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Cortisol secretion patterns in addiction and addiction risk

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Abstract

Addiction to alcohol or nicotine involves altered functioning of the brain's motivational systems. Altered functioning of the hypothalamic–pituitary–adrenocortical (HPA) axis may hold clues to the nature of the motivational changes accompanying addiction and vulnerability to addiction. Alcohol and nicotine show at least three forms of interaction with HPA functioning. Acute intake of both substances causes stress-like cortisol responses. Their persistent use may dysregulate the HPA. Finally, the risk for dependence and for relapse after quitting may be associated with deficient cortisol reactivity to a variety of stressors. The HPA is regulated at the hypothalamus by diurnal and metabolic signals, but during acute emotional states, its regulation is superseded by signals from the limbic system and prefrontal cortex. This top–down organization makes the HPA responsive to inputs that reflect motivational processes. The HPA is accordingly a useful system for studying psychophysiological reactivity in persons who may vary in cognitive, emotional, and behavioral tendencies associated with addiction and risk for addiction. Chronic, heavy intake of alcohol and nicotine may cause modifications in these frontal–limbic interactions and may account for HPA response differences in seen in alcoholics and smokers. In addition, preexisting alterations in frontal–limbic interactions with the HPA may reflect addiction-proneness, as shown in studies of offspring of alcohol- and drug-abusing parents. Continuing research on the relationship between HPA function, stress responsivity, and the addictions may yield insights into how the brain's motivational systems support addictions and risk for addictions.

Keywords

Hypothalamic–pituitary–adrenal axis; Addictions; Nicotine; Alcohol; Cortisol; Stress

1. Introduction

The hypothalamus controls the secretion of cortisol; a hormone necessary for life that regulates the functioning of all cells in the body. The secretion of cortisol is acutely sensitive to inputs from the limbic system and the prefrontal cortex during times of stress. This motivationally relevant communication between the limbic system and the hypothalamic–pituitary–adrenocortical axis (HPA) interacts with alcohol use and abuse in at least three ways. Ingestion of alcohol causes an acute cortisol response. Long-term abuse of alcohol dysregulates the basal and stress-reactive secretion of cortisol. Genetic propensity for alcohol and drug abuse may be accompanied by a reduced HPA response to stress. This paper reviews the basal and stress-reactive control of the HPA in relation to alcoholism with reference to nicotine and other addictions.

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1.1. Diurnal and stress-related regulation of the HPA

Cortisol secretion reflects the activity of the HPA. This activity is driven by diurnal and metabolic inputs as well as by stress responses (De Kloet and Reul, 1987; Linkowski et al., 1993). Cortisol's basal, or diurnal, secretion, shown in Fig. 1, peaks in the morning about the time of awakening and declines gradually through the waking hours to achieve a daily minimum during the first half of the sleep cycle (Czeisler et al., 1976). Cortisol's morning burst is driven by the action of clock genes in the suprachiasmatic nucleus of the hypothalamus initiating neuronal signals to the paraventricular nucleus (PVN) (Linkowski et al., 1993). Specialized PVN neurons respond to these signals. Their axons terminate in the median eminence of the hypothalamus, where they release CRF into the portal circulation, causing the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH is transported to the adrenal gland where it causes the adrenal cortex to increase the synthesis and release of cortisol into the circulation. This diurnal pattern is modulated throughout the day by metabolic inputs arising in relation to blood glucose levels (Van Cauter et al., 1992). Finally, cortisol helps to regulate its own secretion by exerting negative feedback at the pituitary, hypothalamus, and hippocampus (Bradbury et al., 1994). For these reasons, we refer to this basal pattern of HPA regulation as diurnal and metabolic in nature. Chronic disturbances of this diurnal secretion pattern may reflect disorder at one or more levels in this system.

