



# Are we eating more than we think? Illegitimate signaling and xenohormesis as participants in the pathogenesis of obesity

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**Summary** Resource utilization may represent a central force driving evolution. A tight link between sensing energy availability and managing energy acquisition and utilization constitutes a common feature among all organisms. While such a link was likely adaptive during prehistoric evolution, modern lifestyles may decouple perceived cues from actual energy availability so as to promote obesity in humans. A particular illegitimate signal is chronic stress, which may shift body phenotype to suit a more conservative state of energy management. In prehistoric times, such a response likely aided survival during periods of low resource availability. However, new sources of chronic stress have emerged that bear little relationship to contextual energy, which is generally abundant in the modern world. In addition, modern techniques of husbandry and agriculture can produce stress in the food chain, such that food itself can act as an illegitimate signal of chronic stress. Obese livestock and unusual fat profiles in farmed fish, meat, and eggs may reflect stress phenotypes. Consumers of stressed foods may sense those signals – a phenomenon known as xenohormesis – and assume the stressed phenotype. This maladaptive process may promote obesity by erroneously biasing hosts towards caloric accumulation in the context of energy abundance. Regional tissue accumulation of fat may indicate local tissue stress. Atherosclerosis may result from stress signals that induce sympathetic bias and regional fat accumulation in vessel adventitia. Medications such as neuroleptics and foods such as diet drinks may generate illegitimate signals by mimicking molecules used for energy management. Implications for the prevention and treatment of dysfunctions related to these derangements are discussed. New strategies for manufacturing biologics by manipulating stress conditions or controlling fatty acid attachments to proteins are envisioned.

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## Hypothesis

### Evolutionary dislocations of cues that relate to energy

We have previously discussed the idea that energy efficiency may represent the currency of evolution [1]. Our bodies have developed systems to manage

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our acquisition and utilization of energy. Energy intake is governed by two principal factors: how much food we eat, and how many calories our gastrointestinal system extracts. Deployment of energy intake depends on both metabolic rate and level of activity. Environmental factors significantly modulate these intake and expenditure variables.

The increasing prevalence of obesity may arise from numerous evolutionary dislocations associated with modern living. Modern human lifestyles have become substantially remodeled such that energy intake and expenditure characteristics have substantially changed. Furthermore, many cues once linked to the energetic state of the environment no longer reflect actual resource availability. Despite a ready access to energy in the external milieu and a surfeit of activities that require significant energy expenditure, our bodies may extract and use energy in a fashion that may contribute to a variety of metabolic diseases. We focus on the potential for evolutionary dislocation of cues to produce behaviors incongruent with the availability of energy in the environment and consequent metabolic derangements.

## Evidence

### Chronic stress as a source of obesity

Stress is often invoked as a culprit for causing obesity [2]. In higher organisms,, the dominant form of acute stress is the “fight-or-flight” response that induces a shift into a specific mode of energy use best suited for such a situation. Chronic stress during prehistoric evolution likely arose from prolonged decreased access to energy, which induced a shift into a more conservative mode of energy absorption and use. The autonomic nervous system and neurohormonal factors such as cortisol represent control systems that modulate this process so as to optimize metabolic rate, body phenotype, energy storage patterns, and behaviors such as hibernation accordingly. Decreased energy content in the environment may promote increased consumption and absorption of energy as an adaptive response. Such a response likely proved beneficial in prehistoric times to survive prolonged periods of low resource availability.

However, distinctly modern sources of chronic stress have emerged that possess a weak link to caloric availability at best. Furthermore, calories are no longer scarce in the industrial world. This combination of circumstances may render the prehistoric chronic stress response maladaptive and

promote caloric accumulation and obesity. This principle may help explain why low socioeconomic status, aging, mood disorders, and smoking cessation – all source of chronic stress – accordingly demonstrate an association with obesity [3–6]. As an example of the inverse phenomenon, smoking causes low birth weights. Notably, anxiolytics can blunt the weight gain associated with smoking cessation [7]. Emergent modern stressors, such as high density living, may represent illegitimate signals of future caloric scarcity and induce a response that favors caloric accumulation. The benefits of exercise may arise from reduction of chronic stress independent of the caloric expenditure produced by such activity.

