Brazilian Journal of Medical and Biological Research (1997) 30: 1391-1405
ISSN 0100-879X

Food and the circadian activity of the hypothalamic-pituitary-adrenal axis

A.M.O. Leal and A.C. Moreira

Divisão de Endocrinologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil

Abstract

Temporal organization is an important feature of biological systems and its main function is to facilitate adaptation of the organism to the environment. The daily variation of biological variables arises from an internal time-keeping system. The major action of the environment is to synchronize the internal clock to a period of exactly 24 h. The light-dark cycle, food ingestion, barometric pressure, acoustic stimuli, scents and social cues have been mentioned as synchronizers or "zeitgebers". The circadian rhythmicity of plasma corticosteroids has been well characterized in man and in rats and evidence has been accumulated showing daily rhythmicity at every level of the hypothalamic-pituitary-adrenal (HPA) axis. Studies of restricted feeding in rats are of considerable importance because they reveal feeding as a major synchronizer of rhythms in HPA axis activity. The daily variation of the HPA axis stress response appears to be closely related to food intake as well as to basal activity. In humans, the association of feeding and HPA axis activity has been studied under physiological and pathological conditions such as anorexia nervosa, bulimia, malnutrition, obesity, diabetes mellitus and Cushing's syndrome. Complex neuroanatomical pathways and neurochemical circuitry are involved in feeding-associated HPA axis modulation. In the present review we focus on the interaction among HPA axis rhythmicity, food ingestion, and different nutritional and endocrine states.

Correspondence
A.C. Moreira
Departamento de Clínica Médica
Faculdade de Medicina de
Ribeirão Preto, USP
14049-900 Ribeirão Preto, SP
Brasil

Publication supported by FAPESP.

Received April 8, 1997
Accepted October 16, 1997

Key words
- Feeding
- Glucocorticoids
- CRH
- ACTH
- Circadian rhythm

Introduction

Circadian rhythmicity is present in most organisms living under natural conditions and its most important role is to facilitate adaptation of the organism to periodic fluctuations in the external environment (1). In particular, the food-seeking behavior might have forced the development of specialized functions of the circadian timing system that enable the organism to be prepared for food seeking, digestion and metabolism (2).

Daily variations in plasma corticosteroid levels may be considered a paradigm of circadian rhythms and evidence has been accumulated showing the close relationship between the hypothalamic-pituitary-adrenal (HPA) axis and the nutritional status of mammals, including humans (3).

In this review we focus on the interaction among HPA axis rhythmicity under basal and stress conditions, food ingestion, and different nutritional and endocrine states. In the first part of this paper we introduce the

reader to basic concepts of chronobiology (for extensive reviews, see Refs. 1,4-6).

Circadian rhythms

General features: anatomical pathways and rhythm synchronizers

Biological rhythms range extensively in periodicity from a fraction of a second to several years; however, the circadian rhythms (from the Latin circadian meaning "around a day") have a predominant role and can be demonstrated not only in physiological states but also in pathological processes which fluctuate during the course of a day (7).

The daily variations of biological variables are not simply a response to 24-h changes in the environment due to the rotation of the earth on its axis, but rather arise from an internal time-keeping system (4) and persist under constant environmental conditions ("free-running"). The major action of the environment is to synchronize the internal system to a period of exactly 24 h.

In mammals, the suprachiasmatic nucleus (SCN) was initially supposed to be the only master circadian pacemaker (4). The SCN is a complex structure involving two small bilaterally paired nuclei situated in the anterior hypothalamus above the optic chiasm and lateral to the third ventricle (5). The role of the SCN as the circadian clock has been demonstrated by lesion experiments and studies involving transplantation of the SCN (8-10). Although other neural loci have not been identified as sites of the central biological clock, there is evidence demonstrating resynchronization of corticosteroid circadian rhythmicity after SCN destruction. These results may indicate the possibility of the presence of other circadian clocks in brain areas outside the SCN (11). Probably a more complex timing circuitry exists and may support the existence of a multioscillator system where a master oscillator could be responsible for synchronization among other oscillators present in various organs and tissues (12). In addition to the pacemaker hypothesis, the network hypothesis was recently proposed: the interaction between the pacemaker and non-pacemaker cells may be the key factor in the generation of a precise circadian rhythm within the SCN (13).

In mammals the SCN receives entraining information from the light-dark cycle via pathways separated from the visual system. These pathways include the retinohypothalamic tract and the geniculohypothalamic tract which arises from a subdivision of the lateral geniculate nucleus (4). The neurotransmitters and photoreceptors involved in the circadian rhythms of mammals have not been completely established. There are some data suggesting the presence of neurons containing glutamate, gamma-aminobutyric acid, vasoactive intestinal peptide and neuropeptide Y (NPY) in the circadian timing system (13).

The output pathways leaving the SCN project mainly to the medial hypothalamus (14,15) and the localization of the SCN suggests that this nucleus has an important integrative function.

Little is known about the mechanisms whereby nonphotic stimuli influence the circadian clock system and how the SCN exerts its integrative influence. It is generally accepted that the generation of HPA axis periodicity occurs in the central nervous system (CNS) (16). However, specific neuroanatomical pathways and neurotransmitters involved in the expression of pituitary-adrenal circadian rhythmicity have not been clearly demonstrated. Numerous investigators have reported that lesions in various areas of the hypothalamus inhibit daily adrenocorticotropin (ACTH) and corticosterone variation. These procedures include anterior hypothalamic deafferentation and SCN lesions (8,17,18), lesions of ventromedial and dorsomedial nuclei (19), anterior hypothalamic lesions (20) and basal hypothalamic lesions (21). The maintenance of a free-running circadian rhythm for corticosterone in rats with

isolation of the medial basal hypothalamus, including the SCN, from the rest of the central nervous system (22) indicates that these neural structures are essential for the manifestation of a light entrainable corticosterone rhythm. In addition, a direct input from the SCN to the paraventricular nucleus (PVN) has been described (14). Catecholaminergic inputs from the brainstem (23,24) and serotonergic projections from the dorsal raphe (25) have also been described as modulators of HPA axis rhythm.

There is evidence that circadian rhythmicity is an inherited characteristic of diverse species, including humans (26). In fact, a period mutation was described in golden hamsters, referred to as the tau mutant, in which the 24-h free-running periods of the activity rhythm are shortened to 20 h and to 22 h, in homozygous and heterozygous animals, respectively (27). However, genetic analysis and identification (cloning) of genes responsible for the determination of circadian rhythm have been restricted to invertebrates (28,29).

Since the endogenous circadian period observed under constant conditions is not exactly 24 h, external physical environmental factors must operate to synchronize (entrain) the internal clock system. The light-dark cycle is the primary agent that synchronizes most circadian rhythms. However, other agents such as food ingestion (30), barometric pressure (31), acoustic stimuli (32) and scents (33) have been cited as synchronizers or "zeitgebers". The effects of these synchronizers on circadian rhythms may differ considerably both in quality and strength between nocturnal and diurnal mammals. In humans, social cues seem to be even stronger stimuli than the light-dark cycle, as clearly observed in experiments with night workers and travelers across time zones (jet lag effect).

Molecular and cellular mechanisms underlying entrainment are poorly defined. However, some studies have shown that light is able to induce the expression of the proto-oncogenes c-fos and jun-B and to influence light entrainment and locomotor activity (34,35).

The role of food presentation as a synchronizer under natural conditions is not yet clear. However, under laboratory conditions, Krieger's first studies (30) showed that periodic meal timing could act as an important rhythm synchronizer in rats. The adaptive feature of food synchronization is of obvious importance for the survival of any species.

Diurnal rhythms of the hypothalamic-pituitary-adrenal axis and the role of food

The circadian rhythmicity of the HPA axis is one of the best documented cyclic neuroendocrine activities. Daily variation in plasma corticosteroid has been well characterized in man and in rats, presenting as peak concentrations prior to or at the time of onset of activity, with a decline over the remainder of the 24-h period. After the first description of daily variation in urinary ketosteroid excretion (36), evidence has been accumulated showing daily rhythmicity at every level of the HPA axis.

