Neuroendocrine aspects of the control of eating in eating disorders

Basic research on the neuroendocrine mechanisms controlling eating has made great advances in recent years. Here we briefly review examples of this progress that highlight points of connection with the disordered control of eating in eating disorders (ED), especially anorexia nervosa (AN) and bulimia nervosa (BN). We consider both peripheral neural and endocrine signals that affect eating and brain processing of these signals.

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Because most eating is organized as meals, the principal questions for eating research are: when are meals initiated, what foods are chosen, and how much is eaten. Individual experience undoubtedly explains much or most of human eating. In addition, however, unlearned physiological processes contribute, and form the basis for much of what is learned. These physiological processes include hunger, satiety and food reward (or, hedonic, palatability) processes.

We emphasize peripheral, sensory signals in the controls of eating because several of them are well understood and because they provide a way into the analysis of brain function. Such signals include palatability stimuli as well as signals arising from gastrointestinal (GI) and metabolic processes. These signals reach the brain via both hormonal and neural pathways. Peripheral controls can be divided into within-meal signals, which affect eating during the same meal that elicits the signal, and across-meal signals, which affect eating in later meals. The slowest feedback signals are adiposity signals, which are eating controls related to body fat content (1, 2). We review evidence that in patients with ED there are disturbances in each of these types of signals.

The normally close relationship between eating behavior and eating-related subjective experiences suggests that these phenomena have common neurological foundations. With respect to ED patients, however, even the more physiological aspects of eating-related subjective experiences are often disturbed. For example, ED patients' ratings of the intensity of hunger and satiety may not show the usual inverse relation (i.e., satiety increases as hunger decreases) and may not change coherently during meals (i.e., hunger may not decrease). Similarly, ratings of food reward are under unusually strong cognitive control. For example, in ED universally preferred flavors such as sweet are often reported to be unpalatable. These sorts of abnormal experiences greatly complicate the interpretation of both biological and psychological data. The application of powerful new methods, such as functional brain imaging, may help in understanding how such disordered feelings arise and what their role is in the disordered eating of ED patients.

Food Reward

Although characterizing the palatability of even simple flavors is difficult in ED patients, some fascinating results have emerged (3, 4). For example, BN patients give lower palatability ratings for fat flavors than healthy controls, but increased ratings for sweet (assuming they have no history of AN; those with previous AN gave lower sweet ratings). In one study, BN patients also gave elevated reports of the non-hedonic intensity of some fats, and this persisted after resolution of symptoms. AN patients also rate fat palatability lower, but usually rate sweet palatability relatively normally. The low fat ratings may persist after weight restoration.

Food hedonics are under potent cognitive control in ED. For example, AN patients ratings of sweet palatability may increase if the food is tasted but not swallowed vs. actually ingested. AN patients also avoid foods perceived to contain sugar, but may consume remarkable quantities of artificial sweetener. Here food volume apparently also plays a role, as fewer AN patients than controls report use of diet beverages, whereas more BN patients than controls do (5).

Functional brain imaging may provide insights about some of these subjective changes. One recent study tested brain activation after tasting a sweet fluid vs. water in women whose physical and behavioral AN symptoms had resolved for > 1 year (6). In comparison to control women, recovered AN women had similar palatability ratings, but reduced activation in two brain areas associated with hedonic processing, the insula and dorsal striatum (in the latter area, animal studies reveal dopaminergic processing of sweet reward). Furthermore, hedonic ratings and brain activation intensity were correlated in controls, but not in recovered AN. Such work seems to hold great potential for the future. Particularly interesting is the possibility that some brain differences are permanent «trait» characteristics of ED, as further discussed below.

Cholecystokinin (CCK)

Hormonal CCK, which is released from the small intestine during meals and acts on CCK-1 receptors in the upper gut to produce a vagal signal to the brain, is without a doubt the best established endocrine control of eating. Administration of doses of CCK mimicking prandial levels reduces meal size in humans, and antagonism of CCK-1 receptors increases meal size in animals and humans (7).