### Manipulated food as an environmental dislocation

Consumption of farmed fish and meats may exert a differential effect on coronary heart disease compared with ingestion of their wild-type counterparts, as suggested by their effect on markers of atherogenesis [8,9]. This distinction may stem from differences in fat content and profile, specifically with respect to the ratio of omega-3 to omega-6 fatty acids [10]. Virgin olive oil, made from olives grown on uniquely nurtured trees and processed immediately after harvesting, possesses anti-inflammatory properties not found in its “regular” counterpart. However, we remain unaware of any teleologic explanation as to why eating alternative phenotypes of the same food may exert differential impacts.

We propose that the nature of food may signal the relative stress state of the food chain. Organisms may use this information to assimilate the body phenotype of the food they consume. During evolution, the “consumer” would gain a benefit by recognizing signs of stress, such as caloric deprivation in a routine food source. Early recognition of a “stressed” state of consumed food would allow the “consumer” to enter into an adaptive behavior pathway. Likewise, the production of such signals may have also provided benefit to the organism being consumed, as they might have caused the “consumer” to look elsewhere for a food source.

In the modern setting where the stress signal is an artifice of husbandry, perhaps people become obese – a stressed phenotype – and develop stress-related diseases, such as atherosclerosis, from consuming stressed foods. Eating food that exhibits a stressed phenotype may confer signals of chronic stress to the consumer, who then assimilates the stress phenotype in a Darwinian rendition of “you are what you eat”. In addition, stressed

food may have promoted either migratory behavior or conservative metabolic utilization during evolution. In modern society, migratory response to stressed food may be reduced to frequent motions while at a desk – a phenomenon that is negatively correlated with body fat accumulation [11]. In contrast, a response of conservative metabolic utilization to stressed food would produce obesity.

Other food may also harbor cues that have become evolutionarily displaced. Eggs may express a specific molecular phenotype in their yolk composition in order to convey information on resource availability and maternal stress to their progeny. Our model would predict that free range eggs would have a lower tendency to cause obesity and other diseases associated with sympathetic stimulation, such as atherosclerosis. Genetically engineered plants bred for hardiness may likewise concurrently acquire transmissible stress response mechanisms. Upon ingestion, the stress signal may impact our own perception of and response to stress. In a similar fashion, fermented beverages may impart stress signaling in the form of alcohol and other chemical byproducts that our bodies would normally encounter only under conditions of nutritional deprivation. Eating foods that carry signals that suggest scarcity or the impending need for hibernation, such as plant products indigenously unique to the autumnal season, may lead to the adoption of behaviors that promote hoarding of calories and the consequent development of obesity. Indeed, the stressed food concept may apply throughout the food chain to both plants and animals; modern humans may be consuming inordinate amounts of stress accumulated iteratively through the food chain due to human development.

We have previously proposed that the gastrointestinal system may represent an information filter as well as a conduit for absorption of energy [12]. Dietary iodine may serve as a proxy for energy availability in the environment and that organisms may use dietary iodine intake to tailor their life history strategies using thyroid hormone [13]. Similarly, we believe that life history strategies are intentionally altered by dietary antibiotic intake – a common occurrence in nature – that may signal certain useful information about the state of the food chain. The altered body phenotype and growth trajectory evident on livestock fed with antibiotics are traditionally attributed to changes in gut flora [14], but we believe that the effect may also represent a neurohormonal response to host perceptions of ecologic opportunity. In addition, the traditional chemistry-focused paradigm interprets the so-called nutritional content of food in terms of the roles of its components as media-

tors of enzymatic reactions or repositories of energy. This paradigm neglects the higher-order significance of food components, such as fat, with respect to their functions as biologic signals unto themselves. The ingestion of fat may not lead to obesity due to the caloric density of fat, but rather due to the instructions that fat conveys to alter the programming of the body.

The dissociation of taste from caloric content may also serve as a Darwinian dislocation. Taste can provoke a neurohormonal response including insulin release [15]. In the case of artificial sweeteners, an imbalance of insulin relative to calorie intake may develop, which in turn may lead to metabolic dysfunctions. Supplementation with salt and other additives likely also causes significant distortions in the information conveyed by food. In prehistoric times, we likely gained significant information regarding energetic content from the flavors of that which we consumed, and adjusted our programs of energy management appropriately. However, nowadays the energetic content of ingested material often bears little relationship to the characteristics perceived by our eyes, nose, and tongue, and may cause derangements of metabolic programming. We believe that illegitimate signaling is a concept that applies broadly within the food chain.

