Intranasal Leptin: Blood-Brain Barrier Bypass (BBBB) for Obesity?

Although the discovery of leptin (1) has failed, so far, to fulfill its promise as the magic bullet for the treatment of obesity, it has focused attention on the blood-brain barrier (BBB) and the role of endogenous peptides/polypeptides in food ingestion. The article by Fiedner, Schulz, and Lehnert (2) in this issue of *Endocrinology* does more than add to the 20,000 papers on the BBB, 10,000 on leptin, and 100 on the BBB + leptin; it offers a possible approach that may lead to a practical solution to the problem of leptin resistance.

The first big disillusionment with leptin was the observation that fat laboratory animals and human beings had high, not low, concentrations in their blood. An increase of blood leptin failed to reduce feeding (3–7) or be reflected in increased levels of leptin in the cerebrospinal fluid (CSF) (5, 8, 9). If leptin is delivered directly into the brain, it reduces feeding, but delivery into blood is essentially without effect (3, 6, 7). The most parsimonious explanation for these results is a block at the BBB. The first direct examination of the relation of leptin with the BBB by well-validated, sensitive methods (10) showed that leptin entered the brain in intact form (11). More importantly for the concept of leptin resistance, it also showed that this influx is saturable, being decreased in the presence of excess leptin in blood as is found in obesity. Partial saturation of leptin transport may even occur in normal weight mice (12).

Unlike leptin, many ingestive peptides do not cross the BBB by a saturable transport mechanism. Some, like neuropeptide Y (13), orexin A (14), and cocaine- and amphetamine-regulated transcript (15), enter by simple passive diffusion, based on physicochemical properties like lipophilicity, hydrogen bonding, and conformation. Some, like melanin-concentrating hormone, are tightly bound to blood proteins (16) or, like agouti-related protein, aggregate in blood (17). Some, like adrenomedullin, tend to remain in the cerebral vasculature (18), and some, like the recently described obestatin (19), don't cross at all (20).

The field of brain peptides has come a long way, and, in a sense, the paper by Fiedner et al. (2) illustrates how the field could be construed as having arrived full circle regarding the relation of leptin with the BBB. For years, the field was plagued by many misleading concepts (21), including the dogma that peripherally administered peptides could not exert any effect on the central nervous system (CNS). It took a long time for it to be finally accepted that peptides elsewhere in the body can, indeed, influence the brain. But then it was insisted that such actions must be indirect and could not possibly occur by passage across the BBB. The controversy became reminiscent of the four steps to unorthodox scientific discovery attributed to J. B. S. Haldane: 1) This is worthless nonsense; 2) This is an interesting, but perverse, point of view; 3) This is true, but quite unimportant; and 4) I always said so. Now that the BBB is recognized to play a dynamic regulatory role, it might seem somewhat paradoxical that techniques such as intranasal administration are being used to bypass its more archaic role as a wall.

Another misconception is that the hypothalamus is “leaky.” If so, then an intranasal approach might be unnecessary because the arcuate nucleus of the hypothalamus is the main site of action for the effects of leptin on food ingestion. It continues to be mistakenly believed by a few investigators, without substantial proof, that the basal hypothalamus with its arcuate nucleus is not protected by a complete BBB, in which case leptin should be able to seep through. However, there is convincing anatomical evidence from several outstanding laboratories that even the median eminence is solidly separated from the adjacent hypothalamus, including the arcuate nucleus (22–26).

Perhaps part of the reason for persistence of the “leaky hypothalamus myth” is that the median eminence is a circumventricular organ (CVO). CVOs don’t have a traditional BBB, so that there is penetration from the blood for the short distance of a few cell layers; however, the ependyma/tanycytes, particularly β1 tanycytes (27), form a continuous membrane of tight junctions, preventing direct penetration into brain parenchyma. Once in the CVO, a plasma-derived peptide is trapped inside, not able to pass into CSF and brain regions adjacent to the CVO (28). Moreover, the surface area of the CVOs is at least 5000 times smaller than that of the BBB, minimizing its influx role (29, 30).

The existence of saturable BBB transport systems is exciting because such an influx is subject to regulation under physiological conditions. However, saturable systems are also susceptible to pharmacological constraints limiting the total amount of added material reaching the brain. Fiedner et al. (2) show that intranasally administered leptin enters the brain even in the presence of the high levels of this polypeptide that would occur in the blood of most forms of obesity. The mechanism by which this influx occurs, however, requires further elucidation. They provide evidence that passage is unlikely to occur through the blood or even the CSF, supported by results from Frey’s group (31). Both groups favor direct access from the nose into brain tissue as the most probable route. This results in regional differences, not subject to differential regional enzymatic regulation by the microvascular endothelial cells composing the BBB (32), so that some areas such as the deep brain structures may not benefit from intranasal delivery.

Bypassing the BBB with leptin has therapeutic implications, not the least of which might be to reduce the necessity for coronary bypass procedures, leading to our whimsical abbreviation BBBB. Other methods to facilitate brain influx, summa-

**Abbreviations:** BBB, Blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CVO, circumventricular organ.

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rized elsewhere (33), include chemical alterations of the ligand, liposome-mediated delivery, antibodies to endothelial markers, fusion proteins, viral-mediated delivery, and osmotic opening of the BBB. Less than 1% of administered peptides and polypeptides (which we define as 2–200 amino acids and 100–200 amino acids, respectively) reach the brain, including those known to exert potent CNS actions. Thus, the CNS is exquisitely sensitive to the small amounts allowed to cross its protective BBB.

Fliedner et al. (2) show that intranasal leptin, bypassing the ceiling effect of a saturable BBB transport system, allows increasing amounts to reach the brain, although there was a large discrepancy between their two experiments. It remains to be seen whether this translates into a linear dose-response for reduction of food ingestion. A larger dose of a peripherally administered peptide does not always produce a larger CNS effect but can result in an inverted-U shaped dose-response relationship (21). Other variables, like time of administration, are applicable for other cytokines in other CNS disorders (33). Defects in leptin signaling in the brain may also be involved. Moreover, a subject’s sex could be another factor, as suggested by the report that intranasal insulin reduces body fat in men but not women (34).

The pharmaceutical industry has seemed reluctant to develop potential peptide therapies. Lack of ease of administration is one reason offered, although millions of patients with diabetes mellitus have tolerated frequent sc administration of insulin. Another reason sometimes mentioned is the short half-life of peptides in blood, which ignores the lack of correlation with the longer duration of their CNS actions (21). Intranasal administration of a peptide to treat a disorder originating in the brain is not a novel concept; the vasopressin analog desmopressin has been used clinically by this route for several decades to treat diabetes insipidus. Desmopressin, however, does not need to bypass the BBB to exert its therapeutic effect, which, at a higher dose, is the same as by the systemic route. A saturated transport system at the BBB in obese subjects poses a different sort of problem that may be obviated by the approach shown here. Resistance to the small amounts allowed to cross its protective BBB may be limited. J Clin Endocrinol Metab 83:3220–3225

References

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