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Review

Neurobiology of the metabolic syndrome: An allostatic perspective

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Abstract

The metabolic syndrome is a cluster of more or less related metabolic and cardiovascular derangements including visceral obesity, insulin resistance, blood and tissue dislipidemia, high blood pressure and it is often associated with neuroendocrine and immunological dysregulations. The aetiology of this syndrome is clinically highly relevant because it predisposes to life-threatening complications, such as Diabetes Mellitus, kidney failure, cardiovascular disease, and certain types of cancer. Contributing factors include a sedentary life-style combined with increased dietary fat intake and psychosocial stress. From a biological viewpoint, however, the metabolic syndrome can be considered as a maladaptive consequence of an initially successful adaptation to high environmental demands. As opposed to pre-historic times — when environmental demands were usually energy-costly (e.g., fight/flight/hunt) and nutritional resource often inadequate — energy-utilizing actions serve no longer an optimal solution to deal with environmental demands of current human society. This paper describes the interactions between psychosocial stress and nutrition and how these may affect emotional and metabolic components of the metabolic syndrome. A deeper understanding of these interactions is necessary to come to effective treatment and prevention of the metabolic syndrome in the future.

Keywords: Psychosocial stress; Obesity; Energy balance; Human; (Rat)

Contents

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1. Introduction

The metabolic syndrome or "syndrome X" is a condition characterized by a number of related metabolic and cardiovascular abnormalities, including visceral obesity, insulin resistance, glucose intolerance, hypertension, an athrogenic plasma lipid profile, low-grade inflammatory state, and certain neuroendocrine derangements including elevated levels of "stress" hormones (Bjorntorp and Rosmond, 2000; Moller and Kaufman, 2005). A critical issue for the health of individuals who have several of these abnormalities in concert is that they have a highly increased risk of developing debilitating diseases including type-2 diabetes mellitus, cardiovascular complications, kidney failure, certain types of cancer and cognitive impairments (WHO Technical Report series, 2002; James et al., 2004; Marchesini et al., 2004; Yaffe et al., 2004). The underlying causes of this syndrome are as yet unknown, but factors related to a change in life-style have spurred the idea that the metabolic syndrome is actually a life-style induced disease. Despite the fact that clinical professionals and health care organisations warn continuously for the devastating consequences of an "unhealthy" life-style, recent surveys of the World Health Organisation indicate that the prevalence of humans with the metabolic syndrome is increasing at an alarming rate (WHO Technical Report series, 2002). If no serious break-through is reached soon, it is estimated that more than half of our population will be affected within the near future, and the costs associated with the treatment of the associated illnesses become staggering to our society. While the aetiology of the metabolic syndrome is relevant from a clinical standpoint, it may be proposed that it is, in fact, a maladaptive consequence of an initially successful adaptation to regulate energy balance under conditions of increased environmental demands. A thorough understanding of the underpinnings of the metabolic syndrome would require insight in its original adaptive nature as well. In this paper, we will discuss neurobiological strategies of energy balance in demanding environments and put these into a mechanistic framework of how this could lead to obesity and metabolic derangements.

2. Thrift in demanding environments

Throughout the course of animal history, environmental demands have continuously shaped species by natural selection (Darwin, 1859). This has, among others, provided many species including humans with highly efficient mechanisms to find, ingest, and absorb nutrients. When absorbed nutrients exceed immediate metabolic requirements, they can be packed into storage tissues, and later released for metabolic purposes. These features allow animal species to eat their food in bouts interspaced by intermeal-intervals, and nonetheless maintain long-term energy balance (Strubbe and van Dijk, 2002; Woods et al., 2000). Ingesting nutritionally rich food items clearly has the advantage for maintaining body energy stores most optimally. It has been suggested that this enabled animals to live through periods of famine and the most thrifty individuals would have the highest survival chances. In 1962 James Neel proposed that humans surviving repeated periods of starvation had "thrifty genes" which enabled them to do so by storing excess nutrients more efficiently in their bodies in times of plenty than others (Neel, 1962). This efficient storage capacity would involve enhanced insulin responses during eating behavior. The downside of this increased capacity to store fuels is that it could lead to metabolic derangements such as Diabetes Mellitus when these periods of famine are no longer occurring (Neel, 1962). This "thrifty genotype" hypothesis has attracted tremendous attention over the last decades, since it held a promise to find the genetic underpinnings of — and potential treatment strategies to combat — the current epidemic of obesity and metabolic diseases (Cummings and Schwartz, 2003). A problem with this theory might be that specific polymorphic "thrifty genes" have not been discovered on a large scale in the obese population, and it has therefore been questioned whether these exist at all (Speakman, 2006). Moreover, past episodes of famine by lack of natural reserves might have happened too infrequent to favour selection of "thrifty genes" (as opposed to certain diseases) (Speakman, 2006). Although it is too early to call off the search for these genes in our opinion, environmental factors might be equally or even more prominently involved in determining how thrifty one is, without necessarily altering the gene pool. A compelling case has for instance been made for early perinatal programming of life-long regulation of energy balance by Hales and Barker (Hales and Barker, 1992). They hypothesized — and found evidence — that poor foetal growth due to placental dysfunctioning or malnutrition during pregnancy could propel a "thrifty phenotype" and associated metabolic derangements later in life in the offspring. The adaptive component (i.e., thriftiness) makes sense from a survival point of view. The maladaptive component is a "catch-22" since maternal obesity and type 2 Diabetes Mellitus obtained from poor foetal growth could lead to relatively heavy newborns with also increased risk for development of obesity and metabolic diseases later in life (Dabelea and Pettitt, 2001; Hutcheon et al., 2006). In either case, the magnitude by which potential "thrifty genes" (if they exist) and/or perinatal/epigenetic programming events will eventually lead to obesity and cardiovascular and metabolic complications relies upon the environmental settings which individuals will face later in life.

