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*Review Article*

# The Selfish Brain: Competition for Energy Resources

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*ABSTRACT* Obesity and type 2 diabetes have become the major health problems in many industrialized countries. Here, I present the unconventional concept that a healthy organism maintains its systemic homeostasis by a "competent brain-pull", i.e., the brain's ability to properly demand glucose from the body, and that the underlying cause of obesity is "incompetent brain-pull." I describe the energy fluxes from the environment, through the body, toward the brain as the final consumer in a "supply chain" model. There is data-based support for the hypothesis, which states that under conditions of food abundance incompetent brain-pull will lead to build ups in the supply chain culminating in obesity and type 2 diabetes. There is also support for the related hypothesis, which states that under conditions of food deprivation, a competent brain-pull mechanism is indispensable for the continuation of the brain's high energy level. To experimentally determine how the competent brain-pull functions to demand for cerebral energy, healthy young men undergoing psychosocial stress were studied. It was found that the brain under stressful conditions demands for energy from the body by using a brain-pull mechanism, which is referred to as "cerebral insulin suppression" and in so doing it can satisfy its excessive needs during stress. This article gives an overview about the recent work on the "Selfish Brain" theory dealing with the maintenance of the cerebral and peripheral energy homeostasis. Am. J. Hum. Biol. 23:29–34, 2011. 

## THE BRAIN AS THE PRIMARY GLUCOSE CONSUMER

The brain consumes 130 g of glucose daily (Reinmuth et al., 1965). A human of normal weight and height needs a total of ~200 g of glucose per day. Thus, the brain takes up 2/3 of the circulating glucose. Under mild stress conditions, e.g., during an oral examination, the global brain-glucose uptake increases by 12% (Madsen et al., 1995). During deep sleep, the brain decreases its energy uptake by 40% (Boyle et al., 1994). Thus, by using the gold-standard method of Kety-Schmidt to investigate cerebral glucose metabolism, it could be shown that the brain is the primary glucose consumer in the organism (Madsen, 1995).

How can the brain adjust its energy supply to its high energy needs? To address this question, we recently made use of established knowledge about economic supply chains (Peters and Langemann, 2009). In the cerebral supply chain, energy passes from the environment into the body and from there into the brain as the final consumer (Fig. 1). From this logistic perspective, human energy metabolism resembles supply chains of economic production processes. Economathematics has dealt with such supply chains for >80 years. Among the principles, which are important for supply chains are the following two (Slack et al., 2004): first, the "push-principle," describing that the flux of goods or energy depends on the supplier; second, the "pull-principle," describing that the flux depends on the receiver. The relation between push and pull components can be for example 50:50, where half of the flux is determined by the supplier and the other half by the receiver. If the receiver has a high energy need, the relation between push and pull component varies, so that 90% of the flux is determined by the receiver and only 10% by the supplier. In the economy, it has turned out that supply chain processes, which are governed by strong pull components are particularly efficient, fast, and they lack build-ups or delays. In the following, we will regard the human energy metabolism as a supply chain. We recently could show that in such a cerebral supply chain a competent brain-pull component is indispensible for maintaining brain and body homeostasis (Peters and Langemann, 2009).

For decades, research on glucose metabolism was based on the "glucostatic theory" of the renowned physiologist Jean Mayer (Mayer, 1953). He proposed that food intake is controlled by hypothalamic receptors, which are capable of detecting glucose concentrations in the blood. In this way, the hypothalamus was considered to control food intake with the target to keep blood glucose concentrations constant within a narrow range. Interestingly, Mayer also considered the brain in his theoretical concept. In his view, food intake was at the service of cerebral energy supply. Accordingly, brain supply was expected to be sufficient, if blood glucose concentrations were also sufficient. But Mayer admitted in his article on the glucostatic theory that he was unable to explain why patients with diabetes, who display high blood glucose concentrations, do eat at all: high blood glucose concentrations should virtually suppress appetite.

