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Neural Circuitry in the Regulation of Adrenal Corticosterone Rhythmicity

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Adrenal cortical secretion of glucocorticoids is an essential adaptive response of an organism to stress. Although the hypothalamic–pituitary–adrenal axis regulates the adrenal cortex via release of ACTH, there is strong evidence supporting a role for sympathetic innervation in modulating adrenal glucocorticoid secretion. The dissociation between changes in ACTH and glucocorticoids under non-stress and stress conditions has reinforced the concept that neural control of the adrenal cortex acts to modulate steroidogenic responses to circulating ACTH. A dual control of the adrenal cortex has been implicated in the prominent circadian rhythm in glucocorticoids. However, the central neural substrate for circadian changes in glucocorticoids that are mediated by peripheral neural innervation of the adrenal cortex has not been conclusively delineated. The hypothesis to be addressed is that neurons in the paraventricular nucleus of the hypothalamus receive input from the suprachiasmatic nucleus and project to sympathetic preganglionic neurons in the spinal cord to provide inhibitory and excitatory input to the adrenal cortex that drives the circadian rhythm. This review examines anatomical and physiological evidence that forms the basis for this putative neural circuit.

Key Words: Adrenal innervation; sympathetic activity; hypothalamic paraventricular nucleus; suprachiasmatic nucleus; circadian rhythms.

Introduction

The hypothalamic–pituitary–adrenal (HPA) system is characterized by a prominent circadian rhythm with peak plasma corticosterone occurring immediately prior to the onset of an animal's activity cycle *(1–3)*. The rhythm is entrained by the light–dark cycle *(4)* and driven by diurnal activity of neurons in the suprachiasmatic nucleus (SCN) *(5,6)*. Because corticosterone is the prominent glucocorticoid in rodents, daily variation in corticosterone is critical for homeostatic regulation of metabolic, cardiovascular, and neural processes affected by glucocorticoids *(7,8)*. The diurnal variation in plasma corticosterone is mediated in part by a rhythm in plasma ACTH *(9)*. The ACTH rhythm appears to be driven by hypothalamic neurons in the paraventricular nucleus (PVN) that secrete corticotropin-releasing hormone (CRH), because rhythms in CRH heteronuclear RNA *(10)*, mRNA *(10,11)*, and CRH peptide content *(12)* have been observed. Also, immunoneutralization of CRH blocks the circadian rhythm in ACTH and corticosterone *(13–15)*. In addition to ACTH, the rhythm in plasma corticosterone is amplified by an in-phase rhythm in adrenal sensitivity to ACTH *(1,9,16)*. Dexamethasone treatment blocks the ACTH rhythm without affecting the adrenal sensitivity rhythm, suggesting that ACTH is not responsible for changes in adrenal sensitivity *(1)*.

Innervation of the Adrenal Cortex and Diurnal Corticosterone Rhythm

In addition to hormonal control, the adrenal cortex is regulated by an extensive innervation that includes sympathetic and sensory nerves. Sympathetic innervation consists of cholinergic preganglionic fibers *(17)* and catecholaminergic postganglionic fibers positive for tyrosine hydroxylase (TH) and neuropeptide Y (NPY) *(18,19)*. Sensory innervation consists of primary afferent fibers positive for calcitonin gene–related peptide (CGRP) and substance P *(20,21)*. In addition, intrinsic innervation of the adrenal cortex arises from two types of medullary ganglion cells: type I cells are noradrenergic and NPY-positive, whereas type II cells produce neuronal nitric oxide synthase (nNOS) and vasoactive intestinal peptide (VIP) *(19)*. Because both preganglionic sympathetic and primary afferent fibers are carried in the thoracic splanchnic nerve *(22)*, altering splanchnic nerve activity has been used to assess the effect of neural input on adrenocortical function. Electrical stimulation of the splanchnic nerve in anesthetized calves *(23)* and dogs *(24)* increases cortisol secretion by modulating adrenal responsiveness to ACTH. In neonatal rats, maternal separation–induced increases in adrenal sensitivity to ACTH are suppressed by chemical sympathectomy *(25)*. Chemical sympathectomy also reduces corticosteroid responses to hypoxia in neonatal

