

FEATURE REVIEW

Approaching the shared biology of obesity and depression: the stress axis as the locus of gene–environment interactions

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Obesity and depression are serious public health problems and also constitute cardiovascular disease risk factors. Research organizations have called for efforts to explore the interrelationship between obesity and depression. A useful starting point is the fact that in both disorders there is dysregulation of stress systems. We review molecular and clinical evidence indicating that the mediators of the stress response are a key locus for gene–environment interactions in the shared biology of depression and obesity. Scientific milestones include translational paradigms such as mice knockouts, imaging and pharmacogenomic approaches that can identify new therapeutic strategies for those burdened by these two afflictions of contemporary civilization. Perspectives for the future are promising. Our ability to dissect the underpinnings of common and complex diseases with shared substrates will be greatly enhanced by the Genes and Environment Initiative, the emerging Large Scale Studies of Genes and Environment in Common Disease, and the UK Biobank Project.

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Introduction

The study of common and complex disorders has gained particular impetus with the recent emergence of plans for large-scale studies of gene–environmental interactions, including the new Genes and Environment Initiative. The National Human Genome Research Institute (NHGRI/NIH) plans to study the genome and the environment of over 500 000 Americans through the proposed Large Scale Studies of Genes and Environment in Common Disease aimed at unraveling the fundamental mechanisms underlying common and complex disorders.¹ There is in current plan for the 2007 NIH budget an allocation of 68 million dollars to fund the Genes and Environment Initiative. In addition, a new Request for Applications has been recently issued by the National Human Genome Research Institute (NHGRI) for ‘Public Consultation to Inform the Design of Possible Large Scale Studies of Genes and Environment in Common Disease’. It was also recently announced that British

doctors have started recruiting 500 000 subjects for the UK Biobank project. These initiatives are set to completely revolutionize translational research on common and complex diseases, including obesity and depression. The issue that the scientific community will face – as exemplified by these two diseases – is whether such conditions should be studied jointly or in isolation. In other words, is it time to use the emerging tools of the Genes and Environment Initiative, the emerging Large Scale Studies of Genes and Environment in Common Disease, and the UK Biobank project to investigate obesity and depression as representing a spectrum of underlying shared environmental and genetic factors, or is it a case of two completely independent disorders that happen to occur in the same individual by chance, and which should therefore be best studied independently?

Our goal in this article is to advance the concept that diseases such as these may actually share key pathophysiological elements at the interface of gene–environment interactions that justify their study in a joint manner. We propose here that the hypothalamic–pituitary–adrenal (HPA) axis is a model system for the mediation of gene–environment interactions, and that dysregulation of this stress-responsive system is a key element in the shared biology of obesity and depression. The Genes and Environment Initiative, the emerging Large Scale Studies of Genes and Environment in Common Disease proposed by Francis Collins and the NIH, and the UK Biobank

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project will give us the tools to test these ideas in ways never possible before. We will provide a brief overview of both diseases, discuss how both involve HPA dysregulation, and comment on opportunities presented by large-scale population studies to definitively address old questions of nature-versus-nature, shared biology or epiphenomenon, joint etiology or coincidence, and integrated treatments or isolated approaches.

The scope of the problem: obesity and depression

Over the course of the past decade, obesity has become a global epidemic with two grim potential outcomes – obesity can completely break the financial basis of health care delivery systems due to the rise in morbidity. Additionally, all gains in life expectancy achieved in recent decades by increased standards of living, public health, and medical progress will likely be offset by the adverse health consequences of obesity. As individuals, we have progressively gained weight during the past several decades, but the exponential rate of weight gain in the population has only been fully appreciated in recent years (Table 1).

At the same time, the full scope of the immense medical, social, and economic burden of another chronic disease, namely major depression, has only become apparent in recent decades. A joint study conducted by the World Bank and the World Health Organization showed that depression is the second largest cause of disease burden in developed countries and the fourth in developing countries. Current estimates hold that depression will be the second most important cause of disease burden worldwide in the next twenty years. Gerald Klerman, a pioneer in the field of psychiatric research, perceptively named the current era as the ‘age of melancholy’.²

Table 1 Interrelationship between depression and obesity

- (1) Depression and obesity frequently co-exist.
- (2) Both disorders are substantial health problems worldwide.
- (3) Obesity can follow depression that occurred earlier in life.
- (4) Depressed mood can be a side effect of obesity treatments.
- (5) Weight gain and obesity can be a side effect of antidepressant treatments.
- (6) Several neuropeptidergic and neurotransmitter systems involving molecules as CRH, NPY, serotonin, and norepinephrine are involved in the regulation of mood as well as body weight.
- (7) Depression and obesity are important risk factors for cardiovascular disease, potentially causing or worsening the metabolic syndrome.
- (8) Genetic polymorphisms may underlie the predisposition both to cardiovascular disease and to depression.
- (9) Drugs used in depression studies predominantly affect either serotonin or norepinephrine in the CNS.
- (10) Obesity treatment includes central inhibition of both serotonin and norepinephrine reuptake.

