The effects of high fat diets on the blood–brain barrier transport of leptin: Failure or adaptation?

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Abstract

Leptin is a pluripotent regulatory protein secreted by fat and exerts many effects through the CNS. Interpretation of the characteristics by which it crosses the blood–brain barrier (BBB) supports the view that leptin most potently signals the brain at serum levels well below those associated with the current definition of ideal body weight. This fits with the perspective that low serum levels of leptin are a signal to brain that a sufficient store of calories are available for the organism to expend energy for efforts unrelated to acquisition of calories. This would explain why low serum levels of leptin are permissive in many of the non-feeding actions of leptin, such as enhancing CNS-mediated immune function, memory, bone growth, reproduction, breathing, and neurogenesis. Triglycerides inhibit the transport of leptin across the BBB and so could be key in the onset of the peripheral leptin resistance, which is a hallmark of obesity. These results explain the paradox of why obesity should induce resistance to an anorectic: hypertriglyceridemia also occurs with starvation and we postulate that triglyceride-induced resistance to leptin transport across the BBB initially evolved to limit the signal of an anorectic to the brain during starvation.

1. Introduction

Resistance to the anorectic and thermogenic actions of leptin is thought to be a major factor in the acquisition and maintenance of obesity. But leptin is unlikely to have evolved as an adipostat and leptin has many functions not readily ascribable to an adipostat. A fuller understanding of how leptin works and why resistance occurs is likely to require a consideration of what leptin does in populations which do not subsist on Western diets. Such an analysis leads us to believe that leptin resistance initially arose as an adaptive response to starvation as signaled by hypertriglyceridemia.

2. Leptin's feedback loop on adiposity

Fig. 1 illustrates the relations among leptin, fat mass, the blood–brain barrier (BBB), and the arcuate nucleus. Adipocytes secrete leptin into the blood [1–4]. As it circulates through the cerebrovasculature, transporters for leptin carry it across the BBB to enter the interstitial fluid of the brain [5]. There it interacts with leptin receptors, including those located at the arcuate nucleus. Among leptin’s various functions are its ability to suppress appetite by stimulation of anorectics and inhibition of orexigens [6–9]. Anorexia and increased thermogenesis result in enhanced burning of stored calories and, hence, a reduction in fat mass [2,4,10,11]. The decreased fat mass results in lower leptin, completing a negative feedback loop. If resistance to leptin did not occur, this system would, in theory, maintain adiposity within a very tight range.

Obesity is associated with a failure in this feedback loop. Feedback loop failures in general fall into two broad categories: i) a deficiency of the regulatory hormone and ii) a resistance to the actions of the regulatory hormone. Examples of both of these causes of feedback failure are known to occur for leptin in humans and animals. A loss of the ability of fat tissue to secrete leptin is the hallmark of the Ob/Ob rodent and occurs rarely in humans. The vast majority of humans, however, show the pattern of leptin-resistant obesity, as evidenced by elevated levels of serum leptin in the face of increased adiposity. Most models of diet-induced obesity in rodents also show resistance...
to leptin. It is this paradox of leptin resistance occurring with diet-induced obesity, that is when a adipostat is most needed, that teleologically brings into question the role of leptin as an adipostat. It may also be that this induction of leptin resistance, and so interruption of the negative feedback loop, that underlies the current epidemic of obesity. The question which must be addressed is why does leptin fail in the face of obesity, the very condition that an adipostat would supposedly safeguard against? Is it that the leptin feedback loop is fragile and simply overwhelmed by a Western diet too high in fat or does the leptin feedback loop defend against a condition other than obesity?

Work on the BBB characteristics of leptin transport in conjunction with selected other studies suggest an alternative scenario for the utility of leptin and leptin resistance. This work suggests: i) that low serum levels of leptin are useful in signaling to the brain that caloric reserves are adequate to pursue activities other than those immediately related to acquisition of calories, ii) that leptin resistance at the BBB (that is, a decreased ability of the BBB to transport leptin) evolved as a defense against starvation, and iii) that leptin resistance at the BBB is induced by triglycerides. This scenario would explain the BBB portion of the leptin resistance of obesity as occurring because of the unfortunate coincidence that hypertriglyceridemia also occurs with obesity.

