Stress and eating behavior
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Abstract
How stress, the stress response, and the adaptation of the stress response influence our eating behavior is a central question in brain research and medicine. In this report, we highlight recent advances showing the close links between eating behavior, the stress system, and neurometabolism.

Introduction and context
When humans undergo acute mild mental stress, their global cerebral metabolic rate for glucose increases by 12% [1]. As the brain has limited storage capacity, the cerebral energy demand from the body should closely match the cerebral needs. That the brain is capable of controlling its energy supply could be seen from the early observation that during inanition all organs of the body (heart, liver, kidney, and pancreas) lose 40% of their weight whereas the weight of the brain changes by only 1% or less [2].

To demand energy from the body, the brain can activate its stress system (i.e., the sympathetic nervous system [SNS] and the hypothalamus pituitary adrenal [HPA] system). Once the stress networks in the upper brain stem, including the ventromedial hypothalamus (VMH) and the paraventricular nucleus, are activated, energy – particularly glucose – is allocated to the brain. With SNS activation, insulin secretion from beta cells is suppressed [3] and insulin-dependent glucose uptake via glucose transporter type 4 (GLUT4) into the body periphery becomes limited [4,5]. In this way, glucose is available via insulin-independent GLUT1 transport across the blood-brain barrier [6,7].

The failure of the brain to match its energy demand with its need becomes evident in patients with Addison’s disease. Addison patients, who are known to display disintegration of the entire stress system, have been shown not only to lack sympathoadrenal activity but also to suffer from neuroglycopenic symptoms (‘neuroglycopenia’ refers to a shortage of energy [glucose] in the brain) [8]. It is noteworthy that this deficit in cerebral energy could be alleviated partly by the intake of high-calorie food [8].

As excess cerebral glucose uptake has been observed during acute mental stress in humans [1], subsequent animal studies have provided evidence that functional brain activation leads to cerebral accumulation of products in intermediary metabolic pools that are subsequently consumed and oxidized during recovery [9].

After acute stress, energy homeostasis should be restored. The excess glucose extracted by the brain has to be replenished in the body stores. One possible solution is taking up energy from the near environment (i.e., eating food) [10]. The SNS/HPA response and the eating response to stress are sequentially activated, with glucocorticoids being crucial in integrating these modes of energy procurement [11]. These two stress responses are finely tuned and adapted in order to match the exogenous and endogenous energy fluxes toward the brain. Almost certainly, this tuning and adaptation process is executed by the stress and emotional networks located in the cerebral hemispheres.

Major recent advances
The logistics of brain energy
In 2009, a paper was published making use of supply chain principles and laws, taken from the fields of logistics
and economics, to describe the central and peripheral energy metabolism [12]. The supply chain of the brain – with the central nervous system as the final consumer – describes the energy fluxes from the remote environment to the near environment, through the body, toward the brain (Figure 1). The supply chain is branched; that is, it is possible to store energy in side buffers such as muscle and fat tissue. It is a general principle in economic supply chains that the flux can be determined by both the supplier (push component) and the receiver (pull component). In other words, the fluxes are regulated by offer and demand (insert in Figure 1). The fluxes transport the energy in various forms. This publication on neuroenergetics presented the concept that a healthy organism is maintained by an ‘efficient brain pull’ which serves systemic homeostasis and that the underlying cause of obesity is ‘inefficient brain pull’ (i.e., that the brain is unable to properly demand and receive glucose from the body).

**Brain-pull mechanisms**

In the last two years, the mechanisms of brain pull have been better understood due to major scientific contributions. The brain pull functions to demand energy from the body. Two brain-pull mechanisms have been detected so far: first, allocative brain-pull mechanisms, which activate the SNS and the HPA axis to favor glucose allocation to the brain, and, second, astrocytic mechanisms, which enhance glucose transport via GLUT1 through the blood-brain barrier.