There is a rate of 60% for overweight and 15% for a lifetime diagnosis of major depression in the American population. We will review the evidence for a possible basis for the overlap in these conditions. Epidemiological surveys in several countries have gathered ample evidence that adolescents with depression are at a greater risk of becoming obese, and obese individuals are more likely to develop depression as non-obese individuals.³ Why is that? Both disorders are thought to be the result of disrupted interactions between genes and the environment, so which one is the culprit here – nature, nurture... or both?

Let us examine the environment. Our current society structure is more complex and connected. We have undergone fundamental and systematic changes in lifestyle, such as eating behavior, sedentary living conditions, globalization and migration. All of those changes could influence the activation and programming of the hormonal stress axis during early life. Early events are now proven to alter the ability of the body to respond to stress throughout the lifetime. Events happening in adulthood, from major to minor, also have an impact on our biology. As a small example, even the supposedly harmless buzzes and jingles from our personal electronic gadgets appear to play a role in increasing our stress response and activating the cardiovascular system.⁴ Global tourism is on the rise, as are commuting and migration (Figure 1a). Mobility is seen as an essential personal asset in our globalized environment. Emerging evidence shows that moving from one society to another bears an increased risk for both obesity and mood disorder associated with elevated stress hormones.⁵ Indeed, the alarmingly high rates of both disorders points to a connection between the two and that realization has triggered major funding agencies in the US and Europe to request research projects to explain the relationship between depression and obesity in modern society.⁶

The HPA axis as a distal mediator of gene–environment interactions

Stress is conveyed in the body in many ways. The two most studied classical systems include the interconnected norepinephrine system and the stress-related neuroendocrine system known as the HPA axis, which seems to play a dominant role in the shared biology of depression and obesity. Even with the ever-increasing identification of myriad neurotransmitters, neuropeptides, cytokines, receptor molecules, enzyme systems, binding proteins and transcription factors involved in both disorders, all of these factors share one common denominator – their contribution to the modulation of the HPA axis. Numerous studies support the dysregulation of the HPA axis in both obesity and depression, and both anti-obesity drugs and antidepressants regulate the HPA axis. Contrary to expectation, the strikingly integrative role of the HPA axis shared by common and complex disorders