Since the work of Hans Selye, we have been aware that the HPA is supremely reactive to stressors that challenge the well-being of the organism (Selye, 1936). Stressors form two major classes, those that originate in bodily disturbances, such as hemorrhage, and those that originate as external threats, such as confrontation by a predator. The former may be considered bottom-up stressors because their inputs ascend from the body to the brain. In contrast external threats and psychological distress can be thought of as being top–down in nature; they activate the stress axis because of how they are perceived and interpreted (Lazarus and Folkman, 1984; Lovallo and Gerin, 2003). Psychological stressors gain their influence because of how we interpret them in relation to our long-term plans and expectations about the world (Lazarus and Folkman, 1984). It is noteworthy that cortisol is quite responsive to acute psychological distress, suggesting that the source of HPA activation in such cases must involve connections from the limbic system and prefrontal cortex to the hypothalamus.

Our understanding of cortisol responses to psychological stress was increased by the discovery that cortisol has a widespread system of receptors above the hypothalamus. These are found in the hippocampus, the limbic system, and the prefrontal cortex (McEwen et al., 1968; Sanchez et al., 2000). The distribution of these receptors argues strongly that higher brain centers play a role during the psychological stress response and cause responses of the HPA. In fact, during periods of psychological distress, cortisol's diurnal pattern is overridden by signals to the hypothalamus that originate in the limbic system. The signals arise in the amygdala and the bed nuclei of the stria terminalis, structures that are activated by conditioned and unconditioned stimuli and that convey information having survival value (Amaral et al., 1992; Halgren, 1992; LeDoux, 1993). The amygdala therefore stands at the center of a neural network that generates approach and avoidance reactions to innate and learned stimuli (Rolls and Stringer, 2001). Outputs from the amygdala and bed nuclei interact with nearby structures, such as the nucleus accumbens, that, in turn communicate extensively with the prefrontal cortex (Carboni et al., 2000; Figueiredo et al., 2003; Herman et al., 2003). The bed nuclei also provide the primary inputs to the PVN that generate an HPA response to psychological stress. These frontal–limbic processes therefore form the neurophysiological mechanism through which psychological events can generate cortisol responses (Lovallo and Thomas, 2000). These influences are augmented during periods of psychological stress by norepinephrine inputs that ascend from the locus ceruleus in the brainstem to activate the cerebral cortex and limbic system

(Harris and Aston-Jones, 1994; Pacak et al., 1995). The stress response is further integrated across the central nervous system by an extensive system of CRF-secreting neurons found in the cerebral cortex and limbic system (Petrusz and Merchenthaler, 1992). Because of the frontal–limbic origin of psychological stress responses, variations in the acute cortisol response to stress may reveal differences between individuals in their limbic system reactivity and psychological controls over their behavior.

The foregoing indicates that the HPA is responsive to the most fundamental motivational processes, such as seeking food, ingestion of nutrients, metabolic regulation, and threats to well being. Addictions to alcohol, nicotine, and other drugs necessarily involve a reworking of these relationships. We may therefore view altered HPA functioning in substance use disorders to be of prime importance in understanding the underlying brain mechanisms.

2. Features of the addictions

Alcoholism is a socially defined construct reflecting a person's progressive loss of behavioral control over use of a socially sanctioned drug (American_Psychiatric_Association, 1994). Use of alcohol and illicit drugs, and to a lesser extent, nicotine addiction may involve: (1) use beyond accepted norms or unsanctioned use; (2) forsaking of usual activities; (3) disruption of family life, employment, and legal difficulties; (4) inability to curtail or stop the activity despite repeated attempts; and (5) withdrawal symptoms on cessation of use. The likelihood that common vulnerabilities underlie various addictions is supported by the high rates of comorbid abuse (Burns and Teesson, 2002; Tapert et al., 2002). The common occurrence of multiple addictions also suggests that common vulnerabilities may underlie any one addiction.

3. Addiction and the brain's motivational systems

The emerging view of the commonalities among addictions is promoted by research showing that addictions involve genetic and acquired alterations in motivational systems within the brain. In a series of influential papers, George Koob and colleagues showed that reward mechanisms are disrupted in rat strains that are prone to self-administer alcohol and other drugs. This dysregulation is worsened by prolonged low-level exposure to drugs of abuse (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 dependent on drugs of abuse (Koob and Le Moal, 1997).

