Editorial: The Corticotropin-Releasing Hormone System and Feeding Behavior—A Complex Web Begins to Unravel

The CRH system is best known for the role of CRH as the hypothalamic-releasing factor that is the primary regulator of the hypothalamic-pituitary-adrenal (HPA) axis (1), and of the stress-regulated control of adrenal glucocorticoid production. Glucocorticoids have an important role both peripherally and centrally in the control of energy homeostasis; however, the CRH system is also involved in energy homeostasis via direct central actions independent of HPA axis control. Thus, genetic manipulations in the mouse have been an important tool in the study of this complex system (for a review see Ref. 2). In this issue of Endocrinology (3) and in recent articles in Nature Genetics (4, 5), unique roles for each of the two CRH receptors in the central control of feeding behavior have been suggested by careful analysis of the Crhr1 and Crhr2 knockout mice.

As of this writing, the CRH system in mammals appears to be defined by the CRH peptide, a related peptide called urocortin, two G protein-coupled receptors, Crhr1 and Crhr2, and a binding protein, CRH-BP, that binds both CRH and urocortin with affinities comparable to ligand binding of the receptor. The neurosecretory CRH cells responsible for regulation of pituitary ACTH release are found in the paraventricular nucleus of the hypothalamus (PVH); however, this peptide is also found in the cortex, brain stem, and amygdala, for example. The urocortin peptide is more restricted centrally, being expressed primarily in the Edinger-Westphal nucleus, as well as in lower amounts elsewhere, and is also found peripherally in sites including the gastrointestinal and immune systems. The Crhr1, which binds both peptides with equal affinity, is the pituitary receptor for CRH and is also expressed in the cortex and a handful of other brain regions. The Crhr2, which has a much higher affinity for urocortin than for CRH, is widely expressed in the periphery in sites such as the heart, muscle, and GI tract, and in the brain in sites including the ventromedial hypothalamus, lateral septum, and the cerebral vasculature. The CRH-BP is coexpressed with the peptides and receptors at many sites in the brain and periphery.

Glucocorticoid production in the adult regulates carbohydrate and protein metabolism, and disorders such as Cushing's disease that lead to chronic elevation of circulating glucocorticoids cause obesity. Not surprisingly, a variety of mouse models have been created that cause a Cushing's-type obesity in the mouse. For example, a transgenic mouse expressing an antisense cDNA for the type II glucocorticoid receptor expressed behind the neurofilament gene promoter was found to have close to twice the level of normal circulating corticosterone and reached twice the weight (65 g) of normal littermates (35 g) by 6 months of age (6). Presumably, the lack of autoinhibitory glucocorticoid receptors in pituitary and hypothalamus elevated glucocorticoid production, which acted peripherally to increase adipose mass. Several other models with varying degrees of Cushing's-type obesity have also been created. These include selective knockout of the type II glucocorticoid receptor in the brain (7), knockout of 7B2, a protein required for production of the prohormone convertase PC2 (8) necessary for conversion of ACTH into α-MSH, pituitary-directed transgenic expression of leukemia inhibitory factor (9), resulting in development of excessive numbers of corticotrophs, and transgenic overexpression of CRH behind the metallothionein promoter (10). In brief, any manipulation of the HPA axis at the level of the hypothalamus or pituitary that elevates circulating glucocorticoids appears to produce a Cushing's syndrome type of obesity.

Importantly, however, centrally administered CRH (11) or urocortin (12) inhibits feeding and stimulates metabolism, in opposition to the role of CRH released from neurosecretory PVN neurons in stimulating glucocorticoid release and enhancing energy storage. Furthermore, central administration of a CRH antagonist blocks stress-induced inhibition of feeding (13), implying that some of the inhibitory effects of stress on feeding may be mediated by central CRH pathways. Thus, it has been of great interest to attempt to determine the respective contribution of the component parts of the CRH system in the central control of energy homeostasis.

Several genetic models in the mouse also address these issues, including transgenic mice overexpressing CRH binding protein behind either a pituitary promoter (14), or metallothionein promoter (15). The transgenic expressing CRH-BP in the pituitary demonstrated a normal HPA axis, but a compensatory elevation in CRH in the PVN. These animals exhibited an alteration in the normal diurnal pattern of food intake, but no change in total food intake. Mice expressing the protein behind the metallothionein promoter exhibited a sexually dimorphic obesity syndrome, with obesity developing at 3 months in the males and at 12 months in the females. In CRH-BP knockout mice, basal and restraint-stress induced corticosterone levels are still normal; however, reduced weight gain is seen specifically in the males (15%), as is hypophagia (16).

Surprisingly, no defects in feeding behavior were seen in the Crhr1 knockout mice (17, 18) or CRH knockout mice (19). More recent work demonstrated reduced weight loss in a protein deprivation model in the Crhr1 knockout; however, this appeared to correlate with the reduced glu-
corticoid levels in the animals, and not be due to the absence of central Crhr1. In a paper from Vale and colleagues in this issue, however, the first centrally mediated feeding behavior phenotype is reported for the Crhr1−/− mouse (3). A careful analysis of wild-type and Crhr1−/− mice demonstrated no effect of genotype or provision of corticosterone in the drinking water on weight loss during a fast, or on restoration of normal weight following refeeding. Likewise, there were no effects of genotype on anorexia resulting from a 7-day chronic intracerebroventricular CRH administration. However, the Crhr1−/− mice lacked the early phase acute anorexigenic response (0–1.5 h) to centrally administered urocortin seen in wild-type mice (3). Both wild-type and Crhr1−/− mice exhibited a comparable reduction in feeding at 3–11 h post administration. Control experiments demonstrated that the early phase response in wild-type mice could not be duplicated elevating corticosterone, ruling out the possibility that the lack of response in the Crhr1−/− resulted from an inability to elevate corticosterone in response to central urocortin administration.

Recent studies on the Crhr2−/− mouse are also providing more details on the role of the central CRH pathways in energy homeostasis. The Crhr2−/− mouse has an altered refeeding response to a 24 h fast, consuming only 75% of control values of food in the first 24 h of refeeding (4). Remarkably, the late phase of anorexia resulting from central administration of urocortin appeared to depend on the presence of the Crhr2 (5). Urocortin administration inhibited food intake in wild-type mice for 10 h. In the Crhr2−/−, urocortin inhibited food intake for approximately 4 h but returned to near vehicle treated levels by 6 h. Thus, signaling through the Crhr1 and Crhr2 appears to exert a biphasic control on feeding behavior, with the Crhr1 mediating urocortin’s effects from 2–4 h after treatment, and the Crhr2 receptor mediating the effects from 6–10 h.

These exciting results show clear potential for these two receptors in the regulation of feeding behavior. However, what is the physiological role of central CRH pathways in feeding, and what is the nature of the downstream pathways regulated by CRH? Certainly, the dense expression of CRH and Crhr1 in the amygdala suggests a role for the system in coordinating the effects of stress on feeding behavior; however, other roles, such as effects on gastric emptying may also be important.

Regarding potential downstream effector pathways, it appears that CRH may be interacting with leptin responsive circuits. The CRH-α-helical antagonist appears to block inhibition of feeding mediated by leptin administration (20). Furthermore, MC4-R deficient mice are hypersensitive to the anorectic effects of CRH (21), and the obese AY mice are hypersensitive to the effects of mild stressors on food intake (22), suggesting cross-talk between central melancortin and CRH pathways. Clearly the Crhr1−/− and Crhr2−/− mice will be valuable tools for some time to come in unraveling the complex web of the central CRH system and its actions in the regulation of feeding behavior and energy homeostasis.

References

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