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Review

A Metabolic Perspective on Reward Abnormalities in Anorexia Nervosa

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Anorexia nervosa (AN) is the psychiatric disorder with the highest mortality rate; however, the mechanisms responsible for its pathogenesis remain largely unknown. Large-scale genome-wide association studies (GWAS) have identified genetic loci associated with metabolic features in AN. Metabolic alterations that occur in AN have been mostly considered as consequences of the chronic undernutrition state but until recently have not been linked to the etiology of the disorder. We review the molecular basis of AN based on human genetics, with an emphasis on the molecular components controlling energy homeostasis, highlight the main metabolic and endocrine alterations occurring in AN, and decipher the possible connection between metabolic factors and abnormalities of reward processes that are central in AN.

Historical Concepts in Anorexia Nervosa

Anorexia nervosa (AN) is a life-threatening mental illness affecting mostly young women in the absence of any unambiguous pathophysiological explanation. The disorder is characterized by body image disturbances and compulsive food restriction that is often associated with over-exercising, and that results in an abnormally low body weight (Box 1). There is a general belief that AN corresponds to a recent social phenomenon related to obsessive slimming among young girls, where sociocultural influence, such as the recent promotion of thinness for women, may be a trigger. However, food avoidance by young girls and women is a very old story. Skrabanek (1983) described three main periods in the history of AN. Between the 5th and the 13th centuries, food avoidance was described in theological literature and interpreted as a 'supranatural manifestation' [1]. From the 16th to the 18th centuries, medical descriptions insisted on a phenomenon called anorexia mirabilis or inedia prodigiosa. This period of 'holy anorexics' has been retrospectively described as food avoidance associated with an ascetic state, the ability to perform severe self-discipline, and abstention for different behaviors or pleasures, a route to God. In the 19th century, Marcé, a French alienist (psychiatrist), provided the first clinical description of AN (1859): a 'form of hypochondriacal delirium occurring consecutive to dyspepsia, and characterized by refusal of food' [2]. Later, Lasègue and Gull introduced the concept of AN as a clinical entity [3]. In 1873, Lasègue included for the first time 'excessive physical activity' and Gull coined the term 'anorexia nervosa'. For Marcé, AN was not a somatic disease but a mental disorder. He mentioned the integrity of stomach function as a proof of normal somatic activity. At the beginning of the 20th century, AN was believed, alternatively, to be a psychological or **endocrine** (see Glossary) disorder. As an example, Simmonds suggested in 1914 that a pituitary insufficiency was the cause of the disorder, whereas Berkman, in 1930, proposed that signs of hypopituitarism were only a consequence of starvation [4,5]. In 1938, Farquharson described AN as a 'metabolic disorder of psychological origin' [6]. With the emergence of psychoanalysis, the metabolic manifestations of the disorder were considered to be an epiphenomenon. Until recently this disorder was considered to be purely psychiatric disorder, neglecting all the metabolic and endocrine manifestations as possible contributing mechanisms of the disorder. The different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have helped to define the clinical symptoms of this disorder more precisely (Box 1). DSM-V does not integrate an objective criterion of excessive physical activity, a behavior which has been linked to poor outcome.

Recently, a novel research framework, the 2009 Research Domain Criteria (RDoC), promoted by the National Institute of Mental Health, suggested a new approach to the investigation of mental disorders. This explores the basic dimensions of functioning that span the full range of human behavior from normal to abnormal. It aims to understand illness in terms of varying degrees of dysfunction in general psychological/biological systems. Dimensions can be included in a post-diagnostic era

Highlights

AN is a complex and multifactorial psychiatric disorder characterized by compulsive self-restriction of food intake often associated with hyperactivity, leading to life-threatening consequences. It encompasses social, psychological, and also biological and genetic/epigenetic factors.

Although AN is primarily considered to be a psychiatric disorder, it has also important metabolic and endocrine components that may be considered as strategies to adapt to undernutrition, but these may also participate in the pathophysiology of the disorder.

Recent genetic studies have highlighted AN as a disorder of both psychiatric and metabolic etiology, with genetic correlations with a broad range of metabolic phenotypes.

The mechanisms underlying the pathophysiology of AN are largely unknown, but abnormalities in the reward system have been suggested to contribute to the maintenance and chronicity of the disease that could explain the high relapse rate.

Metabolic sensors that signal energy deficit target mesocorticolimbic dopaminergic structures that control reward processes, and these could mechanistically be involved in reward abnormalities in AN by acquiring reinforcing properties.

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Box 1. Eating Disorders and DSM-V Criteria for Anorexia Nervosa

The latest version of Diagnostic and Statistical Manuel of Mental Disorders (DSM-V, 2013) describes criteria for the diagnosis of eating disorders. Eating disorders encompass several categories: anorexia nervosa (AN) and avoidant restrictive food-intake disorder (ARFID), bulimia nervosa (BN), binge-eating disorder (BED), pica, rumination disorder, other specified feeding or eating disorder (OSFED), and unspecified feeding or eating disorder (UFED).

AN is associated with; (i) restriction of energy intake leading to significantly reduced body weight (in the context of what is minimally expected given the age, sex, developmental trajectory, and physical health of the patient), (ii) an intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain (despite significantly low weight), and (iii) a disturbance in the way in which body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of current low body weight.

AN includes two main subtypes: restricting-type and binge-eating/purging type. A bidirectional crossover between AN subtypes occurs in approximately half of the patients [97]. The restricting-type (AN-R) is dominated by dieting, fasting, and/or excessive exercise. The binge-eating/purging-type (AN-BP) includes recurrent episodes of binge eating (i.e., eating large amounts of food in a discrete period of time when not feeling physically hungry accompanied by a sense of lack of control) and/or with purging behavior (e.g., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). Other features that are not part of DSM-V criteria, such as personality or temperament traits, are sometimes associated with AN: inflexible thinking, compulsivity, low self-directedness, and perfectionism that can hamper flexible adaptation to a changing environment. Compared with AN-R, AN-BP patients have higher rates of impulsivity and may be more likely to develop substance abuse.

where diagnosis is less important than pathological traits, which can be studied deeply and targeted for therapeutic intervention [7]. In the case of AN, a growing body of studies indicate abnormal **reward** pathway and reward valuation, monitored by **delay discounting**, as core elements [8] that might constitute a target for therapeutic intervention [9].

