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THE SELFISH BRAIN THEORY

This is an extract (the introduction) of the review “ The selfish brain: competition for energy resources “ by A. Peters, U. Schweiger, L. Pellerin, C. Hubold, K.M. Oltmanns, M. Conrad, B. Schultes, J. Born, H.L. Fehm.
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The selfish brain: competition for energy resources

1. Introduction

How does the human organism control its energy supply? The answer to this question is the key to treating many diseases: obesity and the so-called metabolic syndrome with diabetes mellitus, hyperlipoproteinemia, hypertension and cardiovascular diseases belonging to these disorders. Gynecological diseases including polycystic ovaries or psychiatric disorders such as depression or eating disorders are also associated with disrupted regulation of energy supplies. Two different processes can be distinguished that regulate energy metabolism: energy supply (appetite, intake of foods) and allocation (assignment). The various organs of the body must compete for the allocation of a limited number of energy resources.

The brain occupies a special position amongst all the organs concerning energy metabolism. It is the central organ for regulating energy supply, and it is able to receive information about the peripheral organs via peripheral (e.g. hepatic) sensors and their afferent neuronal pathways. Conversely, it can also control the functions of many peripheral organs, e.g. the skeletal musculature, the heart, the gastrointestinal tract or the sexual organs, via its efferent nerve pathways. It is probable that this control is not just restricted to physical movements and the function of many inner organs, but that it also includes the regulation of energy metabolism. The neuronal discharge and release of neurotransmitters and neuropeptides requires exceptionally large amounts of energy [1]. The energy consumption of the brain, related to its small proportion of the entire body mass, is much larger than the energy consumption of all other organs (e.g. muscle). The proportion of energy consumed by the human brain exceeds the proportion found in all other known

species. This fact may be relevant for the origin of characteristics and disorders of metabolism found primarily in humans, e.g. obesity. The brain is separated from the general circulation by the blood–brain barrier. Specific substrates (such as glucose and lactate) or hormonal signals (such as insulin or leptin) are transported exclusively by specific transportation mechanisms across the blood–brain barrier [2,3]. Thus, the transfer of substrates and hormones into the brain is very strictly controlled. The capacity of the brain to store energy is extremely limited, but maintenance of the energy supply to the brain is of prime importance to the survival of the whole organism. It is not therefore surprising that the energy content immediately available to the brain, i.e. in the form of adenosine triphosphate (ATP), is strictly regulated within extremely narrow boundaries. The brain is almost exclusively dependent on the metabolization of glucose. As such, selection of substrates by the brain is highly specific, while peripheral organs (muscle) can metabolize glucose, fat or proteins. Fatty acids can not traverse the blood–brain barrier. Only in special situations, such as with hypo or hypernutrition, does the organism produce significant amounts of alternative substrates such as ketones or lactate that can traverse the blood–brain barrier and assume a role in supplying energy to the brain. Finally, the brain is able to memorize information about its control actions and their subsequent effects, and to learn from the outcomes. It can use its plasticity to optimize its control behavior.

Overall, therefore, the unique position of the brain is characterized by
1. its physical barrier properties,
2. its high energy consumption,
3. its low energy storage capacity,
4. its substrate specificity,
5. its plasticity, and
6. its ability to record information from and to control peripheral organs.

In order to account for the idiosyncrasies of the brain's energy supply and to establish the meaning of these for the entire organism, we propose here a new paradigm for the regulation of energy supply in the organism:

- The brain prioritizes adjustment of its own ATP concentration. For this reason it activates its stress system and in so doing competes for energy resources with the rest of the organism (allocation).
- The brain then alters the appetite (food intake) so that it can alleviate the stress system and return it to a state of rest.

