Medical Hypotheses (2006) **66,** 263–269

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medical hypotheses

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# Obesity and ADHD may represent different manifestations of a common environmental oversampling syndrome: a model for revealing mechanistic overlap among cognitive, metabolic, and inflammatory disorders

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Received 11 February 2005; accepted 21 February 2005

**Summary** Obesity and attention-deficit hyperactivity disorder (ADHD) are both increasing in prevalence. Childhood exposure to television has shown linkage to both ADHD and obesity with the former ascribed to dysfunctional cognitive hyperstimulation and the latter to altered patterns of diet and exercise. Empirical evidence has contradicted prior presumptions that the hyperactivity of ADHD would decrease the risk of obesity. Instead, obesity and ADHD demonstrate significant comorbidity. We propose that obesity and ADHD represent different manifestations of the same underlying dysfunction, a phenomenon we term environmental oversampling syndrome. Oversupply of information in the form of nutritional content and sensory content may independently predispose to both obesity and ADHD. Moreover, the pathogenic mechanisms of these conditions may overlap such that nutritional excess contributes to ADHD and cognitive hyperstimulation contributes to obesity. The overlapping effects of medications provide further evidence towards the existence of shared etiologic pathways. Metabolism and cognition may represent parallel systems of intelligence, and oversampling of content may constitute the source of parallel dysfunctions. The emerging association between psychiatric and metabolic disorders suggests a fundamental biologic link between these two systems. In addition, the immune system may represent yet another form of intelligence. The designation of syndrome X subsumes seemingly unrelated metabolic and inflammatory entities. Environmental oversampling syndrome may represent an even more inclusive concept that encompasses various metabolic, inflammatory, and behavioral conditions. Apparently disparate conditions such as insulin resistance, diabetes, hypertension, syndrome X, obesity, ADHD, depression, psychosis, sleep apnea, inflammation, autism, and schizophrenia may operate through common pathways, and treatments used exclusively for one of these conditions may prove beneficial for the others.


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0306-9877/$ - see front matter 
doi:10.1016/j.mehy.2005.02.042

## Hypothesis

We propose that obesity and ADHD effectively represent different manifestations of the same underlying dysfunction, a phenomenon we term environmental oversampling syndrome. An excess of exogenously supplied information in the form of nutritional content and sensory content may independently predispose to both obesity and ADHD.

## Evidence

### Obesity, and ADHD: information oversupply may cause dysfunction

The rising prevalence of obesity is generally attributed to greater nutritional accessibility and more sedentary lifestyles, but many aspects of the condition remain enigmatic, and effective treatment continues to prove elusive [1]. Other putative contributors to this heterogeneous disease, including environmental and genetic factors, have become a focus of intense research [2]. Attention deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder of childhood. Genetic, structural, and neurophysiologic factors are thought to play roles in its pathogenesis, but empiric evidence has proven inconclusive [3]. Therefore, studies have increasingly turned to examining the role of environmental influences [4].

With few exceptions [5], numerous national studies have suggested that childhood exposure to television is associated with obesity, lipid disturbances, and poor cardiovascular health during adulthood [6,7]. Although the associations may reflect numerous confounding factors, some authors have suggested that television viewing may have causal effects on obesity [8,9]. The success of obesity interventions based on reducing television exposure supports these arguments for causality [10]. The blame has largely rested on the idea that television promotes marked lifestyle changes featuring an imbalance of caloric intake and expenditure [11].

In similar fashion, an association appears to exist between childhood exposure to television and ADHD [12]. Although the correlation may reflect confounding factors, debate has centered on the role of dysfunctional cognitive hyperstimulation as the causal factor [13]. Numerous studies have shown that the nature and extent of stimulation from the environment during early development modulates the density of neuronal synapse formation [14].

We have previously argued that digestion and cognitive perception can be construed as parallel systems of intelligence [15]. Contrary to prior speculation that ADHD would decrease the risk of obesity, new empirical evidence suggests that ADHD has an association with an increased risk of obesity [16]: a recent study shows that ADHD shows a particular prevalence amongst those adults with extreme obesity [17].