Other studies show pervasive alterations of HPA stress responsivity in relation to drug exposure and addiction (Valdez et al., 2003). These alterations involve changes in dopaminergic and opiodergic regulation of CNS function (Oswald and Wand, 2004). Several findings illustrate these points. First and foremost, acute administration of drugs of abuse often causes an HPA response, leading to increased cortisol secretion (Broadbear et al., 2004; Mendelson et al., 1971). Both behavioral stress and drug withdrawal are interchangeable in their effects, as indexed by their mutual ability to evoke anxiety-like behaviors in rats (Breese et al., 2004). Furthermore, rapid drug withdrawal causes release of CRF in widespread brain regions, precipitating a systemic stress reaction (Rodriguez de Fonseca et al., 1997). Stress by itself increases cocaine cravings in human abusers (Sinha et al., 2000), and it increases drug self-administration in animal models (Piazza and Le Moal, 1998). In turn, self-administration appears to depend on the neural signals generated by cortisol feedback to the central nervous system (CNS), because decreasing the production of CNS glucocorticoid receptors also causes a reduction in cocaine self-administration (Deroche-Gamonet et al., 2003). Acute cortisol administration precipitates craving in cocaine-dependent humans (Elman et al., 2003), again suggesting an active role for the HPA in enhanced drug intake. At this time it is not firmly established whether self-administration and drug cravings reflect: (1) the CRF activation associated with generation of a stress response, or (2) if they depend more on cortisol negative

feedback to the CNS that is responsible for regulating the duration and intensity of stress responses, or (3) if the character of this feedback is altered due to glucocorticoid receptor variations.

The interaction between stress and drug self-administration depends on the same dopamine pathway that responds during drug seeking and intake. Both stress and the acute administration of several abused drugs increase the excitability of dopamine neurons originating in the ventral tegmental area of the brainstem (Saal et al., 2003). Glucocorticoid receptor blockade prevents the stress-enhancement of dopamine neuron excitability, although it does not prevent the drug-induced effect on this excitability. This suggests that stress and drugs of abuse may initiate their effects in different ways but that they both act on brain dopamine systems as a common pathway to self-administration (Saal et al., 2003).

The evidence above indicates that the limbic system response to emotional stimuli and HPA responses to stress are both of interest in relation to drug intake, addiction vulnerability, and potential for relapse in humans. Consistent with this brain-based model, there is a tendency for addiction proneness to run in families, suggesting that the genes conferring this increased risk affect the same brain systems that are altered in consequence of addiction (Cloninger, 1987; Cloninger et al., 1981). Studies discussed below indicate the possibility that persons with a family history of alcoholism may have altered central opioid function that affects both the frontal–limbic processes necessary for evaluating events and dopaminergic activity that supports drug self-administration.

4. Cortisol regulation in persons at high risk for addiction

There are several lines of evidence that suggest alterations in HPA axis responsiveness in relation to current and past addictions as well as risk for addiction by virtue of a positive family history. Evidence for interaction between HPA function and use of alcohol, nicotine, and illicit drugs begins with the fact that all such substances cause acute HPA responses due to pharmacologic activation (Rivier, 1996). The second point of interaction is that the HPA may plausibly be dysregulated by persistent, high-level use of these substances (Adinoff and Risher-Flowers, 1991). Altered reactivity of the HPA in former abusers or persons at risk for abuse by virtue of a family history may derive from underlying psychobiological characteristics, therefore appearing in the absence of current abuse (Adinoff et al., 2005b; King et al., 2002).

This line of thought begins with findings that acute alcohol administration increases HPA function in rats (Rivier et al., 1984) and humans (Mendelson et al., 1971, 1966). Persons dependent on alcohol, nicotine, and other drugs may show chronic activation of the HPA during periods of heavy intake (Steptoe and Ussher, 2006; Wand and Dobs, 1991) and during withdrawal, with the loss of a normal diurnal secretion pattern for days to weeks afterward (Adinoff and Risher-Flowers, 1991). The usual diurnal pattern is reestablished if abstinence is maintained. Alcoholics regain a relatively normal pattern of diurnal cortisol secretion at about one to four weeks of abstinence (Adinoff et al., 2005a,b; Iranmanesh et al., 1989). However, HPA regulation may not be completely normal even after the diurnal pattern has recovered. Adinoff reported that abstinent alcoholics have a deficient cortisol response to HPA stimulation by CRF (Adinoff et al., 2005a,b).