Frequently mentioned life-style factors that propel obesity and the metabolic syndrome are increased intake of dietary fat and sweeteners and sedentariness (WHO Technical Report series, 2002). Evidence is increasing, however, that also psychological factors play a role in the development and propagation of obesity and the metabolic syndrome (Bjorntorp, 1992; Brunner et al., 2002). It can be imagined that over the course of animal evolution, psychological stress had an intimate relationship with nutrition as selection criteria for survival. It may for example be expected that a relative mild food shortage easily changed the relation between animals from co-consumers to competitors fighting for these shrinking natural reserves, which finally affects the relation with animals higher — up in the food chain (for example due to increased exposure to predation) (Sweitzer, 1996). Subjects with the greatest ability to select under those

pressures nutritionally rich food — of course in a trade-off fashion with effort to obtain it — had, and probably still do for many wild life animals, the highest chance to live through these stressful episodes. Especially finding dietary fat would qualify, because it contains the most energy per unit weight among nutrients, and therefore adds most to filling of reserve tissues (Rolls, 2000). When nutritionally rich (and usually palatable) food is abundant, but the environmental demands are changing such that energy-utilizing actions (i.e., fight, flight, or hunt) are no longer required, these biologically adaptive mechanisms can easily become maladaptive, and trigger obesity and associated metabolic derangements. Such a situation might very well apply to humans in our society of plenty, in which a sedentary life-style combined with a "rat-race" competition and high responsibilities may put extremely high psychological pressures on individuals. This idea seems confirmed by epidemiological studies in which the metabolic syndrome was found most prevalent among individuals under psychosocial pressure or chronic stress (Bjorntorp, 1992; Brunner et al., 2002).

3. Neuroendocrinology of energy balance

3.1. Basic mechanisms

Before beginning to understand the mechanisms that may drive the aetiology of the metabolic syndrome, we will first discuss the mechanisms by which animals are capable of maintaining energy balance. Several decades ago, Kennedy was one of the first to recognize the stability of energy balance of animals over most of their adult life (Kennedy, 1953). He realized that the amount of energy an animal utilizes is almost exactly matched by the amount of energy it consumes. Since the smallest distortion of this match leads to alterations in the amount of body fat, Kennedy hypothesized that the amount of body fat is the regulated factor underlying energy balance (Kennedy, 1953). Around the time Kennedy proposed this mechanism, Hetherington and Ranson had already discovered that lesions in the ventromedial hypothalamus caused rats to become extremely hyperphagic and obese (Hetherington and Ranson, 1983). Thus, it was proposed further that a factor related to the amount of stored body fat would act in the ventromedial hypothalamus where it would reduce food intake, stimulate metabolism or both. This idea was reinforced in 1994 by Friedman and colleagues, who discovered that adipocytes produce a hormone which they called "leptin" (coming from the Greek word leptos meaning "thin") (Zhang et al., 1994). Leptin circulates in the blood stream roughly in proportion to body adiposity, and enters the brain where it acts on specific leptin receptors which, among other, are found, among other, in the ventromediobasal part of the hypothalamus. Indeed, minute infusion of leptin into the hypothalamus causes rodents (Van Dijk, 2001) and primates (Tang-Christensen et al., 1999) to reduce their food intake and stimulate their metabolism. The mechanisms underlying this effect include leptin interacting with neuropeptidergic neural pathways that arise from several hypothalamic regions, and these pathways project to most other regions in the brain (Schwartz et al., 2000). This negative feedback loop involving leptin production and signalling is working in humans as well since rare mutations in leptin synthesis or leptin receptors result in extreme forms of obesity (Farooqi and O'Rahilly, 2004).

