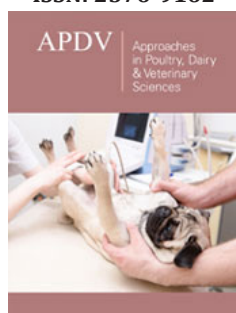


# Factors Affecting the Transfer of Leptin Through Blood-Brain Barrier (BBB). The Implication for Leptin Resistance

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## Introduction

The base of the leptin resistance hypothesis promulgated several years ago consists of two tenets: the extinction of leptin-induced intracellular signaling downstream of leptin binding to the long form of neuronal receptor (LTRb) in the hypothalamus and impedance to leptin entry imposed at the blood-brain barrier (BBB). A recent comprehensive literature review [1] has led to the conclusion that central leptin insufficiency associated with the metabolic syndrome is due to reduced BBB leptin transport efficiency, and not just to leptin insensitivity in the hypothalamus. Furthermore, it has been shown that transport performance is not restored after significant weight loss by calorie restriction and provided evidence of deep central hypoleptinemia in sheep who have lost weight (“obese slimmers”), which can be expected to counteract persistent weight loss [2]. However, due to the wide range of ambiguities in the implications that STAT3/SOCS3 (signal transducer and transcription activator 3/cytokine signaling suppressor 3), intracellular signaling confers central leptin resistance, along with several possible alternative options such as compensatory functionality and anatomical reorganization in appetite regulating network (ARN), rearrangement of afferent hormonal feedback signaling involved in weight homeostasis and modifications of leptin transport to the hypothalamus by BBB, the claim that impairment of intracellular signaling downstream the entry of leptin to ARN accelerates the environment-induced energy homeostasis disorder remains unfounded and requires further evidence.

Based on the results of previous studies [3-8] and new discoveries in rodents and sheep [9,10], it has been suggested that one of the factors of leptin resistance is autosuppression, in which leptin stimulates the expression of SOCS3 factors that inhibit leptin signaling. Increased expression of SOCS3 in response to leptin may be a key cause of resistance/insensitivity to the anorectic effect of this hormone, which is a pathological condition in obese ones and a physiological phenomenon in sheep during the long-day season (LD) [4]. The occurrence of unique, reversible and season-dependent leptin resistance in sheep is associated with adapting these animals to annual changes in energy supply and demand; however, the neuroendocrine foundations of this phenomenon remain unknown. Our previous work [3-8] showed the role of SOCS3 factors in modulating the hypothalamus and pituitary gland sensitivity to leptin in vivo and in vitro depending on the season. Recent work on mice and sheep has shown that resistin can cause central leptin resistance by increasing circulating leptin concentrations and contributes to the hypothalamus insensitivity to leptin by inhibiting leptin signal by STAT3/SOCS3 [9,10].

Leptin secreted from peripheral adipose tissue acts centrally within the mammalian hypothalamus as an adipostat, reducing appetite and promoting negative energy balance. However, the typically elevated circulating leptin concentrations in obese individuals beings fail to act in this way, reflecting a state of leptin resistance. To act centrally, leptin from

circulating blood must first enter the brain, passing through the blood-cerebrospinal fluid (blood-CSF) barrier at the choroid plexus (CP) and/or the blood-brain barrier at the cerebral endothelium. It was suggested the desensitization of leptin receptors or a dysfunction of leptin-receptor signaling as the cause of reduced sensitivity [11], and indicated disturbance of the transport of the hormone across the BBB [12]. Loss of the anorectic properties of leptin is most likely not caused by a single mechanism, but rather results from a combination of the above-mentioned factors.

Resistin is a hormone that belongs to the family of small, cysteine-rich secreted proteins, collectively called resistin-like molecules [13]. The source of resistin differs between rodents and humans. In mice and ruminants, resistin is mainly expressed by adipocytes, whereas in humans, monocytes and macrophages are the main sources of resistin. Despite this difference in species and expression profile, resistin derives its name from a positive correlation with obese insulin-resistant in both mice [13] and humans [14]. Mouse studies confirm the direct role of resistin in insulin resistance. Although the mechanisms by which resistin causes insulin resistance have not yet been completely elucidated, work on rodents suggests that the central action of resistin in mice drives peripheral metabolic responses via the hypothalamus [15].

Studies of obese humans indicate a decreased lumbar CSF-to-blood leptin concentration ratio that is indicative of decreased blood-CSF leptin transfer. Using sheep as a large animal model with a body weight [BW] and adiposity similar to those of humans, Adam and Findlay (2010) were able to explore the dynamics of endogenous leptin blood-brain transport longitudinally in vivo using concurrent peripheral blood and CSF samples while also repeatedly testing intra-hypothalamic leptin sensitivity by direct intracerebroventricular (ICV) administration. Few studies have investigated the restoration of central leptin sensitivity after weight loss in obese subjects, although serum leptin concentrations have been reported to decrease disproportionately relative to body fat levels after weight loss caused by caloric restriction in obese women. The resulting hypoleptinemia would be exacerbated centrally if leptin resistance persisted at the blood-brain transport level, which could contribute to feelings of hunger. Adam and Findlay (2010) demonstrated that leptin concentrations in CSF increased initially along with concentrations in plasma as obesity in sheep developed. Unlike the concentrations in plasma, the rate of increase in the CSF was not sustained. This result reflects a transfer of leptin from the BBB decreased proportionally with increased leptinemia. The reduced CSF-to-blood leptin concentration ratio in obese sheep endorses earlier reports of reduced distal CSF-to-blood leptin ratios in obese humans and of decreased blood-CSF leptin transfer in obese rats. Further they demonstrated that in sheep, some leptin still entered the CSF of obese animals, but the decreased magnitude of the increments within the brain compared with the periphery was insufficient to elicit an anorexic response [2]. In contrast, the acute increase in suprphysiological concentrations within the brain after ICV leptin injection was clearly sufficient to elicit a response. Obesity in ovine model was characterized by high BW,

high external adiposity scores and relatively high 'bad' (low-density lipoprotein; LDL) cholesterol concentrations in circulating plasma [2]. Therefore, the results those authors presented support the hypothesis that the loss of the anorectic properties of central leptin associated with obesity is attributable to decreased efficiency of blood-brain leptin transport and thus not solely caused by leptin insensitivity within the hypothalamus.