The glucostatic theory contains an implicit assumption, which turns out to be problematic from the modern perspective of neuroenergetics. It is the assumption that the energy flux from the body to the brain is a passive process only. From this assumption, it would follow that the energy, according to the push principle, would be equally distributed among the brain and the rest of the body. But as early as in 1921, experimental evidence was published showing that the brain occupies a special hierarchical position in human energy metabolism. Marie Krieger, student of one of the pioneers of pathology Robert Rössle, showed that in humans who died from starvation all

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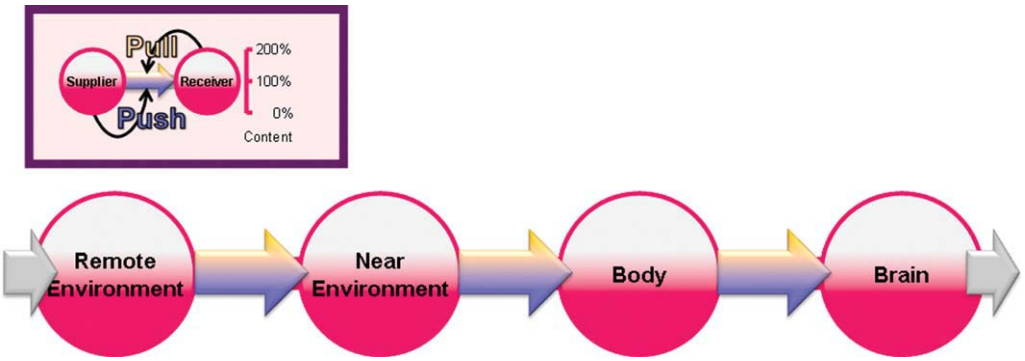


Fig. 1. Supply chain of the human brain. Energy from the remote environment is brought to the immediate environment, it is then taken up by the body, and from there a large part of it enters the brain. In a general supply chain, the flux of energy is determined principally by the supplier (previous step) and the receiver (proximate step). Insert: The share of the flux which is determined by the supplier is called the push component (blue part of the arrows); the share which is determined by the receiver is called the pull component (yellow part of the arrows). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

organs like heart, liver, spleen, and kidney markedly lost mass (40%), except the brain which lost only 1% or less (Krieger, 1921). Using modern magnet resonance technology, these findings had been confirmed in humans and animals, both in adult and fetal life (Gong et al., 1998; Muhlau et al., 2007; Kind et al., 2005; Miller et al., 2002).

Marie Krieger's findings show that the energy distribution within the organism is a matter of competition for energy resources among the brain and the other organs. Her findings can only be explained, if the supply chain exhibits a strong brain-pull component, with which the brain demands energy from the body in an active manner (Peters and Langemann). The priority of the brain is not only evident in the chronic process of starvation, but also under acute challenging conditions of glucose metabolism like fasting and hypo- or hyperglycemia (Bodoky et al., 1995; Hilsted et al., 1988; Oltmanns et al., 2008). Patients with Addison disease, who display a disintegration of the entire sympathoadrenal system, are unable to fulfill proper brain-pull function and accordingly display a state of cerebral energy deficiency (Klement et al., 2010). These findings show that the central nervous system prioritizes the regulation of its own energy content. In this way, the brain behaves in a "selfish" manner. This "selfishness" is the key aspect in the neuroenergetically founded selfish brain theory. The theory was founded in the period 1998-2004, published in 2004 (Peters et al., 2004), its scope of validity was expanded by experimental testing (Hitze et al., 2010; Schweiger et al., 2008; Oltmanns et al., 2008; Peters et al., 2007a; Steinkamp et al., 2007; Klement et al., 2010), and it was further developed in 2009 (Peters and Langemann, 2009).

## BIOLOGICAL CORRELATES OF BRAIN-PULL MECHANISMS

There are two brain-pull mechanisms, a direct and an allocative one. These two components act synergistically to safeguard the brain's supply.

### *Direct brain-pull mechanisms*

These brain-pull mechanisms are operative on the cell-to-cell level. Astrocytes play a crucial role in the energy supply of the neurons (Fig. 2). These cells make contact with the end feet of their extensions to the endothelial cells of the brain capillaries. Through these extensions astrocytes can take up glucose molecules from the blood circulation and provide them to their neighboring neuron. Other astrocytic end feet make contact to the neuronal synapse. Astrocytes can both supply the pre- and postsynaptic neuron with energy. For the transport of glucose from the blood into the astrocytes, the glucose transporter 1 (GLUT1) molecules are essential. The GLUT 1 molecule is located at the luminal and abluminal side of the blood brain barrier and also on the end feet of the astrocytes, which surround the brain capillaries. GLUT1 molecules are like pores inserted in the cell membrane. They are