Even before the corticotropin-releasing hormone (CRH) had been characterized, rhythmicity of hypothalamic CRH activity had been suggested in rats (37-39) by bioassays. After CRH characterization, circadian periodicity in hypothalamic CRH content and plasma CRH was described (40-43). More recently a daily rhythm in CRH mRNA expression was demonstrated by different techniques (44,45). However, these studies showed no consensus about nadirs of the daily CRH pattern and others did not detect daily variation of hypothalamic or plasma CRH (46-48). These controversies may be related to different time sampling and sensitivities of assay methods. In spite of these controversies, the blockade of plasma ACTH

rhythm by passive immunization with CRH antiserum and the restoration of the rhythm by pulsatile administration of CRH indicate the participation of CRH in the determination of ACTH rhythm (49,50). The possibility remains that this influence occurs at the pituitary level; however, the data about the daily variation in pituitary responsiveness to CRH are also contradictory (46,47,51-53). In addition, the finding of a persistent daily rhythm of ACTH during continuous administration of CRH (54) suggests that other factors are also involved in the ACTH rhythm. Among these factors, the role of vasopressin was investigated but not well defined (55).

Many studies have confirmed a pattern of plasma ACTH rhythmicity similar to that of corticosteroids (47,56) and have indicated the presence of a daily rhythm in the pituitary secretion of other proopiomelanocortin (POMC)-related peptides, such as ß-lipotropin (57) and ß-endorphin (58,59). In man, the daily rhythm of the corticotropic axis seems to be under the control of amplitude, but not frequency, modulation of ACTH secretion (59,60). In addition, in-phase daily variation of the adrenal responsiveness to ACTH which amplifies the corticosterone rhythm has been well established (21,61). On the other hand, morning cortisol peaks in ACTH-deficient patients treated with exogenous ACTH suggest that extrapituitary factors may act in conjunction with ACTH (62).

The negative feedback mechanism that controls the secretion of ACTH by adrenal steroids also presents daily variation, with higher efficacy at nadir time (46,63). It was demonstrated in rats that the occupation of type I (high affinity) corticosteroid receptors is able to control basal activity in the HPA axis in the morning and that in the evening type I occupation potentiates the inhibition of plasma ACTH by occupation of type II receptors (lower affinity) (64).

Although most evidence indicates that HPA axis rhythmicity is under a hierarchical order, other evidence indicates functional independence at every level of HPA axis organization, including the adrenals. Although the rhythmic secretion of corticosterone in adrenal organ cultures is controversial (47,65,66), the periodicity of corticosterone in hypophysectomized rats implanted with ACTH has been described (67). In addition, it was demonstrated that the rhythm in ACTH, CRH and CRH mRNA persists after adrenalectomy in rats (38,39,68,69). The daily ACTH variation was also maintained in patients with ACTH hypersecretion due to different degrees of cortisol production deficiency as found in Addison's disease (70) or different types of congenital adrenal hyperplasia (71). Thus ACTH rhythmicity is partially independent of negative feedback.

Finally, it should be remembered that variations in the metabolic clearance rate of corticosteroids have been reported and could contribute to its rhythmic pattern (72-74).

Moreover, the circadian variation of the HPA axis changes with the manipulation of rhythm by phase-shifting a synchronizer such as the light-dark, sleep-wake and rest-activity cycles, and food schedule (75). In humans, an adult cortisol circadian pattern (peak of plasma cortisol at early morning) is established and maintained at a mean age of 8 weeks in healthy infants (76). Although it has been suggested that the development of the circadian pattern in adrenocortical activity in humans is parallel to the development of sleeping and feeding patterns and is also related to maternal adrenocortical activity (77), the ontogeny of HPA axis circadian rhythm deserves further investigation both in humans and in rats.

Although neither the mechanism nor the site of feeding-associated daily rhythm is known, studies have indicated feeding as a major organizer of rhythms of HPA axis activity. There are two classes of animals in terms of food behavior. Diurnal mammals, including human beings, are active in the daytime and sleep at night. Nocturnal animals (including many ranging in size from

bears to mice) rest in the daytime and are active and take most of their daily food in the dark period. Thus, the feeding synchronizer effect on the HPA axis may differ considerably both in quality and strength between nocturnal and diurnal mammals, especially rats and men.

Rats are nocturnal animals and eat more than 70% of their daily food intake during the night (78). Rats with free access to food manifest a daily peak of plasma corticosterone at 20:00 h, just prior to the time of onset of predominant food intake. Approximately twenty years ago, the pioneering work of Krieger (30) demonstrated that restriction of food access in the morning hours from 9:00 to 11:00 h was able to cause a 12-h shift of plasma corticosterone peak in rats. This observation was initially associated with the changes of locomotor activity and sleep-wake cycle that accompany the eating pattern. Other studies showed that this explanation was not completely correct, since peak corticosterone levels are observed prior to food presentation regardless of its relation to the lighting period (79,80). Furthermore, Honma et al. (22) demonstrated that the rhythm of plasma corticosterone is not a direct consequence of the rhythm of locomotor activity.

Additionally, it was found that food-shifted rhythms of plasma corticosteroid concentrations and of body temperature persisted in animals with SCN lesions and if the animals had become arrhythmic because of SCN lesions, a restricted-feeding schedule could restore circadian rhythmicity. Furthermore, it was observed that daily food cyclicity did not affect SCN neural activity (81,82). These studies indicate the primacy of food as a zeitgeber and suggest the existence of a biological clock other than the SCN. Nevertheless, the abolition of food-shifted daily corticosterone and activity rhythmicity by ventromedial hypothalamic lesions (83,84) indicates the involvement of the hypothalamic area in the generation of food shift rhythms.

Despite much work in the intervening 20 years, our knowledge of the mechanisms and pathways by which food induces synchronization of adrenal axis rhythms is still incomplete. Honma et al. (85) correlated the duration of food restriction and amount of food ingested to the corticosterone rhythm. On the other hand, the prefeeding corticosterone peak does not appear to be related to the availability of certain food constituents (80). Furthermore, the time interval between food presentation and prefeeding corticosterone peak is incompatible with new neurotransmitter synthesis.

We have recently investigated the effect of food restriction on the various functional levels of the HPA axis. Although the 12-h shift of plasma corticosterone peak was clear and plasma ACTH was high in the morning, there was no significant difference between morning and afternoon plasma ACTH levels (47). Furthermore, there was no detectable daily variation of hypothalamic CRH or pituitary ACTH contents and plasma ACTH response to synthetic CRH in free-fed or food-restricted rats. These findings led us to investigate the effect of food restriction on the adrenal responsiveness to ACTH. We demonstrated a 12-h shift in the adrenal response to synthetic ACTH [1-24] induced by the time of feeding as previously suggested by Wilkinson et al. (86). We also originally showed that this shift of corticosterone response to exogenous ACTH may not be influenced by endogenous plasma ACTH levels during the preceding 12 h since it was maintained after dexamethasone pretreatment. This pattern of response, however, was abolished by chlorpromazine-morphine-pentobarbital anesthesia. In addition, in *in vitro* experiments, incubated adrenal slices obtained from free-fed and food-restricted rats showed no daily variation in adrenal responsiveness to ACTH [1-24]. These results indicate that the daily variation in adrenal responsiveness to ACTH is due to

modulation by neural (central or peripheral), vascular or humoral factors other than ACTH.

On the other hand, there is now a considerable body of evidence suggesting the importance of adrenal innervation in the modulation of the HPA axis (87-92), including the adrenal sensitivity to ACTH. Additionally, the pituitary-adrenal axis appears to have a daily pattern of response to stress, with a higher ACTH response in the morning in free-fed rats, that is not dependent on corticosterone (93-96).

As well as the basal activity, the daily variation of the HPA axis stress response appears to be closely related to food intake (96,97). In a previous study we found that food restriction for 2 weeks abolished the a.m.-p.m. difference in plasma ACTH levels attained after immobilization stress in rats by a still uncharacterized mechanism (96). It is suggested that food restriction may also modify the ACTH response to stress along the day.

Although it has been shown that an intact vagus nerve is not necessary for the establishment of the daily rhythmicity of plasma corticosterone in free-fed or food-restricted rats (98), there is extensive evidence indicating the relationship among HPA axis, catecholamines and feeding (99-103). Food intake was shown to be affected by central administration of catecholamines (103) and the permissive role of corticosterone in norepinephrine-elicited feeding which exhibited a circadian pattern has been demonstrated (99,100). Furthermore, the prefeeding increase in paraventricular norepinephrine release and the abolition of the prefeeding corticosterone peak by destruction of catecholaminergic innervation of the PVN in rats under food restriction strongly suggest the participation of catecholamines in the expression of feeding-related corticosterone rhythms (101).

The mechanisms responsible for modulation of the HPA axis by feeding are very complex and probably involve uncharacterized central nervous system pathways, including medial basal hypothalamic nuclei and autonomic pathways. Moreover, feeding patterns result from a balance between anorectic (CRH, cholecystokinin, neurotensin) and orectic (NPY, pancreatic polypeptide, galanine) factors forming a complex circuitry (104-111), many of them being closely related to HPA axis activity.