Reduced prandial secretion of CCK is associated with reduced satiety in BN (8). Both abnormalities resolved after binge frequency was reduced. This indicates that these abnormalities are not the initial cause of BN. Nevertheless, it is possible that they facilitate worsening of the disorder once it has begun and impede recovery from it. Surprisingly, plasma CCK may increase

Abstrakt
Neurophysiologische Aspekte des Essverhaltens bei Essstörungen
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In den letzten Jahren hat die Grundlagenforschung auf dem Gebiet der Neuroendokrinologie grosse Fortschritte gemacht. Diese Übersichtsarbeit stellt Beispiele dieser neuen Erkenntnisse vor, die möglicherweise eine Erklärung bieten können für die abnormale Steuerung des Essverhaltens bei Personen, die an Anorexia nervosa und Bulimia nervosa leiden. Die Autoren beschreiben einige der für Hunger und Sättigung verantwortlichen peripheren, neuronalen und endokrinen Signale sowie deren zentrale Verarbeitung und zeigen auf, dass bei essgestörten Patienten häufig die physiologischen Aspekte der essbezogenen subjektiven Erfahrungen gestört sind. Das heisst, dass beispielsweise bei Essgestörten oft die normalerweise übliche inverse Korrelation zwischen Hunger und zunehmender Sättigung während der Nahrungsaufnahme fehlt – die Hungergefühle bleiben also erhalten.
Periphere Hunger- und Sättigungssignale beeinflussen im Gehirn die für die Steuerung des Essverhaltens massgeblichen Neuropeptide und Neurotransmitter und lösen damit entsprechende Verhalten und subjektive Erfahrungen aus. Dazu gehören Hormone wie Cholezystokinin, Ghrelin und Leptin, die – wie entsprechende Untersuchungen gezeigt haben – bei essgestörten Patienten oft anormale Plasmaspiegel aufweisen.
So wird beispielsweise das Peptidhormon Cholezystokinin (CKK), das während der Nahrungsaufnahme im Magen-Darm-Trakt freigesetzt wird und die Entwicklung des Sättigungsgefühls induziert, bei Patienten mit Bulimia nervosa in geringeren Konzentrationen sezerniert, was mit einem deutlich reduzierten Sättigungsgefühl einhergeht. Bei Patienten mit Anorexia nervosa sind die CKK-Spiegel dagegen oft deutlich höher als bei gesunden Kontrollen. Andererseits sind bei Bulimie-Patienten die Plasmaspiegel des «Hungerhormons» Ghrelin erhöht, was die ständigen Hungergefühle und die «Fressanfälle» mindestens zum Teil erklären könnte. Bei Anorexiepatienten finden sich dagegen signifikant reduzierte Leptinspiegel, was sich durch ihr stark reduziertes Körpergewicht erklären lässt. Darüber hinaus beschreiben und bewerten die Autoren verschiedene neu entdeckte Aspekte der zentralen neurophysiologischen Mechanismen, die an Hunger- und Sättigungsregulation beteiligt und bei pathologischem Essverhalten teilweise gestört sind. Gerade in diesem Gebiet sind neue Schlüsselergebnisse zu erwarten, zum Beispiel mithilfe funktioneller Gehirntomografiestudien.

more in AN after meals than in controls, suggesting that a complementary disturbance may occur in AN.

Gastric volume

The stomach is richly innervated with mechanoreceptors that signal the brain via vagal afferents. Although these signals alone do not appear to contribute importantly to eating, they may interact synergistically with other signals to do so. For example, many vagal fibers are sensitive to both gastric volume and plasma CCK, and signaling frequency is increased when both occur together. Decreased gastric emptying has been reported in both AN and BN patients. The significance of this for the control of eating and appetite is unclear. The changes appear to resolve with recovery. BN patients also have an increased gastric capacity, which may contribute (perhaps in part due to decreased gastric emptying and consequently decreased CCK secretion) to the decreased feelings of fullness and satiety during meals and to their larger meal sizes (9).

Ghrelin

Ghrelin is a hormone synthesized predominantly by gastric mucosal cells. It is unique among gut hormones in that it is secreted in response to emptying of the gut. Ghrelin administration stimulates eating, leading to the hypothesis that it is the «hunger hormone». Ghrelin levels decrease rapidly as ingested nutrients enter the duodenum. Ghrelin appears to act on receptors in the arcuate nucleus of the hypothalamus (ARC, see below) and may also serve as an adiposity signal because its basal levels are inversely associated with body fat mass. In some reports fasting ghrelin levels in BN patients were elevated, which could indicate increased hunger and potentially exacerbate binging. Fasting ghrelin levels are also elevated in patients with AN, again consistent with increased hunger, and approach normal with weight gain, as expected of an adiposity signal. Meal-induced decreases in plasma ghrelin levels were similar in AN patients before and after treatment (and weight gain) (10). Thus, because pre-meal ghrelin levels were highest before treatment, postprandial ghrelin levels were negatively associated with body weight, again suggesting increased hunger signaling in AN. In contrast, postprandial reductions in plasma ghrelin were attenuated in BN patients, perhaps as a consequence of their reduced gastric emptying (11). If high post-meal ghrelin levels contribute to an abnormal maintenance of hunger, it could contribute at least permissively to binging.