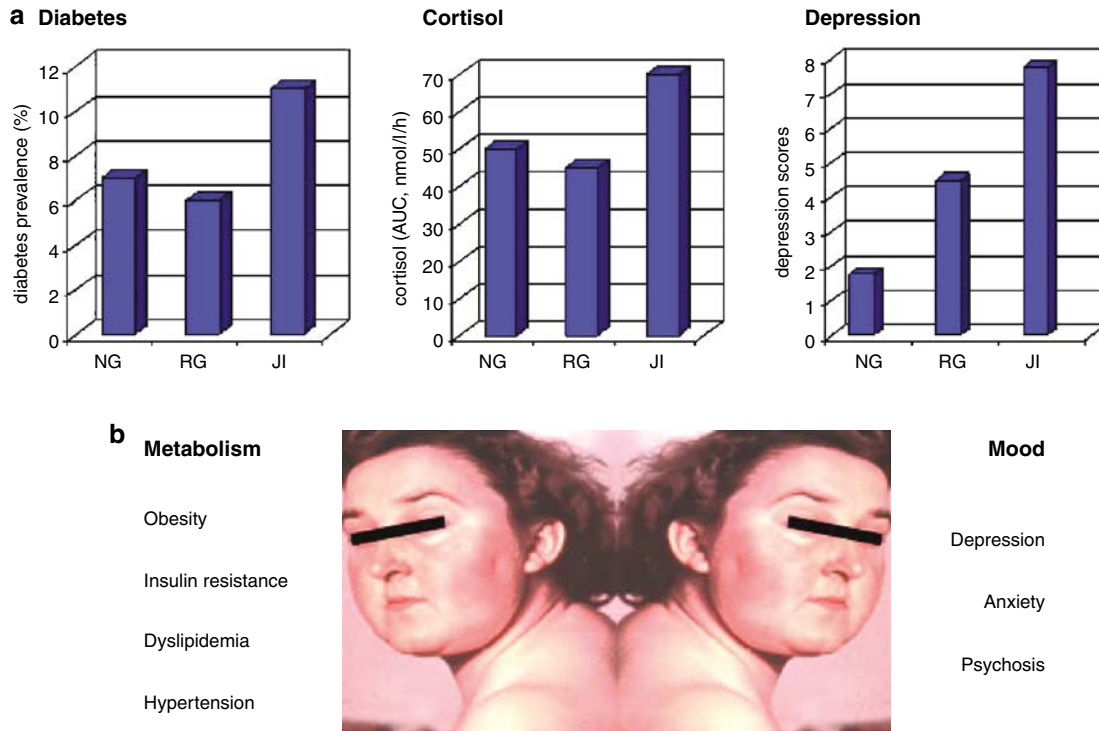


Figure 1 Modern lifestyles involve traveling and migration. Immigrant groups to Germany (NG: native German; JI: post-Soviet immigrants with Jewish family background; RG: post-Soviet immigrants with Russian-German family background) have an increased prevalence of diabetes and depression associated with elevated free cortisol levels (a)² Cushing's syndrome is a classical paradigm for the shared biology of obesity and depression (b).

has been under-explored. There is a unique model of persistent, tumor-driven hyperactivity of the HPA axis, Cushing's disease and revealingly the clinical presentation of this natural model of HPA dysregulation includes both obesity and depression.

The issues in this field are the following: How does one go beyond descriptions of existing diseases towards the identification of shared pathophysiological mechanisms that connect obesity and major depression? Are these mechanisms related to the etiology or to the metabolic consequences of these disorders? Is this current surge in the rates of obesity and depression related to the combination of ever-increasing stress levels in modern society in combination with the oversupply of low-cost, calorie-dense foods? A useful way to address this conundrum is to start by examining a classical clinical paradigm.

Cushing's syndrome – a model disease of sustained HPA axis dysregulation causing both depression and obesity

Cushing's syndrome involves cortisol excess resulting from endogenous hyperactivation of the hypothalamic pituitary adrenal (HPA) axis or treatment with corticosteroids. Like the metabolic syndrome, insulin resistance is increased in Cushing's syndrome, as are blood cholesterol levels and blood pressure. These patients often show mood-related symptoms.

Disordered mood in Cushing's syndrome very often consists of a full-blown diagnosis of major depression, which can be the initial clinical presentation of the overall syndrome and the reason some patients seek medical attention;⁷ patients' disordered mood may also have features of anxiety or psychosis (Figure 1b). Interestingly, such psychiatric presentations can be successfully treated by removal of the pituitary or adrenal tumors or by corticosteroid production inhibitors such as ketoconazol, metyrapone, and aminoglutethimide, rather than by use of classical antidepressants. These findings clearly suggest a connection between obesity and depression mediated by the HPA axis in Cushing's syndrome. In contrast, the degree of HPA axis dysregulation in the majority of patients with obesity or depression unrelated to Cushing's syndrome appears to be less clear at the present time.

HPA axis dysregulation in obesity and depression

It is well established that the exogenous administration of glucocorticoids results in metabolic changes typical of obesity, such as hyperinsulinemia, beta-cell hyperplasia, and insulin resistance.⁸ Furthermore, stroma cells in human adipose tissue develop the characteristic features of adipocytes after glucocorticoid stimulation.⁹ Surgical removal of the adrenal can, to some extent, normalize or prevent weight gain

and metabolic changes in obesity,^{10–12} and glucocorticoid treatment in animals after removal of the adrenal glands results in the reappearance of the obesity syndrome.¹³ These facts highlight the crucial role of adrenal steroids in the development of obesity and insulin resistance, but do not conclusively establish a causative role of a hyperactive HPA axis in obesity.

Hypercortisolism which is common in genetically obese *fa/fa* rats and *db/db* and *ob/ob* mice, has also been reported in obese humans with insulin resistance.^{14,15} However, studies have also suggested that elevated cortisol levels in obese individuals are related to increased body mass, increased turnover and/or changes in cortisol-binding globulin.¹⁶ A blunted long-term response of adrenal glucocorticoid release has been reported in obesity.¹⁷ There is a clear correlation between the nutritional status in mammals and stress hormone regulation. The activity of the HPA axis is modulated by factors involved in weight regulation, although there is controversy on whether weight gain results from early activation of the HPA axis or from comfort eating as a way to contain and control stress.¹⁵ HPA axis dysregulation may contribute to the current epidemic increase of obesity rates.