Neuropeptide Y is a potent orexigenic agent with a dense distribution in hypothalamic nuclei (112,113) and is responsible for stimulating food intake in the rat (104,114). A daily rhythm in NPY content in the parvocellular portion of the PVN with a unimodal peak prior to the onset of dark has been described (115). In rats under food restriction, elevated NPY content and release in the PVN were observed before the introduction of food, with decreasing levels during the course of eating (116). In addition, anatomical and pharmacological studies suggest that NPY can modulate CRH, ACTH and corticosterone secretion (117, 118). On the other hand, glucocorticoids are required for an increase in prepro NPY mRNA levels induced by food deprivation (119,120) and the hypothalamic NPY-feeding system is dependent upon corticosterone. We have investigated the role of vasopressin using the food-restriction model (47). However, we found that the daily patterns of plasma vasopressin and ACTH-corticosterone did not coincide in terms of basal activity and stress response. Vasopressin may not be involved in the pituitary-adrenal adaptations that occur in food restriction (47,96).

We have recently shown a significant correlation between daily variation of plasma atrial natriuretic peptide (ANP) and corticosterone in rats on a free or restricted feeding regimen (121). However, the nature of the relationship between ANP and feeding is far from clear. It is hypothesized that ANP may interact with ACTH and other central neuropeptides (122).

Corticosteroids exert metabolic effects

on food intake and intermediary metabolism, which together act to provide an adequate supply of energy (123). The studies of restricted feeding are of considerable importance because they reveal feeding as a synchronizer link between hormonal systems and metabolic machinery. Once the food restriction schedule is set, neurohumoral and metabolic variables are temporarily reorganized to ensure anticipative adaptation of the animal. Thus, rats under food restriction develop high rates of lipogenesis in adipose tissue and in liver (124), resistance to liver glycogen depletion during fasting (125) and increased storage of glycogen in liver, muscle and adipose tissue during the postprandial period (126-128), higher efficiency in food utilization and a higher capacity to recover from hypoglycemia (129,130). In addition, delayed gastric emptying (128) and an increase in intestinal absorbing area due to mucosal hypertrophy have been observed (131). The periodicity of food presentation is an important factor for the establishment of the metabolic changes, since the same amount of food given randomly in time to food-restricted rats promotes a different adaptive metabolic pattern (132). Corticosteroids seem to be required for the metabolic adaptation since adrenalectomized animals do not survive food restriction due to lack of lipogenesis, gluconeogenesis and glucogenolysis (133) to efficiently supply energy in the intermeal period.

Dallman et al. (3) suggest that the interactions among insulin, glucocorticoids and NPY are responsible for the metabolic aspects related to food intake. It was observed that rats under food restriction present higher circulating levels of insulin and greater insulin sensitivity (134). Furthermore, many lines of evidence support the hypothesis that insulin is an afferent central signal which regulates normal energy balance (135). It was recently observed that high-dose dexamethasone administration decreases the efficiency of CNS insulin transport (136).

Furthermore, it is hypothesized that the metabolic actions of corticosteroids rely on concentration-dependent interactions with type I and type II glucocorticoid receptors (137).

The association of feeding and HPA axis activity has been studied in humans under physiological and pathological conditions. The demonstration of a large peak of plasma cortisol coinciding with the noon meal and a smaller peak after the evening meal gives evidence for the influence of meal timing on the daily plasma cortisol pattern (138-140). The mechanism by which ingestion of food stimulates cortisol secretion is unknown. Higher postprandial plasma ACTH and cortisol increments related to high-protein meals have been demonstrated (141,142) and a role of gut peptides and neurotransmitter substrates as neuroendocrine links between gut and brain has been proposed. The role played by these peptides in HPA axis activity is supported by the finding that parenteral feeding during a restricted time of day completely abolished blood corticosterone rhythm in rats (143). In humans, the parenteral nutritional support did not alter the circadian rhythm of cortisol as compared with enteral nutrition (144). Al-Damluji et al. (104) suggested a stimulatory effect of alpha-1 adrenoceptors on the ACTH and cortisol postprandial peak. However, the physiological mechanisms leading to postprandial ACTH and cortisol release remain to be determined. Corticosteroids appear to play an important role in regulating the circadian fluctuations of brain-gut peptides and cell cycle of the gastrointestinal mucosa (145).

Anorexia nervosa has long been known to be associated with hypothalamic-pituitary-adrenal axis abnormalities. Anorectic patients present elevated levels of plasma cortisol with the loss of normal daily rhythm, failure of suppression of plasma ACTH and cortisol levels by dexamethasone, a deficient response of plasma cortisol to insulin-induced hypoglycemia and blunted ACTH

and cortisol responses to CRH (146-149). Although little is known about the pathophysiology of hypercortisolism of anorexia nervosa, evidence points to a disorder at or above the hypothalamus leading to hypersecretion of CRH (146,149-152). Since these abnormalities of cortisol secretion are reversed with improvement in nutrition and body weight, they could be regarded only as secondary to malnutrition. However, as pointed out by Gold et al. (149), CRH hypersecretion may be a defect associated with primary affective disorder, given the clinical and pathophysiologic similarities between anorexia nervosa and depression.

The investigation of HPA axis function in bulimia has revealed abnormalities that are independent of weight disturbances (153,154). Although the cortisol circadian variation appears to be normal, 24-h integrated plasma ACTH and cortisol levels are elevated and ACTH and cortisol responses to CRH are blunted (153). These findings are in disagreement with those of Gold et al. (149). A prominent finding in bulimia is the lack of cortisol suppression by dexamethasone (155). However, it is difficult to state if this abnormality is related to psychic distress or to eating behavior itself (154). Interestingly, bulimics do not present the usual cortisol increase in response to a mixed meal (153).

The changes of adrenal function in malnutrition include increased serum cortisol concentration, abolition of daily rhythm, decreased cortisol metabolic clearance, decreased cortisol responsiveness to CRH and incomplete dexamethasone suppression (156,157). This pattern of HPA axis activity has been attributed to endogenous CRH hypersecretion (158). These alterations are all reversible with refeeding. Some of these changes are also observed in normal men after fasting (159).

Although the mechanisms of the altered adrenal function common to fasting, malnutrition and eating disorders are not known, the role of corticosteroids may be considered to be an adaptive response important for the metabolic adjustments for fuel storage to assure survival (160,161).

There is evidence that HPA axis activity is altered by obesity. On the other hand, it is well known that HPA axis components, in particular CRH and corticosteroids, influence the patterns of calorie and nutrient intake. The control of food intake is complex and involves numerous brain neurotransmitters and central and peripheral neural structures. Glucocorticoids are believed to interact with hypothalamus neurotransmitters to mediate their effects on nutrient intake (108,109). Obese humans have normal plasma ACTH and cortisol circadian rhythm, higher cortisol production rate (162), normal cortisol response to hypothalamic-pituitary stimulation by hypoglycemia and direct adrenal stimulation by ACTH, and impaired cortisol response to pituitary stimulation by CRH (163). In addition, obese individuals may fail to suppress plasma cortisol following dexamethasone administration (164). The various animal models of obesity have provided important data to elucidate metabolic disorders in this human disease. Corticosterone has been shown to be necessary for the expression of genetic and hypothalamic lesion-induced obesity (165). The genetically obese fa/fa rat presents many metabolic and endocrine abnormalities that are dependent on adrenal glucocorticoids. Most of these metabolic impairments are reversed by adrenalectomy and restored by corticosterone treatment (166). Adrenalectomy, through the loss of corticosterone, may act on food intake, sympathetic activity and insulin (167) and NPY (3) secretion. In spite of controversial findings in the literature, studies of hypercorticism in genetically obese rats have suggested alterations in the central regulation of the HPA axis (168-171) by still unidentified mechanisms. A regulatory role of glucocorticoids in obese gene expression and leptin secretion has been indicated (172). An

interaction between leptin and NPY has also been suggested (173), with inhibition of NPY synthesis and release by leptin.

In normal man, glucose tolerance varies with time of day. Plasma glucose responses to oral and intravenous glucose or meals are higher in the evening than in the morning (174,175). Van Cauter et al. (176) demonstrated that the daily variation in glucose levels during constant glucose infusion is paralleled by a similar variation in insulin secretion, which is inversely related to the circadian rhythm of cortisol secretion. Under controlled conditions, a similar result was obtained in response to mixed meal ingestion in the morning and in the evening. These studies suggest that factors other than cortisol and gastrointestinal hormones are implicated in the circadian changes in glucose tolerance. Such factors could affect the insulin response through changes in the pancreatic beta cell sensitivity to glucose (177). Additionally, in a recent study our group suggested a modulatory role of cortisol in the IGF-IGF binding protein system under physiological conditions, especially in situations of low insulin concentrations (178).