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rats without affecting plasma ACTH *(26)*. Both studies support the hypothesis that adrenal innervation facilitates the adrenal response during stress in neonatal rats. In adult rats, water deprivation–induced increases in plasma corticosterone are reduced by splanchnicectomy *(27)*. The neural effect results in part from a decrease in adrenal sensitivity to ACTH. Topical treatment of the splanchnic nerve with capsaicin selectively removes primary afferent nerves, but does not affect the corticosterone response to dehydration. These results support the hypothesis that the splanchnic neural effects are mediated by changing preganglionic sympathetic neural activity. The excitatory effect on corticosteroid responses during stress is due in part to increasing adrenal sensitivity to ACTH. Because adrenal medullectomy prevents splanchnicectomy-induced effects *(27)*, neural input could affect cortical function by changing medullary function. This possibility is supported by anatomical studies showing extensive contact between chromaffin and cortical cells *(28,29)*, and physiological studies showing potent effects of chromaffin cell secretory products on steroidogenesis (reviewed in ref. *30*).

The finding that adrenal sensitivity to ACTH can be affected by changes in splanchnic nerve activity during stress supports the hypothesis that splanchnic neural input to the adrenal contributes to the circadian rhythm in plasma corticosterone. Because episodic secretion of corticosteroids underlies the circadian rhythm in humans *(31)* and rats *(32)*, our initial studies used adrenal microdialysis to monitor pulsatile secretion of corticosterone in rats *(33)*. The amplitude of corticosterone pulses in the AM (at the nadir of the rhythm) was reduced compared to the PM (at the peak). Splanchnicectomy increased the frequency of corticosterone pulses in the AM, revealing an inhibitory function of adrenal innervation *(34)* that resulted in part from decreases in adrenal sensitivity to ACTH *(35)*; no consistent effect of splanchnicectomy was observed in the PM using microdialysis. In contrast, Dijkstra and associates *(36)* showed that splanchnicectomy results in decreases in plasma corticosterone in the PM, suggesting that an excitatory neural input activates the diurnal increase in plasma corticosterone. Our studies have confirmed this finding; in addition, the excitatory effect in the PM results from increases in adrenal sensitivity to ACTH *(37)*. However, plasma corticosterone in the AM was not affected by splanchnicectomy, a finding in conflict with our earlier work using adrenal microdialysis *(34)*. In the microdialysis experiments, rats were sampled repeatedly to resolve pulses of corticosterone. Because pulses in the AM are intermittent *(34)*, it is possible that a single sample of trunk blood (used in ref. *37*) would not resolve the effect of splanchnicectomy. To address this apparent discrepancy, we have initiated experiments to assess the response to splanchnicectomy by repeated blood sampling in chronically cannulated rats. When adrenal responses are estimated by a series of corticosterone values measured over 60 min, splanchnicectomy not only reduces plasma corticosterone in the PM, but also results in increased plasma corticosterone in the AM (Ulrich-Lai, Arnhold, and Engeland, manuscript in preparation). These results support a bidirectional role for splanchnic neural activity that could be responsible for diurnal changes in adrenal sensitivity to ACTH; in the AM, neural activity is inhibitory, whereas in the PM, neural activity is excitatory.

Neural Circuitry in the Control of Adrenal Corticosterone Rhythmicity

In order for splanchnic neural activity to modulate circadian variation in adrenal function, a central neural circuit must be present to drive the peripheral neural response. A series of studies by Buijs, Kalsbeek, and associates (summarized in refs. *38* and *39*) form the foundation for the premise that neurons in the paraventricular nucleus of the hypothalamus receive input from the suprachiasmatic nucleus and project to the spinal cord to provide inhibitory and excitatory input to the adrenal cortex that drives the circadian rhythm. The balance of this review will examine anatomical and physiological evidence that forms the basis for this putative neural circuit (shown in Fig. 1) with the goal of directing attention to issues that remain unresolved. Discussion will be organized by focusing on three elements that are required to establish the functional circuit.