Similarly, there is extensive evidence for HPA axis dysregulation in depression. Corticotropin-releasing hormone (CRH), a hypothalamic peptide, has been identified as the key regulator in control of HPA axis function.^{18,19} Several lines of evidence converge to strongly suggest a role for dysregulated central CRH function in the biology of depression.

Compared to healthy controls, patients with major depression have a blunted ACTH response, but normal cortisol response to CRH stimulation tests.^{20–22} This blunted ACTH response could be caused by the downregulation of pituitary CRH receptors due to chronic hypersecretion in depressed persons.²³ This hypothesis correlates with findings in post-mortem studies on suicide victims that have revealed decreased CRH receptor density in the frontal cortex.²⁴ Also, compared to healthy subjects, depressed patients have shown enhanced ACTH and cortisol secretion compared to healthy subjects in response to CRH stimulation preceded by the administration of 1 mg oral dexamethasone before 100 µg CRH stimulation the following day.²⁵ Interestingly, asymptomatic first-degree relatives of depressed patients also showed slightly abnormal levels that endured over time in this test. This might indicate a heritable cause for HPA axis dysregulation.^{26,27} Further, it could be shown that the CRH levels in pontine brain areas of suicide victims with major depression in their medical history were up to 45% higher than in controls.²⁸ In living depressed patients there is significant increase in CRH concentrations in cerebrospinal fluid; this represents another line of evidence for the connection of HPA dysregulation and major depression.^{29,30}

The resolution of all previously dysregulated HPA axis parameters including hypercortisolemia, blunted

ACTH response to CRH, hypersecretion of CRH, and adrenal hypertrophy following successful antidepressant treatment provides independent support for the involvement of the HPA axis in depression.^{31–33} Antidepressant treatment of rats both at basal conditions and during chronic stress results in downregulation of CRH gene expression in the paraventricular nucleus (PVN) of the hypothalamus.^{34,35} Moreover, treatment of healthy individuals with the classic tricyclic antidepressant, imipramine, results in endocrine evidence of the HPA axis.³⁶ Taken together these results strongly indicate that HPA downregulation is a direct effect of antidepressant treatment, not just an epiphenomenon of stress that might be ameliorated as depression improves. Finally, pharmacogenomic evidence suggests a role for genetic variants in elements of the HPA axis, including the CRH receptor type 1 (CRHR1) in the response to antidepressants.^{37,38}

Given the abundant data supporting a role for CRH dysregulation in depression, CRH receptor antagonists have been developed as a new strategy for pharmacotherapy of depression. Such drugs have already been tested in clinical trials.

Features of obesity and depression in animal models with overexpression or gene deletion at different levels of the HPA axis

Is there a way to dissect the complexity of the neuroendocrine stress system? It is important to understand metabolic and behavioral features of several animal models created recently, as they may help us identify the key players involved in the shared biology of obesity and depression.

The hypothalamus controls the endocrine stress axis that produces CRH, which then controls pituitary ACTH and adrenal glucocorticoid secretion (Figure 2a, b). Glucocorticoids act through receptors on peripheral target cells and are metabolized, activated or deactivated by intracellular enzymes and binding globulins. Hormones, receptors, transcription factors, binding proteins or enzymes have been overexpressed or deleted to analyze their function in the entire organism at each level. Here we will describe some of the most relevant models affecting HPA function, summarizing their metabolic and behavioral changes.

Starting at the level of the hypothalamus, increased food intake, weight gain, and development of increased insulin resistance have been demonstrated in mice with corticotropin-releasing hormone (CRH) overexpression.^{39,40} Interestingly, these mice also displayed increased anxiety levels with impaired stress coping and learning potential^{41,42} (Figure 2). CRH acts through two receptors (CRHR1 and CRHR2) that are expressed in various tissues. In mice lacking corticotropin-releasing hormone receptor (CRHR1^{-/-}), food intake seems to be time-dependent, with decreased appetite in the late phase post-stress; on the other hand, CRHR2^{-/-} mice show decreased appetite in early post-stress phase.^{43,44} There is