With these two postulates, the brain simultaneously represents the highest regulatory authority and the consumer with the highest priority. The brain looks after itself first. Such selfishness is reminiscent of an earlier concept in which the brain's selfishness was addressed with respect to addiction [4]. We chose our title by analogy but applied it in a different context, i.e. the competition for energy resources. During stress and times of shortage it safeguards its own supply even at the expense of all the other organs. The brain's obligation to alleviate its stress system in a second step and allow it to return to a state of rest is not trivial. From a regulatory-theoretic standpoint we presume that the stress system is adjusted

around a so-called setpoint at which it is at a state of rest. In the second step the brain therefore pursues the objective of satisfying its own energetic needs and those of the entire organism on a long-term basis in the most economic way possible. The regulation of the mass of the various body compartments such as the adipose tissue is then considered to be a secondary objective with this paradigm.

According to traditional paradigms the brain regulates body mass by changing the intake of foods. Maintenance of blood glucose within narrow limits is also of key importance for maintaining health. The 'lipostatic' theory was originally formulated by Kennedy 1953 [5]. Jeffrey Friedman and coworkers of the New York Rockefeller University supported this view in 1994 with their ground-breaking finding of the hormone leptin [6]. With leptin, a hormone was discovered in fat and muscle tissue that sends a feedback signal to the brain so that the brain is informed about the status quo of peripherally stored energy. Most researchers considered this to be a closed regulatory system in which the absorption of nutrients is the regulator, body mass is the controlled parameter, and leptin is the feedback signal. Notably, before leptin was discovered, the research team of Stephen Woods and Daniel Porte at the University of Washington, Seattle, presented compelling evidence for insulin being an adiposity signal [7,8]. With the 'glucostatic' theory, blood glucose is considered to be the regulated parameter in the center of the regulatory system and it is assumed that endocrine changes (for example insulin, glucagon, growth hormone, and cortisol) and behavioral changes are mainly responsible for maintaining the concentration of blood glucose within narrow limits. The implicit assumption that an adequate energy supply to the brain automatically results from the constant behavior of the fat reserves and the blood glucose is common to both the glucostatic and the lipostatic theory. Another common feature is the assumption that with obesity a defect can be traced to the closed feedback loop. It can indeed be shown that with most overweight people leptin is not able to restrict the intake of foods. This phenomenon has been termed 'leptin resistance'. Such a leptin resistance is found both as an inherited phenomenon with monogenetic defects [9,10] and as an acquired phenomenon after overfeeding [11]. A large number of neurotransmitters, neuropeptides and their receptors that mediate the leptin effect in the brain, e.g. anorexigens such as 'Melanocyte Stimulating Hormone' (α-MSH), have been studied in detail over the last few years [12]. The phenomenon of leptin resistance has as such been well described, but its origin has so far escaped explanation.

The glucostatic and the lipostatic theories have explicitly or implicitly provided the basis for a large number of research strategies and therapeutic interventions for diabetes mellitus, obesity and other diseases. Against this, however, a range of observations have accumulated that can not be satisfactorily explained by these views and research approaches:

*** If healthy people are advised in a study to overeat considerably over a period of months, they do increase substantially in weight during this time, but within a few months they can return again to their initial body weight [13]. Clinical experience on the other hand shows that although many people show good body mass regulation at the start of their life, in later life (e.g. in the third decade), their body mass increases. If these people then attempt to reduce their body weight by dieting, the 'yo-yo' effect then sets in, and one gets the impression that body weight is regulated at a new, raised virtual setpoint [14]. Phenomena such as the yo-yo effect show that

the system of body mass regulation is more complex than previously assumed. If only a simple defect within the regulatory system for weight regulation exists, such persons should be able to return to and maintain their initial body weight with their normal nutrition after a diet. However, the body mass often exceeds the previous maximum. The fact that only few people succeed in reaching and maintaining their initial body weight means that the traditional view that changes can be found within the assumed closed loop of the body mass regulatory system (e.g. single or multiple gene mutations) is too simple.

*** The study of metabolic, endocrine and behavioral phenomena in repeated hypoglycemia has shown that the brain has mechanisms for protecting its functionality actively within certain limits despite the existence of very variable blood glucose concentrations. The energy supply of the brain therefore represents more than just a by-product of the energy supply of the whole organism.