Since ADHD is associated with the risk of obesity, oversampling of sensory content through venues such as television may contribute to obesity, independent of any sedentary lifestyle factors. Indeed, television content appears to have a stronger association with obesity than sedentary lifestyle factors [18], suggesting that cognitive oversampling plays an underrecognized role. Cognitive impairments associated with ADHD may result in social disabilities [19] and self-destructive compulsive behaviors [20] that predispose to overeating and obesity. While innate compulsive tendencies are often blamed in these conditions, perhaps these tendencies also result from environmental oversampling.

### Potential mechanisms of overlap

The dopamine receptor gene DRD4 has shown linkage to both obesity and ADHD, suggesting the existence of a potential common pathway for both diseases [21—23]. Thought to lead to insufficient reward satiety normally mediated by dopamine, the DRD2 receptor dysfunction induces a hunger for reward, or reinforcing information, that the activities of risk taking, substance abuse, and abnormal eating habits might satiate [24]. Indeed, patients with ADHD or obesity commonly exhibit such behaviors [24]. Obesity appears to induce downregulation of DRD2 receptors, which may induce dopamine-pathway neurologic dysfunctions such as ADHD and further exacerbate obesity [25]. D2 agonists, which modulate various psychiatric symptoms, also appear to reduce insulin resistance associated with obesity [26]. Dysregulations of the hypothalamic—pituitary axis may represent a nexus of metabolic dysfunctions and psychiatric diseases, and thus may play a role in the association between obesity and ADHD.

Long-term potentiation (LTP) in the brain represents another potential site of mechanistic overlap between behavioral disorders and obesity. LTP dysfunction has shown linkage to various mood and anxiety disorders that also show an association with obesity [27]. Although the behavioral disorders

presumably predispose to obesity, behavioral disorders also potentially arise from obesity [28]. Cytokines such as IL-8 can dampen long-term potentiation (LTP) [29], and inhibition or dysfunction of hippocampal LTP have correlated with the development of ADHD and impulsive behaviors [30]. Since patients with obesity and overfeeding syndromes exhibit dysfunctional regulation of numerous cytokines including IL-8 [31], cytokine-induced LTP dysregulation represents a plausible mechanism by which nutritional oversampling can induce ADHD. Feeding also induces release of gut—brain hormones such as melatonin, secretin, cholecystokinin (CCK), leptin, ghrelin, vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP), somatostatin, and neuropeptide Y (NPY). Many of these compounds also inhibit or modulate LTP [32,33]. Melatonin may also regulate obesity [34]. Low plasma tryptophan level, which predicts brain uptake and production of serotonin (a precursor of melatonin), has shown an association with obesity [35]. Interestingly, dysfunctions of melatonin and zinc, which promotes LTP [36], have been implicated in ADHD [37]. Although LTP represents a plausible pathway by which nutritional oversampling can induce behavioral disorders, further empiric observations are necessary to support this view.

As evidence that psychotropic and metabolic drugs exhibit crossover effects emerges, the notion of an overlap of their respective pathways of action has become more likely. Evidence suggests that methylphenidate, a drug commonly prescribed for ADHD, can reduce obesity [38]. Clonidine, prescribed for ADHD, appears to also reduce insulin resistance [39]. Selective serotonin reuptake inhibitors (SSRIs), antiepileptics, and bupropion, have demonstrated benefits in both ADHD [40,41] and obesity [42,43]. Interestingly, some psychotropic medicines that have shown benefits in ADHD such as antipsychotics and tricyclics [44] tend to induce weight gain or insulin resistance [45,46]. Whether effects on metabolic function arises from compensatory responses remains unknown, but even paradoxical cases further strengthen the notion that metabolic and psychiatric dysfunctions may operate through overlapping pathways.

The psychotropic effects of metabolic drugs have undergone less study but show similar effects. Metformin, which is prescribed for insulin resistance and obesity, have shown benefit in mood disorders [47]. Conversely, dexfenfluramine, an appetite suppressant banned by the Food and Drug Administration due to its association with cardiac valvular dysfunction, appears to worsen psychiatric dysfunctions [48]. The crossover effects of metabolic and psychotropic agents provide further evidence for our hypothesis.