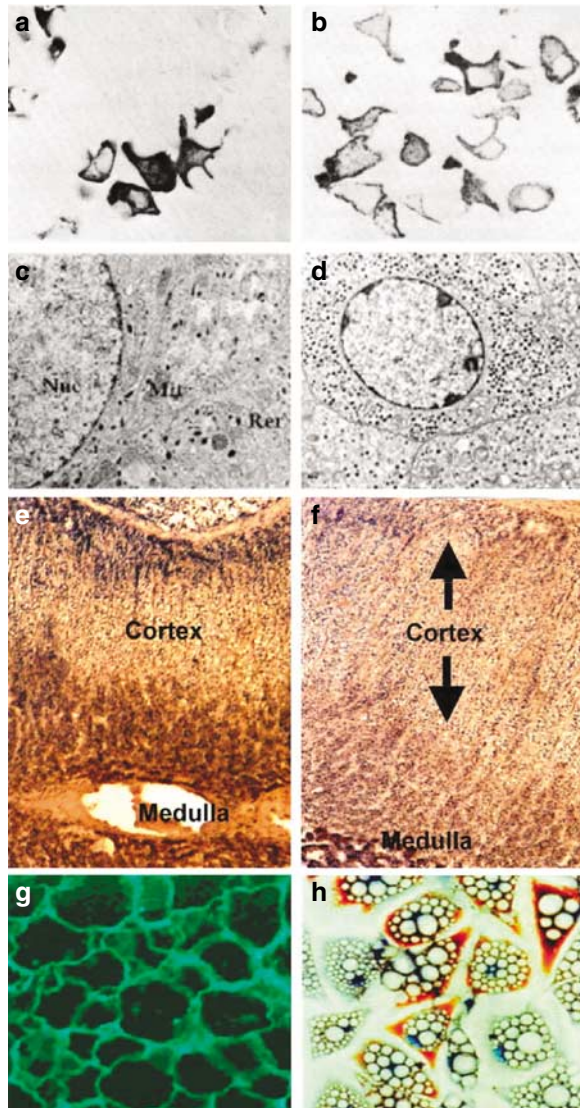


Figure 2 Corticotropin cells from rat pituitary stained with an antibody against ACTH (a, b). During stress, CRH induces rapid marginalization of ACTH around cell membranes before release into the systemic circulation. CRH system deletion involves not only impairment of HPA function itself, but also alterations in the neuroendocrine cell system. This leads to significant depletion in new secretory granules containing catecholamines and neuropeptides in chromaffin cells in CRH receptor knockout mice (c) compared to wild-type animals (d).¹⁰⁷ There is striking hyperplasia in depression patients' adrenals¹⁰⁸ (f) compared to nondepressed individuals (e). Human fat cells express CRH receptors¹⁰⁹ (green immunofluorescence) (g) and cytokines such as IL6 (brown immunostaining) (h). These are major regulators of HPA axis function, and have been implicated in the shared biology of depression and obesity.

evidence that anxiety levels are clearly reduced in CRHR1^{-/-} mice, while CRHR2^{-/-} mice show increased anxiety levels.^{45–47}

At the level of the pituitary, striking behavioral changes have been described with the disruption of

the proopiomelanocortin (POMC) gene, which encodes several products including β -endorphin and ACTH. POMC-knockout mice (POMC^{-/-}) show hyperphagia – excessive eating – with weight gain.⁴⁸ Five receptors have been identified for melanocortins, a group of pituitary peptide products. After administration of MCR4 receptor antagonists, animals display reduced anxiety levels, while stress coping and pain reduction are enhanced.⁴⁹ Mice without melanocortin-4 receptors (MCR4) show increased food intake along with weight gain and increased insulin resistance. Metabolic and behavioral changes seen in these animals are not only a result of defects in the HPA axis, but are also due to complex alterations in the neurobiology of these animals. Gene deletions for CRH receptors, transcription factors (such as steroidogenic factors), and steroidogenic enzymes (such as 21-hydroxylase) that play a crucial role in the release and regulation of glucocorticoids also affect the release and regulation of catecholamines and neuropeptides.^{50,51} Those different transgenic animals display conspicuous alterations in ultrastructure (Figure 2c, d) and hormone expression in various neuroendocrine cell systems. Impairment of catecholamine and neuropeptide release and regulation therefore appear to contribute to the metabolic and behavioral symptoms seen in animal models and patients with altered HPA axis function.⁵²

Finally, not only central components of the HPA axis are vital to the development of abdominal obesity and associated disorders such as depression,⁵³ but tissue-specific concentrations of cortisol mediated by enzymes such as 11 β -hydroxydehydrogenase 1 (11 β -HSD1) and 11 β -hydroxydehydrogenase 2 (11 β -HSD2) also play a crucial role in the development of the metabolic syndrome and glucocorticoid-associated CNS disorders.⁵⁴