Finally, the study of hypothalamic-pituitary-adrenocortical activity in diabetic patients has revealed a state of hypercorticism (179,180). The origin of the increased activity of the HPA axis is not clear. It was suggested that fluctuations in blood sugar could be the cause (179). In addition, temporal and quantitative correlations between glucose and circadian cortisol variations were observed in patients with noninsulin-dependent diabetes and normal subjects submitted to fasting. Altogether, these findings indicate the role of glucocorticoids in the control of the daily variations in glucose levels and fuel availability (181,182) and, therefore, the importance of time of day in the diagnosis and treatment of diabetes mellitus.

Cushing's syndrome is characterized by, among other things, HPA rhythmicity abnormalities, insulin resistance and hyperglycemia secondary to hypercortisolism. Hypercortisolemia is associated with increased glucose production, decreased glucose transport and utilization, decreased protein synthesis and increased protein degradation in muscle. It was demonstrated that glucocorticoids may interfere with the early steps of insulin signal transduction in liver and muscle (183). Centrally localized adipose tissue is another feature of corticosteroid excess and this typical fat distribution has been attributed to elevated adipocyte lipoprotein lipase activity and low lipolytic activity (184). After the noon meal, the normal postprandial elevation in cortisol is depressed or absent in pituitary-dependent Cushing's syndrome patients (185).

Interestingly, two recent studies demonstrated that a rare pituitary-independent type of Cushing's syndrome can be food-dependent (186,187). In this uncommon case the development of abnormal adrenal sensitivity to the stimulatory action of secreted gastric inhibitory polypeptide (GIP) was possibly secondary to aberrant expression of GIP receptors on adrenal cells. Thus, in this newly described nodular adrenal hyperplasia cortisol production depends on how much and how often the patients eat.

In conclusion, the present review examined the role of food ingestion as an important synchronizing agent for HPA axis regulation. The modulation of the HPA axis by feeding is complex and may involve a neurohumoral circuitry with both central and peripheral components.

References

1. Aschoff J (1979). Circadian rhythms: general features and endocrinological aspects. In: Krieger DT (Editor), *Endocrine Rhythms*. Raven Press, New York.
2. Moore-Ede MC (1986). Physiology of the circadian timing system: predictive versus reactive homeostasis. *American Journal of Physiology*, 250: R737-R752.
3. Dallman MF, Strack AM, Akana SF, Bradbury MJ, Hanson ES, Scribner KA & Smith M (1993). Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. *Frontiers in Neuroendocrinology*, 14: 303-347.
4. Menaker M, Takahashi JS & Eskin A (1978). The physiology of circadian pacemakers. *Annual Review of Physiology*, 40: 501-526.
5. Rusak B & Zucker I (1979). Neural regulation of circadian rhythms. *Physiological Reviews*, 59: 449-526.
6. Turek FW (1994). Circadian rhythms. *Recent Progress in Hormone Research*, 49: 43-90.
7. Minors DS (1985). Chronobiology: its importance in clinical medicine. *Clinical Science*, 69: 369-376.
8. Moore RY & Eichler VB (1972). Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Research*, 42: 201-206.
9. Stephan FK & Zucker I (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proceedings of the National Academy of Sciences, USA*, 69: 1583-1586.
10. Ralph MR, Foster RG, Davis FC & Menaker M (1990). Transplanted suprachiasmatic nucleus determines circadian period. *Science*, 247: 975-978.
11. Krieger DT, Hauser H & Krey LC (1977). Suprachiasmatic nuclear lesions do not abolish food-shifted circadian adrenal and temperature rhythmicity. *Science*, 197: 398-399.
12. Moore-Ede MC, Schmelzer WS, Kass DA & Herd JA (1976). Internal organization of the circadian timing system in multicellular animals. *Federation Proceedings*, 35: 2333-2338.
13. Aronson BD, Bell-Pedersen D, Block GD, Bos NPA, Dunlap JC, Eskin A, Garceau NY, Geusz ME, Johnson KA, Khalsa SBS, Koster-Van Hoffen GC, Koumenis C, Lee TM, LeSauter J, Lindgren KM, Lin Q, Loros JJ, Michel SH, Mirmiran M, Moore RY, Ruby NF, Silver R, Turek FW, Zatz M & Zucker I (1993). Circadian rhythms. *Brain Research Reviews*, 18: 315-333.
14. Berk ML & Finkelstein JA (1981). An autoradiographic determination of the efferent projections of the suprachiasmatic nucleus of the hypothalamus. *Brain Research*, 226: 1-13.
15. Stephan FK, Berkley KJ & Moss RL (1981). Efferent connections of the rat suprachiasmatic nucleus. *Neuroscience*, 6: 2625-2641.
16. Dallman MF, Akana SF, Cascio CS, Darlington DN, Jacobson L & Levin N (1987). Regulation of ACTH secretion: variations on a theme of B. *Recent Progress in Hormone Research*, 43: 113-173.
17. Cascio CS, Shinsako J & Dallman MF (1987). The suprachiasmatic nuclei stimulate evening ACTH secretion in the rat. *Brain Research*, 423: 173-178.
18. Abe K, Kroning J, Greer MA & Critchlow V (1979). Effects of destruction of the suprachiasmatic nuclei on the circadian rhythms in plasma corticosterone, body temperature, feeding and plasma thyrotropin. *Neuroendocrinology*, 29: 119-131.
19. Bellinger LL, Bernardis LL & Mendel VE (1976). Effect of ventromedial and dorsomedial hypothalamic lesions on circadian corticosterone rhythms. *Neuroendocrinology*, 22: 216-225.
20. Slusher MA (1964). Effects of chronic hypothalamic lesions on daily and stress corticosteroid levels. *American Journal of Physiology*, 206: 1161-1164.
21. Kaneko M, Hiroshige T, Shinsako J & Dallman MF (1980). Daily changes in amplification of hormone rhythms in the adrenocortical system. *American Journal of Physiology*, 239: R309-R316.
22. Honma S, Honma K-I & Hiroshige T (1984). Dissociation of circadian rhythms in rats with a hypothalamic island. *American Journal of Physiology*, 246: R949-R954.
23. Szafarczyk A, Alonso G, Ixart G, Malaval F & Assenmacher I (1985). Daily-stimulated and stress-induced ACTH release in rats is mediated by ventral noradrenergic bundle. *American Journal of Physiology*, 249: E219-E226.
24. Szafarczyk A, Guillaume V, Conte-Devolx B, Alonso G, Malaval F, Pares-Herbute N, Oliver C & Assenmacher I (1988). Central catecholaminergic system stimulates secretion of CRH at different sites. *American Journal of Physiology*, 255: E463-E468.
25. Szafarczyk A, Ixart G, Malaval F, Nouguier-Soule J & Assenmacher I (1979). Effects of lesions of the suprachiasmatic nuclei and of p-chlorophenylalanine on the circadian rhythms of adrenocorticotrophic hormone and corticosterone in the plasma, and on locomotor activity of rats. *Journal of Endocrinology*, 83: 1-16.
26. Linkowski P, Van Onderbergen A, Kerkhafs M, Bosson D, Mendlewicz J & Van Cauter E (1993). Twin study of the 24-h cortisol profile: Evidence for genetic control of the human circadian clock. *American Journal of Physiology*, 264: E173-E181.
27. Ralph MR & Menaker M (1988). A mutation in the circadian system of the golden hamster. *Science*, 241: 1225-1227.
28. Hall JC (1990). Genetics of circadian rhythms. *Annual Review of Genetics*, 24: 659-697.
29. Konopka RJ & Benzer S (1971). Clock mutants of *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences, USA*, 68: 2112-2116.
30. Krieger DT (1974). Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. *Endocrinology*, 95: 1195-1201.
31. Hayden P & Lindberg RG (1969). Circadian rhythm in mammalian body temperature entrained by cyclic pressure changes. *Science*, 164: 1288-1289.
32. Gwinner E (1966). Periodicity of a circadian rhythm in birds by species-specific song cycles (Aves, Fringillidae: *Carduelis spinus*, *Serinus serinus*). *Experientia*, 22: 765-766.
33. McClintock MK (1971). Menstrual synchrony and suppression. *Nature*, 229: 244-245.
34. Earnest DJ, Iadarola M, Yeh HH & Olschowka JA (1990). Photic regulation of c-fos expression in neural components governing the entrainment of circadian rhythms. *Experimental Neurology*, 109: 353-361.
35. Kornhauser JM, Nelson DE, Mayo KE & Takahashi JS (1992). Regulation of jun-B messenger RNA and AP-1 activity by light and a circadian clock. *Science*, 255: 1581-1584.
36. Pincus G (1943). A daily rhythm in the excretion of urinary ketosteroids by young men. *Journal of Clinical Endocrinology*, 3: 195-199.
37. David-Nelson MA & Brodish A (1969). Evidence for a daily rhythm of corticotrophin-releasing factor (CRF) in the hypothalamus. *Endocrinology*, 85: 861-866.

