Netherlands. In agreement with the other papers in this issue, these authors report that smokers have higher levels of cortisol production. They then separated the disaster victims into those with no psychopathology vs. those with posttraumatic stress disorder, with or without major depressive disorder. They observed a flattened diurnal curve in the depressed victims, but they were only able to discern this difference after correcting the data for smoking. This work indicates that smoking may be a form of self-medication and that smoking may obscure differences in cortisol secretion between individuals with various forms of psychopathology.

The papers in this issue suggest two important relationships between alcohol and nicotine intake and HPA function. One group of papers suggests that addiction tendencies are associated with reduced HPA responsivity to stress and to alcohol. These studies may tell us about central nervous system differences in persons predisposed to substance abuse. The second group of papers shows that alcohol and nicotine acutely increase cortisol secretion with more normal levels of output being achieved after intake is stopped. They suggest that heavy intake of alcohol and nicotine may cause prolonged increases in cortisol secretion, exerting a negative impact on other systems, such as the immune system. Both sets of papers suggest that research on the HPA in relation to addiction will provide a rich source of information about addiction processes for some time to come.

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