How valid this scenario is remains to be seen. But it can be used to place leptin in an evolutionary context, to explain why leptin resistance occurs in obesity, why leptin has so many functions within the brain unrelated to caloric acquisition, why leptin can reverse many of the findings of starvation, why only low levels of serum leptin are needed for induction of many of leptin’s non-feeding functions, why leptin’s role seems more permissive than direct, and can give some insight into why leptin receptors are in multiple brain regions. This view emphasizes leptin’s role as a measure of adiposity as opposed to a role in the regulation of adiposity; that is, leptin as an adipometer rather than an adipostat. The remainder of this review examines leptin’s role in this context.

3. The ideal in blood to brain signaling

Several peptides and regulatory proteins are known which are produced by peripheral tissues and cross the BBB to induce a CNS function. Many of these substances are transported across the BBB by saturable processes. The most efficient blood-to-brain signaling occurs when the relation between blood levels and CNS levels are most linear. It is in this region where a rise in the serum level of a substance is mirrored by the greatest rise in its CNS level. For leptin, this linear portion ends before a serum level of 10 ng/ml, a level typical of persons of ideal body weight. Fig. 2 shows the relation of CNS leptin and vascular leptin in mice studied by brain perfusion [12]. It shows that the percent of leptin in the vascular space transported across the BBB approaches about 15% at very low blood levels. At about 10 ng/ml, the rate of transport has fallen to about half of this and about half of the maximal amount of leptin entering the brain has already been reached. At levels representing even mild obesity, transport is near saturation. This suggests that the most robust blood-to-brain signaling as mediated by the saturable transport of leptin occurs at relatively low blood levels, not at levels typically associated with obesity.

4. The ideal body weight in the wild

The above finding raises the question of why leptin transport should be attuned to be most efficient at low serum levels. One possibility is that evolution occurred at much lower levels of serum leptin than we now consider normal. A person of ideal body weight has an adipose mass that is about 20% of total body weight [13]. However, wild animals living in non-famine conditions are
much leaner. Adult baboons living in the wild typically have an adipose mass that is about 1.9% of total body weight and leptin levels below 2 ng/ml [14–16]. These levels increase in captivity or when calories are easily obtained. Baboons living in the wild but raiding garbage dumps at nearby villages have about 23% of their total body weight as adipose tissue and leptin levels that average about 12 ng/ml [15,17]. Therefore, it is likely that the leptin transporter at the BBB evolved to deal with transport at these lower levels.

Starvation is a much more common event than an unrestricted number of calories in most wild populations. With only a few percent of excess body weight available as a reserve, a long period of negative caloric balance would result in death by starvation. Therefore, any system regulating feeding and body weight would need to be biased toward acquisition and retention of calories. The ancestral regulatory system must have also been very flexible to have adapted to the caloric storage needs of different life styles in the wild. For example, a bulk-feeder carnivore living in a seasonal climate has different energy storage needs than an herbivore living in the tropics.

Given the low reserve of body fat, an animal would need to have a monitor of their relative caloric reserve. They would need a strong signal of starvation and a clear indicator of how much caloric reserve they have. The signal would likely act permissively towards important nonfeeding behaviors when caloric reserves were adequate. Leptin appears to have all of these characteristics.

5. Brain effects of leptin: beyond feeding

Leptin has many effects on brain other than those related to calories and thermogenesis (Fig. 3, upper panel). For example, leptin has effects on various aspects of reproduction [18–23], memory [24], neurogenesis and brain growth [25], the immune system [26], bone density [27], and breathing [28,29]. These effects are mediated through the central nervous system and at relatively low levels of leptin. Furthermore, leptin administration to starving animals can activate some of these systems [30]. Some of these functions, especially immune functions and reproduction for the female, require a large number of calories. Shutting down or attenuating these systems can conserve energy reserves and increase the likelihood of survival. Forcing activation of, for example, the immune system in a starving animal can result in death [31]. But for an animal with extra caloric reserves, activation to a more robust immune system is a good investment. It makes sense, therefore, that extra calories as indicated by an increase in leptin serum levels would activate a host of functions which are of long-term benefit to the individual and species but which can be attenuated short-term when calories are low.