Diurnal Variation in Adrenal Cortical Function and Daily Variation in Preganglionic Sympathetic Neural Activity

The *first element* is that *diurnal variation in adrenal cortical function results from daily variation in preganglionic sympathetic neural activity* (Fig. 1). There are many observations that support this possibility. Exposure of rats to light enhances sympathetic efferent activity in the adrenal branch of the splanchnic nerve, whereas lesions of the SCN prevent the response *(40)*. Although there is no prominent rhythm in plasma catecholamines *(41)*, frequent sampling reveals a diurnal rhythm in plasma epinephrine that parallels that of corticosterone *(42)*; these data support the contention that the activity of preganglionic sympathetic neurons innervating chromaffin cells varies diurnally. Retrograde labeling studies have shown that preganglionic sympathetic nerves that innervate the adrenal are localized in the intermediolateral cell column in the spinal cord from thoracic level 1 to 13 *(43,44)*. The intermediolateral neurons regulate chromaffin cell secretion of catecholamines and neuropeptides *(45,46)* and the activity of postganglionic neurons that innervate the adrenal *(47,48)*. Based on responses to splanchnicectomy *(34,36,37)*, a working hypothesis would be that activation of preganglionic sympathetic neurons in the AM mediates inhibitory effects on cortical function, whereas activation of neurons in the PM elicits excitatory effects. Because chromaffin cells and postganglionic neurons release multiple neurotransmitters that can suppress or facilitate