*** If the energy supply of the brain is threatened, lipostatic signals do not play any significant role in behavioral regulation: ravenous hunger with hypoglycemia occurs independently of the adipose tissue mass of the organism.

*** Traditional treatment concepts of type 2 diabetes mellitus are derived from the glucostatic theory and aim at normalization of blood glucose concentrations. The United Kingdom Prospective Diabetes Study showed that ‘tight’ blood glucose control results in a reduction in the risk of microvascular but not of macrovascular diseases [15].No effects on the overall mortality were observed. As side effects of such concepts using hypoglycemic agents or insulin, undersupply of the brain (recurrent neuroglucopenic comas) or oversupply of fat stores (body mass gain) occurred [15]. Peter G. Kopelman from the Bartholomew’s and the Royal London School of Medicine commented in the editorial that the ‘inevitable rise in glycosylated HBA1c witnessed throughout the study period, despite strict glycemic control, emphasizes the need for a better understanding of the pathogenesis of type 2 diabetes in susceptible individuals’ [16].

*** Traumatization and psychiatric conditions such as depressive or eating disorders lead to modifications in the stress hormone system and various central transmitter systems. They can also lead to considerable increases and also reductions in body fat, even where defects in the fundamental mechanisms of lipostasis or glucostasis have not yet been observed until now. These observations cast doubt on the priority of lipostatic signals in particular.

*** Despite intense research and the outstanding methodology that is now available, genetic defects have been able to explain only a small proportion of obesity and diabetes cases up until now. The observed obesity epidemic throughout the entire industrialized world illustrates this [17,18]. The fact that people of a similar genetic background under defined environmental conditions remain of normal weight or develop excessive overweight early on, however (e.g. Nauruans or Pima Indians) [19], supports a significant role of genetic factors. The traditional view fails to consider that a disorder might also lie outside the feedback system for weight regulation, e.g. in a higher-ranking regulatory system providing it with commands.