38. Hiroshige T & Sakakura M (1971). Circadian rhythm of corticotropin-releasing activity in the hypothalamus of normal and adrenalectomized rats. *Neuroendocrinology*, 7: 25-36.
39. Takebe K, Sakakura M & Mashimo K (1972). Continuance of daily rhythmicity of CRF activity in hypophysectomized rats. *Endocrinology*, 90: 1515-1520.
40. Moldow RL & Fischman AJ (1982). Physiological changes in rat hypothalamic CRF: circadian, stress and steroid suppression. *Peptides*, 3: 837-840.
41. Owens MJ, Bartolome J, Schanberg SM & Nemeroff CB (1990). Corticotropin-releasing factor concentrations exhibit an apparent daily rhythm in hypothalamic and extrahypothalamic brain regions: differential sensitivity to corticosterone. *Neuroendocrinology*, 52: 626-631.
42. Honma K-I, Noe Y, Honma S, Katsuno Y & Hiroshige T (1992). Roles of paraventricular catecholamines in feeding-associated corticosterone rhythm in rats. *American Journal of Physiology*, 262: E948-E955.
43. Watabe T, Tanaka K, Kumagae M, Itoh S, Hasegawa M, Horiuchi T, Miyabe S, Ohno H & Shimizu N (1987). Daily rhythm of plasma immunoreactive corticotropin-releasing factor in normal subjects. *Life Sciences*, 40: 1651-1655.
44. Watts AG & Swanson LW (1989). Daily variations in the content of preprocorticotropin-releasing hormone messenger ribonucleic acids in the hypothalamic paraventricular nucleus of rats of both sexes as measured by *in situ* hybridization. *Endocrinology*, 125: 1734-1738.
45. Kwak SP, Young EA, Morano I, Watson SJ & Akil H (1992). Daily corticotropin-releasing hormone mRNA variation in the hypothalamus exhibits a rhythm distinct from that of plasma corticosterone. *Neuroendocrinology*, 55: 74-83.
46. Akana SF, Cascio CS, Du JZ, Levin N & Dallman MF (1986). Reset of feedback in the adrenocortical system: an apparent shift in sensitivity of adrenocorticotropin to inhibition by corticosterone between morning and evening. *Endocrinology*, 119: 2325-2332.
47. Leal AMO & Moreira AC (1996). Feeding and the daily variation of the hypothalamic-pituitary-adrenal axis and its responses to CRH and ACTH in rats. *Neuroendocrinology*, 64: 14-19.
48. Charlton BG, Leake A, Ferrier IN, Linton EA & Lowry PJ (1986). Corticotropin-releasing factor in plasma of depressed patients and controls. *Lancet*, i: 161-162.
49. Bagdy G, Chrousos GP & Calogero AE (1991). Circadian patterns of plasma immunoreactive corticotropin, beta-endorphin, corticosterone and prolactin after immunoneutralization of corticotropin-releasing hormone. *Neuroendocrinology*, 53: 573-578.
50. Avgerinos PC, Schurmeyer TH, Gold PW, Tomai TP, Loriaux DL, Sherins RJ, Cutler GB & Chrousos GP (1986). Administration of human corticotropin-releasing hormone in patients with secondary adrenal insufficiency: restoration of the normal cortisol secretory pattern. *Journal of Clinical Endocrinology and Metabolism*, 62: 816-821.
51. Nicholson S, Lin J-H, Mahmoud S, Campbel E, Gillham B & Jones M (1985). Daily variations in responsiveness of the hypothalamo-pituitary-adrenocortical axis of the rat. *Neuroendocrinology*, 40: 217-224.
52. DeCherney GS, Debold CR, Jackson RV, Sheldon WR, Island DP & Orth DN (1985). Daily variation in the response of plasma adrenocorticotropin and cortisol to intravenous ovine corticotropin-releasing hormone. *Journal of Clinical Endocrinology and Metabolism*, 61: 273-279.
53. Desir D, Van Cauter E, Beyloos M, Bosson D, Golstein J & Copinschi G (1986). Prolonged pulsatile administration of ovine corticotropin-releasing hormone in normal man. *Journal of Clinical Endocrinology and Metabolism*, 63: 1292-1299.
54. Shulte HM, Chrousos GP, Gold PW, Booth JD, Oldfield EH, Cutler GB & Loriaux DL (1985). Continuous administration of synthetic ovine corticotropin-releasing factor in man. *Journal of Clinical Investigation*, 75: 1781-1785.
55. Salata RA, Jarret DB, Verbalis JG & Robinson AG (1988). Vasopressin stimulation of adrenocorticotropin hormone (ACTH) in humans. *Journal of Clinical Investigation*, 81: 766-774.
56. Dallman MF, Engeland WC, Rose JC, Wilkinson CW, Shinsako J & Siedenburg F (1978). Nycthemeral rhythm in adrenal responsiveness to ACTH. *American Journal of Physiology*, 135: R210-R218.
57. Tanaka K, Nicholson WE & Orth DN (1978). Daily rhythm and disappearance half-time of endogenous plasma immunoreactive ß-MSH (LPH) and ACTH. *Journal of Clinical Endocrinology and Metabolism*, 46: 883-890.
58. Dent RRM, Guilleminault C, Albert LH, Posner BI, Cox BM & Goldstein A (1981). Daily rhythm of plasma immunoreactive ß-endorphin and its relationship to sleep stages and plasma rhythms of cortisol and prolactin. *Journal of Clinical Endocrinology and Metabolism*, 52: 942-947.
59. Veldhuis JD, Iranmanesh A, Johnson ML & Lizarralde G (1990). Amplitude, but not frequency, modulation of adrenocorticotropin secretory bursts gives rise to the nyctohemeral rhythm of the corticotropic axis in man. *Journal of Clinical Endocrinology and Metabolism*, 71: 452-463.
60. Veldhuis JD, Iranmanesh A, Johnson ML & Lizarralde G (1990). Twenty-four-hour rhythms in plasma concentrations of adenohypophyseal hormones are generated by distinct amplitude and/or frequency modulation of underlying pituitary secretory bursts. *Journal of Clinical Endocrinology and Metabolism*, 71: 1616-1623.
61. Kaneko M, Kaneko K, Shinsako J & Dallman MF (1981). Adrenal sensitivity to adrenocorticotropin varies daily. *Endocrinology*, 109: 70-75.
62. Fehm HL, Klein E, Holl R & Voigt KH (1984). Evidence for extrapituitary mechanisms mediating the morning peak of plasma cortisol in man. *Journal of Clinical Endocrinology and Metabolism*, 58: 410-414.
63. Dallman MF, Levin N, Cascio CS, Akana SF, Jacobson L & Kuhn RW (1989). Pharmacological evidence that the inhibition of daily corticotropin secretion by corticosteroids is mediated via type I, corticosterone-preferring receptors. *Endocrinology*, 124: 2844-2850.
64. Bradbury MJ, Akana SF & Dallman MF (1994). Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo-pituitary-adrenal axis during the daily trough and the peak: Evidence for a nonadditive effect of combined receptor occupation. *Endocrinology*, 134: 1286-1296.
65. Andrews RV (1968). Temporal secretory responses of cultured hamster adrenals. *Comparative Biochemistry and Physiology*, 26: 179-193.
66. O'Hare MJ & Hornsby PJ (1975). Absence of a circadian rhythm of corticosterone secretion in monolayer cultures of adult rat adrenocortical cells. *Experientia*, 31: 378-380.
67. Meier AH (1976). Daily variation in concentrations of plasma corticosteroid in hypophysectomized rats. *Endocrinology*, 98: 1475-1479.