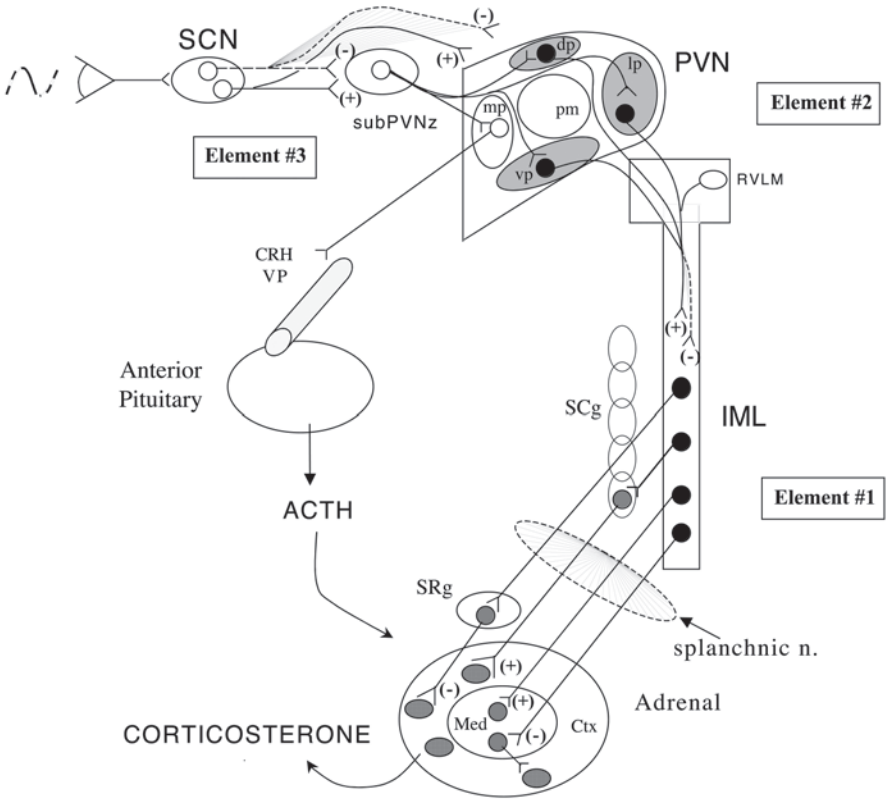

Fig. 1. Schematic of proposed neural circuit from the suprachiasmatic nucleus to the autonomic paraventricular nucleus that regulates sympathetic preganglionic neurons that innervate the adrenal to control diurnal variation in corticosterone secretion. SCN, suprachiasmatic nucleus; subPVNz, subparaventricular zone; mp, medial parvocellular paraventricular nucleus(PVN); dp, dorsal parvocellular PVN; pm, posterior magnocellular PVN, vp, ventral parvocellular PVN; lp, lateral parvocellular PVN; RVLM, rostral ventrolateral medulla; IML, intermediolateral nucleus SCg, sympathetic chain ganglia; SRg, suprarenal ganglia; Ctx, adrenal cortex; Med, adrenal medulla; CORT, corticosterone or cortisol; CRH, corticotropin-releasing hormone; VP, vasopressin; ACTH, adrenocorticotropin.

corticosteroid secretion *(30)*, selective activation of subpopulations of intermediolateral neurons could mediate the diurnal responses. Specific populations of intermediolateral neurons have discrete chemical codes that are associated with specific adrenal medullary targets. Whereas noradrenergic chromaffin and type I ganglion cells are innervated by cholinergic/nNOS/calretinin fibers *(49)*, adrenergic chromaffin cells are innervated by cholinergic/nNOS/enkephalin fibers *(50)*. It is likely that subpopulations of intermediolateral neurons are responsible for bidirectional adrenal cortical responses such that neurons mediating inhibitory responses are active in the AM, whereas neurons mediating excitatory responses are active in the PM.

Activity of PVN Neurons and Diurnal Variation in Adrenal Cortical Function

The *second element* is that *the activity of PVN neurons is required for diurnal variation in adrenal cortical function*. There is extensive literature supporting a role for PVN neurons acting as sympathetic premotor neurons controlling autonomic function. The PVN consists of separate and topographically distinct subpopulations of neurons that have different terminal sites of projection *(51)*. The medial parvocellular division of the PVN (mpPVN) synthesizes CRH and vasopressin, projects to the median eminence, and controls pituitary secretion of ACTH *(52)*. In contrast, autonomic PVN neurons in the dorsal, ventral, and lateral parvocellular subdivisions project directly to the IML or indirectly to the IML via brainstem nuclei like the ventrolateral medulla and vagal complex *(53)*. Using retrograde labeling and immunohistochemistry or *in situ* hybridization to define neuronal phenotype, autonomic PVN neurons with terminals in the IML have been shown to express neurotransmitters that include vasopressin, oxytocin, and the enkephalins *(54–56)*. Specific connections between PVN neurons and adrenal preganglionic sympathetic neurons were conclusively demonstrated by Strack, Loewy, and colleagues *(57)* using transneuronal labeling with pseudorabies virus *(58)*. Following injection of pseudorabies viurus into the adrenal, virus was localized in sympathetic preganglionic neurons of the spinal cord at the $T_{4–13}$ levels and spinal interneurons; viral labeling identified second-order neurons in five brain areas: the caudal raphe nuclei, ventromedial medulla, rostral ventrolateral medulla, A5 cell group, and the PVN. Using anterograde labeling from the PVN in combination with retrograde labeling from the adrenal, experiments have confirmed a monosynaptic pathway from the PVN to adrenal preganglionic neurons *(59)*. These observations support the

contention that autonomic PVN neurons could be a component of the neural circuit that mediates circadian regulation of adrenal steroidogenesis (Fig. 1).