There are many other factors that are integral to the above-mentioned regulation. When an animal senses food, this information is processed in the brain and the animal can approach it, or hunt it down, and ingest it. Its decision to do so obviously depends upon its history. Thus, when an animal has finished a meal just prior to seeing the next food item, signals related to the filling of the gastrointestinal tract (Dockray, 2004) and the metabolic status of the liver (Scharrer, 1999) are conveyed via afferents which connect these organs to the brainstem. In turn, regions in the brainstem (including the nucleus of the solitary tract, area postrema, locus coeruleus, and the parabrachial nucleus) relay this information and pass it on to the hypothalamus and limbic structures, and finalize it into a sensation or perception of satiety in higher brain regions, and the animal may decide not to eat it (Berthoud, 2004). However, when the animal remembers from other occasions that the palatability of this next food item is very high, satiety can be overruled by a sensation of reward which the animal gets (or "anticipates" to get) from ingesting it (Berthoud, 2004; Schultz, 2002). The animal will eat it, despite the fact it is satiated. The mechanisms underlying reward include regions in the fore- and midbrain, such as the ventral tegmental area/substantia nigra and the nucleus accumbens. It is currently believed that both gastrointestinal/hepatic satiety and nutritional reward signals are regulated by leptin (Figlewicz, 2003; Matson et al., 2000). Besides regulating energy balance, evidence is increasing that leptin action in the brain has a major effect on neuroendocrine/autonomic outflow (Van Dijk et al., 1997; Van Dijk et al., 2003). Indeed, the above-mentioned neuropeptidergic pathways project to the preganglionics of the autonomic nervous system, and they regulate the activity of several neuroendocrine axes (Elmquist, 2001). This way, leptin acting in the brain can regulate peripheral fuel fluxes in and between organs (Van Dijk et al., 2003). When central leptin action is blocked, this not only leads to increased filling of adipose tissue (i.e., through increased food intake and reduced metabolism), but it also leads to overflow of fat fuels from adipose tissue to non-adipose organs such as the liver, muscle, and pancreas (Cohen et al., 2001). Since the intracellular fatty acid level in insulin sensitive organs (such as the liver and muscle) directly interferes with insulin signalling, it is most likely that this latter mechanism is the prime culprit underlying whole body insulin resistance and dyslipidemia (Boden and Shulman, 2002). Whereas the mechanisms behind this phenomenon are still not entirely clear, a teleological explanation may be that filling of extra-adipose tissue is simply enlarging the total storage capacity of fat fuels in the body. This might make sense from an evolutionary point of view, as has been pointed out before by Neel (1962).

3.2. Environmental context

Besides regulating energy balance and fuel homeostasis, another function of the brain is, of course, to protect animals

from threats in the environment. Through the senses, information regarding (potentially) dangerous situations or threats in the environment is processed in limbic brain structures (including the hippocampus, the amygdala and the prefrontal cortex), which finally leads to the sensation of "fear". Among the emotions, fear is probably the best studied (LeDoux, 2003; McEwen, 2003; Miller et al., 2005), and is highly relevant in acute situations like threat of predation or social conflict. When facing immediate danger, an animal can defend itself or run. In either case, a "stress response" is initiated by the brain which serves to alarm the body in an anticipatory fashion for its internal defence. The initiation of this response occurs at the level of the hypothalamus, where neuronal cell bodies release corticotropin-releasing hormone (CRH) which eventually leads to the stimulation of glucocorticoid production (cortisol in primates, and corticosterone in rodents) and epinephrine release from the adrenal gland (Sawchenko et al., 1993). These hormones activate the cardiovascular system and respiration, serve to mobilize energy to muscles, and they set immunological priorities (Bohus et al., 1993; Pollard, 1997). Low-priority functions like gastrointestinal functioning and reproduction are decreased under those conditions. Glucocorticoids also feedback to the brain where they can inhibit the neural systems where the stress response was initiated (Young and Vazquez, 1996). On the other hand, glucocorticoids improve memory functions (Roozendaal and McGaugh, 1997), ensuring that future threats are detected as early as possible, and can be coped with effectively (i.e., avoided or passively/actively dealt with).