Consistent with this finding, abstinent alcoholics have a blunted cortisol response to physical and psychological stressors for at least 4 weeks postwithdrawal (Bernardy et al., 1996; Errico et al., 1993; Lovallo et al., 2000; Margraf et al., 1967). In these studies, the controls and patients reported equal amounts of psychological distress in response to the stressor exposure, therefore ruling out differential interpretations or mood responses as causes of the blunted responsivity. Other studies of this type are also in agreement that cortisol responses are reduced to public

speaking stress in abstinent users of 3,4-methylenedioxymethamphetamine (‘ecstasy’) (Gerra et al., 2003b) and to negative emotions induced by photographs in abstinent heroin addicts (Gerra et al., 2003a). Abstinent heroin addicts also had reduced cortisol responses during a hostility-inducing game (Gerra et al., 2004). It would appear that abstinent alcoholics, heroin addicts, and users of ecstasy all show a persistent hyporesponsiveness to behavioral stress and related affect inductions. These findings collectively point to a persistent disruption of the usual limbic-system inputs to the hypothalamus in persons with an elevated abuse potential. Because these patients had a prolonged history of alcohol or drug intake, it is unclear if their cortisol response deficits were a consequence of drinking or drug addiction, if HPA responses would recover over time, or if the response deficit points to preexisting alterations of limbic system control over the HPA.

A recent study of abstinent alcoholics provides an alternative perspective (Munro et al., 2005). Similar ACTH and cortisol responses were seen in healthy controls and alcoholics abstinent for an average of 3.5 years and ranging up to 17 years. It is perhaps noteworthy that these alcoholics in remission did not differ from controls in their reported symptoms of depression, a characteristic that differs from most studies of alcoholics. It is not immediately clear if the alcoholics had recovered a normal level of HPA response with prolonged abstinence, if they had been normal all along, or if their lack of psychological comorbidity indicated that they were less affected by secondary characteristics related to a hyporesponsive HPA axis. However, the null results raise helpful questions about possible sources of heterogeneity within the alcoholic population. Variation in HPA response to stress, and to opioid challenge, may be related to comorbid depression or externalizing tendencies, such as novelty seeking (Oswald et al., 2004) and low sociability (Sorocco et al., 2006). This suggests useful avenues for future work on the causes of HPA hyporeactivity in relation to addiction.

5. Blunted cortisol reactivity and addiction severity

The studies showing blunted HPA reactivity in substance use disorders raise the question of whether the reactivity difference is a consequence of addiction or a characteristic of the persons in question. Limited, but suggestive, evidence indicates that a hyporesponsive HPA signals the severity of the underlying addictive process. Alcoholics in treatment tend to relapse more rapidly when they have smaller cortisol responses to public speaking stress (Junghanns et al., 2003) or in response to alcohol cues in a cue exposure procedure (Junghanns et al., 2005). Studies on abstinent smokers, reported in this issue, show that small stress cortisol responses signal greater relapse potential as well (al'Absi, 2006). Relapse was also related to the magnitude of cortisol reduction after cessation from smoking, indicating relatively lower tonic cortisol levels in persons with greater relapse potential (Steptoe and Ussher, 2006).

6. Opioid blockade, cortisol response, and a positive family history of alcoholism

Studies using the opioid blocking agents, naloxone and naltrexone, provide insight into the nature of the blunted HPA responsiveness observed in alcoholics, and they support the idea that such deficits predate heavy drinking. Wand and colleagues administered intravenous naloxone to nonabusing young adults with (FH+) and without (FH−) a family history of alcoholism and found that the FH+ had a large and rapid cortisol response over the next 120 min, compared to the FH− (Wand et al., 1998). Other tests ruled out peripheral response differences as a source of these findings (Oswald and Wand, 2004). King also has reported that oral naltrexone causes larger and more prolonged cortisol responses in FH+ than in FH− (King et al., 2002). Her FH+ subjects reported a greater decline in feelings of vigor, again pointing to central nervous system effects of the opioid blockade. These results show altered central regulation of the HPA in FH+ who have no personal history of heavy drinking.