68. Cheifetz P, Gaffud N & Dingman JF (1968). Effects of bilateral adrenalectomy and continuous light on the circadian rhythm of corticotropin in female rats. *Endocrinology*, 82: 1117-1124.
69. Kwak SP, Morano MI, Young EA, Watson SJ & Akil H (1993). Daily CRH mRNA rhythm in the hypothalamus: decreased expression in the evening is not dependent on endogenous glucocorticoids. *Neuroendocrinology*, 57: 96-105.
70. Krieger DT & Gewirtz GP (1974). The nature of the circadian periodicity and suppressibility of immunoreactive ACTH levels in Addison's disease. *Journal of Clinical Endocrinology and Metabolism*, 39: 46-52.
71. Moreira AC, Leal AMO & Castro M (1990). Characterization of adrenocorticotropin secretion in a patient with 17 α-hydroxylase deficiency. *Journal of Clinical Endocrinology and Metabolism*, 71: 86-91.
72. Woodward CJH, Hervey GR, Oakey RE & Whitaker EM (1991). The effects of fasting on plasma corticosterone kinetics in rats. *British Journal of Nutrition*, 66: 117-127.
73. Marotta SF, Hiles LG, Lanuza DM & Boonayathap U (1975). The relation of hepatic *in vitro* inactivation of corticosteroids to the circadian rhythm of plasma corticosterone. *Hormone and Metabolic Research*, 7: 334-337.
74. Lacerda L, Kowarski A & Migeon CJ (1973). Daily variation of the metabolic clearance rate of cortisol. Effect on measurement of cortisol production rate. *Journal of Clinical Endocrinology and Metabolism*, 36: 1043-1049.
75. Krieger DT (1979). Rhythms in CRF, ACTH and corticosteroids. In: Krieger DT (Editor), *Endocrine Rhythms*. Raven Press, New York, 123-142.
76. Santiago LB, Jorge SM & Moreira AC (1996). Longitudinal evaluation of the development of salivary cortisol circadian rhythm in infancy. *Clinical Endocrinology*, 44: 157-161.
77. Spangler G (1991). The emergence of adrenocortical circadian function in newborns and infants and its relationship to sleep, feeding and maternal adrenocortical activity. *Early Human Development*, 25: 197-208.
78. Morimoto Y, Arisue K & Yamamura Y (1977). Relationship between circadian rhythm of food intake and that of plasma corticosterone and effect of food restriction on circadian adrenocortical rhythm in the rat. *Neuroendocrinology*, 23: 212-222.
79. Nelson W, Scheving L & Halberg F (1975). Circadian rhythms in mice fed a single daily meal at different stages of lighting regimen. *Journal of Nutrition*, 105: 171-184.
80. Gallo PV & Weinberg J (1981). Corticosterone rhythmicity in the rat: Interactive effects of dietary restriction and schedule of feeding. *Journal of Nutrition*, 111: 208-218.
81. Inouye ST (1982). Restricted daily feeding does not entrain circadian rhythms of the suprachiasmatic nucleus in the rat. *Brain Research*, 232: 194-199.
82. Shibata S, Liou SY, Ueki S & Oomura Y (1983). Effects of restricted feeding on single neuron activity of suprachiasmatic neurons in rat hypothalamus slice preparation. *Physiology and Behavior*, 31: 523-528.
83. Krieger DT (1980). Ventromedial hypothalamic lesions abolish food-shifted circadian adrenal and temperature rhythmicity. *Endocrinology*, 106: 649-654.
84. Inouye ST (1982). Ventromedial hypothalamic lesions eliminate anticipatory activities of restricted daily feeding schedules in the rat. *Brain Research*, 250: 183-187.
85. Honma K-I, Honma S & Hiroshige T (1983). Critical role of food amount for prefeeding corticosterone peak in rats. *American Journal of Physiology*, 245: R339-R344.
86. Wilkinson CW, Shinsako J & Dallman MF (1979). Daily rhythms in adrenal responsiveness to adrenocorticotropin are determined primarily by the time of feeding in the rat. *Endocrinology*, 104: 350-359.
87. Ottenweller JE & Meier A (1982). Adrenal innervation may be an extrapituitary mechanism able to regulate adrenocortical rhythmicity in rats. *Endocrinology*, 111: 1334-1338.
88. Holzwarth MA, Cunningham LA & Kleitman N (1987). The role of adrenal nerves in the regulation of adrenocortical functions. *Annals of the New York Academy of Sciences*, 512: 449-464.
89. Vinson GP, Hinson JP & Tóth IE (1994). The neuroendocrinology of the adrenal cortex. *Journal of Neuroendocrinology*, 6: 235-246.
90. Charlton BG (1989). Adrenal cortical innervation and glucocorticoid secretion. *Journal of Endocrinology*, 126: 5-8.
91. Engeland WC & Gann DS (1989). Splanchnic nerve stimulation modulates steroid secretion in hypophysectomized dogs. *Neuroendocrinology*, 50: 124-131.
92. Edwards AV, Jones CT & Bloom SR (1986). Reduced adrenal cortical sensitivity to ACTH in lambs with cut splanchnic nerves. *Journal of Endocrinology*, 110: 81-85.
93. Dunn J, Scheving L & Millet P (1972). Circadian variation in stress-evoked increases in plasma corticosterone. *American Journal of Physiology*, 222: 402-406.
94. Yasuda N, Takebe K & Greer MA (1976). Evidence of nycterohemeral periodicity in stress-induced pituitary-adrenal activation. *Neuroendocrinology*, 21: 214-224.
95. Bradbury MJ, Cascio CS, Scribner KA & Dallman MF (1991). Stress-induced adrenocorticotropin secretion: daily responses and decreases during stress in the evening are not dependent on corticosterone. *Endocrinology*, 128: 680-688.
96. Leal AMO, Forsling ML & Moreira AC (1995). Daily variation of the pituitary-adrenal and AVP responses to stress in rats under food restriction. *Life Sciences*, 56: 191-198.
97. Hanson ES, Bradbury MJ, Akana SF, Scribner KA, Strack AM & Dallman MF (1994). The daily rhythm in adrenocorticotropin responses to restraint in adrenalectomized rats is determined by caloric intake. *Endocrinology*, 134: 2214-2220.
98. Moreira AC & Krieger DT (1982). The effects of subdiaphragmatic vagotomy on circadian corticosterone rhythmicity in rats with continuous or restricted food access. *Physiology and Behavior*, 28: 787-790.
99. Leibowitz SF, Roland CR, Hor L & Schillari V (1984). Noradrenergic feeding elicited via the paraventricular nucleus is dependent upon circulating corticosterone. *Physiology and Behavior*, 32: 857-864.
100. Bhakthavatsalam P & Leibowitz SF (1986). α_2-Noradrenergic feeding rhythm in paraventricular nucleus: relation to corticosterone. *American Journal of Physiology*, 250: R83-R88.
101. Mitome M, Honma S, Yoshihara T & Honma K-I (1994). Prefeeding increase in paraventricular NE release is regulated by a feeding-associated rhythm in rats. *American Journal of Physiology*, 226: E606-E611.
102. Stanley BG, Schwartz DH, Hernandez L, Hoebel BG & Leibowitz SF (1989). Patterns of extracellular norepinephrine in the paraventricular hypothalamus: relationship to circadian rhythm and deprivation-induced eating behavior. *Life Sciences*, 45: 275-282.