In 1865, Claude Bernard published his "Introduction à l'étude de la médecine expérimentale" in which he realized that maintenance of a stable milieu inside the body in the face of external changes was a necessary condition for a free life (Bernard, 1865). This concept was further outlined by Walter B. Cannon, who introduced the term "homeostasis" ("homeo" means "same"), and popularized it further in the early twentieth century (Cannon, 1932). The concept of homeostasis is nowadays largely used by scientists who study the regulation of fuel fluxes in the body and the capacity of the body to maintain energy balance (see previous paragraph) mainly through negative feedback-regulatory mechanisms. Although there is still a lot of debate around this subject, the ability of the body to respond to threats in an anticipatory fashion in order to keep the "internal milieu" stable has been termed allostasis ("allos" and "stasis" are Greek words for "change" and "stable"), and is used since the early 1980s. It is more complete than the term homeostasis. The classic image of an allostasis mechanism is that of a predator running after its prey. Both animals allow deliberate disruptions of "fuel homeostasis" on the short term to enable these fight/flight responses. In his book "The end of stress as we know it", McEwen points out that the situations that ignite stress responses nowadays are increasingly ones for which neither fight nor flight is an option. These stressors are often psychological in nature (e.g., working for an overbearing boss, or caring for a family member who is seriously ill, etc). As a result, the stress response can become more prevalent and stronger, or even become chronic. Frequently or continuously elevated plasma levels of epinephrine and the resulting surges in blood pressure can damage the blood vessels of heart and brain, and eventually lead to atherosclerosis, a major risk factor for heart attack and stroke (McEwen and Lasley, 2002). Excessive and prolonged amounts of circulating glucocorticoids impair the immune system, reduce insulin action, and cause visceral fat storage to accumulate. Within the brain, high levels of glucocorticoids can cause damage to vulnerable brain structures such as the hippocampus (Sapolsky, 1996). The damage that the allostatic response causes when stressors are inescapable is termed "allostatic load", and this resembles, in fact, many aspects of the metabolic syndrome (Korte et al., 2005; McEwen and Lasley, 2002).

4. Interactions between stress and nutrition

Current knowledge of the neurobiology of stress and regulation of energy balance has finally advanced to a level to allow an integration of the two. The systems that serve the regulation of energy balance are strongly interconnected to the ones that regulate the allostatic responses to environmental demands. For example, Dallman and colleagues have pointed out that glucocorticoids are key in shifting fuel homeostasis from a fed to a fasting state (Akana et al., 1994). This shift would be necessary to maintain fuel homeostasis during fasting. When food becomes available, glucocorticoids increase feeding behavior (Tempel et al., 1992), thereby offsetting its own increase. A similar mechanism involving glucocorticoids could also be active during stress situation as pointed out earlier. Evidence is available that the effect of glucocorticoids is mediated by a number of neural pathways in the brain that serve the effects of leptin as well, but in opposing directions (Jeanrenaud and Rohner-Jeanrenaud, 2000). In addition to increased food intake, also several signs of the metabolic syndrome are found upon chronic central glucocorticoid administration (Jeanrenaud and Rohner-Jeanrenaud, 2000), an effect that is consistent with certain diseases characterized by hypersecretion (or action) of glucocorticoids (Chrousos, 2000). Leptin is more efficacious to reduce feeding behavior in animals without adrenals than in sham operated animals (Drazen et al., 2003). This increased efficacy is counteracted by treatment of dexamethasone, a synthetic glucocorticoid (Drazen et al., 2003). Finally, the obesity resulting from leptin deficiency, as well as most other monogenetic or central lesion-induced (Dallman et al., 1993) models of obesity can be corrected when the adrenal glands of obese animals are removed.

As a whole, these interactions seem to indicate that a high glucocorticoid/leptin signalling ratio might underlie the aetiology of the metabolic syndrome (Zakrzewska et al., 1997). However, do these interactions also underlie the metabolic syndrome in ecologically relevant situations?

At this moment, several laboratories world-wide are concerned with the study of the aetiology of the metabolic syndrome resulting from allostatic mechanisms. In general, investigations are conducted using genetically selected/modified rodents in laboratory conditions or in humans in clinical settings. Although there is no doubt that this work has greatly