Recent advances in human genetics incriminate metabolic and endocrine factors in AN. It can be hypothesized that the latter may interfere with reward valuation and act at two stages of the disorder: early stage (precipitating factors) and late stage (perpetuation factors). Could metabolism be the cement of the reward valuation alteration in AN? Reward processing and valuation might be controlled by metabolic aspects in the early phase, and prevent attempts to change cognitive processes in the late phase. The metabolic alterations induced by undernutrition might interact with a predisposed genetic background, thus promoting the development and maintenance of the disorder. The resurgence of metabolic factors as an etiological dimension of AN encourages us to explore bridges between metabolism, cognitive processes, and feeding behavior.

Feeding Behavior: Key Concepts

Eating: A Question of Survival

Survival is strongly linked to the most essential motivated behavior, namely eating. The regulation of food intake requires a finely tuned interaction between molecules produced by the digestive tract and specific brain areas. **Homeostatic** sensors are directly linked to the energy needs of the body, whereas 'nonhomeostatic factors' are related to experience, learning, **habits**, stress, biological rhythms, or sociocultural environment. Dysregulation of any one of these elements could contribute to the occurrence of an eating disorder such as AN. The hypothalamic arcuate nucleus (ARC) is the primary target of peripheral sensors of energy status through the modulation of specific neuronal populations, such as neuropeptide Y/agouti-related peptide (NPY/AgRP) and pro-opiomelanocortin (POMC) neurons, which increase and decrease food intake respectively. These neurons are essential to convey metabolic and nutritional information of the organism to other hypothalamic areas such as the paraventricular nucleus that, in particular, is involved in the stress response, as well as to extrahypothalamic structures such as the amygdala or dorsal raphe that are involved in the modulation of

reward and emotions. In addition, AgRP neurons are essential to connect metabolic needs and **goal-directed behaviors** (Box 2). They modulate mesolimbic dopamine activity and food palatability, both related to the motivational processes that are mandatory for seeking food [10,11].

The preprandial phase, that usually occurs about 1 h before a meal, requires central integration of extrinsic factors, such as the sight, smell, ideation, time of day, motivation to eat, pleasure expectation, and intrinsic physiological and endocrine factors [12]. These signals are necessary to: (i) sense the central and peripheral energy deficit, through a mechanism referred to as 'cerebral insulin suppression', to limit glucose fluxes into peripheral tissues (muscle, fat, liver) and enhance cerebral glucose supply [13]; (ii) attribute a positive or negative emotional **valence** to food, and (iii) allow the development of appropriate motor and motivated behaviors oriented to the consumption of nutrients. Several gastrointestinal hormones are released before a meal to prepare the organism for the metabolic challenge triggered by the caloric load of a meal [12]. Insulin, a pancreatic hormone, is released a few minutes before an anticipated meal [12] to cope efficiently with the glucose load triggered by the meal. Furthermore, the systemic concentration of ghrelin, a powerful orexigenic hormone mainly produced by the stomach, increases around 30 minutes before the meal not only to initiate feeding behavior [14] but also to improve sensitivity to smell and odors leading to feeding when food becomes available [12,15].

Stopping Eating: Satiation and Satiety

Satiation and **satiety** are parts of the sequence of feeding that elicit the termination of a meal. To become satiated is not only a question of acute variations of gastrointestinal hormones that occur during the meal or post-meal but also includes pleasure and sensory integration of odors and taste as part of sensory-specific satiety, that may be altered in AN [16,17].

Various redundant peptide hormones that are released postprandially by the intestine signal satiation through either humoral or vagal–brainstem afferent fibers: these include glucagon-like peptide-1, peptide YY (3–36), and cholescystokinin (CCK) [18]. Furthermore, the kinetics of the decrease in circulating ghrelin following a meal are important to achieve satiety because, in rodents, pharmacological reduction of ghrelin exerts an anorexigenic effect associated with a reduction in meal frequency but without affecting satiation [19]. Finally, the post-meal release of insulin and leptin, that are considered to be adiposity hormones and whose secretion is proportional to the amount of body fat, also contributes to the reduction in food intake by modulating NPY/AgRP and POMC ARC neurons [12].

Emotional Feelings in Feeding Behavior

Feeding is strongly influenced by emotional feelings. Indeed, emotions influence our cognition and induce physiological changes that can heighten motivated behaviors for food intake. From an

Box 2. AgRP Neurons Connect Metabolic Needs and Goal-Oriented Behaviors

AgRP neurons are a discrete population of hypothalamic neurons within the arcuate nucleus (ARC) that are modulated by peripheral metabolic sensors such as ghrelin, leptin, and insulin to signal energy deficit (or excess) in order to promote hunger (or satiety) and reduce (or increase) energy expenditure. Acute pharmacological activation of this neuronal population leads to increased feeding, whereas specific ablation of AgRP neurons results in profound anorexia [98]. When food is unavailable, optogenetic stimulation of AgRP neurons creates a state of aversion, suggesting that these neurons, in addition to positively controlling food intake, also encode the negative valence associated with hunger [99]. Furthermore, activation elicits food consumption and instrumental food seeking, indicating that these neurons are an entry point to motivational processes resulting from homeostatic deficit [100]. In a context in which AgRP neuronal activity is impaired and is unable to signal metabolic demands, circulating signals reflecting energy needs, such as ghrelin, can directly stimulate DA neurons and promote reward-directed behaviors [11]. Under these conditions, feeding seems to largely depend on reward and emotional drives, and no longer depends on energy needs [11].