11 β -HSD1 is a bidirectional enzyme that regenerates active corticosterone, whereas 11 β -HSD2 deactivates corticosterone.^{55,56} Transgenic mice that overproduce 11 β -HSD1 show symptoms of Cushing's syndrome – such as increased food intake, weight gain and behavioral changes,^{57–59} and also exhibit increased neurotoxicity.⁶⁰ Mice that overproduce 11 β -HSD2 show decreased food intake and they also have improved glucose tolerance and insulin sensitivity.^{61,62} The brain seems to be protected when there is efficient deactivation of cortisol.⁶³

In addition to the effects of the enzymes described above, glucocorticoid receptor function has a major impact on the effects of glucocorticoids. Genetic dissection of corticosteroid receptor function in mice has given us new insights into the role of glucocorticoids.⁶⁴ Inactivation of glucocorticoid receptors in mouse liver cells leads to hypoglycemia; moreover, hyperglycemia is reduced in streptozotocin-induced diabetes. These findings show the essential role of the glucocorticoid receptor in glucose metabolism in the liver, and offer new treatment approaches for diabetic hyperglycemia with glucocorticoid receptor antagonists.⁶⁵

Similarly, increased glucocorticoid receptor expression in hepatocytes may contribute to the phenotype of type 2 diabetes in *db/db* mice.⁶⁶ Finally, aged transgenic mice that display increased sensitivity to glucocorticoids in pancreatic beta-cells develop diabetes.⁶⁷

These results can be relevant for humans – a recent study has shown that a polymorphism in the glucocorticoid receptor gene is associated with decreased sensitivity to glucocorticoids and decreased insulin and cholesterol levels *in vivo*.⁶⁸ A single nucleotide polymorphism on exon 2 of the glucocorticoid receptor gene is associated with increased sensitivity to glucocorticoids and obesity in non-diabetic subjects.⁶⁹ Mice with genetically altered overexpression of the glucocorticoid receptor showed reduced helplessness after stress exposure and enhanced HPA system feedback regulation, whereas mice heterozygous for the glucocorticoid receptor *GR*^{+/-} exhibit normal baseline behavior, but show increased helplessness after stress exposure.⁷⁰

In similar fashion, patients with major depression show glucocorticoid receptor impairment with decreased glucocorticoid sensitivity,⁷¹ which is compatible with the hypercortisolemia described in depression.⁷² It is noteworthy that deficits in the negative feedback of the HPA axis caused by impairment in glucocorticoid receptor function due to depression are resolved after treatment with antidepressants.⁷³ These findings indicate that disturbances at every level of the HPA axis are relevant for both obesity and depression.

The HPA axis as a key locus for gene environment interactions in the phenotypes of obesity and depression

Numerous neuropeptides, neurotransmitters, cytokines and adipokines, such as agouti-related protein, CART, ghrelin, adiponectin, NPY, ANP, melanocortin, leptin, orexin, serotonin and interleukin 6 (IL-6) (Figure 2g, h), play a crucial role in HPA axis regulation, and may be involved in the regulation of both obesity and mood disorders (Figure 3). A detailed review of the key role the HPA axis plays in the crosstalk of all these factors is beyond the scope of this article, but we will briefly cover the most relevant ones.

The adipokine leptin is the principal anorexigenic substance that modulates the HPA axis both in the brain and the periphery. Leptin concentrations are elevated in obese patients; recombinant human leptin has been used for treatment in genetic disorders such as lipodystrophy and leptin deficiency.^{74,75} Plasma leptin concentrations are subject to pulsatile and diurnal variation; a blunted nocturnal rise in leptin levels correlates with weight gain.⁷⁶ Leptin itself acts directly on the adrenal gland and suppresses cortisol production.⁷⁷ These findings suggest that increased leptin release cannot suppress cortisol secretion sufficiently, and weight gain occurs due to elevated cortisol levels.