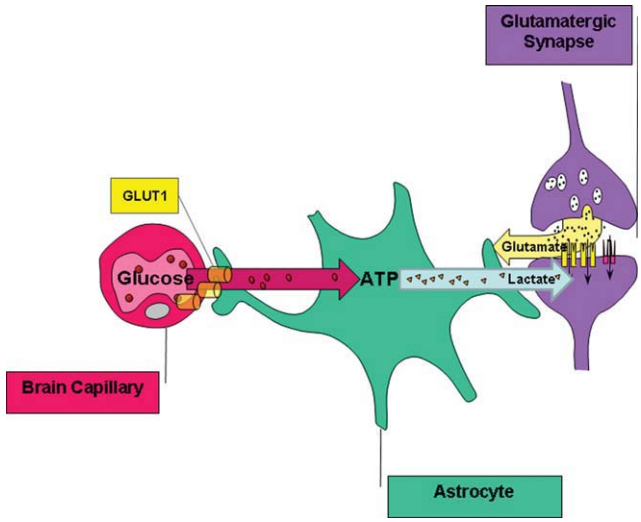


Fig. 2. Astrocytes and neurons demand for energy. On excitation of the glutamatergic neuron, the astrocyte takes up glutamate from the synaptic cleft. Glutamate represents an energy on demand signal. The recycling of glutamate to the neuron results in a small ATP decline within the astrocyte. Thereon, the astrocytic GLUT-1-pores open and the astrocyte gets glucose from the brain capillary. Then, the astrocyte converts glucose to lactate, ready to be used by the neuron. In this way, the active neuron is provided with energy when needed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

equipped with an intracellular ATP (adenosinetriphosphat) binding cassette (Blodgett et al., 2007). Once the binding cassette lacks ATP as a ligand, the pore of the GLUT1 opens by a change in molecule confirmation. In this way, glucose can enter the cell when needed. This molecular mechanism is a pull mechanism, because the energy flux depends on the fill content of the receiver, i.e., the astrocyte.

The astrocyte provides energy in a process which is dependent on the activity of the adjacant neuron (Pellerin and Magistretti, 1999). If the neuron is firing, glutamate is released into the synaptic cleft. Because the high energy consuming process of de- and repolarization, a high energy need develops in the neuron. The glutamate molecule is taken up by the astrocyte, and thereafter is recycled to the neuron. The recycling of glutamate is a process, which itself consumes a small amount of astrocytic energy. In case of high neuronal activity, a high energy need in the neuron corresponds to a small energy need in the astrocyte. When the ATP in the astrocyte tends to decrease, the ATP-dependent astrocytic pull mechanisms open up the GLUT1 pore and in so doing they increase the energy supply from the blood. Glucose is taken up by the astrocyte, and it is here converted into lactate, which still contains 95% of the energy that has been contained in glucose. In this way, the astrocyte covers its small energy need by the ATP from glycolysis. Then the astrocyte provides lactate to the neuron. Lactate covers exactly the high energy need for neuronal activity. Thus, the neuron can cover its high energy need with the help of its neighboring astrocyte in a process which is "on demand." This energy on demand process was discovered by Luc Pellerin and Pierre Magistretti in 1994 (Magistretti et al., 1994).

### *Allocative brain-pull mechanism*

Brain-pull mechanisms do also exist on the systemic level. They organize the energy flux from the body to the brain. Like the neuron demands for energy from the blood, the brain as a whole demands energy from the body's energy depots. This process is referred to as "allocation," i.e., partitioning of energy between the brain and the body. While astrocytic ATP is the decisive energy substrate for the energy demand on the cell-to-cell level, it is neuronal ATP which initiates the brain's energy demand from the body on a systemic level.

Allocative brain-pull mechanisms are capable of limiting GLUT4-mediated energy uptake into muscle and adipose tissue. In this way, these pull mechanisms increase the energy supply of the brain via GLUT1 (Peters et al., 2007b). In the ventromedial hypothalamus (VMH), glucose-responsive neurons are responsive to changes in intracellular ATP (Miki et al., 2001). If the cerebral intracellular ATP concentrations drop, these VMH neurons depolarize due to GABAergic disinhibition (Chan et al., 2007). Via glutamatergic mechanisms they activate the sympathoadrenal system (Tong et al., 2007) and in doing so inhibit insulin secretion (Ahren, 2000). The sympathetic efferences project to the β cells in the endocrine pancreas. Under conditions of cerebral energy deprivation, these sympathetic nerves inhibit insulin secretion (Woods and Porte, 1974; Frühwald-Schultes et al., 2000). VMH-controlled sympathetic efferences also project to muscle and fat tissue. There they inhibit the insulin-dependent glucose transport via GLUT 4 (Mulder et al., 2005). The catecholamines released at nerve endings adjacent to adipocytes interfere with trafficking of GLUT 4 molecules, i.e., they block the translocation of GLUT 4 from the inside of the cell to its cell membrane. Thus, the VMH neurons are capable of limiting the flux of glucose from the blood into the energy stores (muscle and fat tissue). These VMH triggered mechanisms can be regarded as brain-pull mechanisms because they guarantee sufficient glucose supply for the brain when needed.