Glossary

Cognitive control: allows the mind to override impulses and thus allows decision making to be based on goals rather than on habits or reactions. Allows selection and successful monitoring of behaviors that facilitate the attainment of chosen goals.
Compulsive behavior: defined as performing an act persistently and repetitively without it necessarily leading to an actual reward or pleasure, and the excess activity is not connected to the purpose for which it appears to be directed.
Decision making: in psychology, decision making is regarded as the cognitive process resulting in the selection of a belief or a course of action among several alternative possibilities. Every decision-making process produces a final choice, which may or may not prompt action. Decision making is the process of identifying and choosing between alternatives based on the values, preferences, and beliefs of the decision-maker.
Delay discounting: a cognitive phenomenon where the relative value of a reward decreases as the delay in receiving it increases. Delay-discounting reward is the preference for an immediate, smaller (greater discounting of a delayed reward, DRD), and larger but less certain (less discounting of a less probable reward, PRD) reward. Steep discounting of delayed rewards is associated with increased impulsivity and poor self-control, whereas shallow discounting of probabilistic rewards is related to increased risk-taking behavior.
Endocrine: the secretion of effector molecules (e.g., hormones) directly into the bloodstream to regulate the function of cells and tissues throughout the body.
Exome sequencing: also known as whole-exome sequencing (WES), this is a genomic technique for sequencing all the protein-coding region of genes in a genome or of all the exons (known as the exome). This allows the characterization in a patient of all polymorphisms among the 30 million coding nucleotides of the exome. To confirm a specific genetic vulnerability, variants located in

evolutionary perspective, eating requires that fear/anxiety behavior is suppressed and that motivational systems engage locomotor activity such that a source of food can be reached. This motor behavior encompasses foraging behaviors that involve particularly frontal brain areas, and food anticipatory activity occurring before the presentation of food. In AN patients and in animal models of food restriction, physical activity is inappropriately high in relation to the state of undernutrition [20–22]. Although the role of physical activity as a means to reduce anxious behavior has been debated, excessive physical activity in AN is generally associated with higher scores on anxiety, perfectionism, and compulsions [23]. The decision to move to eat or not corresponds to an intermingled complex network in which the structures that regulate homeostasis and emotional feeling, stress, motivation, and cognition (goal-directed behavior, learning, memory, impulsivity, and disinhibition) are strongly interconnected. Eating properly necessitates moderate stress and/or moderately intense emotions because hunger and negative emotions such as fear can be viewed as incompatible states that convey opposite information within neural circuits. Finally, negative emotional states are thought to increase food intake, especially palatable food, because of impaired **cognitive control**.

Genetics of AN: A Psychiatric Disorder of Metabolic Etiology?

Epidemiological studies strongly suggest that genetic factors are involved in the etiology of AN because the disorder has an estimated **heritability** of about 0.7 [24]. Genetic predisposition in AN can be identified with the classical molecular tools of human genetics. Screening of functional genetic variants in genes implicated in the control of feeding behavior suggests that key metabolic sensors play a role in vulnerability to the disorder.

The genes *LEP* and *LEPR* encode leptin and its receptor, respectively, and discrepancies of associations between AN and *LEP* or *LEPR* variants have been reported [25,26]. Adiponectin is another hormone secreted by adipocytes that is increased in AN patients. Variants in the adiponectin gene, *ADIPOQ*, were not different between AN and controls [27].

Different variants of the preproghrelin (*GHRL)* gene that substitute amino acids have been investigated. The Met allele of variant rs696217/Leu72Met was found to be overtransmitted in a family-based study of AN, especially in the binge-eating/purging AN (AN-BP) subtype [28]. Furthermore, an excess of transmission of the Gln90Leu72 preproghrelin **haplotype** in patients with AN was reported, and the Gln90Leu polymorphism was associated with reduced body mass index (BMI) among AN patients. However, no association was observed in a large family-based and case–control study between AN and three *GHRL* Single Nucleotide Polymorphisms (SNPs) (Gln90Leu/rs4684677, Leu72Met/rs696217, and Arg51Gln/rs34911341) [26,29,30]. The rs495225/171T/C variant of the *GHSR* gene, coding for the ghrelin receptor, was not associated with AN [31]. Finally, the enzyme ghrelin O-acyltransferase (GOAT), encoded by the *MBOAT4* gene, is involved in acylation of ghrelin at serine 3 that permits it to bind to and activate GHSR. An association between the *GOAT* rs10096097 variant and AN was reported [32].

In the ARC, first-order neurons that respond negatively to leptin coexpress AgRP, a ligand that is an inverse agonist at the melanocortin 4 receptor (MC4R). Variants in the *AGRP* gene were found to be associated with AN or low BMI [26,28,33]. Other genetic studies of candidate genes involved in hypothalamic hunger and satiety regulatory systems, including *NPY1R* and *NPY5R* genes (that encode the neuropeptide Y receptors 1 and 5), *MC4R* and *MC3R*, and *POMC* (encoding proopiomelanocortin) did not find any association between polymorphisms and AN [25,26]. By contrast, a large screening of 182 candidate genes in AN patients and subsets showed an association between a SNP in *POMC* and restrictive AN (AN-R) subtype, and AN was associated with polymorphisms in the *GLP2R* gene which encodes the glucagon-like peptide (GLP) 2 receptor, a regulator of glucose and fatty acid concentrations [34].

The first large international consortium on **genome-wide association studies (GWAS)** in AN found an association between AN and variants of the *PPP3CA* gene that encodes the α isoform of a subunit of calcineurin [35]. No statistically significant associations with genetic variants of candidate genes involved in the regulation of hunger and satiety were found [35]. GWAS analysis of low-frequency

the same gene then need to be identified in several patients.
Genome-wide association study (GWAS): screening of genetic variants spanning the genome by using hundreds thousands of SNPs in families, or in case–control studies comparing thousands of patients and controls, to characterize segregation of transmission or association between variants and the disorder or a specific phenotype. This allows the identification of regions, loci, and candidate genes that are possibly involved in the disorder.
Goal-directed behaviors: purposeful actions driven by the anticipation and evaluation of a rewarding outcome. They are observed when individuals are engaged in reaching a specific goal.
Habits: learned (instrumental) behaviors that are repeatedly engaged and consequently become fixed (not flexible) behaviors. Habit-based behaviors (HBs) occur without conscious effort, are elicited by external stimuli, and are independent from the rewarding value of the outcome.
Haplotype: a set of linked SNPs that tend to always occur together (i.e., that are associated statistically).
Heritability: a statistic used in the field of genetics that estimates the degree of variation in a phenotypic trait within a population that is due to genetic variation between individuals in that population and is not explained by the environment or random chance.
Homeostasis: the ability to maintain a constant internal environment despite external changes. It is a unifying principle of biology. The nervous and endocrine systems control homeostasis in the body through feedback mechanisms involving various organs and organ systems.
Incentive salience: a cognitive process that confers a 'desire' or 'want' attribute, which includes a motivational component, to a rewarding stimulus. The 'wanting' of incentive salience differs from 'liking' in the sense that liking is the pleasure that is immediately gained from the acquisition or consumption of a rewarding stimulus.