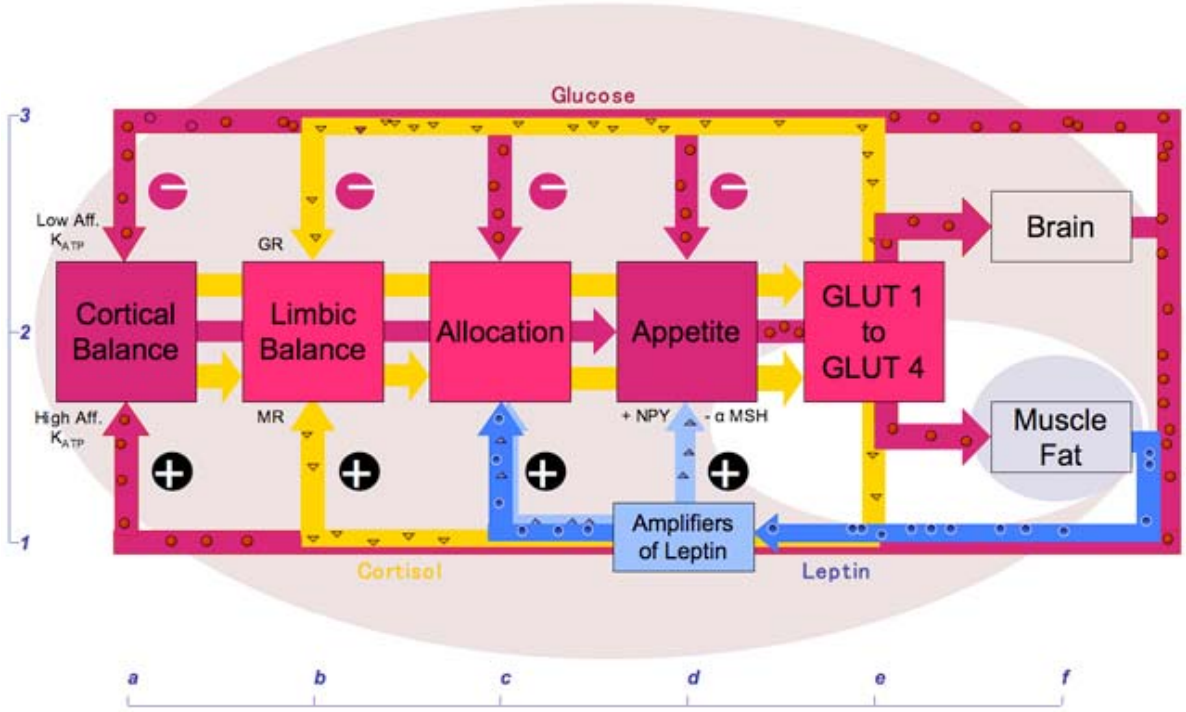

Fig. 1. The 'Fishbone Model' of glucose metabolism. The cerebral cortex sends a 'glutamate command' signal to the subordinate regulatory subsystems: 1. The allocation subsystem assigns glucose via the glucose transporter 1 (GLUT1) to the brain, and via GLUT4 to the muscle and adipose tissue (yellow arrow). 2. The appetite regulatory subsystem controls the total amount of glucose available for allocation (red arrow). The energy content of the brain and peripheral tissues is measured with multiple sensors. The limbic-hypothalamic-pituitary-adrenal (LHPA) system, which includes the sympathetic nervous system, plays a decisive role in allocating glucose. The activity of the LHPA-system is indicated by the serum cortisol concentration. Feedback signals on the energy status in the brain (glucose), the peripheral organs (leptin), and on the activity of the LHPA system (cortisol) act on the various hierarchical levels of the system, i.e. the cerebral cortex, the limbic system and the hypothalamic sites for allocation (ventromedial hypothalamus) and intake (lateral hypothalamus) of foods.

*** Cortical balance. If the brain-ATP is too low, the glutamate command signal is stimulated in the cerebral cortex via high-affinity ATP-sensitive potassium channels; if the brain-ATP is too high, it is suppressed via low-affinity ATP-sensitive potassium (KATP) channels. In this way the system strives for a balance whereby the opposing effects of high-affinity and low-affinity KATP channels are of the same magnitude.

*** Limbic balance. If the serum cortisol is too low, the LHPA system is stimulated via high-affinity brain mineralocorticoid receptors (MR); if the serum cortisol is too high, it is suppressed via low-affinity brain glucocorticoid receptors (GR). Here, the LHPA system strives to achieve a balance whereby the stimulating and suppressing feedback signals are of the same magnitude.

*** Allocation. If the energy content is too great in the muscle and adipose tissue, leptin activates the ventromedial hypothalamus (VMH) that allocates glucose to the brain; if the energy content of the brain is too large, the brain ATP suppresses the VMH, so that glucose is allocated more to the musculature and adipose tissue. Thus, the allocation-subsystem strives for a balance whereby the feedback signals from the brain and the periphery are of the same magnitude.

*** Appetite. If the energy content is too low in peripheral tissues, the appetite stimulating lateral hypothalamus (LH) is activated via NPY; if the energy content is too large in the periphery, the LH is inhibited via α-MSH. The NPY- and a-MSH-signals are filtered in the arcuate nucleus (ARC) and conveyed only under certain circumstances to the LH. The key feedback-signal for regulating the intake of foods is brain glucose.

If the stimulatory and inhibitory feedback-signals in the cerebral cortex, in the LHPA system, and in the hypothalamus are balanced, the organism achieves a state of energetic homeostasis. Coordinates indicate positions in the model that are referred to in the text.

While most research continues to focus on crucial hypothalamic circuits, a small group of scientists have already broken new ground, since recent work has clearly shown that ingestive behavior is influenced by a widely distributed neural network, which includes the caudal brainstem, limbic and cortical structures [20–22].