Two new papers showed that the cerebral need for energy is sensed and metabolically assessed by intracellular ATP.
On the one hand, Sherwin and colleagues [13] reported that activation of the SNS in the glucose-deficient state is mediated by ATP-sensitive potassium channels that are located on GABAergic neurons adjacent to VMH neurons. On the other hand, Carruthers and colleagues [14] demonstrated that the GLUT1 pore is not a fixed pore allowing glucose to enter cells but that this transport molecule displays an intercellular ATP-binding site that opens up the GLUT1 pore when intracellular ATP is absent. The discovery of this mechanism demonstrates that astrocytes which are equipped with GLUT1 are able to actively demand or ‘pull’ energy according to their needs. It has further been shown that astrocytes connect among each other to form astrocytic networks that supply neurons on demand [15]. In summary, mechanisms have been recently detected that fulfill a brain-pull function and allow the brain and its neurons to systemically and locally order more energy in an ATP-dependent manner.

**Ingestive-pull and storage-push mechanisms**

Besides the brain-pull mechanisms, there is an additional pull mechanism that conveys the demand for energy from the near environment: eating. It is not surprising that eating behavior, which constitutes a distinct step in the cerebral supply chain, is controlled by energy sensors located in a different compartment. Denis Burdakov and colleagues [16] showed that glucose receptors are found on the surface of neurons in the lateral hypothalamus and that these drive eating behavior by sensing glucose in the cerebral extracellular space. Thus, astrocytic and neuronal mechanisms driven by intracellular ATP fulfill the function of brain pull while mechanisms driven by extracellular cerebral glucose, which is closely related to blood glucose, fulfill the function of ingestive pull.

Recently, an essential work was published on how energy is stored in the side buffers of the supply chain (i.e., muscle and fat tissue) and how feeding behavior is affected. Insulin-deficient rats were provided with different amounts of insulin. The researchers could clearly show that insulin promotes body weight gain and increases the ingestion of sucrose but not fat [17]. In this way, it becomes clear that insulin fulfills the function of a storage hormone by mediating a push component of the energy flux from blood to the energy stores: the higher the energy content in the blood (glucose), the more insulin is secreted in order to enhance glucose uptake via GLUT4 into peripheral tissues. In all, recent research has expanded our knowledge of brain pull and other push/pull components that are operative in the supply chain of the brain.

**Stress needs and brain pull**

By means of the invasive Kety-Schmidt technique in humans, global cerebral metabolic rate for glucose has been found to be increased during mental stress [1]. It is likely that under stress conditions, the SNS/HPA response mediates the brain-pull function and is essentially involved in augmenting the body-to-brain energy flux. Since there is experimental evidence that the brain does actually consume the extracted excess glucose [9], it is also likely that the cerebral need is increased during and after mental stress.

When the behavior of the cerebral supply chain under conditions of increased cerebral need due to brain activation is studied, various changes can be observed (Figure 2): the brain pull is increased, the energy flux from the body toward the brain augmented, the energetic equilibrium in the blood and muscle/fat compartment burdened, and the peripheral energy stores reduced. These observations within the supply chain are similar to those that occurred in approximately 40% of students who participated in two British studies and reported decreased food intake during stress, or weight loss [18,19]. Thus, it is conceivable that weight loss in an individual is driven by a persistent SNS/HPA stress response or, in other words, by a persistent overactive brain pull. There were, however, other participants (approximately 50%) in these British studies who, in contrast, reported increased food intake during stress, or weight gain [18,19]. What was different in these individuals? Did they respond differently with their SNS and HPA axis to a given stressor? Is there experimental support of this latter view?

**Adaptation of the stress response: from brain pull to comfort eating**

People with chronic stress often develop depressive symptoms [20], and hyperactivity of the hypothalamic-pituitary-adrenal axis is one of the most consistent biological findings in major depression psychiatry [21]. When the stressor persists, some people adapt with their stress responses (i.e., their SNS/HPA responsiveness decreases) whereas others do not [22]. Does the brain in some cases use a metabolic coping strategy combining ‘comfort eating’ (increased intake of calorie-rich foods) with an unburdening of the stress system (brain pull) and in this way allow stabilization of mood and cerebral energy homeostasis?