and rare variants associated with AN identified specific associations with two genes, *CCKAR* (that encodes the cholecystokinin A receptor, a regulator of satiety) and ankyrin repeat domain-containing protein 50 (*ANKRD50*) (which is involved in the endosome-to-plasma membrane trafficking, including an interaction with the transporter of glucose GLUT1 [36]). Interestingly, recent GWAS studies demonstrate that AN correlates with a broad range of metabolic phenotypes. Indeed, positive genetic correlations were observed between AN and high-density lipoprotein cholesterol, and negative genetic correlations with BMI, fasting insulin and glucose, and insulin resistance HOMA index (HOMA-IR), as well as with an altered lipid phenotype [37]. Finally, a recent GWAS meta-analysis strategy enabled the identification of specific genes in two main pathways, suggesting that AN should be considered as a metabo-psychiatric disorder, in other words a disorder with both a psychiatric and a metabolic etiology [38].

Recently, **exome sequencing** provided identification of rare variants in genes encoding neuropeptides, neurotrophic factors, and receptors involved in appetite regulation, such as glucagon (*GCG*), proopiomelanocortin (*POMC*), inositol 1,4,5-trisphosphate receptor type 3 (*ITPR3*), brain-derived neurotrophic factor (BDNF) and BDNF signaling (NTRK2, Neurotrophic Receptor Tyrosine Kinase 2) [39,40].

AN: A Disorder of Reward Processes

Recent research suggests that reward processing is disordered in AN patients [41]. Patients with **remitted** AN have reduced sensitivity to the motivational drive for hunger [42], and favor delayed (*versus* immediate) rewards compared with controls. Habit-preferences ('stimulus–response') are furthermore preferred compared with goal-directed ('action–outcome') choices [43,44] in accordance with the observation that compulsivity characterizes many traits of the disorder, such as relentless self-starvation and overexercise [45], despite adverse outcomes. The developmental period of onset of AN indeed includes an initial phase of reward seeking in the form of weight loss which is experienced as rewarding and pleasurable [8] (Figure 1, Key Figure). Such behavior has been proposed to originate from a dysregulation of mesocorticolimbic dopamine circuits that encode positive/negative valence and control reward and **decision-making** behaviors [46,47] (Box 3). Thus, self-starvation and overexercise behaviors, core features of AN, may act as positive **reinforcers** of these **compulsive behaviors** and participate in the process that leads to the maintenance and chronicity of the disorder (Figure 1).

Interestingly, human neuroimaging studies have highlighted alterations in the structure and function of reward circuits that are associated with food restriction or binge-eating and purging, and that are observed in the acute phase of the disorder but seem to persist after recovery [48,49]. Abnormally increased activity of the striatum for delayed reward was also observed, and this abnormal decision processing was reversed with weight restoration [50]. Furthermore, there is direct evidence that the balance between goal-directed and habitual control in humans is dopamine-dependent [51]. Brain imaging through MRI (magnetic resonance imaging), fMRI (functional MRI), and DTI (diffusion tensor imaging) also shows that, when patients with AN need to make a food choice, there is higher activity in the dorsal striatum relative to age-matched healthy controls [52] as well as reduced capacity of the orbitofrontal cortex to modulate the nucleus accumbens (NAcc) [53]. Interestingly, in an animal model of decision taking, avoidance choices correlated with the number of perseverative errors [54]. Finally, AN patients display altered connectivity within circuits that link homeostatic and reward control of eating drive [47]. The authors suggest that cognitive/emotional control affects reward and eating drive, and overrides hypothalamic inputs to the reward circuit so as to prolong food restriction. Similarly, a rodent model that combines caloric restriction and access to a running wheel, and that mimics the core symptoms of restricting-type AN (AN-R) (excessive exercise, weight loss, anhedonia, etc.), namely the activity-based anorexia (ABA) model, exhibits altered mesolimbic reward circuitry which may contribute to disease susceptibility [11,55].

Possible Mechanism of Reward Abnormalities in AN: Role of Metabolic Sensors

Metabolic and Endocrine Adaptations in AN

Many studies have documented metabolic and neuroendocrine alterations in patients with AN [56,57] (Table 1). The chronic state of calorie restriction has been associated with hypogonadotropic

Reinforcer: a stimulus (such as a reward) that will strengthen the future behavior of an organism whenever that behavior is preceded by a specific stimulus. There are two types of reinforcer – positive reinforcers and negative reinforcers; positive is where a reward is offered upon expression of the wanted behavior, whereas negative involves removal of an undesirable element in a person's environment whenever the desired behavior is achieved.
Remission: the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity.
Reward: any stimulus, object, event, activity, or situation that has the potential to induce approach and/or consumption.
Reward learning: a process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behavior is modified when a novel reward occurs, or outcomes are better than expected. Reward learning is a type of reinforcement learning.
Satiation: from Benelam, 2009 [119], the process that leads to the termination of eating, which may be accompanied by a feeling of satisfaction.
Satiety: from Benelam, 2009 [119], the feeling of fullness that persists after eating, potentially suppressing further energy intake until hunger returns.
Set-shifting: in neuropsychological investigations, set-shifting, mediated by the medial prefrontal cortex (mPFC), is the ability to shift thoughts and actions in response to changing contexts.
Valence (positive/negative): in psychology, especially in discussing emotions, valence means the intrinsic attractiveness/'goodness' (positive valence) or averseness/'badness' (negative valence) of an event, object, or situation. The term also characterizes and categorizes specific emotions.