Results from the study of the BBB suggest that these various CNS functions of leptin are not exclusively mediated through the hypothalamus. Leptin is transported into every region of the brain to varying degrees [12], consistent with other regions of the brain having leptin receptors [32–34] and mediating the effects of leptin [35]. It may be that different functions are mediated by different regions of the brain. For example, whereas effects of leptin on feeding have been primarily associated with the hypothalamus, leptin’s effects on memory are mediated through the hippocampus [24]. Furthermore, the linear portion, Vmax, and Km of the relation between blood and brain levels varies with brain region [12]. This means that the blood level at which the blood-to-brain signal mediated by leptin is most efficient varies among brain regions. This situation allows the possibility that higher blood levels are needed to activate some brain regions or, conversely, that some brain regions remain relatively sensitive to changes in blood levels of leptin after other regions have become saturated with leptin.
6. Banking and caloric reserves

The above supports a view that leptin acts as monitor of caloric wealth, letting the brain know when there is enough of a reserve to begin investing in high energy pursuits not directly related to energy acquisition. This view minimizes leptin as an adipostat and also suggests it is a starvation signal only by its absence [36]. This view casts leptin in a role which is analogous to bank statements on checking accounts. The main use of a checking account statement is to help the owner monitor the balance between inflow and outflow of ready cash. Usually some low level of excess is desirable because of the huge penalty for a deficit. Long term deficits can lead to bankruptcy, the economic equivalent of death by starvation. Excesses in the account often lead to the money being diverted to other economic uses. The purpose of the statement is not to let the owner know when there is no money in the account nor is there a mechanism for diverting excess funds out of the checking account. Likewise, leptin seems to act as a statement to the brain of caloric wealth, allowing increased expenditures on high caloric pursuits without curtailing further deposits into the caloric reserve.

7. Hypertriglyceridemia in fasting and feasting

The above supports a view that the information which leptin provides the brain is most critical at that juncture where an animal has enough fat reserves to devote calories to important functions other than seeking food. Many of these functions are long term commitments. If calories are expended faster than they are acquired, fat mass decreases and leptin levels will fall. But an interesting feature of the leptin axis is what happens when calories are suddenly and totally stopped and the animal is forced into starvation. In humans, leptin secretion by fat is curtailed after about 12 h without food [11]. Thus, even if fat stores are still significant, leptin signals to the brain that there is a state of starvation. Studies of the BBB reinforce this. With short-term fasting, leptin transport across the BBB unchanged or slightly increased. But with starvation, leptin transport across the BBB is decreased and, eventually, stopped altogether [37,38].

Triglycerides are a regulator of the rate at which leptin is transported across the BBB [38]. Serum triglyceride levels and the transport rate of leptin across the BBB are inversely related, so that high triglycerides attenuate leptin transport. Triglyceride levels increase with fasting as fat reserves are mobilized from adipose tissue. Thus, elevated serum triglyceride levels indicate starvation (Fig. 3, lower panel). The ability of triglycerides to halt leptin transport into the brain means that they would not only remove an anorectic signal from the brain and result in decreased thermogenesis, but also attenuate the calorically demanding functions leptin permits. Thus, leptin resistance to hypertriglyceridemia is adaptive in starvation.

Triglycerides are also elevated with obesity. However, obesity as a cause of hypertriglyceridemia has probably been a much more rare event during evolution than starvation. As such, the hypertriglyceridemia of obesity may be mistaken as a starvation signal by the BBB and so induce leptin resistance. Consistent with this, a lack of body fat and leptin produces conditions which are typically associated with obesity: insulin resistance, hyperglycemia, increased caloric intake, fatty liver, hypertriglyceridemia [39]. These conditions of alipodystrophy or dyslipodystrophy are likely viewed by the brain as starvation. Leptin treatment alone partially corrects all of these abnormalities.

Leptin resistance in obesity may also have an adaptive aspect. No matter how great the caloric reserves of an animal, it must still eat to acquire nutrients which are less efficiently stored than fat, such as glucose and water soluble vitamins. If caloric reserves and serum leptin levels were the only determinant of anorexia, then obese animals might stop eating entirely. This could lead to muscle catabolism to produce glucose and vitamin and mineral deficiencies.

8. Summary

Obesity is associated with resistance to leptin. The results from the dynamics of BBB transport of leptin in normal body weight animals, obese animals, and starving animals support leptin not so much as an adipostat as an adipometer. That is, its most important function may be to inform the brain of that critical point when calories are in such excess that they can be diverted to tasks other than seeking food. The obverse of this is that absence of leptin and hypertriglyceridemia signal starvation to the brain. These signals can arise rapidly with a shift to negative energy balance and are not dependent on depletion of body fat.

References