The paradigm proposed by us places the regulation of ATP-concentration in the brain at the focal point. The brain initially adjusts its own ATP-concentration by burdening its own stress system and competing for energy resources within the body. The brain changes eating behavior so that it can then alleviate the stress system and return it to a state of balance. The regulatory principles of this paradigm have been formulated mathematically as a dynamic system and graphically illustrated in the form of a so-called ‘fishbone model’ [23] (an overview is given in Fig. 1, more details are explained in chapter 2).

Readers and authors are faced with a dilemma regarding the needs of simplicity and complexity, i.e. between merely a suggestive and an explicit representation of specific mechanisms. The fishbone model has a simple but not a trivial structure: it represents a hierarchically organized system with a forward pathway (similar to the spine of a fish) and multiple paired stimulatory and inhibitory feedback pathways (the fishbones). Flow charts of complicated control systems can be simplified by mathematical transformations [24]. The most simple model for allocating energy resources to 2 organs, e.g. to the brain and muscle, has a ‘fishbone’-like structure. Such a special model structure is suitable for dealing with different levels of complexity.

Is the model oversimplified or too abstract?

One point of view might be that important hormones (e.g. resistin, ghrelin) escape mention here so that the true complexity of energy metabolism is not delved into. We reviewed the literature and indeed often found two or more biological mechanisms for each individual component in the mathematical model. As such there appears to be much redundancy in glucose regulation. Redundant signal pathways can be added to the fishbone model (new fishbones) without changing the basic model structure. The activation of the sympathetic nervous system is mediated by leptin and insulin as well. In the model, the hormone leptin conveys a signal to the brain that energy has been stored in peripheral organs, particularly in the adipose tissue, and is not therefore available at that time as a substrate for the brain. Correspondingly, leptin conveys a signal to certain hypothalamic neurons [25] and in this way invokes an increase in sympathetic nervous system activity and thereby an increased allocation of glucose to the brain. Insulin sends a similar signal analogous to this. Insulin in the same way informs the brain that glucose is stored and unavailable for supplying the brain. Correspondingly, insulin can influence the same hypothalamic neurons in the same manner [26], so that the sympathetic nervous system is stimulated and the appropriation of glucose by the brain is ensured. This example shows that leptin and insulin transmit related or similar signals to the brain. There may be distinguished differences in the timing of their

feedback signals, however, in principle they transmit redundant messages. The stimulatory insulin feedback pathway can be integrated into the fishbone model without changing its fundamental structure. Only the degree of redundancy, and not the relevancy of the model, is changed through such additions.

Is the model too complex or explicit?

We have in fact refrained from including a large number of biological mechanisms that might also fulfill functions in the model. A list of various possible redundant signals was presented in an earlier manuscript [23]. However, we decided to assign only a single functional mechanism and a single anatomical structure to a single signal pathway in the model. Leptin acts for example as a 'substitute' for a class of signals that contains insulin amongst other elements, and which can fulfill all the functions described in the model. We are aware that there might be a better selection for such a substitute, and that in the future hormones might be discovered that fulfill this function better and so have a greater biological relevance than the ones mentioned here. This may likewise account for the selection of brain structures referred to in this paper. The limbic system and the hippocampus for example are extremely complex structures per se, supporting many other specific functions not relevant here, and of course, those relevant here may in part be fulfilled by other redundant structures. We are also aware that the assignments proposed here might be the subject of some debate, but we feel that the specificities of the model presented are less important than the general basic principle proposed here for energy metabolism. We followed the advice that 'everything should be made as simple as possible, but not simpler' [27].

The newly presented theory regarding the regulation of energy supply is only valid within a certain scope. For example, many experiments that are cited here in support of the model have only been carried out under special experimental conditions in in-vitro or in animal studies, but have not yet been confirmed in humans. Also, many studies in humans cited here have only been performed in men but not in women. Several hypotheses can be derived from the presented model. In the future, testing of such hypotheses shall allow a redefinition of the scope within which the theory is valid, whether it should be broadened or narrowed. In this review article we would like to apply the 'selfish brain theory' to offer new explanations for phenomena which until now have escaped clarification.

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