Key Figure

Genetic, Epigenetic, and Metabolic factors in the Onset, Development, and Maintenance of Anorexia Nervosa (AN)

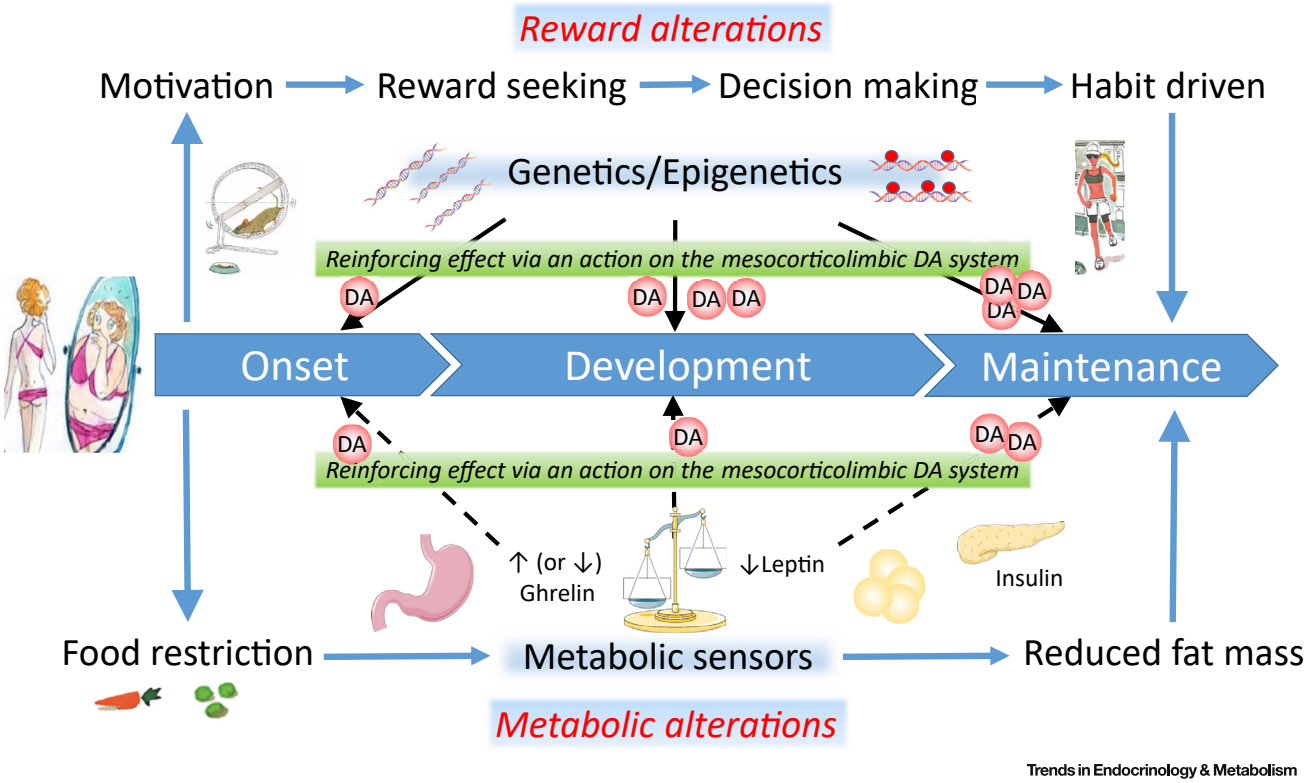

Figure 1. AN is a multifactorial psychiatric disorder that affects mostly young women and encompasses several risk factors including genetic/epigenetic, environmental, and biological factors. AN is characterized by self-starvation and over-exercise behaviors. In fact, an initial phase of reward seeking in the form of weight loss is experienced as rewarding and pleasurable. Such behavior is associated with dysregulation of mesocorticolimbic dopamine (DA) circuits that control reward and decision-making behaviors [46,47]. Indeed, although individuals with AN have the ability to delay reward, their impairment in decision making leads the patient to develop excessive habit formation instead of goal-oriented behaviors, and may lead them to engage in compulsive weight-loss behaviors despite adverse outcomes [45,48,96]. Thus undernutrition in vulnerable AN may act as a positive reinforcer of their compulsive behavior and participate in the process that leads to development and maintenance of the disorder. Metabolic sensors that signal the undernutrition state [increased ghrelin in restricting-type AN (AN-R) versus reduced ghrelin in binge-eating/purging AN (AN-BP), or reduced adiposity and energy deprivation (decreased leptin in both AN-R and AN-BP)], do not succeed in promoting feeding in AN-R patients. Because they control reward-related behaviors via action on the mesocorticolimbic DA system, they may possibly acquire reinforcing properties to maintain reward abnormalities when dysregulated because of modifications in nutritional and energy status. The thick blue arrows in the center of the figure illustrate, from left to right, the evolution of AN from onset to maintenance. Onset is associated with food restriction and/or overexercise that are initially rewarding and develop into habits. The top of the figure illustrates the sequence of reward alterations (from left to right, depicted by the thin blue arrows) which parallel the development and maintenance of the disorder and are under the control of genetic, epigenetic, and neurobiological factors such as dopamine (DA, in pink circles). The bottom of the figure illustrates metabolic alterations (increased or decreased metabolic sensors as depicted by the scale) induced acutely by food restriction (such as ghrelin produced by the stomach) and more chronically by reduced fat stores (such as leptin or insulin produced by the adipose tissue and pancreas, respectively) (*drawings from Servier Medical Arts*). Metabolic sensors can, in turn, impact on the mesocorticolimbic DA system by modulating DA release and/or action.

hypogonadism, increased growth hormone (GH), and reduced insulin-like growth factor (IGF-1) plasma concentrations, as well as nutritionally acquired GH resistance, hypercortisolemia, increased plasma concentrations of ghrelin, GLP-1, and adiponectin, and decreased plasma concentrations of

Box 3. Neurobiological Basis of Reward/Motivation and Decision Making

Several studies point to the dopamine (DA) system as a key player in controlling eating behavior and weight. Indeed, the reinforcing and motivational aspects of food are closely tied to the release of this neurotransmitter by midbrain DA neurons in the ventral tegmental area (VTA). DA is considered to be key to the rewarding effects of both natural and drug-derived reward [101]. Feeding and palatable food ingestion are associated with DA release in the striatum, and the degree of pleasure is strongly correlated with the amount of DA release [102–104].