Leptin

Leptin is an adipocyte hormone that is hypothesized to be an adiposity signal because plasma leptin levels are normally correlated with fat mass and leptin administration reduces eating. In AN patients, plasma leptin levels are markedly reduced, as might be expected from the decrease in the patients' fat mass. Unexpectedly, however, the normal diurnal variation in plasma leptin is reduced and plasma levels of the soluble leptin receptor are increased, further reducing available hormone. Leptin is thought to affect eating mainly by acting in the ARC, so it is also

relevant that the concentration of leptin in the CSF is reduced in AN. Leptin levels recover with weight gain; indeed there may be a relative hyperleptinemia in plasma or CSF leptin, which might lead to resistance to further weight gain (12). Finally, in BN patients plasma leptin levels have been reported to be inversely correlated with the illness duration and frequency of binging.

Central Processing

Novel molecular genetic methods have led to the discovery of many aspects of the central neuroendocrine (i.e, chemical signaling) mechanisms of eating, especially in the hypothalamus. Two chemically distinct neuronal groups in the ARC contribute to the control of eating. One includes neurons that express pro-opiomelanocortin (POMC), the precursor of α-melanocyte stimulating hormone (α-MSH), which decreases eating in animals. The other group expresses neuropeptide Y (NPY) and agouti-related peptide (AgRP), both of which stimulate eating in animals. The two groups act in concert: leptin and ghrelin act in part by activating receptors in both groups; NPY/AgRP neurons exert inhibitory effects on the POMC neurons; both populations receive ascending inputs from the hindbrain, including e.g. serotonergic (5HT) and dopaminergic (DA) inputs; and both project to several other hypothalamic areas, in each of which additional signaling molecules are involved.

One of the few techniques available to study brain neuroendocrine function in humans is to measure neurochemicals in the cerebral spinal fluid (CSF). Changes in CSF levels of several ARC neuropeptides have been investigated in ED. For example, CSF NPY levels are increased in AN patients, whereas CSF levels of POMC derived peptides are decreased in AN patients. Both normalize after weight recovery (13). CSF levels of the 5HT metabolite 5-hydroxyindoleacetic acid were reduced in AN patients, but were elevated after recovery in both AN or BN patients, suggesting that disturbed 5HT signaling might be part of the cause of these disorders. More recently, functional brain imaging has confirmed preexisting or persistent changes in 5HT receptor function that suggest decreased signaling specifically in forebrain areas linked to hedonics and mood in both ill and recovered AN and BN patients (14). Both CSF and imaging studies also indicate similar changes in DA signaling, also consistent with alterations in food hedonics.

Discussion

We reviewed several examples associating ED with changes in peripheral and central neuroendocrine controls of eating. Some of these changes, so-called trait effects, persist after recovery of at least the core behavioral and physical diagnostic criteria (DC), suggesting that these changes may contribute to the initial pathogenesis of the ED. None is alone sufficient, however, as they exist in the absence of most of the DC. Additionally, especially subjective components of ED resolve very slowly or not at all, so these trait changes could contribute to the maintenance of these aspects. Other neuroendocrine changes disappear with recovery (so-called state changes). It is premature, however, to dismiss the importance of these in ED. Rather, they may contribute causally to pathologies that develop regularly in the course of these progressive disorders. Thus, treatment of such pathologies may facilitate recovery.

We emphasize that this is a rapidly evolving research area, and that our review is incomplete. We do not treat, for example, genetic studies that have revealed polymorphisms in genes related to neuroendocrine function (15). Nor do we treat sex differences in the neuroendocrinology of eating (16), although these may well be related to the marked sex differences in the incidence of ED. Finally, as neuroendocrinological research continues to be done mainly in animals, it is important to note that a variety of powerful animal models are providing translational approaches to the understanding of ED (17). ■

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