advanced the knowledge within the field of regulation of energy balance and neuroendocrine regulation of metabolism and ingestive behavior, these studies have not been very instrumental in elucidating the true underpinnings of the metabolic syndrome. A major problem of revealing these underpinnings is that they become obscured and untraceable as soon as the metabolic syndrome becomes a fact. In a new approach, we have recently initiated investigation of psychosocial pressure on aetiology of the metabolic syndrome in genetically normal rats. Our laboratory embraces a model of psychosocial stress in which rats are subjected to social defeat on 2–3 occasions by a dominant rat in a resident–intruder paradigm (Buwalda et al., 2001; Koolhaas et al., 1997). Following social defeat, stressed rats feeding a healthy carbohydrate-rich diet developed transient loss of appetite, behavioral inactivity and fever, and temporarily or chronically lose body weight (Koolhaas et al., 1997). They showed long-term deterioration of mood (Meerlo et al., 1996), and displayed a reduced performance in a so-called novel object recognition paradigm (van Dijk and Buwalda, unpublished observation). Upon reintroduction with the dominant rat by which they were defeated previously, the rats responded with strong conditioned behavioral and neuroendocrine responses (van Dijk and Buwalda, unpublished observation). Although psychosocial stress is clearly a heavy stressor, and causes profound allostatic responses, the rats feeding a "healthy" diet did not show signs of the metabolic syndrome, as evidenced by similar plasma insulin responses to intravenously infused glucose and plasma adiponectin levels as compared to undefeated controls. A different picture emerged, however, when rats undergoing psychosocial stress were feeding a high-fat diet. In this case, psychosocial stress caused a profound lowering of plasma adiponectin levels (i.e., which is a strong indication for development of type-II diabetes mellitus in humans (Hotta et al., 2000), and a markedly increased plasma insulin response following an intravenous glucose challenge, indicating insulin resistance. None of these effects were observed in rats feeding the same high-fat, but had not undergone social defeat stress (van Dijk and Buwalda, unpublished observation). These data therefore suggest that psychosocial stress leads to characteristics of the metabolic syndrome provided that these rats are feeding an "unhealthy" high-fat diet.

5. Towards ecologically relevant models

The use of psychosocial stress in the resident–intruder paradigm has the advantage for the investigator to exert reasonable experimental control, and as explained above, this can be an excellent asset to the study of the aetiology of the metabolic syndrome. To investigate these interactions in a model with a higher face-validity for the human situation, interactions between psychosocial stress and dietary fat on energy balance and the aetiology of the metabolic syndrome can be investigated in colony-housed rats. Psychosocial stress is common in many animal species living in colonies and typically results from competition for resources such as space, access to a reproductive partner, food or water. A number of animal models have been developed to capitalize on the tendency of different species to form social hierarchies when housed in groups, including rats (Blanchard and Blanchard, 1990; Fokkema et al., 1995; Tamashiro et al., 2004), mice (Ely and Henry, 1978; Van Oortmerssen, 1971), and non-human primates (Barrett et al., 2002). Establishing and maintaining dominance in a group setting is psychologically and physically stressful for all parties, including both the dominant and the subordinate animals. Furthermore, since animals are group-housed for extended periods of time, the members of the group are continuously exposed to stress as opposed to intermittent acute exposures as mentioned in the resident–intruder paradigm. A potential problem with studying colonies is that the experimental control of the investigator is reduced. Sakai and colleagues partly resolved this issue by studying colony-housed rats kept in semi-natural "visible burrows" (Tamashiro et al., 2004). Briefly, the visible burrow system (VBS) includes a large surface area, to which smaller chambers are connected by a number of tunnels. It involves housing of mixed-gender (typically four or five males and two females) groups of rats in a semi-naturalistic burrow environment continuously for 14 days or longer. Within a few days after colony formation, a dominance hierarchy forms among the males of the group resulting in 1 dominant and 3–4 subordinate animals.

Controls are single males pair-housed with a single female. The VBS model has the advantage of forming stable hierarchies over time: i.e., it has been used for investigating the effects of single as well as repeated episodes of exposures to psychosocial stress (Tamashiro et al., 2005). There is no indication that the animals habituate to VBS housing conditions as indicated by the persistence of significant stress-induced behavioral and physiological changes that occur during VBS housing. These include decreased body weight and elevated basal glucocorticoid levels in subordinate males (Tamashiro et al., 2004).

Interestingly, subordinate animals rapidly regained body weight during a recovery phase (outside the VBS), but, compared to dominant animals, they mainly did so by significantly elevating visceral fat content. The latter effects were stronger when animals were feeding a high-fat diet (Tamashiro et al., 2006).

6. Dissociating emotional and metabolic aspects of stress and diet interactions

The data of Sakai and colleagues point out that metabolic derangements might particularly develop in the emotional recovery phase following psychosocial stress, with dietary fat and sedentariness as propagating factors. Our studies using the resident–intruder paradigm may also involve a comparable recovery component which could act independent of the metabolic consequences of stress and dietary fat. In fact, in contrast to the deleterious permissive effects of feeding a high-fat diet on the development of the metabolic syndrome in psychosocially stressed rats, we unexpectedly observed that a number of other "negative" effects of the psychosocial stress were markedly attenuated by feeding the high-fat diet. Thus, psychosocially stressed rats feeding the high-fat diet appeared