Anatomical studies have shown multiple pathways from the SCN that could influence PVN activity *(60,61)*. Because there is no extensive direct SCN–PVN connection, areas that project directly to the PVN and receive SCN projections could be elements in the circuit that mediate diurnal control of PVN activity. These areas include the subparaventricular zone (subPVNz), a region between the SCN and the PVN and between the periventricular nucleus and the anterior hypothalamus *(61)* and the dorsomedial hypothalamic nucleus *(60–62)*. Neurons in the rat SCN demonstrate changes in electrical activity that are synchronized with the light–dark cycle with increased neural activity during the light *(63,64)*. The expression of cFos has been used as a marker of diurnal neuronal activity in the SCN, because cFos mRNA and protein increase in the SCN during the light and decrease during the dark *(65–67)*. Monitoring cFos expression for diurnal changes in the subPVNz have resulted in inconsistent findings; some studies show changes that parallel the SCN activity *(67,68)*, whereas others find no variation in cFos expression in this area *(69,70)*. Although these experiments have monitored activity in subregions of the subPVNz, it is possible that the variability arises in part from differential responses of neuronal subpopulations within the area *(68)*. In contrast to the SCN, other brain areas display changes in cFos expression that parallel the rest–activity cycle being highest during the hours of activity *(71)*. Surprisingly, few studies have examined specific hypothalamic nuclei associated with pituitary–adrenal activity for diurnal changes in cFos expression. In a recent survey, diurnal variation in cFos protein expression was observed in the dorsomedial nucleus, mpPVN, and pmPVN, but not in the ventromedial nucleus, arcuate nucleus, or medial preoptic area *(70)*. Changes in cFos expression in these nuclei were out of phase with the SCN rhythm, an observation that could reflect a role in mediating the rhythm in pituitary–adrenal activity. Additional experiments are needed to determine whether diurnal variation in cFos expression occurs in autonomic PVN subnuclei, a finding that would support the hypothesis that neurons in these regions participate in adrenal neural control of corticosteroid rhythmicity. To directly test this hypothesis, one could lesion specific autonomic subnuclei and assess the effect on the plasma ACTH and corticosterone rhythm. These experiments would be challenging, because lesions of the mpPVN will destroy CRH neurons and affect ACTH secretion. Although studies have clearly shown that PVN lesions block the stress response *(72)*, few attempts have been made to assess the circadian rhythm after PVN lesions. In a study directed toward this goal, lesions that included mpPVN neurons reduced both the plasma ACTH and the corticosterone rhythm *(73)*; however, the effect on corticosterone was minor relative to ACTH, suggesting that the lesion may have spared neurons in autonomic subnuclei of the PVN. Additional experiments that target specific subnuclei of the PVN will be required to determine if rhythms in corticosterone can be dissected from rhythms in ACTH.

SCN Neurons and Adrenal Diurnal Rhythmicity

The *third element* of the hypothesis is that *SCN neurons that project to the autonomic PVN initiate the changes in adrenal diurnal rhythmicity*. As discussed above, the PVN, including neurons in autonomic subnuclei *(60,74,75)*, receives polysynaptic and monosynaptic connections from neurons in the SCN *(74,76)*. Because lesions of the SCN abolish the corticosterone rhythm *(5,6,77)*, input from the SCN to the PVN drives the rhythm. Subpopulations of SCN neurons projecting to the PVN synthesize the neuropeptides, vasopressin and vasoactive-intestinal polypeptide (VIP) *(61, 66,78–80)*. In addition, both anatomical *(81,82)* and physiological *(83)* studies have implicated GABA and glutamate as mediators of fast monosynaptic neurotransmission from the SCN to the PVN. Although some of the GABAergic and glutaminergic neurons in SCN innervate PVN neurons that project to the spinal cord *(84)*, experiments to define the SCN–PVN link required for control of adrenal corticosterone rhythmicity have focused on neuropeptidergic mechanisms. Buijs, Kalsbeek, and co-workers have proposed that the corticosterone rhythm results in part from the release of vasopressin from SCN neurons during light onset to inhibit plasma corticosterone. Their data show that SCN lesions increase the nadir of the corticosterone rhythm *(85)* and that VP injection into the PVN offsets the lesion effect *(86)*. Because the effects on the corticosterone rhythm are more prominent compared to the ACTH rhythm, these investigators have proposed that the inhibitory effect of vasopressin is mediated via changes in adrenal neural activity *(3,85,86)*. Subsequent studies have shown that vasopressin antagonist given late in the light period has a more potent stimulatory effect on plasma corticosterone *(3,87)*, suggesting that the peak in HPA activity results from the reduction in vasopressin release with the concomitant release of an excitatory neurotransmitter from SCN neurons. Because VIP stimulates HPA activity by acting in the PVN *(88)*, it has been proposed that VIP released from SCN neurons prior to dark onset stimulates plasma corticosterone to produce the peak in the circadian rhythm. In addition to revealing functional connections between the SCN and PVN required for the circadian rhythm, parallel studies using transneuronal labeling confirmed the existence of a polysynaptic connection between the SCN and the adrenal *(39)*. These observations support the hypothesis that SCN neurons drive the corticosterone rhythm through the autonomic PVN via changing adrenal neural activity (Fig. 1). However, additional experiments are needed that directly test the requirement for adrenal innervation in this circuit. Studies are needed to determine the interactive effect of SCN lesions and adrenal denervation on the diurnal rhythm in plasma ACTH and corticosterone.