103. Shor-Posner G, Grinker JA, Marinescu C & Leibowitz SF (1985). Role of hypothalamic norepinephrine in control of meal patterns. *Physiology and Behavior*, 35: 209-214.
104. Al-Damluji S, Iveson T, Thomas JM, Pendlebury DJ, Rees LH & Besser GM (1987). Food-induced cortisol secretion is mediated by central alpha-1 adrenoceptor modulation of pituitary ACTH secretion. *Clinical Endocrinology*, 26: 629-636.
105. Morley JE (1987). Neuropeptide regulation of appetite and weight. *Endocrine Reviews*, 8: 256-287.
106. Nagai K & Nakagawa H (1992). *Central Regulation of Energy Metabolism with Special Reference to Circadian Rhythm*. CRC Press, Boca Raton.
107. Antoni FA (1986). Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. *Endocrine Reviews*, 7: 351-378.
108. Leibowitz SF (1987). Hypothalamic neurotransmitters in relation to normal and disturbed eating patterns. *Annals of the New York Academy of Sciences*, 499: 137-143.
109. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP & Ravussin E (1996). Effects of glucocorticoids on energy metabolism and food intake in humans. *American Journal of Physiology*, 34: E317-E325.
110. Koenig JI (1990). Regulation of the hypothalamo-pituitary-adrenal axis by neuropeptide Y. *Annals of the New York Academy of Sciences*, 611: 317-328.
111. Brady LS, Smith MA, Gold PW & Herkenham M (1990). Altered expression of hypothalamic neuropeptide mRNAs in food-restricted and food deprived rats. *Neuroendocrinology*, 52: 441-447.
112. Dequidt ME & Emson PC (1986). Distribution of neuropeptide Y-like immunoreactivity in the rat central nervous system. II. Immunohistochemical analysis. *Neuroscience*, 18: 545-618.
113. Clark JT, Kalra PS & Kalra SP (1985). Neuropeptide Y stimulates feeding but inhibits sexual behavior in rats. *Endocrinology*, 117: 2435-2442.
114. Sahu A & Kalra SP (1993). Neuropeptidergic regulation of feeding behavior: neuropeptide Y. *Trends in Endocrinology and Metabolism*, 4: 217-224.
115. Jhanwar-Uniyal M, Beck B, Burlet C & Leibowitz SF (1990). Daily rhythm of neuropeptide Y-like immunoreactivity in the suprachiasmatic, arcuate and paraventricular nuclei and other hypothalamic sites. *Brain Research*, 536: 331-334.
116. Kalra SP, Dube MG, Sahu A, Phelps CP & Kalra PS (1991). Neuropeptide Y secretion increases in the paraventricular nucleus in association with increased appetite for food. *Proceedings of the National Academy of Sciences, USA*, 88: 10931-10935.
117. Wahlestedt C, Skagerberg G, Ekman R, Heilig M, Sundler F & Hakanson R (1987). Neuropeptide Y (NPY) in the area of the hypothalamic paraventricular nucleus activates the pituitary-adrenocortical axis in the rat. *Brain Research*, 417: 33-38.
118. Haas DA & George SR (1989). Neuropeptide Y-induced effects on hypothalamic corticotropin-releasing factor content and release are dependent on noradrenergic/adrenergic neurotransmission. *Brain Research*, 498: 333-338.
119. Ponsalle P, Srivastava LS, Uht RM & White JD (1992). Glucocorticoids are required for food deprivation-induced increases in hypothalamic neuropeptide Y expression. *Journal of Neuroendocrinology*, 4: 585-591.
120. Stanley BG, Lanthier D, Chin AS & Leibowitz SF (1989). Suppression of neuropeptide Y-elicited eating by adrenalectomy or hypophysectomy: reversal with corticosterone. *Brain Research*, 501: 32-36.
121. Oliveira MHA, Antunes-Rodrigues J, Leal AMO, Elias LLK & Moreira AC (1993). Circadian variation of plasma atrial natriuretic peptide and corticosterone in rats with continuous or restricted access to food. *Life Sciences*, 53: 1795-1801.
122. Oliveira MHA, Antunes-Rodrigues J, Gutkowska J, Leal AMO, Elias LLK & Moreira AC (1997). Atrial natriuretic peptide and feeding activity patterns in rats. *Brazilian Journal of Medical and Biological Research*, 30: 1-5.
123. Dallman MF, Darlington DN, Suemaru S, Cascio CS & Levin N (1989). Corticosteroids in homeostasis. *Acta Physiologica Scandinavica*, 136: 227-234.
124. Leveille GA (1967). *In vivo* fatty acid synthesis in adipose tissue and liver of meal-fed rats. *Proceedings of the Society for Experimental Biology and Medicine*, 125: 85-88.
125. Leveille GA (1966). Glycogen metabolism in meal-fed rats and chicks and the time sequence of lipogenic and enzymatic adaptive changes. *Journal of Nutrition*, 90: 449-460.
126. Leveille GA & Chakrabarty K (1967). Daily variations in tissue glycogen and liver weight of meal-fed rats. *Journal of Nutrition*, 93: 546-554.
127. Stevenson JAF, Feleki V, Szlavko A & Beaton JR (1964). Food restriction and lipogenesis in the rat. *Proceedings of the Society for Experimental Biology and Medicine*, 116: 178-182.
128. Lima FB, Hell NS, Timo-Iaria C, Scivoletto R, Dolnikoff MS & Pupo AA (1981). Metabolic consequences of food restriction in rats. *Physiology and Behavior*, 27: 115-123.
129. Hell NS, Oliveira LBC, Dolnikoff MS, Scivoletto R & Timo-Iaria C (1980). Changes of carbohydrate metabolism caused by food restriction, as detected by insulin administration. *Physiology and Behavior*, 24: 473-477.
130. Curi R, Hell NS, Bazotte RB & Timo-Iaria C (1984). Metabolic performance of free fed rats subjected to prolonged fast as compared to the metabolic pattern in rats under long term food restriction. *Physiology and Behavior*, 33: 525-531.
131. Leveille GA & Chakrabarty K (1968). Absorption and utilization of glucose by meal-fed and nibbling rats. *Journal of Nutrition*, 96: 69-75.
132. Bazotte RB, Curi R & Hell NS (1989). Metabolic changes caused by irregular-feeding schedule as compared with meal-feeding. *Physiology and Behavior*, 46: 109-113.
133. Berdanier CD, Wurdeman R & Tobin RB (1976). Further studies on the role of the adrenal hormones in the responses of rats to meal-feeding. *Journal of Nutrition*, 106: 1791-1800.
134. Wiley JH & Leveille GA (1970). Significance of insulin in the metabolic adaptation of rats to meal ingestion. *Journal of Nutrition*, 100: 1073-1080.
135. Schwartz MW, Figlewicz DP, Baskin DG, Woods SC & Porte Jr D (1992). Insulin in the brain: A hormonal regulator of energy balance. *Endocrine Reviews*, 13: 387-414.
136. Baura GD, Foster DM, Kaiyala K, Porte D, Kahn SE & Schwartz MW (1996). Insulin transport from plasma into the central nervous system is inhibited by dexamethasone in dogs. *Diabetes*, 45: 86-90.