to have lower neuroendocrine and behavioral responses when being reintroduced with the dominant rat by which they were previously defeated than psychosocially stressed rats feeding the high-carbohydrate chow. One potential mechanism through which feeding a high-fat diet mediates these effects, is that it is "comforting" for them. This idea has been proposed by Dallman and colleagues (Pecoraro et al., 2005), who hypothesized a role for glucocorticoids in these effects. While this certainly can be a potential mechanism, experiments of the group of Dallman do not point to dissociation between the types of nutrients; i.e., rats would find a solution to reduce their emotional allostatic load in any nutrient with a higher palatability, including fats and sugars. Indeed, when supplied in solution, restrained-stressed rats (Pecoraro et al., 2005) can ingest sucrose avidly. Our data point to a more specific role of fats in alleviating emotional stress, and this in agreement with the findings of Levin et al. (2000), showing reduced fear and stress responses in diet-induced obese rats. In addition, our psychosocially stressed rats feeding a high-fat diet performed significantly better in a behavioral test, in which their performance was assessed to identify a novel object. Finally, psychosocially stressed rats feeding the high-carbohydrate diet showed a down-regulation of the hypothermic response to the serotonergic (5HT) agonist, 8-OH-DPAT, which is clinically used as a marker for deterioration of mood (Lesch, 1991). This down-regulation was not observed in psychosocially stressed rats feeding the high-fat diet (Buwalda et al., 2001). Thus, despite the fact that rats feeding the high-fat diet were on a fast lane towards the development of the metabolic syndrome, they appeared to handle the psychosocial stress better on cognitive and affective fronts. In this event, the concept of allostasis may come to mind again and may provide a conceptual framework. On the one side, these findings might be explained to indicate that high-fat feeding reduces the emotional allostatic load, and simultaneously increases the metabolic allostatic load following psychosocial stress on the other side.

These simultaneous effects of a high-fat diet on emotional and metabolic allostatic loads have a number of implications. First of all, when a high-fat diet causes animals to cope easier with stress because it reduces the animal's emotional allostatic load, it can be imagined that rats as well as humans "like" or "want" (Berridge, 2004) to ingest increasing amounts of fat under conditions of elevated environmental demands. There are a few reports that indeed point to this effect (Oliver et al., 2000; Wardle et al., 2000; La Fleur et al., 2005). At this point, it is very important to consider the type of environmental demand or stress. If the environment allows an active coping strategy which drains a lot of energy (such as during fight/flight/or hunt), the metabolic allostatic load will not easily develop, even if the animal would ingest a high-fat diet (see Fig. 1A). However, if the environment does not permit an active coping strategy (such as during inescapable psychosocial stress) and thus no drain of energy takes place, there is no break on the development of the metabolic allostatic load (Fig. 1B).

In addition, threats faced by an active coping strategy generally take less time to end than those that are faced by passive coping strategies, and lasting threats could add to the emotional allostatic load more easily (Fig. 1B). The worst-case scenario is the situation in which the threat becomes chronic, and cannot be off-set by the passive coping strategy (Fig. 1C). If food is available in unlimited quantity and choice, it is conceivable that individuals crave for "comforting" food items, and dietary fat may represent an alternative default