The anatomical basis for central control of the circadian rhythm in corticosteroid secretion by adrenal innervation is conclusive, whereas functional data remain incomplete. Clearly, splanchnicectomy and lesions of the SCN affect plasma corticosterone at the nadir and the peak of the circadian rhythm. However, it is unclear whether the autonomic PVN mediates the adrenal neural response or whether adrenal neural activity is a required response element of the SCN-driven circuit. It is likely that inhibitory and excitatory signals at hypothalamic and spinal levels act in concert to mediate rhythms in plasma ACTH and adrenal sensitivity to ACTH. For inhibition of AM corticosterone secretion to be mediated both by SCN-derived vasopressin acting in the autonomic PVN *(86)* and by increases in splanchnic neural activity *(34)*, an inhibitory link between the PVN and the intermediolateral nucleus must be required. Inhibition could be mediated by release of inhibitory neurotransmitters in the intermediolateral nucleus directly from autonomic PVN neurons *(89)* or indirectly from brainstem neurons that receive PVN projections *(90)* or from inhibitory interneurons. Brainstem neurons could include GABAergic or glycinergic neurons from the rostral ventromedial medulla that have been identified by transneuronal labeling to innervate adrenal sympathetic preganglionic neurons *(91)*. Transneuronal labeling has also identified GABAergic interneurons in the central region of the spinal cord that project to and inhibit adrenal preganglionic neurons *(92)*. Additional studies are required to establish elements of the neural circuit required both for inhibition of adrenal corticosterone secretion in the AM and excitation in the PM.

Clinical Relevance

Although the clinical relevance of neural control of adrenocortical function remains speculative, there are numerous neurological disorders in which a dissociation between plasma ACTH and cortisol have been reported. When changes in cortisol occur that cannot be accounted for by changes in ACTH, it is possible that altered adrenal sensitivity mediated by adrenal neural activity is involved. In depression and in Alzheimer's disease, plasma ACTH responses to stress and to CRH administration are reduced, whereas plasma cortisol responses are normal or augmented *(93–95)*. Because a differential responsiveness of the pituitary and the adrenal has been noted in these disorders, the augmented plasma cortisol responses may result from increases in adrenal responsiveness to ACTH *(96–98)*. It is likely that changes in adrenal responsivity are involved, but the mechanism responsible for changing adrenal responsiveness to ACTH has not been defined. Because increased basal sympathetic neural activity in Alzheimer's patients has been associated with augmented plasma cortisol responses to stress *(99)*, it is possible that the sympathetic nervous system modulates adrenal cortisol production via adrenal innervation. In contrast to disorders associated with adrenal hypersecretion, patients with posttraumatic stress disorder (PTSD) show reduced basal plasma cortisol *(100,101)* that has been attributed in part to reduced adrenal responsiveness to ACTH *(102)*. Patients with PTSD also have elevated norepinephrine in cerebrospinal fluid that is correlated with the severity of the disorder *(103)*, suggesting that central noradrenergic activity is augmented. Because increases in adrenal medullary function also have been observed in PTSD *(104)*, the direct involvement of sympathetic activity on adrenal cortical function cannot be excluded.

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