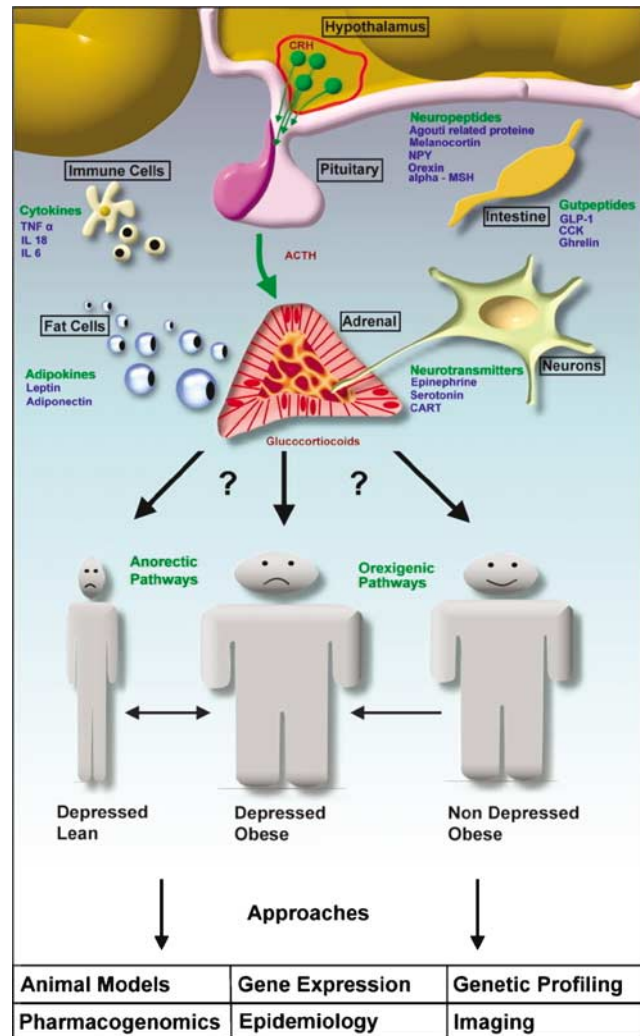


Figure 3 This diagram shows groups of cytokines, neuropeptides and neurotransmitters implicated in both obesity and depression. These substances interact with the HPA axis. Owing to early biological programming, chronic stress and differential gene expression, individuals may develop isolated or combined forms of depression and obesity. Translational research strategies and large studies of gene-environment interactions should enable us to unravel the mechanisms involved in this relationship.

Among the members of the neuropeptide group, orexin is a classical appetite stimulant that is also surprisingly linked to narcolepsy, a sleep-related disorder. Alterations in sleep are among the diagnostic features of major depression. There are reduced numbers and size of hypothalamic orexin neurons in human depression and in animal depression models.^{78,79} While orexin activates catecholamines and endocannabinoids, catecholamines and serotonin exert a negative feedback on the orexin system.^{80,81} These findings suggest a central role for the orexin systems in the shared biology of feeding and mood disorders.

The classical neurotransmitter serotonin modulates various body functions including sleep, weight and

mood via the HPA axis. Among the neurotransmitters, the importance of the role of serotonin interfacing with the HPA axis in both syndromes has emerged. Serotonin-blocking agents have been associated with weight increase; several selective serotonin re-uptake inhibitor (SSRI) antidepressants have also been used in weight reduction.

IL-6, an inflammatory cytokine and a strong HPA axis activator, has been found in abundant amounts in fat cells, and is likely involved in the fat metabolism.⁸² Increased IL-6 levels are one of the features of metabolic syndrome; both IL-6 and local cortisol production support the stress-mediated complications of obesity, including diabetes and cardiovascular events. Significant increases in IL-6 levels are also reportedly involved in major depression.⁸³ Compared to healthy controls, depressed patients show highly elevated IL-6 levels and reversed circadian rhythmicity, with levels peaking at the daytime, even in the absence of overt hypercortisolism. Activation of the immune system by pro-inflammatory mediators is a feature of both the metabolic syndrome and affective disorders. This suggests that cytokines such as IL-6 may be a shared element in the biology of both syndromes.

The HPA axis as a mediator of antidepressant and antiobesity treatment

Several antiobesity and antidepressant drugs affect HPA axis function. Rimonabant, an antiobesity drug, increases CRH levels⁸⁴ while decreasing ACTH and cortisol at low doses, but increases both at high doses.⁸⁵ Traditional antidepressants such as fluoxetine, citalopram and imipramine all decrease CRH, ACTH and cortisol levels.^{86–89} A slight rise in CRH may be detected immediately after starting treatment with citalopram, which turns into a decrease after continuous administration.⁹⁰ We have demonstrated that leptin replacement therapy in leptin-deficient adults with established pathological obesity results not only in profound weight loss and behavioral effects, but also in changes on the endocrine stress axis.⁹¹ These findings show that both antiobesity and antidepressive medication decrease the activation of the HPA axis to a great extent, leading to a reduction in ACTH and cortisol. Although there is striking evidence that alterations on the HPA axis occur in obesity and depression, establishing the clinical significance of these findings still requires considerable work: the traditional two-dimensional concept of either activation or suppression of the HPA axis may fall far short in addressing the involvement of this system in depression and obesity.