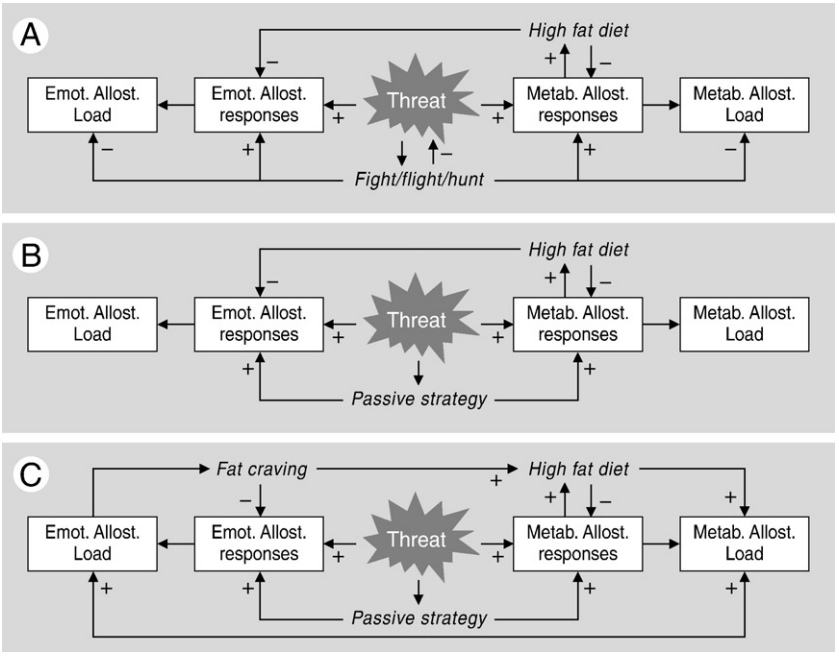

Fig. 1. Models of interaction between high-fat feeding and environmental threat. A) The course of events when an active strategy (fight/flight/hunt) to the environmental threat is possible, and quick relief is found. High-fat feeding serves as a high energy source to meet metabolically demanding events. B) When the environment does not allow an active strategy (such as during inescapable psychosocial stress). No quick relief is found. Note that the negative breaks on emotional and metabolic allostatic loads are lost. C) This situation becomes worse if a passive strategy becomes a static state, and environmental threats can not be relieved at all. The emotional and metabolic allostatic loads are hypothesized to reinforce one another.

mechanism for "enduring the threat". This increased dietary fat intake adds further to metabolic allostatic load, etc. In this way, all breaks on the system are lost and a pathological vicious circle is initiated. We propose that emotional and metabolic allostatic loads start adding on to each other, potentially due to intracellular wear and tear of metabolic machinery, which eventually will lead to all characteristics of the metabolic syndrome, including deterioration of mood.

7. Potential brain mechanisms subserving allostatic responses

As pointed out above, high-fat feeding and psychosocial stress increase the metabolic allostatic load in rats, and there is growing evidence that this can also occur in humans (Brunner et al., 2002; Vitaliano et al., 2002). It is assumed that these interactions are ignited within the brain and are reflected in the peripheral body, and these latter effects eventually impose upon the brain again. One potential mechanism underlying the development of the metabolic syndrome may be a reduction of leptin signalling in the brain. Indeed, we have previously shown that central leptin insensitivity predicts development of several characteristics of the metabolic syndrome in normal rats (Van Dijk et al., 2005). Then how could feeding a high-fat diet result in a decline of leptin signalling in psychosocially stressed (genetically normal) animals, and at the same time be protective against deterioration of mood?

As mentioned earlier, pathways responsible for brain leptin signalling include several neuropeptide systems that arise form hypothalamic nuclei (Schwartz et al., 2000). Among these is the brain melanocortin system. Gene expression of proopiomelanocortin (POMC) — from which the melanocortin receptor agonist alpha-melanocyte stimulating hormone (MSH) is spliced post-translationally — is stimulated by leptin (Van Dijk et al., 1999), and treatment with a specific melanocortin receptor blocker can prevent leptin's anorexigenic action (Adage et al., 2001; Seeley et al., 1997). While obesity in animal models of obesity via leptin resistance can normally be corrected by removing the adrenals of the obese animals (Jeanrenaud and Rohner-Jeanrenaud, 2000; Zakrzewska et al., 1997), obesity and metabolic syndrome that follows from a disturbance in brain melanocortin system seems to be an exception to this rule (Yaswen et al., 1999). Mice with targeted deletion of POMC are obese, but do not have adrenals (Challis et al., 2004). The latter is probably due to the fact that POMC expression in the pituitary, which normally gives rise to ACTH production, is required for adrenal development (Karpac et al., 2007). Because psychosocially stressed rats feeding the high-fat diet initially appeared to increase their metabolic allostatic load without lasting elevated glucocorticoid levels (in fact the reactivity of the HPA axis was reduced in our psychosocially stressed rats feeding the high-fat diet upon reintroduction with the dominant rat), there could be a potential role for diminished brain melanocortin activity in the initial aetiology of the metabolic syndrome in high-fat feeding rats subjected to psychosocial stress.

There are a number of observations that back up this idea. First of all, we have previously observed that chronic central pharmacological blockade of melanocortin receptors in rats increases visceral adiposity in these animals, and that these effects are markedly enhanced upon feeding a high-fat diet (on which they became significantly more hyperphagic) relative to those feeding a high-carbohydrate diet (Morens et al., 2005). This effect of the high-fat diet was not seen in animals not infused with the melanocortin receptor antagonist. Since many others have shown that increased high-fat diet intake reduces POMC gene expression in the arcuate nucleus — see e.g. (Huang et al., 2004; Parton et al., 2007) — this situation could become intrinsically reinforcing (Adan and van Dijk, 2006). This effect, however, probably depends on glucocorticoid action since mice that lack 11β-hydroxysteroid dehydrogenase Type 1 (the catalyzing enzyme for regenerating active intracellular glucocorticoids) do not show reduced POMC expression when subjected to high-fat feeding (Densmore et al., 2006). Thus, although we stated that obesity and the metabolic syndrome could result from POMC deficiency independent of glucocorticoid action, this does not mean that glucocorticoids may not be required for the effect of high-fat feeding to lower the activity of the POMC neuron. While acute stress (which leads to increased levels of glucocorticoids) is able to increase arcuate nucleus POMC expression (Larsen and Mau, 1994), we propose that this increase is transient, and eventually becomes reduced below basal levels when this is associated with feeding a high-fat diet. A lowering of POMC expression and thus a subsequent reduction of brain melanocortin activity may have two consequences, namely it would induce hyperinsulinemia and thriftiness (Fan et al., 2000), and, secondly, animals would lighten up emotionally (Kokare et al., 2005). In fact, reduced brain melanocortin activity has been suggested to be anti-depressive (Chaki and Okubo, 2007) and to reduce the effects of stress on affective (Liu et al., 2007) and ingestive (Vergoni et al., 1999) behaviors.