Anticipation and reward processing involve several brain structures. The corticostriatal circuit is composed of both a striatal (involving the ventral striatum/nucleus accumbens) and prefrontal (anterior cingulate cortex/ventromedial prefrontal cortex) component. Projections of DA neurons from the VTA to the NAcc mediate the rewarding and reinforcing effects of food. The caudate nucleus (striatal component) is suggested to drive compulsive behaviors, whereas the orbitofrontal cortex (prefrontal component) controls or inhibits this behavior. The prefrontal cortex integrates motivation and cognitive control in the service of decision making, and is likely to be dysregulated in disorders involving reward abnormalities. Among DA receptors, D1 and D2 receptors are involved in **reward learning** and **incentive salience**. Dopamine receptor D2 (DRD2) has been associated with food-anticipatory behavior, food restriction, reward, and motivation [105]. Interestingly, DA neurons of the VTA express receptors for metabolic/endocrine signals such as insulin receptor (Ins-R), leptin receptor (Lept-R or Ob-R), and ghrelin-R (GHSR1a) [106,107]. Furthermore, GHSR1a/DRD2 heterodimers have also been identified in subsets of hypothalamic neurons that regulate appetite, suggesting direct interactions between ghrelin and DA signaling pathways in homeostatic circuits [108].

leptin and triiodothyronine [56,57]. Interestingly, distinct metabolic adaptations (for instance, for gastrointestinal hormones) have been observed according to the subtype (restricting versus binge-eating/purging) or the study (Table 1). Although these endocrine and metabolic alterations are directly associated with nutritional status and play a key role in the survival of the organism in situations of food scarcity (Box 4), they are only partly adaptive to the state of chronic undernutrition because weight restoration normalizes some of these dysfunctions but not others. In the following we discuss how these metabolic sensors have the potential to contribute to reward abnormalities in AN (Table 2).

Mechanism of Reward Abnormalities

Insulin Modulates Food Valuation and Learning about Food Reward

This satiety endocrine sensor plays a key role in food reward by increasing dopamine (DA) release in the striatum (NAcc, caudate, and putamen) [58]. In rodents, insulin reinforces preference for a flavor that signals a glycemic load through an action on insulin receptors located on DA axons in the NAcc [58]. Furthermore, insulin appears to modulate reward-based learning without impacting on the reward value of palatable foods [59]. Interestingly, chronic food restriction promotes hypoinsulinemia and increases the sensitivity of striatal DA release to insulin [58]. Because insulin promotes learning about food reward, it has the potential to reinforce repetitive ingestive behaviors and/or restrictive behaviors in AN patients.

Consistent with these mechanistic observations in rodents, blood oxygen-level dependent (BOLD) imaging studies in healthy humans demonstrate an inverse correlation between post-meal insulin levels and activation of reward circuitry, such as the insula and orbitofrontal cortex [60], whereas intranasal insulin reduces activation in the orbitofrontal cortex [61]. In healthy individuals, intranasal insulin administration induces a reduction in the valuation of food palatability, which is associated with decreased food value signals in the mesolimbic system. In AN patients with chronic food restriction, increased whole-body insulin sensitivity has been reported (Table 1 and Box 4). Because insulin alters food value and palatability [62], possible modifications of insulin sensitivity affecting specifically the reward system, if they occur, could explain the reduced motivation to eat in AN patients [61] or reduced reward-based learning about restrictive behaviors under conditions of restricted feeding. In conclusion, insulin seems to be important in communicating the caloric value of a diet/meal.

Table 1. Differential Endocrine and Metabolic Alterations in Anorexia Nervosa Subtypes[a]

	Parameter	AN-R	AN-BP
Body parameters	Body mass index	↓ BMI	↓ BMI
Somatotropic axis	GH	↑ GH	↑ GH
	IGF-1	↓ IGF-1	↓ IGF-1
Thyroid axis	Free T3	↓ Free T3	↓ Free T3
HPA axis	Cortisol	↑ Cortisol	↑ Cortisol
HPG axis	17β-Estradiol	↓ 17β-Estradiol	↓ 17β-Estradiol
	LH, FSH	↓ LH and FSH	
Adipose tissue	Fat mass	↓ Fat mass	↓ Fat mass
	Leptin	↓ Leptin	↓ Leptin
	Adiponectin	↑(++)/= Adiponectin	↑(+) Adiponectin
Glucose metabolism	Glucose	↓/= Fasting blood glucose	= Fasting glucose
	Insulin	↓/= Fasting insulin ↓ Postprandial insulin Normal (or ↑) insulin sensitivity	= Fasting insulin
	GLP-1	↑ Fasting and postprandial GLP-1	
Metabolic gastrointestinal hormones	Ghrelin-derived peptides	↑ Fasting acyl and desacyl ghrelin ↑ Fasting obestatin	↓ Fasting acyl and total ghrelin ↓ Fasting obestatin
	PYY	↓/↑ Fasting PYY	↓ Fasting PYY
	CCK	↑/↓ Or = fasting CCK ↑ Postprandial CCK	

[a]Abbreviations and key: ↑, increase; ↓, decrease; =, no change; AN-BP, anorexia nervosa binge-eating/purging-type; AN-R, anorexia nervosa restricting-type; CCK, cholecystokinin; FSH, follicle stimulating hormone; HPA, hypothalamus–pituitary–adrenal axis; HPG, hypothalamus–pituitary–gonadal axis; LH, luteinizing hormone; PYY, peptide YY; T3, triiodothyronine; BMI, body mass index; GH, growth hormone; GLP-1; glucagon-like peptide 1; IGF-1, insulin-like growth factor-1.

The post-meal insulin response may not only encode the glycemic level of a meal to induce satiety but also modulate reinforcement of behaviors that promote further food consumption. Thus, pathological conditions of chronically low insulin plasma concentrations associated with altered striatal insulin receptor sensitivity may promote pathological eating.