Future perspectives and challenges

Both depression and obesity may feature hyperactivation of the HPA axis with hypercortisolemia, and in many cases, they do. However, this does not mean that a simple approach involving antiglucocorticoid

therapy will be sufficient treatment for either or both disorders, or for effectively preventing these disorders.

Depressed overeaters show lower cerebrospinal CRH and catecholamine concentrations as well as reduced HPA activity. Comfort food ingestion that causes abdominal obesity decreases CRH mRNA expression in the rat hypothalamus.⁹² Therefore, comfort food eating may indeed be an adaptive mechanism to reduce activity in the chronic stress response network in modern society with its ever-increasing stressful external stimuli.

There are, however, forms of depression and obesity that do not reveal any abnormalities in hormone function tests used to characterize HPA function.

A major benefit from the Genes and Environment Initiative, the emerging Large Scale Studies of Genes and Environment in Common Disease, and the UK Biobank project will be – thanks to the large numbers of subjects studied – the ability to define the time course and familial dispositions of different groups much more closely. Why are some patients with obesity resistant to developing symptoms of depression, and why do some depressed patients remain lean – or are even pathologically underweight? Moreover, why does antidepressant suppression of HPA activity cause further weight gain in a certain group of patients with mood disorders and weight loss in others? All these seemingly conflicting findings may be reconciled in a highly comprehensive study of genetic and environmental factors that regulate of HPA axis as discussed in this review. This will be possible under the auspices of the Genes and Environment Initiative and the emerging Large Scale Studies of Genes and Environment in Common Disease, in which approximately 75 000 thousands of depressed patients and over 300 000 overweight or obese subjects will be systematically studied at the genetic and environmental levels. The recently launched UK Biobank project will also provide another invaluable resource for further progress.

At the translational level, increasing evidence suggests roles for each single receptor system on the HPA axis in the control of food intake, energy expenditure and behavior. Dissecting these systems by gene deletion specific to time and site in animal models will also contribute to finding out the mechanisms that lead to different clinical phenotypes.

Functional genomics provides a promising new platform for elucidating variability according to hereditary differences. Pharmacogenomics is a powerful approach that promises help in predicting an individual's response to antidepressants.⁹³ At the same time, impressive progress has been made in the field of genetics of obesity, localizing major obesity loci on various chromosomes in humans.⁹⁴ Potential targets already have been identified in factors and receptors in the endocrine stress system, including melanocortin 4 receptor as well as catecholamine and serotonin transporter genes;^{95–97} however,

a more systematic approach screening for potential susceptibility genes in the entire HPA axis would be of great value (Figure 3).

Unraveling the shared biology of obesity and depression will not only be based on molecular and biochemical analysis, but will most likely also involve the power of modern imaging techniques. Analyzing brain images by computer may transform current practice in diagnosing and comparing mental disorders,⁹⁸ particularly focusing on brain regions involved in long-term memory and emotion, such as hippocampus and amygdala.⁹⁹ One study has already suggested that prenatal glucocorticoid exposure programs behavioral inhibition due to increased corticotropin-releasing hormone levels in the amygdala, along with impaired coping via altered corticosteroid receptor levels in the hippocampus.¹⁰⁰

Patients with hypercortisolism frequently develop brain atrophy, memory impairment and depression with a reduction in amygdala size;¹⁰¹ children with classic congenital adrenal hyperplasia show decreased amygdala volume.¹⁰² Similarly, obese patients also show brain atrophy.¹⁰³ Critical sites for weight gain are located in the amygdala; minor lesions centered on the posterodorsal region of the medial amygdala result in excessive weight gains in rats.¹⁰⁴ Functional magnetic resonance scanning has shown increased activation of visual food stimuli in the amygdala¹⁰⁵ in obese individuals.

Functional imaging studies have also revealed increased amygdala activity in depression and decreased amygdala activity on remission or antidepressant treatment.¹⁰⁶ The integration of endocrine stress activation, eating behavior and mood-related disorders findings to upcoming imaging studies may provide crucial novel information.

Altogether, there is unequivocal evidence for a key role of the HPA axis in both obesity and depression. Future research designs should focus on a multidimensional approach when analyzing this key integrative system. Shared biology does not mean identical or uniform mechanisms of disease, but rather systems that interact, sometimes augmenting one another, and at other times canceling each other out. Diagnostic strategies should consider the overlap between biological systems, and ought to allow for the characterization of subgroups of these disorders that have not been yet identified. We look forward to the proposed and hopefully upcoming large-scale population studies on gene-environment interactions as a way to dissect the shared biology of common and complex diseases whose biology may at least in part overlap, such as depression and obesity.

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