Like mice, humans bearing a genetic mutation causing POMC deficiency are hypocortisolemic and obese as well (Krude et al., 2003). Together with mutations in the melanocortin-4 receptor, they represent the most common forms of monogenic obesity known today (Farooqi and O'Rahilly, 2004; Farooqi and O'Rahilly, 2005). When polymorphisms in a certain system are far more widespread than those in other systems, but underlie seemingly comparable trait characteristics (in this case obesity), there could be a beneficial side effect associated with these frequent polymorphisms. In the case of the brain melanocortin system, these beneficial side effect might be found on the emotional front.

8. Concluding remarks and future perspectives

It was mentioned in the beginning of this paper that the metabolic syndrome may be a maladaptive consequence of an initially adaptive strategy to deal with environmental demands. These demands probably included frequent episodes of famine and psychosocial threats. Given the intimate relation of these factors such that they could have created common selection criteria for survival over the course of animal history, it is no surprise that the neurobiological mechanisms to deal with

threats (i.e. stress response) and famine (i.e., food seeking behavior, ingesting energy dense food, and large nutrient storage capacity in body depots) are highly linked. While it is not surprising on the same grounds that a relationship exists between these factors in the development of the maladaptive component (i.e., the metabolic syndrome), the precise neurobiological underpinnings are as yet still unsure. In our view this has partly to do with the methodologies used to investigate these underpinnings. Most laboratories concerned with the study of the aetiology of the metabolic syndrome utilize genetically selected/modified rodents in laboratory conditions without social interaction. Since it is becoming clear that "psychosocial stress" is an important component in the development of the metabolic syndrome, it is important to consider experimental paradigms that take account of these issues. Thus, it is therefore necessary to focus on the development of the metabolic syndrome in ecologically relevant animal models which highly translates to the human situation. These conditions are characterized by 1) ad libitum availability of palatable food, 2) low physical activity, and 3) a highly demanding environment in which psychosocial stressors are most common. How could we use this knowledge to prevent the aetiology of the metabolic syndrome? It is evident that minimizing nutrient intake, and particularly that of fat, would alleviate some of these effects, but a reduction in food intake in an attempt to lose body weight and metabolic derangements leads to compensatory metabolic adjustments that minimize weight loss (Leibel et al., 1995). In addition, drastic reduction in fat consumption might even be considered not to be useful in this event since the model represented in Fig. 1 predicts that relief of emotional allostatic load by dietary fat intake could represent some form of comfort control. It seems more plausible based on Fig. 1 that losing energy through exercise, or other metabolically demanding events (Chakravarthy and Booth, 2004) is a more successful way to reduce metabolic allostatic load. Moreover, regular exercise improves mood and could be helpful in coping with stress (Anthony, 1991). Another form of metabolic relief could be provided by subjecting animals to a diet which contain elevated amounts of poly-unsaturated fatty acids (PUFAs). As opposed to saturated fatty acids, which form the bulk of fat source of the high-fat diet which we provide to the animals in our studies, poly-unsaturated fatty acids are known to stimulate the enzymatic machinery involved in the oxidation pathways of fatty acids (Clarke, 2001). Although the underlying mechanisms are not entirely clear, evidence is becoming available that the brain plays a role in the effects of exercise (Scheurink et al., 1999) and of elevated dietary poly-unsaturated fatty acid levels (Wang et al., 2002) on energy balance, and probably include systems downstream from leptin signalling. We are currently assessing these treatment strategies to investigate whether they can prevent the development of the metabolic syndrome in psychosocially stressed rats feeding a high-fat diet, and which central neural pathways can be assigned to contribute to these effects. Effective drugs that tie into the pathways through which exercise and dietary poly-unsaturated fatty acids-enrichment have beneficial effects in curing the metabolic syndrome could be used as potential treatment modalities as well. Above all these options, it would be most optimal to find a societal solution for our "stress" problem, and — given the epigenetic windows of metabolic programming — this should be considered already at a very young age (McEwen, 2000).

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