The above studies suggest that attenuated HPA responses in alcoholics may reflect a difference that predates their heavy drinking. Fig. 2 is adapted from a model developed by Wand that suggests how opioid-producing neurons may act at the hypothalamus, the prefrontal cortex, and the brainstem to influence HPA responsivity in relation to genetic risk for alcoholism. (1) Opioid neurons from the arcuate nucleus of the hypothalamus normally inhibit CRF-neurons of the PVN, restraining CRF delivery to the pituitary gland, thereby reducing ACTH and cortisol release, and possibly diminishing stress responsivity. Opioid blockade thus releases the PVN from this tonic restraint, allowing cortisol production to rise. (2) Opioid neurons in the brainstem normally inhibit the NE-producing cells of the locus ceruleus. Opioid blockade releases the locus ceruleus from this inhibitory influence, allowing NE release to activate the CRF-neurons of the PVN, again allowing cortisol production to increase. (3) A secondary effect of opioid blockade occurs in the prefrontal cortex. Opioid neurons normally activate DA release in the nucleus accumbens. Opioid blockade reduces this DA release, potentially altering moods and processing of reward information. According to Wand's model, opioid blockade would enhance HPA reactivity, reduce the effectiveness of rewards, and have negative effects on mood (King et al., 2002).

Wand proposes that opioid blockade may cause greater cortisol effects in FH+ because of a variation in the μ-opioid receptor gene that codes for the production of a high-affinity opioid receptor on CNS neurons (Oswald and Wand, 2004). In a test of this hypothesis, males having one or two copies of the high-affinity allele had a twofold larger cortisol response to opioid blockade than did the subjects having the low-affinity allele. This provides a plausible mechanism for the greater response to opioid blockade seen in FH+, and it is consistent with the blunted stress response seen in recovering alcoholics. Although this model provides a mechanistic framework for the results of the opiate blockade studies, a differential prevalence of the high-affinity allele is not yet established in FH+ persons. The opioid model is appealing because it is testable in humans and animals, and it provides insights into variations in human HPA response, dopamine mechanisms, and genetic susceptibility to addiction.

7. Altered HPA stress reactivity in persons at risk for addiction

The finding that young adults with alcoholic fathers have exaggerated HPA responses to opioid blockade raises the question of whether they respond differentially to nonpharmacologic stimuli. Several studies show that psychological stress responses are blunted in adolescents and young adults whose parents have a history of alcoholism. Moss, Vanyukov and colleagues have tested cortisol responses to stress in 10- to 12-year-old boys whose fathers were alcoholics or were addicted to drugs (Moss et al., 1995, 1999). In these studies, the subjects entered the hospital to undergo an event-related-potential study that called for the application of scalp electrodes and attachment to complex equipment. The authors accordingly viewed this as a mildly anxiety-provoking stressor. They sampled cortisol from saliva collected before and after the procedure. The authors interpreted an elevation of cortisol before the procedure to be an anxiety-based, anticipatory stress response. The decline in cortisol after the procedure was taken as a return to an unstressed baseline, used to indicate the size of the stress response. The FH+ boys showed a lower level of cortisol before the procedure and an attenuated decline in cortisol afterward, relative to the FH− group. Followup work with the boys showed that attenuated cortisol responses were associated with greater experimentation with cigarettes and marijuana when the boys were 15 to 16 years of age, regardless of FH category (Moss et al., 1999).

This evidence implicates a family history of substance abuse as a factor predisposing to altered CNS responses to potential threats from the environment, with consequent reductions in cortisol response. These authors also implicate antisocial behavior in the father and in the son as further predictors of a stress hyporeactivity. Boys with more symptoms of conduct disorder

and whose fathers displayed more symptoms of antisocial personality disorder had correspondingly reduced cortisol levels and responsivity (Vanyukov et al., 1993), and they had higher levels of predicted risk of future substance use disorder (Dawes et al., 1999). These studies indicate a deficiency in response to potential threats, and they implicate the presence of antisocial tendencies as a contributing characteristic. Antisocial tendencies are indication of reduced emotional response to normally evocative events, they frequent accompany substance use disorders, and they have a known inherited basis (Langbehn et al., 2003).