A recent study in rats established a new physiological concept of energy homeostasis regulation, demonstrating that the nutritional status of an individual modulates the permeability of discrete hypothalamic blood barriers for circulating metabolic signals, thereby enabling the signals direct access to a subset of the arcuate nucleus [ARC] neurons [16]. Many metabolic factors are coordinated by ARC neurons. This regulation is primarily mediated by the balance between anorexigenic neurons that express proopiomelanocortin (POMC) and orexigenic neurons that express neuropeptide Y (NPY) and Agouti-regulated peptide (AgRP). For example, under fasting conditions, reduced systemic levels of nutrients (e.g. glucose) and changes in related hormone concentrations (e.g., lowered leptin and increased ghrelin) act on the activation of NPY/AgRP neurons and inhibit POMC neurons in the hypothalamus. These changes lead to a pronounced anabolic state in the hypothalamus, which translates into a strong stimulus for the animal to seek and take food. The ARC is adjacent to the median eminence [ME], which contains a CSF barrier composed of tanycytes, which are specialized hypothalamic glia lining the bottom of the third ventricle (IIIIV) and prolonging contact with the specialized capillary plexus. The endothelial cells of this ME capillary plexus are unique in that they are fenestrated and their permeability allows for rapid passive extravasation of most nutrients and metabolic hormones circulating in the pituitary gland's blood (i.e., with molecular sizes less than 20 kDa). However, in animals fed ad libitum, limiting capillary fenestration to ME along with tight junctions complexes between adjacent tanycytes that act as a physical barrier, sequesters these molecules in ME and prevents them from diffusing to the rest of the brain by CSF. In contrast, lowering blood glucose concentrations in fasting mice, which are probably detected by the tanycytes themselves due to their glucose detection properties, trigger the expression of vascular endothelial growth factor A (VEGFA) in these cells, and the accumulation of VEGF in ME acts on its endothelial receptors: VEGFR2 to promote the fenestration of capillary loops that reach the ARC. The ARC lies laterally to IIIIV and immediately dorsolateral to ME. VEGF has been shown to be involved in induced endothelial hyperpermeability and is constantly and strongly expressed in the CP, where the blood-CSF barrier is found [17]. Two isoforms are expressed in sheep CP, VEGF<sub>120</sub> and VEGF<sub>164</sub> [18]. VEGF plays an important role in regulating endothelial cell stability in ovine CP [19].

In mice fed ad libitum, the fenestrated ME blood vessels allow local diffusion of macromolecules from circulating blood, while blood vessels in the ARC exhibit BBB barrier properties that block this diffusion. Therefore, high circulating metabolic signals during the fed state (e.g., leptin and glucose) require BBB transport to

gain access to ARC neurons. Under these conditions, tight junctions between tanycytes line the ventricular wall of the median eminence and prevent the diffusion of circulating factors into the IIIV and CSF. During fasting or energy restriction, the levels of orexigenic hormones, such as ghrelin, increase along with the products of lipolysis as leptin and glucose concentrations fall. At the same time, some ME vessels that extend to ARN become fenestrated and the tight junctions barrier along the IIIV simultaneously dorsally extends. These changes allow freer diffusion of circulating signals that indicate energy restriction to ARC cells, including AgRP/NPY neurons that are found in the ventro-medial ARC, while preventing these substances from accessing the rest of the brain through CSF. The focal plasticity of this two-layer hypothalamic-blood barrier therefore increases the orexigenic/anabolic response to energy deficiencies.

Resistance of leptin at both the receptor level and the BBB becomes increasingly profound with advancing obesity. In some animal models, however, BBB resistance predominates in the earlier stages of obesity. The benefits of administering leptin to improve the success of weight loss programs for obese individuals have been recognized. Research efforts have also recognized the need to enhance leptin entry into the brain, such as by intrathecal injection or by modifying the molecule to produce leptin with improved permeation across the BBB, to improve its therapeutic efficacy. Among possible molecules, TAT-leptin [20], P85-leptin [21] and MTS-leptin [22] have been identified and used as proteins that are capable of crossing the BBB independently of the leptin BBB transporter, and these molecules result in decreased feeding and weight loss. Furthermore, because of the wide range of actions and strong biological activity of leptin, the effects of those protein actions must be strictly controlled to prevent the disadvantageous consequences of excessive stimulation of leptin receptors.

## Conclusion

Many newly discovered hormones, as exemplified by leptin, are peptides or regulatory proteins that must access receptors within the brain to exert their effects. Most of the brain, approximately 99.5% of it, is protected by the BBB. As such, many of these peptides and regulatory hormones depend on the ability to cross the BBB to access those deep brain receptors. In many cases, again as exemplified by leptin, these peptides and regulatory proteins depend on transporters located at the BBB to allow them access to the hypothalamus. When those transporters fail by allowing either too much or too little hormone into the brain, disease can arise. "Leakages" across brain barriers are observed in many neurodegenerative disease states, e.g. Parkinson's or Alzheimer's diseases, in multiple sclerosis as well as epilepsy. Overall, modifications of leptin or its analogs would potentially have versatile uses in the development of therapeutic agents targeting the brain that require transport across the BBB.

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