Recently, the behavior of the cerebral supply chain has been experimentally investigated under the conditions of acute psychosocial stress (Hitze et al., 2010). In that study, healthy volunteers were exposed to the Trier Social Stress Test. After 10 min of stress, the subjects were offered a rich buffet. Subjects ate 34.4 g of carbohydrates more than they ate in a nonstress control session. Although stress-extra carbohydrates increased blood glucose concentrations, they did not increase serum insulin concentrations. The ability to suppress insulin secretion in the stressed subjects was found to be linked to their sympathoadrenal stress responses. Furthermore, exogenous energy was shown to counteract an energy-deficient state and mood disturbances which developed during stress. This study shows that the brain under stressful conditions demands for energy from the body by using a mechanism, which is referred to as "cerebral insulin suppression." In this way, the brain can satisfy its excessive needs during psychosocial stress.

### *Body-pull mechanisms: eating behavior*

In the more distal part of the cerebral supply chain, an additional pull mechanism controls the intake of energy from the environment, i.e., eating behavior. This pull mechanism is referred to as body-pull since the flux from the environment into the body is determined by the receiver, i.e., the body. Body-pull is mainly initiated by a decline in blood glucose concentrations. The lateral hypothalamus (LH) contains neurons which release orexin (formerly called "hypocretin"). LH neurons increase food intake, wakefulness, and reward seeking behavior (Lin et al., 1999; Kelley et al., 2005; Cai et al., 1999). These hypothalamic orexin neurons display glucose receptors on their cell surface (Burdakov et al., 2006). The glucose receptors bind extracellular glucose, i.e., glucose from the interstitial extracellular space, which surrounds astrocytes and neurons. The extracellular glucose concentrations tightly correspond to blood glucose concentrations, though the extracellular glucose concentrations are lower by a factor of 3 to 10×.

The LH neurons selectively measure concentrations of glucose (Gonzalez et al., 2008). They do not respond to changes in lactate concentrations. On a decline in extracellular glucose concentrations, tandem-pore-potassium channels (K2P) located on the orexin neuron change their configuration, and consequently the cell depolarizes and starts firing. Hence, a fall in extracellular glucose concentration initiates food intake, increases alertness, and explorative behavior. Through a hypothalamic neuronal network, these orexin neurons also respond to changes in serum leptin, the hormone secreted by adipocytes conveying information about the energy fill content of the adipose tissue. Thus, decreasing energy contents in blood or peripheral energy stores initiate body-pull mechanisms to replenish energy in the body (blood, liver, muscle, and fat tissue).

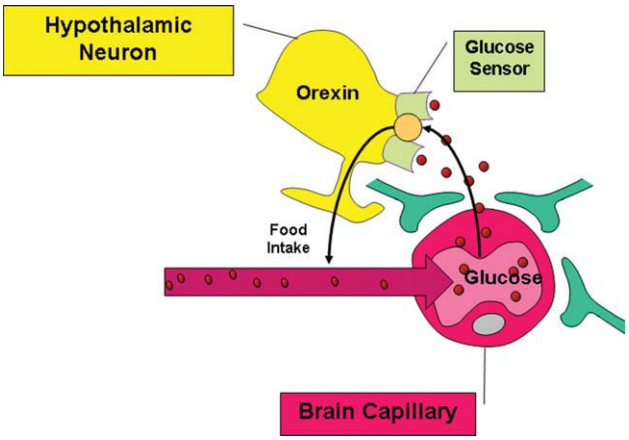


Fig. 3. Neurons of the LH demand for energy by initiating ingestive behavior. LH orexin neurons are equipped with glucose receptors on their cell surface, which monitor extracellular glucose concentrations. On a decline in extracellular cerebral glucose, these orexin neurons depolarize and in so doing increase appetite and food intake. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In summary, the energy supply of the brain is safeguarded by three pull mechanisms, which are located on different levels:

1. Direct brain-pull: Astrocytes demand energy from the blood. Falling intracellular astrocytic ATP concentrations open up the astrocytic GLUT1 pore and in this way increase glucose supply from the blood.
2. Allocative brain-pull: VMH neurons demand for energy from the body. On falling neuronal ATP concentrations glutamatergic VMH neurons activate the sympathoadrenal system and in so doing they limit the glucose flux into muscle and adipose tissue.
3. Body-pull: LH neurons demand for energy from the environment, i.e., they initiate eating behavior. On falling blood glucose concentrations, which are detected by glucose receptors located on LH orexin neurons, these neurons become active and order energy from the environment (Fig. 3).