## Implications

### Regional obesity

In addition to generalized obesity, accumulation of fat in specific regions of the body may also reflect the differential effects of stress or the emergence of dislocations that affect a particular organ or tissue type. Post-traumatic or post-surgical focal fat deposition may arise from the acute energetic change of the specific event followed by the chronic alterations in energetic content imparted by wound healing. The chronic stress created by localized inflammation or infection may lead to fatty accumulation in the liver, pancreas, heart, and other organs.

Atherosclerosis may epitomize this process. Various mechanistic explanations exist for how risk factors for atherosclerosis, such as aging, diet, inactivity, cholesterol levels, hypertension, diabetes, and smoking actually damage the vessels. We recently proposed that the deleterious effects of aging, diabetes, smoking, hypertension, and inactivity manifest through sympathetic bias in the adventitia [16]. We now extend this hypothesis by suggesting that the association of diet with athero-

sclerosis may operate through the induction of adventitial chronic sympathetic activity by stressed foods, independent of direct endothelial fat or cholesterol infiltration. The chronic sympathetic bias in the autonomic insertions of the adventitia may not only explain the secondary endothelial dysfunctions, but may also explain why the adventitia of diseased vessel segments exhibit tremendous regional fat accumulation. The stressed adventitia may locally recruit fat as a maladaptive response to perceptions of local chronic stress.

## Medications

Ketones are produced during times of starvation and have the effect of suppressing appetite and sex drive. Such behaviors may represent adaptations to a nutritionally starved environment. Neuroleptics, which contain functional ketone groups, also blunt sex drive and cause weight gain, suggesting that our bodies may interpret the presence of neuroleptics as an indication of a low energy state.

In addition, the new generation of biologic medicines may contain data that reflects the stress phenotypes of their production hosts, and thus may inadvertently convey these messages to the humans that consume them. For protein-based therapeutics, potential carriers for stress signals include glycosylation, glycation, and various lipid modifications, such as palmitoylation, myristylation, and prenylation. Perhaps we should use expression systems that are not stressed and attempt to derive medicines from natural hosts, so as to avoid the risk of countervailing dislocation.

Alternatively, perhaps we can harness these responses to our advantage. The potential exists for medications to become tailored to convey particular energetic cues so as to intentionally alter energy uptake and metabolism in a specific fashion. Controlling the stress states of production hosts may yield different medicines for different indications. Stress may represent another variable of production potentially amenable to useful manipulation during manufacturing of biologic drugs. Perhaps controlling lipid modification could also alter the therapeutic function of proteins.

## Therapeutic implications

Some avenues to minimize the effects of dislocations appear relatively simple. If they function as potential stress signals to the humans that consume them, calorie restricted animals or non-stressed animals may constitute healthier food

sources, as would organically grown vegetables. Olive oil, a well-established but poorly understood cardioprotective agent, has potent anti-inflammatory properties [17] that may arise in part from signaling effects. Aromatherapy and massage seem to accompany reduction in obesity [18]. Although the association with socioeconomic status may confound proper assessment of such practices, they may also exert effects by inconvertibly confining our perception of the ongoing energetic state within a certain bound of experience, thereby reducing the potential for the intrusion of stress or evolutionary dislocation. Ideally, we may want to live as close as possible to a state of nature to minimize exposure to potentially deleterious dislocations. Realistically, we may eventually gain sufficient awareness to avoid creating dislocations and to remedy existing dislocations. A potential strategy for treating dislocation may involve introducing substitutes or proxies to either properly recontextualize displaced cues, or to displace them to our advantage rather than to our detriment. We envision many methods to harness the phenomenon of xenohormesis to therapeutic advantage.

## The many roles of fat

At one level, fat constitutes energy; at another level, it may serve to convey stress; at still another level, it may also function to compensate for stress. Fat may facilitate the signaling of stress either by serving as a carrier for other molecules that function in this role, or through the direct action of fatty acids and lipids themselves. The accumulation of fat at sites of injury may also function to sequester toxins and other byproducts that would have deleterious consequences if released systemically. Furthermore, because of its capacity for self-assembly and its ability to sequester molecules and environments, fat creates boundaries to enable potentially antagonistic elements to coexist, thereby reducing the potential stresses created by undesired but necessary proximities. In doing so, it may drive the creation of complexity by enabling multiple contradictory processes to simultaneously occur. As such, fat may serve as a key mechanism by which energy efficiency drives evolution.

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