When the behavior of the cerebral supply chain under conditions of both increased cerebral need and decreased brain-pull efficiency is studied, a development and
progression of diverse peripheral metabolic abnormalities can be observed (Figure 3): if the needs of the brain are increased and the brain-pull activity is reduced and food intake is increased, then the brain energy content is found to be preserved. On the other hand, energy is found to accumulate in blood and peripheral tissues as a build-up in the cerebral supply chain. Under these conditions, the brain is supplied by the increased push component from the blood, and the hyperactive brain-pull can remain unburdened. It could be proven analytically that a general property is inherent in the presented cerebral supply chain: the fat compartment increases with decreasing brain-pull efficiency [12]. Hence, the development of obesity is predicted to occur with an inadequate sympathoadrenal stress response.

These observations of occurrences in the supply chain as described here are similar to those abnormalities that have been found in subjects who participated in a large epidemiological study in Norway. The intriguing paper on this large cohort by Amljot Flaa and colleagues [23] demonstrated that low sympathoadrenal activity predicts body weight gain during an 18-year follow-up study. These researchers performed a mental stress test in 99 healthy men of normal weight. In the 18-year follow-up investigation, they found that a body weight gain could be predicted by a low sympathoadrenal response to the stress test at baseline. This study provides decisive support for the view that inadequate sympathoadrenal responsiveness to a mental stressor is a crucial causal factor for the development and progression of obesity.

What are the causal factors that reduce the responsiveness of the SNS/HPA system in people who develop obesity? Chronic stress in adult life may play a major role in adaptation of the stress response. The topical paper by Block et al. [24] provides new insights into the association between stress and long-term weight gain in a large representative cohort. These researches used a longitudinal cohort of 1355 subjects and showed that several domains of psychosocial stress were associated with weight gain over a period of 9 years in both women and men with higher body mass index. Among the people with high baseline body mass index, weight gain was associated with increasing levels of psychosocial stress related to ‘job-related demands’ and ‘difficulty paying bills’. In men, additional factors such as ‘lack of skill discretion’ (variety of work and opportunity for use
of skills) and 'lack of decision authority' were important; in women, 'perceived constraints in life' and 'strain in relations with family' were important. Thus, adaptation to chronic stressors could play a role in reducing brain-pull efficiency and in this way promote the development of obesity.

In another study in British adults, the presence of chronic and repeated episodes of the common mental disorders of depression and anxiety was a risk factor for subsequently being overweight or obese [25]. Moreover, weight gain and the risk of obesity were increased in a dose-response fashion with the number of episodes of these common mental disorders.

Acute episodic stress in early life can also lead to adaptations in the stress response in later life. Two animal experiments have shown that early-life stress or juvenile trauma results in long-lasting changes in the activity of the autonomic nervous system and body weight [26,27]. In an important human study, Sonja Entringer and her colleagues [28] reported that prenatal psychosocial stress exposure is associated with hyperinsulinemia in later life. The researchers investigated healthy young adults whose mothers experienced major stressful life events during their pregnancy. As adults, these individuals displayed hyperinsulinemia, a strong predictor of weight gain [29,30] and a typical marker of brain-pull inefficiency.

**Future directions**

The recent research papers highlighted in the present report support the view that an adaptation of the SNS/HPA stress response to a chronic-persistent or an acute-traumatic stressor involves a strategy of the brain that on the one hand relieves the overloaded brain pull and improves mood but on the other hand makes it necessary to increase eating behavior. Thus, evidence accumulates that the stressed mind can choose a metabolic coping strategy by switching its supply mode from brain pull to 'comfort eating'.

**Abbreviations**

GLUT, glucose transporter; HPA, hypothalamus pituitary adrenal; SNS, sympathetic nervous system; VMH, ventromedial hypothalamus.

**Competing interests**

The authors declare that they have no competing interests.
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