In the supply chain of the brain, the interplay between the three pull mechanisms is finely tuned. The brain-pull mechanisms are indispensible. They improve the chances of survival in times of food deprivation by favoring brain supply and by downsizing of the body. Under the load of stressful conditions the brain demands energy from the body stores. In the recovery phase, the deficits—which have developed in the body during the stressful event—are filled up by eating. The finely tuned interplay between brain pull and body pull, i.e., energy demand from the body or from the environment, is controlled and optimized by the cerebral hemispheres. In this optimization process, cortical learning processes play a crucial role (Peters et al., 2007b).

## BUILD-UPS IN THE SUPPLY CHAIN: OBESITY AND TYPE 2 DIABETES

Brain-pull mechanisms are essential for survival in times of food deprivation. If they fail, they have been shown to cause disturbances in the supply chain (Peters and Langemann). It is a general law in supply chains that the flux of goods or energy is directed in an antegrade manner toward the final consumer. Disturbances, however, due to bottlenecks in the supply chain typically propagate in the retrograde direction, i.e., away from the final consumer. A recent data-based approach provided evidence that in case of an incompetent brain-pull food intake has to be increased in order to safeguard the brain's supply (Peters and Langemann). This switch from brain-pull to body-pull under conditions of food abundance can be regarded as a metabolic coping strategy of the brain. Such a strategy safeguards brain supply on the one hand, however, the adverse effect becomes obvious as a build-up in the supply chain. Energy accumulates in adipose tissue and obesity develops. Glucose accumulates in the blood vessels and diabetes type 2 develops. From the perspective of the outlined logistic approach obesity and type 2 diabetes can be regarded as emergency strategies in case of a bottleneck in the cerebral energy supply. Several causes of brain-pull incompetence have already been identified, which have been summarized and depicted in Figure 4 [according to (Peters and Langemann)].

## BRAIN SIZE, BODY SIZE, AND LONGEVITY

One currently prevailing myth is that a large cerebral capacity should guarantee a long life. Recent analysis suggested that there is indeed a hidden link between brain size and longevity (Peters et al., 2010). In that study, magnetic resonance imaging was applied to measure brain size and indirect calorimetry to measure body metabolism in 208 subjects of widely varying weight (underweight to obesity). It was shown that the body-brain-energy balances (X/Y) were correlated with Quetelet's body mass indexes (BMIs): $X/Y = 0.085\ BMI + 2.961$; $r = 0.553$; $P < 0.001$. If a BMI of 24 kg/m$^2$ is inserted in this regression equation, a body-brain-energy balance (X/Y) of 5.0 is obtained. As such the optimal survival of humans with a BMI of 24 kg/m$^2$, as reported by Wittlock (Whitlock et al., 2009)—is associated with a body-brain energy balance of 5.0, or put in other words with a relative brain energy consumption of 20%. In contrast, underweight subjects showed a higher relative brain energy consumption of 22.0 $\pm$ 0.1%. Obese subjects displayed a lower relative consumption of 17.2 $\pm$ 0.1%. In a second step, this finding was integrated into the more general laws of body-brain allometry (Fig. 5; black solid line). It turned out that the observation Quetelet made in a small data set on humans (Quetelet, 1842), when he described his BMI, fits well with a larger data set assessed in vertebrates (including humans; Fig. 5; gray solid line; dashed line) (Mink et al., 1981). Referring back to a more general biological context, it is not surprising that when analyzing data from humans alone Quetelet was able to find a simple statistically derived variable, that is the BMI, which allowed him to identify humans who were expecting maximal longevity. Although Quetelet's variable is predictive of life-span, it is only a descriptive measure. In that magnet resonance study (Peters et al., 2010), the attempt was made to replace the descriptive ratio BMI (mass divided by an area) with a variable representing a relevant biological feature. Comparison of medical and biological data support the view that the BMI of Quetelet is just a one-to-one mapping of the body-brain energy balance—a biological