A recent study directly compared HPA responsivity to opioid blockade vs. response to the psychological distress of public speaking (Oswald et al., 2004). Two findings stood out. First, persons were comparably more or less reactive to both challenges, showing a correlation of r=.57 in ACTH response, indicating strong individual-difference tendencies despite the disparate challenges. Second, the characteristic of novelty seeking predicted this stable difference across subjects. Novelty seeking is part of a dimension of disinhibition that has been related to substance abuse risk in some studies (Cloninger, 1987). However, in this case, persons higher in novelty seeking were more, not less, reactive than those low in this trait. In addition, the risk groups did not differ in cortisol response. This indicates that both ACTH and cortisol should be sampled when feasible in such studies and that externalizing tendencies may predict altered responsivity to both to biological and psychological challenges. This finding should be tested further in persons at familial risk for the disorder.

In work reported in this special issue, we have examined young adult offspring of alcoholic parents and subjected them to psychological stressors in the lab (Sorocco et al., 2006). These subjects were older than the subjects tested by Moss and colleagues, and they were tested on both a day of stress and a day of rest to obtain a well-defined basal cortisol secretion pattern. The subjects were classified as to antisocial tendencies using the Sociability Scale of the California Personality Inventory (Gough, 1994; Kosson et al., 1994). The subgroup that was FH+ and low in sociability had a significantly attenuated stress cortisol response. The results are in broad agreement with the work in adolescents. Two points deserve mention. (1) Much of the reduction in cortisol responsivity in both studies appears to be associated with the antisocial characteristics of the FH+ groups. (2) The followup study found that cortisol itself was the strongest predictor of nicotine and marijuana use (Moss et al., 1999).

8. Summary

Cortisol measured in saliva is ideal for human studies because it may be sampled noninvasively inside and outside the laboratory and in relation to many behavioral states (Kirschbaum and Hellhammer, 1989). The HPA is an important system to examine in relation to familial risk or existing addiction. As Wand notes, “Studying the release of HPA axis hormones provides a window on CNS function and can uncover differences in neurotransmitter systems as a function of both alcoholism and family history of alcoholism” (Oswald and Wand, 2004).

The risk for alcoholism and other forms of substance abuse appears to be greater in persons with a presumed genetic risk for an addictive disorder, as indicated by a family history of such problems. The inherited risk may be tied to alterations of brain systems that form emotional responses to motivationally relevant situations. In particular, persons with a diminished cortisol response to normal threat cues may those at highest risk for future risky experimentation with drugs and alcohol. The fact that a blunted stress cortisol response appears to be more likely to occur in persons with antisocial characteristics further implicates brain motivational systems as a key link to an inherited risk. Cortisol production is both a measure of response and also a powerful source of feedback to relevant brain systems. This feedback itself may modify long-term responsivity of the prefrontal cortex and limbic system. The relative contributions of cortisol's feedforward and feedback roles in the addictions are not yet determined.

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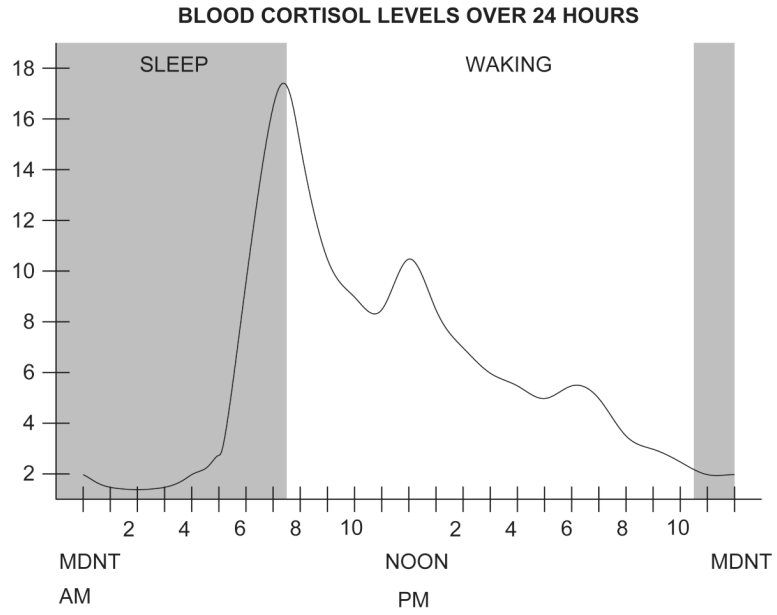