137. Devenport L, Knehans A, Sundstrom A & Thomas T (1989). Corticosterone's dual metabolic actions. *Life Sciences*, 45: 1389-1396.
138. Follenius M, Brandenberger G & Hietter B (1982). Daily cortisol peaks and their relationships to meals. *Journal of Clinical Endocrinology and Metabolism*, 55: 757-761.
139. Quigley ME & Yen SSC (1979). A midday surge in cortisol levels. *Journal of Clinical Endocrinology and Metabolism*, 49: 945-947.
140. Goldman J, Wajchenberg BL, Liberman B, Nery M, Achando S & Germek OA (1985). Contrast analysis for the evaluation of the circadian rhythms of plasma cortisol, androstenedione, and testosterone in normal men and the possible influence of meals. *Journal of Clinical Endocrinology and Metabolism*, 60: 164-167.
141. Slag MF, Ahmed M, Gannon MC & Nuttall FQ (1981). Meal stimulation of cortisol secretion: A protein induced effect. *Metabolism*, 30: 1104-1108.
142. Ishizuka B, Quigley ME & Yen SSC (1983). Pituitary hormone release in response to food ingestion: Evidence for neuroendocrine signals from gut to brain. *Journal of Clinical Endocrinology and Metabolism*, 57: 1111-1116.
143. Saito M, Kato H, Suda M & Yugari Y (1981). Parenteral feeding abolishes the circadian adrenocortical rhythm in rats. *Experientia*, 37: 754-755.
144. Marchini JS, Neto JB & Lara RS (1988). Ritmo nictêmero de cortisol e insulina em pacientes submetidos ao suporte nutricional enteral e parenteral. *Revista do Hospital das Clínicas da Faculdade de Medicina de São Paulo*, 43: 232-236.
145. Pasley JN, Burns ER & Rayford PL (1994). Circadian variations of gastrointestinal peptides and cell proliferation in rats: Effects of adrenalectomy. *Recent Progress in Hormone Research*, 49: 359-365.
146. Frankel RJ & Jenkins JS (1975). Hypothalamic-pituitary function in anorexia nervosa. *Acta Endocrinologica*, 78: 209-221.
147. Berger M, Pirke K, Doerr P, Krieg C & von Zerssen D (1983). Influence of weight loss on the dexamethasone suppression test. *Archives of General Psychiatry*, 40: 585-586.
148. Sirinathsinghyi DJS & Milles IH (1985). Concentration patterns of plasma dehydroepiandrosterone, Δ^5-androstenediol and their sulphates, testosterone and cortisol in normal healthy women and in women with anorexia nervosa. *Acta Endocrinologica*, 108: 255-260.
149. Gold PW, Gwirtsman H, Avgerinos PC, Nieman LK, Gallucci WT, Kaye W, Jimerson D, Ebert M, Rittmaster R, Loriaux L & Chrousos GP (1986). Abnormal hypothalamic-pituitary-adrenal function in anorexia nervosa. *New England Journal of Medicine*, 314: 1335-1342.
150. Hotta M, Shibasaki T, Masuda A, Imaki T, Demura H, Ling N & Shizume K (1986). The response of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. *Journal of Clinical Endocrinology and Metabolism*, 62: 319-324.
151. Kaye VH, Gwirtsman HE, George DT, Ebert MH, Jimerson DC, Tomai TP, Chrousos GP & Gold PW (1987). Elevated cerebrospinal fluid levels of immunoreactive corticotropin-releasing hormone in anorexia nervosa: relation to state of nutrition, adrenal function, and intensity of depression. *Journal of Clinical Endocrinology and Metabolism*, 64: 203-208.
152. Cavagnini F, Invitti C, Passamonti M & Polli EE (1986). Response of ACTH and cortisol to corticotropin-releasing hormone in anorexia nervosa. *New England Journal of Medicine*, 314: 184-185.
153. Mortola JF, Rasmussen DD & Yen SSC (1989). Alterations of the adrenocorticotropin-cortisol axis in normal weight bulimic women: Evidence for a central mechanism. *Journal of Clinical Endocrinology and Metabolism*, 68: 517-522.
154. Gwirtsman HE, Roy-Birne P, Yager J & Gerner RH (1983). Neuroendocrine abnormalities in bulimia. *American Journal of Psychiatry*, 140: 559-563.
155. Walsch BT, Lo SE, Cooper T, Lindy DC, Roose SP, Gladis M & Glassman AH (1987). Dexamethasone suppression test and plasma dexamethasone levels in bulimia. *Archives of General Psychiatry*, 44: 797-800.
156. Smith SR, Bledsoe T & Chhetri MK (1975). Cortisol metabolism and the pituitary-adrenal axis in adults with protein-calorie malnutrition. *Journal of Clinical Endocrinology and Metabolism*, 40: 43-52.
157. Malozowski S, Muzzo S, Burrows R, Leiva L, Loriaux L, Chrousos G, Winterer J & Cassorla F (1990). The hypothalamic-pituitary-adrenal axis in infantile malnutrition. *Clinical Endocrinology*, 32: 461-465.
158. Alleyne GAO & Young VH (1967). Adrenocortical function in children with severe protein-calorie malnutrition. *Clinical Science*, 33: 189-200.
159. Vance ML & Thorner MO (1989). Fasting alters pulsatile and rhythmic cortisol release in normal men. *Journal of Clinical Endocrinology and Metabolism*, 68: 1013-1018.
160. Eigler N, Sacca L & Sherwin R (1979). Synergistic interactions of physiologic increments of glucagon, epinephrine, and cortisol in the dog. *Journal of Clinical Investigation*, 63: 114-123.
161. Brasel JA (1980). Endocrine adaptation to malnutrition. *Pediatric Research*, 14: 1299-1303.
162. Streeten DHP, Stevenson CT, Dalakos TG, Nicholas JJ, Dennick LG & Fellerman H (1969). The diagnosis of hypercortisolism. Biochemical criteria differentiating patients from lean and obese normal subjects and from females on oral contraceptives. *Journal of Clinical Endocrinology and Metabolism*, 29: 1191-1211.
163. Kopelman PG, Grossman A, Lavender P, Besser GM, Rees LH & Coy D (1988). The cortisol response to corticotropin-releasing factor is blunted in obesity. *Clinical Endocrinology*, 28: 15-18.
164. Crapo L (1979). Cushing's syndrome: a review of diagnostic tests. *Metabolism*, 28: 955-977.
165. Dallman MF (1984). Viewing the ventromedial hypothalamus from the adrenal gland. *American Journal of Physiology*, 246: R1-R12.
166. Freedman MR, Horwitz BA & Stern JS (1986). Effect of adrenalectomy and glucocorticoid replacement on development of obesity. *American Journal of Physiology*, 250: R595-R607.
167. Bray GA, York DA & Fisler JS (1989). Experimental obesity: A homeostatic failure due to defective nutrient stimulation of the sympathetic nervous system. *Vitamins and Hormones*, 45: 1-125.
168. Guilhaume-Gentil C, Rohner-Jeanrenaud F, Abramo F, Bestetti GE, Rossi GL & Jeanrenaud B (1990). Abnormal regulation of the hypothalamo-pituitary-adrenal axis in the genetically obese fa/fa rat. *Endocrinology*, 126: 1873-1879.
169. Plotsky PM, Thrivikraman KV, Watts AG & Hauger RL (1992). Hypothalamic-pituitary-adrenal function in the zucker obese rat. *Endocrinology*, 130: 1931-1941.
170. Walker CD, Scribner KA, Stern JS & Dallman MF (1992). Obese zucker (fa/fa) rats exhibit normal target sensitivity to corticosterone and increased drive to adrenocorticotropin during the daily trough. *Endocrinology*, 131: 2629-2637.

171. Havel PJ, Busch BL, Curry DL, Johnson PR, Dallman MF & Stern JS (1996). Predominately glucocorticoid agonist actions of RU-486 in young specific-pathogen-free zucker rats. *American Journal of Physiology*, 271: R710-R717.
172. Slieker LJ, Sloop KW, Surface PL, Kriauciunas A, LaQuier F, Manetta J, Bue-Valleskey J & Stephens TW (1996). Regulation of expression of ob mRNA and protein by glucocorticoids and cAMP. *Journal of Biological Chemistry*, 271: 5301-5304.
173. Stephens TW, Basinsky M, Bristow PK, Bue-Valleskey JM, Burgett SG, Craft L, Hale J, Hoffmann J, Hsiung HM, Kriauciunas A, MacKellar W, Rosteck Jr PR, Schoner B, Smith D, Tinsley FC, Zhang X & Heiman M (1995). The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature*, 377: 530-532.
174. Carrol K & Nestel P (1973). Daily variation in glucose tolerance and in insulin secretion in man. *Diabetes*, 22: 333-348.
175. Van Cauter E, Shapiro ET, Tillil H & Polonsky KS (1992). Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. *American Journal of Physiology*, 262: E467-E475.
176. Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S & Polonsky KS (1991). Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *Journal of Clinical Investigation*, 88: 934-942.
177. Aparício NJ, Puchulu FE, Gagliardino JJ, Ruiz M, Llorens JM, Ruiz J, Lamas A & Miguel R (1974). Circadian variation of the blood glucose, plasma insulin and human growth hormone level in response to an oral glucose load in normal subjects. *Diabetes*, 23: 132-137.
178. Martinelli C, Yateman M, Cotterril A, Moreira A & Camacho-Hubner C (1997). Interaction between the GH-IGF system and spontaneous cortisol secretion in children. Growth Hormone Research Society Conference 96. *Endocrinology and Metabolism*, 4 (Suppl A): 85 (Abstract).
179. Asfeldt VH (1972). Hypophyseo-adrenocortical function in diabetes mellitus. *Acta Medica Scandinavica*, 191: 349-354.
180. Cameron OG, Kronfol Z, Greden JF & Carrol BJ (1984). Hypothalamic-pituitary-adrenocortical activity in patients with diabetes mellitus. *Archives of General Psychiatry*, 41: 1090-1095.
181. Shapiro ET, Polonsky KS, Copinschi G, Bosson D, Tillil H, Blackman J, Lewis G & Van Cauter E (1991). Nocturnal elevation of glucose levels during fasting in noninsulin-dependent diabetes. *Journal of Clinical Endocrinology and Metabolism*, 72: 444-454.
182. Faiman C & Moorhouse JA (1967). Daily variation in the levels of glucose and related substances in healthy and diabetic subjects during starvation. *Clinical Science*, 32: 111-126.
183. Saad MJ, Folli F, Kalin JA & Kahn CR (1993). Modulation of insulin receptor, insulin receptor substrate-1, and phosphatidylinositol 3-kinase in liver and muscle of dexamethasone-treated rats. *Journal of Clinical Investigation*, 92: 2065-2072.
184. Rebuffé-Scrive M, Krotkiewski M, Elfverson J & Björntorp P (1988). Muscle and adipose tissue morphology and metabolism in Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism*, 67: 1122-1127.
185. Liu LH, Kazer RR & Rasmussen DD (1987). Characterization of the twenty-four hour secretion patterns of adrenocorticotropin and cortisol in normal women and patients with Cushing's disease. *Journal of Clinical Endocrinology and Metabolism*, 64: 1027-1035.
186. Lacroix A, Bolté E, Tremblay J, Dupré J, Poitras P, Fournier H, Garon J, Garrel D, Bayard F, Taillefer R, Flanagan RJ & Hamet P (1992). Gastric inhibitory polypeptide-dependent cortisol hypersecretion - a new case of Cushing's syndrome. *New England Journal of Medicine*, 327: 974-980.
187. Reznik Y, Allali-Zerah V, Chayvialle JA, Leroyer R, Leymare P, Travert G, Lebrethon M-E, Budi I, Balliere A-M & Maloudeau J (1992). Food-dependent Cushing's syndrome mediated by aberrant adrenal sensitivity to gastric inhibitory polypeptide. *New England Journal of Medicine*, 327: 981-986.