## Darwinian perspective

Illegitimate signaling constitutes a ubiquitous feature of Darwinian competition. We define illegitimate signaling as the production of a signal by an individual that exploits an existing response to that signal in another individual for the purposes of fitness gain. Predatory fireflies of the *Photinus* genus can decode and exploit the mating signals of fireflies in the genus *Photinus* to lure *Photinus* males to their death [49]. Competition among conspecifics may also create opportunities for fitness gain through illegitimate signals such as the false alarm call of the willow tit, *Parus montanus*, who uses the tactic to hoard food [50]. Illegitimate signaling pervades human societies, and innovations in mass communication and transportation may have furthered this process through the dissolution of kin-based tribal communities. Whereas inclusive fitness considerations and reciprocal altruism mitigated incentives to exploit other members in closely-related tribal communities [51], the benefit-to-cost ratio of illegitimate signaling may escalate in modern human societies as kin networks have dissolved through enhanced mobility. Emergence of mass media further enables the practice of illegitimate signaling and has become an instrument for asymmetric fitness transfer between members of society. Plastic surgery, email spam, political double-speak, pornography, and misleading advertising comprise but a few of the countless examples of the phenomenon.

The use of television programming as a tool for illegitimate signaling seems intuitive. Given the business model driven by viewer attention, primal sensory archetypes that command viewer attention permeate television programming. These sensory archetypes correspond to environmental features that probably once represented significant Darwinian value to the beholder, such as sexual cues, violence cues, bright colors, loud noises or alarm signals, and fast movement. The television industry exploits these preexisting sensory archetypes by supplying an overabundance of attention-demanding signals. Such hyperstimulation of the audience may now apparently induce health consequences among viewers. Without kin-based tribal behavioral incentives in place to keep this asymmetric incentive in check, this trend has continued to escalate.

Parallels exist in the food industry, as food sales depend on sating hunger while catering to sensual preferences. The emergence of the ability to mass produce food has created an imbalance between caloric availability and the innate sensory demand for those calories [52]. Economic incentives drive companies to produce food that serve the sensory demands of the population for salt, fat, and sweets, even if meeting and exceeding those demands carry health consequences. By catering to preexisting sensory demands that hold far less adaptive value today than they did during the prehistoric era, the food industry has effectively exploited illegitimate signals. For both the food and media industries, the desire to stand out among the noise has created incentives to use various signaling tactics to draw attention. As with the oversampling of cognitive content, the oversampling of nutritional content has become a source of many diseases, the most prominent of which is obesity.

Our ability to distinguish meaningful signals from illegitimate signals has not evolved fast enough to counter these trends, and humans may find themselves in a position of unprecedented susceptibility to oversampling stimuli. However, such traits may not necessarily represent maladaptations. Organisms appear to alter life-history strategies depending on how they perceive the availability of energy in the environment. Organisms tend to take on a defensive Darwinian posture during times of resource scarcity that may reflect diminished ecologic opportunity, and pursue a more aggressive strategy during times of resource abundance. Lifespan shortens during calorie-rich environments as compared with calorie-restricted settings [53]. During periods of cooler or widely varying temperatures, potential cues of resource uncertainty, many species skew offspring gender ratio towards the smaller sex, often females [54]. During rising temperatures, surrogates for higher energy states and greater ecologic opportunity, offspring gender bias shows skew towards the larger sex, typically males [55]. At lower temperatures, fungi reproduce asexually as hyphae, a more conservative evolutionary strategy. At higher temperatures, they reproduce sexually as yeast, a more aggressive approach [56]. Similarly, rising temperatures impair the function of heat shock protein (HSP)90, a buffer against phenotypic variation, which further suggests that higher temperatures may promote evolutionary risk-taking [57].

