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

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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.

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 adrenocorticotropic (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 β-lipotropin (57) and β-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 corticosteroi d 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 pre-treatment. 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-elicted 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, neuropeptide Y, 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 adrenoreceptors 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 hypothalamic 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
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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. Hypercortisolism 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.
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