Rewarding Effects of Physical Activity: Role of Leptin Signaling

Food restriction, that engages the encoding of food cues by VTA DA neurons [63], induces an increase in physical activity in both rodents and humans. Older studies demonstrated that endurance running is rewarding in humans [64] and rodents [65], but the mechanistic link between leptin and modulation of physical activity has only been deciphered recently. Leptin has been shown to modulate the motivational and rewarding effects of running [66]. Interestingly, plasma leptin concentrations are inversely correlated with running in both humans [67,68] and rodents [69,70]. In the fed state, leptin increases locomotor activity and voluntary running in humans and rodents. By contrast, under food-restricted conditions, leptin reduces locomotor activity and voluntary wheel running in rats and mice [69–71]. Whereas under conditions of sufficient energy supplies, increased physical activity would be beneficial to increase energy expenditure and reduce energy storage, under conditions

Box 4. Metabolic and Endocrine Adaptations to Undernutrition as a Survival Process

Insulin and Glucose Homeostasis during Undernutrition

In AN patients, insulin secretion has been reported to be either normal, increased, or decreased during the active phase of the disorder [109,110], and to be lowered during an oral glucose-tolerance test [111] depending on the subtype or study (Table 1). In the majority of cases, AN patients maintain euglycemia despite a severe state of undernutrition. Insulin sensitivity has been described to be increased using HOMA (homeostasis model assessment of insulin resistance) assessment, but normal insulin sensitivity and metabolic flexibility measured during euglycemic–hyperinsulinemic clamp has been reported. Optimal insulin action but controlled insulin sensitivity is essential to supply the body in glucose and to control gluconeogenesis, thereby avoiding severely unbalanced glucose homeostasis.

Ghrelin: A Sensor of Undernutrition That Maintains Glucose Metabolism

From a survival mechanism point of view, elevated ghrelin concentrations in situations of chronic undernutrition may represent an important adaptive response to maintain metabolic functions in situations where food is scarce. Ghrelin is a powerful GH secretagog [81] and a postulated function of ghrelin in food-restricted mice is in elevating of GH levels, a hyperglycemic hormone, to prevent hypoglycemia, although this question remains under debate [57,112]. Retaining high GH with low IGF-1 (a hypoglycemic hormone) plasma concentrations may be important to boost β-oxidation and gluconeogenesis (that are enhanced by GH but inhibited by IGF-1) while reducing glucose transport (that is promoted by IGF-1) to maintain euglycemia. A recent study, using targeted invalidation of the GH receptor (GH-R) in AgRP neurons, also suggests that GH is a starvation cue that signals energy deficiency to AgRP neurons. GH signaling on AgRP neurons promotes adaptive responses to conserve limited fuel stores during chronic food restriction in mice [113].

Leptin: A Sensor of Energy Stores That Controls Reproduction

In AN, chronic calorie restriction is accompanied by a dramatic fall in plasma leptin concentrations in proportion to the loss of fat mass (Table 1). The main role of leptin is to signal reduction of energy stores (via falling leptin levels) to the brain [114,115] to initiate behavioral and metabolic responses so as to conserve energy stores and increase survival. Leptin plays a key role in modulating the reproductive axis [116,117]. In AN patients, low plasma leptin concentrations are associated with decreased luteinizing hormone (LH), follicle stimulating hormone (FSH), and gonadal hormone levels [118], amenorrhea, and eventually infertility. A blunted reproductive axis is a necessary adaptation to starvation because sufficient nutrition is key for gestational processes.

of food scarcity the motivational effects of physical activity would be necessary to promote hunting, scavenging, and food hoarding [72].

The involvement of reward pathways in the control of physical activity was suggested many decades ago. Reduced DA overflow in the NAcc associated with a reduced locomotor response to amphetamine has been reported under conditions of leptin deficiency, which is reversed by leptin infusions, supporting the role of leptin as a regulator of reward pathways [73]. Other studies support the idea that leptin signaling in DA neurons reduces voluntary physical activity. Restoring leptin signaling exclusively in DA neurons reduces hedonic feeding and home-cage activity [74]. Data emerging from ABA models suggest that leptin administration directly to the ventral tegmental area (VTA) reduces preprandial locomotor hyperactivity [71] without any change in food intake. Furthermore, reduced LepR–STAT3 signaling in DA neurons appears to be an important mechanism mediating increased physical activity induced by food restriction and reduced plasma leptin levels [75]. Thus, under conditions of food restriction, the mesolimbic DA system promotes motivational processes directed towards obtaining food and more readily responding to leptin to decrease appetitive physical activity. By contrast, during fed states, the actions of leptin may be directed towards hypothalamic pathways to increase physical activity to promote energy expenditure and maintain whole-body energy homeostasis.

Interestingly, addiction to exercise in humans is associated with low fat-adjusted plasma leptin levels [76]. In this regard, the inappropriate physical activity described for 31–80% of AN patients [23,67] has been proposed to be linked to variations of plasma leptin concentrations. However, an absence of a

Table 2. Effects of Metabolic Endocrine Sensors on Energy Homeostasis and Reward[a]

	Effects on energy homeostasis		Effects on reward		
	Food intake	Glucose homeostasis	Food-related	Activity-related	Cognition/emotion
Insulin	↓ Food intake (after central administration)	↓ Glucose	Modulates food valuation and reward-based learning		Correlated with impaired cognitive flexibility
GLP-1	↓ Food intake	↑ Insulin ↓ Glucagon	↓ Hedonic value of food ↓ Food reward		
Leptin	↓ Food intake after peripheral or central administrations	↓ Glucose and insulin ↑ Insulin sensitivity	↓ Food reward	Fed state: ↑ voluntary running Food restriction: ↓ voluntary running ↓ Rewarding effect of running	Correlated with greater inhibitory control
Ghrelin	↑ Food intake after peripheral or central administration	↑ Glucose and insulin ↓ Insulin sensitivity Prevents hypoglycemia during food restriction	↑ Hedonic value of food ↑ Food reward ↑ Food odor conditioning	Food restriction: ↑ food-anticipatory activity	Correlated with reward sensitivity and impulsivity

[a]Abbreviations and key: ↑, increase; ↓, decrease.

simple and linear association between leptin levels and physical hyperactivity has been reported in a large population of AN patients [77]. Rodents and humans share common neurobiological processes such as the rewarding aspect of heightened activity when searching for food. However, the gap often observed between clinical and rodent models could be explained by distinct cognitive or emotional factors such as compulsive attempts to lose weight by overexercising that are typically observed in humans.

Ghrelin: Rewarding Aspects of Feeding and Physical Activity

Data from numerous studies [78] converge to demonstrate direct involvement of ghrelin in the mesolimbic DA signaling by; (i) modulating DA release, (ii) acting on the reinforcing actions of food, and (iii) acting on food choice reward/motivation rather than directly affecting food intake, with notable effects on promoting 'healthy' chow intake.