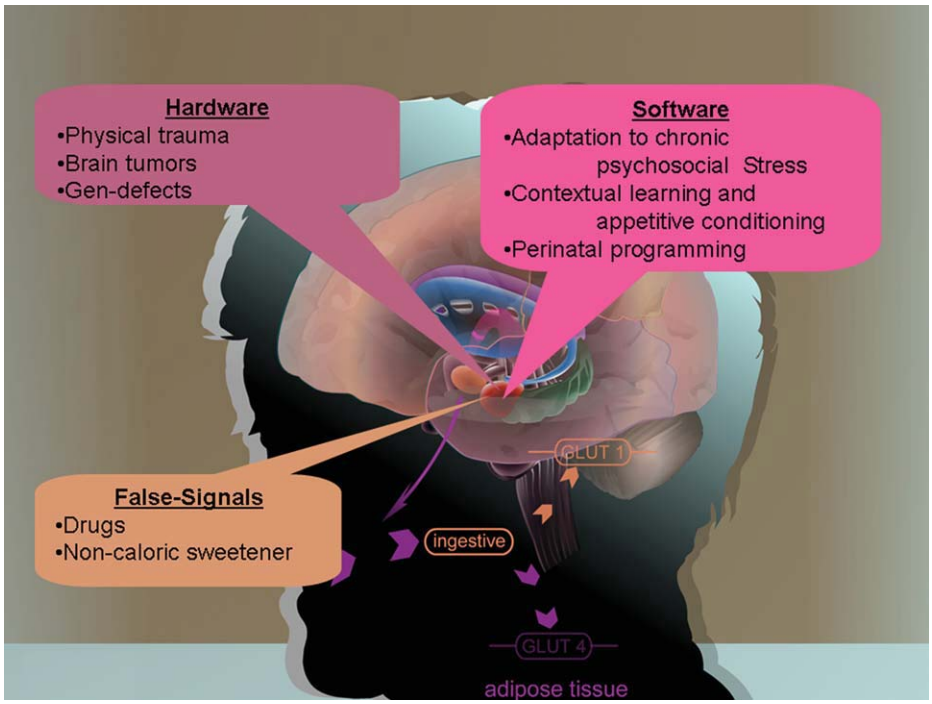


Fig. 4. Incompetent brain-pull mechanisms. Selection of various causes, which lead to brain-pull incompetence; (for details and citations see Peters and Langemann, 2009). These causes can be systematically summarized in three categories, similar to computer problems: hardware, software problems, and false signals. The brain-pull incompetence threatens cerebral energy homeostasis, which can be safeguarded by a compensatory increase in food intake. In this way, the listed causes for brain-pull incompetence can be regarded as the underlying causes for the development of obesity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

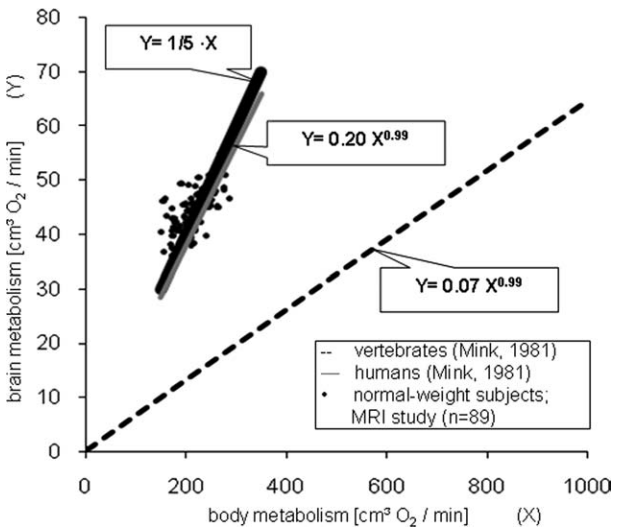


Fig. 5. Isometric brain-to-body functions in vertebrates (dashed graph) and humans (solid gray graph) according to Mink et al. (1981). Note: the dashed graph actually covers a larger scope of values than depicted here, that is, bodies ranging in size from that of a goldfish to an elephant (0.04-6000.00 $cm^3O_2$ $min^{-1}$). The solid black line shows the isometric function, which applies for humans exhibiting a BMI of 24 $kg{\cdot}m^{-2}$, as assessed by the human magnetic-resonance imaging/calorimetric study (Peters et al., 2010). The human-specific function (solid black) assessed here is a good approximation to the function (solid gray) based on the general power law.

variable indicating that an individual maintains a systemic energy homeostasis and therefore is likely to perform well in the coming years. Interestingly, this performance depends largely on an competent brain-pull, i.e., the ability of the brain to competently demand energy from the body, as recent research from the field of neuroenergetics has shown (Peters and Langemann, 2009).

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