If ADHD and obesity represent manifestations of environmental oversampling, these conditions may correlate with risk taking behaviors. Indeed, both ADHD and obesity show correlation with gambling behaviors [58,59]. Bright colors, incessant noises, abundant alcohol and food, and risqué images are ubiquitous features of casinos, which benefit from elicitation of gambling behaviors. Furthermore, variations of DRD2 and DRD4 genes, linked to ''novelty seeking'' traits as previously noted, have shown association with ADHD, substance abuse, and obesity [60]. Death, or programmed self-termination, constitutes a favorable adaptation in certain inclusive frameworks of evolutionary fitness considering the welfare of the entire community [61]. Negative effects of obesity and ADHD on lifespan [62,63], mediated through processes such as insulin resistance and self-destructive behavior such as addiction [58,64], may paradoxically reflect an overall enhancement of fitness.

## Implications

While causal arguments can be made in either direction, we suggest that ADHD and obesity represent different manifestations of a broader oversampling syndrome. Obesity is a component of syndrome X, a classification which mechanistically ties together a myriad of seemingly unrelated metabolic and inflammatory conditions such as sleep apnea, insulin resistance, heart disease, diabetes, and dyslipidemia. Seemingly disparate psychiatric conditions such as depression, ADHD, conduct disorders, autism, bipolar disorder, and psychotic disorders can undergo inclusion within a single behavioral syndrome in a similar fashion similar to syndrome X. Indeed, the behavioral dysfunctions of hyperstimulation and metabolic-inflammatory dysfunctions of syndrome X may eventually merge into the definition of a unified, overarching oversampling syndrome.

Given the inclusion of inflammatory dysfunctions in this framework, some immune dysfunctions may also represent a phenomenon of oversampling. Syndrome X has an affiliation with numerous immune disturbances and inflammation. Inflammatory conditions also occur in conjunction with behavioral disorders. Secondary effects of drugs that influence immunology and behavioral biology further support a relationship between these two categories of phenomena. Immunomodulators such as IL-2 induce behavioral dysfunctions such as depression Alterations of serotonin biology through SSRIs appear to have immunomodulatory effects. The immunomodulatory effects of other psychotropic drugs such as clonidine and bupropion have become increas-

ingly recognized. In addition to the link between ADHD and obesity, an association between ADHD and allergy has also emerged [65].

The teleologic rationale for linking the immune, metabolic, and cognitive pathways remain unknown, but we have developed a working framework that views them as parallel systems of intelligence. Our framework assumes that the immune and metabolic systems, in addition to their respective roles in host defense and energetics, also serve to acquire and process environmental content. Independent from their abilities to incite defense mechanisms and to satiate host biochemical resource needs, the data gathering capability of these systems may partially account for the gut—brain neuroendocrine and autonomic co-regulations. The autonomic system further regulates immune and metabolic functions. Cytokines can impose feedback control and modulate hypothalamic function, as well as influence neuronal regulation of immune, metabolic, and behavioral systems]. Previous reviews have discussed the ability of the immune, metabolic, and neural systems of intelligence to communicate through various other avenues [66].

Our hypothesis suggests that many current treatment strategies devoted to a particular metabolic, inflammatory, or behavioral disorder may ultimately prove suitable for treatment of diseases in all three categories. Indeed, pathogenic theories emergent in one discipline may offer valuable insights towards understanding of the other two. For instance, in addition to the modern changes in diet and lifestyle factors, genetic imprinting and DNA methylation are increasingly being implicated in the modern explosion of obesity and syndrome X [67]. In similar fashion, genetic imprinting and DNA methylation may play a role in the modern proliferation of psychiatric disorders and inflammatory disorders by promoting susceptibility to hyperstimulation. In addition, modern changes in the pattern of light exposure, less during the day and greater during night hours, have been implicated in the emergence of behavioral disorders such as ADHD and inflammatory diseases, possibly operating through melatonin dysfunction [68,69]. These same environmental factors may explain the sudden rise of obesity, inflammatory, and metabolic conditions during modern times. The apparent convergence of science with respect to immunity, metabolism, and behavior suggests that greater research collaboration and cross-disciplinary exchange of ideas among these disciplines may accelerate understanding of common mechanisms underlying many diseases.

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