In the ABA rodent model, weight loss is associated with increased plasma ghrelin concentrations [79], a physiological response to energy deficit also observed in AN patients. Plasma ghrelin concentrations are elevated in AN-R but not in AN-BP [80] (Table 1). This increase in patients with restricted eating is paradoxical, and questions a possible central resistance to ghrelin [41] and/or antagonism of ghrelin by other molecules inhibiting appetite that are produced by the preproghrelin gene, such as desacyl ghrelin and obestatin, which have the ability to block ghrelin-induced feeding [81]. Interestingly, high plasma concentrations of other gastrointestinal peptides, such as GLP-1 – that has been shown to antagonize the effect of ghrelin on food reward in rodents [82] or alter postprandial functional connectivity between homeostatic and reward-related brain regions in humans [83] – may contribute to the reduced motivation to eat in AN-R (Tables 1 and 2). By contrast, differential modulation of these peptides may contribute to increased motivation to binge in AN-BP. Furthermore, the lack of a motivated feeding response to ghrelin despite increased hunger sensation [41] or altered ghrelin secretion following hedonic eating [84] supports the idea that an altered food-related reward response to ghrelin may also contribute to restricted feeding in AN.

In addition to its role in hedonic and motivational eating, ghrelin has been implicated in the modulation of appetitive physical activity in an opposite way to leptin. In food-restricted animals, ghrelin secretion is correlated to food anticipatory activity. Under conditions of ghrelin signaling blockade

(GHSR antagonist or GHSR-deficient mice), this food anticipatory activity is reduced [85]. It has also been postulated that the surge in ghrelin in rodents at dark onset, a time that corresponds to meal initiation, plays a role in the motivation for voluntary exercise via modulation of central DA system [86]. Thus, in AN patients, increased ghrelin secretion may be linked to a higher motivation for physical activity.

Other Reward and Cognitive-Related Effects of Metabolic Factors

Investigations performed in the field of obesity long ago highlighted the link between nutritional and adiposity signals on **decision making** and cognitive control. For example, BMI was found to be positively correlated with impulsivity and decreased activation in frontal inhibitory regions [87]. Interestingly cognitive flexibility, which is important for decision making and goal-directed behavior, is impaired in underweight AN patients. Increased cognitive control and inflexibility may be responsible for their rigid eating behaviors and for increased eating disorder-related psychopathology. Impaired **set-shifting** abilities, assessed by evaluating perseverative errors in the Wisconsin card-sorting test (WCST) have been documented for patients with AN [88].

In rats, repeated hypoglycemia induced by insulin treatments led to impaired set-shifting performance, measured using a maze-based, food-reward set-shift task analogous to the WCST, suggesting impairment in mental flexibility [89]. Furthermore, in AN patients, higher ghrelin levels predict better performance in the Iowa gambling test that evaluates decision making as well as reward and punishment value [88]. Individuals with higher levels of fasting ghrelin are more sensitive to reward but are less sensitive to punishment, and have reduced self-control, in other words increased impulsivity [90]. By contrast, AN patients with lower ghrelin levels display greater impairment in decision making and higher eating disorder-related psychopathology. Recent studies also suggest associations between leptin secretion and inhibitory control in AN patients [91]. Reward association learning has also been studied as a measure of cognitive flexibility in adolescent AN patients and was found to be correlated with abnormal levels of AgRP [92]. Interestingly, activation of AgRP neurons in mice elicits repetitive and compulsive behavior in the absence of food [93] and alters behavioral flexibility in a modified version of the Barnes maze task [94]. Finally, there seem to be interactions between genetic and environment in the perception of body shape and drive for thinness. Indeed, the T3056 T>C SNP in the preproghrelin gene is associated with higher ghrelin concentrations, BMI, and fat mass, and a lower HDL-cholesterol concentration, and is related to increased drive for thinness and body dissatisfaction [95].

Concluding Remarks and Future Perspectives

Although AN is a lethal disorder with an extremely high social burden, the underlying mechanisms of AN are largely unknown. Optimal understanding of how the disorder is established or maintained over the years, and how the chronicity develops, is essential so that effective therapeutic targets can be identified. Despite its complex and multifactorial etiology, studies suggest that AN has both psychiatric and metabolic components. Indeed, recent GWAS analysis has revealed significant genetic correlations between AN and both psychiatric phenotypes and metabolic traits [37,38]. Interestingly, metabolic sensors that are altered following chronic self-starvation play an unquestionable role in reward processes related to food or physical activity that are altered in this psychiatric disorder. However, there are still some gaps and missing pieces regarding the impact of these metabolic factors on specific cognitive aspects of the disorder that are not specifically related to food, such as reduced cognitive flexibility, delayed reward, and preference for habit-driven rather than goal-oriented behaviors (see Outstanding Questions). New technological advances including exome sequencing have allowed the genetic factors underpinning vulnerability to AN to be deciphered. Further investigations into epigenetic mechanisms, such as DNA methylation and transcriptomic gene expression levels, will be important to better characterize how metabolic adaptations induced by extreme nutritional challenge might modulate gene expression and participate in the pathophysiology of AN.

Outstanding Questions

Patients suffering from AN avoid ingesting calories despite the fact that they have a higher physiological state of hunger (increased ghrelin and reduced leptin). Misalignments between environmental cues (peripheral metabolic sensors) and hypothalamic circuits may therefore lead to maladaptive behaviors (repetitive and compulsive behaviors). Does a drive for reward seeking prevail over metabolic demands in the control of feeding in AN patients?

What are the exact neurobiological processes that modify reward responses in AN? Do reward abnormalities alone participate in the maintenance and chronicity of repetitive and compulsive self-restriction?

How can undernutrition contribute to altered reward processes in AN, and can renutrition partly or fully reverse the altered reward abnormalities? What are the exact molecular mechanisms relaying effects of metabolic sensors on reward? What is the contribution of epigenetic modifications to these processes?

There is a paucity of literature on the role of metabolic sensors in specific reward aspects of AN pathology. For example, does chronically elevated ghrelin or reduced leptin trigger delayed reward or reduce cognitive flexibility?

Although AN has been genetically correlated with metabolic phenotypes, the identification of gene variants within a wide range of metabolic factors will be necessary to identify which specific variants within the relevant metabolic pathways are more prevalent in AN, and to test their functionality *in vitro* or in animal models.

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