Fig. 1.

The 24-h plasma cortisol secretion curve in humans. The secretion peak occurs near the time of awakening and has a nadir during the first half of the sleep cycle. Minor rises can be seen in relation to meals at midday and early evening.

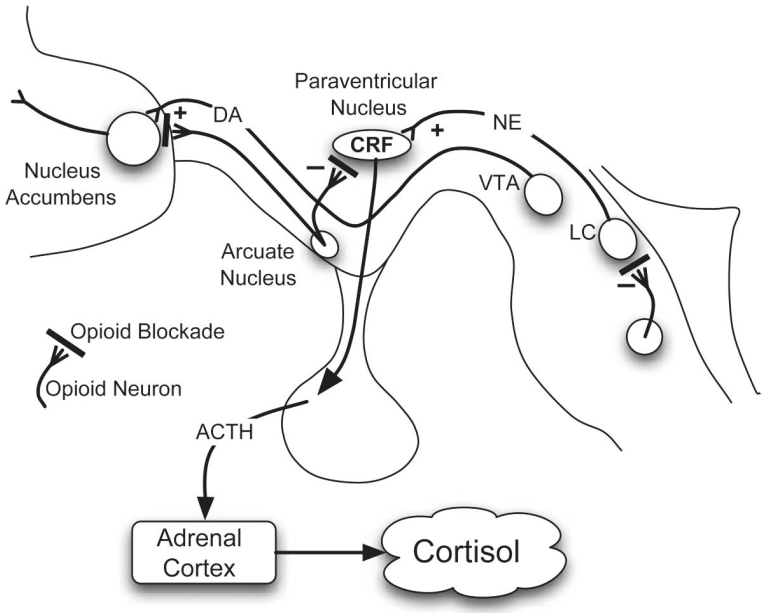

Fig. 2.

Effects of opioid blockade on cortisol secretion. Opioid blockade acts in the brain to increase cortisol secretion and alter mood. (1) Opioid neurons from the arcuate nucleus of the hypothalamus normally inhibit CRF output by neurons of the PVN, reducing CRF secretion at the pituitary gland and thereby reducing ACTH release and cortisol production. Opioid blockade releases the PVN from this inhibitory influence, allowing cortisol production to increase. (2) The locus ceruleus contains about 85% of the NE cell bodies in the central nervous system, and it is largely responsible for the amount of global activation in the brain. Opioid neurons in the brainstem normally inhibit the NE-producing cells of the locus ceruleus. Opioid blockade releases the locus ceruleus from this inhibitory influence, allowing NE to activate the CRF-neurons of the PVN, resulting in increased cortisol production. (3) The nucleus accumbens is a site of DA release in response to all drugs of abuse. This nucleus is in extensive two-way communication with the prefrontal cortex. Opioid neurons from the arcuate nucleus normally activate DA release at the nucleus accumbens. Opioid blockade inhibits this effect, reducing DA release by the nucleus accumbens at the prefrontal cortex. This may alter hedonic states and attention to reward cues. Cortisol feedback to the central nervous system is capable of altering the excitability of dopamine neurons as discussed in the text.
ACTH=adrenocorticotropic hormone; CNS=central nervous system; CRF=corticotropin releasing factor; DA=dopamine; LC=locus ceruleus; NE=norepinephrine; VTA=ventral tegmental area. Adapted with permission of the author (Wand et al., 1998).