Brain Meets Body: The Blood-Brain Barrier as an Endocrine Interface

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The blood-brain barrier (BBB) separates the central nervous system (CNS) from the peripheral tissues. However, this does not prevent hormones from entering the brain, but shifts the main control of entry to the BBB. In general, steroid hormones cross the BBB by transmembrane diffusion, a nonsaturable process resulting in brain levels that reflect blood levels, whereas thyroid hormones and many peptides and regulatory proteins cross using transporters, a saturable process resulting in brain levels that reflect blood levels and transporter characteristics. Protein binding, brain-to-blood transport, and pharmacokinetics modulate BBB penetration. Some hormones have the opposite effect within the CNS than they do in the periphery, suggesting that these hormones cross the BBB to act as their own counterregulators. The cells making up the BBB are also endocrine like, both responding to circulating substances and secreting substances into the circulation and CNS. By dividing a hormone’s receptors into central and peripheral pools, the former of which may not be part of the hormone’s negative feedback loop, the BBB fosters the development of variable hormone resistance syndromes, as exemplified by evidence that altered insulin action in the CNS can contribute to Alzheimer’s disease. In summary, the BBB acts as a regulatory interface in an endocrine-like, humoral-based communication between the CNS and peripheral tissues. (Endocrinology 153: 4111–4119, 2012)

Mechanisms of Hormonal Translocation Across the BBB

Nearly every mechanism by which a substance can cross or interact with the BBB is used by one hormone or the other (Fig. 1). In general, steroid hormones cross the BBB by transmembrane diffusion whereas thyroid hormones, peptide hormones, and regulatory proteins cross by saturable systems. Their small size and lipid solubility allow steroid hormones to easily cross the BBB bidirectionally (i.e. in the brain-to-blood and blood-to-brain directions) by the process of transmembrane diffusion (4). Steroid hormones enter rapidly and throughout the brain by this pathological consequences of these mechanisms, and some disease states that can arise when brain-body communication at the level of the BBB goes awry.
nonsaturable process, the bidirectional and nonsaturable nature of entry allowing brain levels to come into rapid equilibrium with and to directly mirror blood levels, the level of brain retention being dependent more on the presence of receptors than on BBB permeability. Peptides can also cross to some degree by transmembrane diffusion, and enzymatically stable analogs can exert effects on the CNS (5–9).

The rate at which hormones transported by saturable mechanisms cross the BBB vary greatly as a function of the characteristics and distribution of the transporter. In general, the transport rate for the primary ligand of a transporter crosses about 10–40 times faster than it would were it to depend on transmembrane diffusion (10). Likewise, regional hormonal uptake and retention are influenced by the anatomical distribution of the transporter and its avidity for its ligand. The saturable aspect means that brain levels are not necessarily a linear reflection of blood levels both because of the nonlinear nature of transporters and because transporter rates can be modulated by many factors. Transporter dysfunction can lead to CNS dysfunction as discussed below. The list of regulatory substances that cross the BBB by way of saturable transporters such as cortisol and β-estradiol (23, 24).

The brain-to-blood movement of biologically active substances means that the CNS can act as an endocrine-secreting organ. Both IL-6 and TNF-α of CNS origin can contribute significantly to the levels in blood (25–28). Corticotrophin releasing factor transported into blood from brain can affect β-endorphin production by the spleen (29). Other substances transported into the blood from brain that likely contribute significantly to blood levels include IL-2, amyloid β peptide, endorphins, and enkephalins (18, 30–33).

Some very large hormones may cross the BBB by the residual leakiness of the BBB, termed the extracellular pathways (34). The sites for this leakage include the pial surface, the Virchow-Robin spaces, and the subpial cortical gray matter. Erythropoietin, antibodies, binding proteins, and albumin are examples of substances that cross by this mechanism (35). The pharmacokinetics favorable for this pathway have long half-lives in blood and small volumes of distribution. Passage is nonsaturable but independent of lipid solubility or molecular size, and the rate of penetration is low.
Effects of Binding Proteins on Hormone Penetration of the BBB

Albumin and binding proteins influence hormonal penetration across the BBB (36, 37). Cerebrospinal fluid (CSF) levels of albumin are about 0.5% of those in serum, yet this is enough to produce free and bound fractions of hormones in the CSF and brain interstitial fluid. For example, δ-sleep-inducing peptide is about 90% bound in blood and about 50% bound in CSF (38). Binding proteins are very influential in the passage of substances that cross the BBB by way of transmembrane diffusion with only free or loosely-bound hormone being available for transport. For substances with transporters, the relative avidity of the binding protein vs. the transporter dictates the degree to which the bound pool is available for passage across the BBB.

A dramatic example of the interplay between transporter function and binding proteins is that of T4, a hormone that is transported by a saturable mechanism into the CSF. The CSF/serum ratio of total T4 in dogs is 0.025, but the ratio for free T4 is 2.4 (17). In this case, the major source of CSF transthyretin, an important thyroid-binding protein, is not the circulation but the choroid plexus, the anatomical seat of the blood-CSF barrier, with the choroid plexus synthesizing and secreting transthyretin into the CSF (39).

Binding hormones alter pharmacokinetic aspects of their ligands, such as circulating half-life, that ultimately influence the rate and degree of penetration. Sex-binding globulin, for example, slows the rate at which testosterone crosses the BBB but also decreases clearance from blood, allowing more time for testosterone to penetrate the BBB and enter the CNS, ultimately having little affect on the total amount of testosterone entering the brain. However, lower, sustained levels of receptor occupancy vs. shorter-term, higher receptor occupancy can greatly influence hormone action, producing very different pharmacodynamic profiles (40).

These effects of binding hormones affect the pharmacokinetic and pharmacodynamic profiles of drugs derived from the parent hormones. For example, protein binding of insulin detemir prolongs its half-life in blood and its hypoglycemic effects, while decreasing its effects on body weight gain and altering its CNS effects (41–44). The protein binding, however, prevents insulin detemir from rapidly crossing the BBB (45).

Modulation of Saturable Transporter Mechanisms and Targeting to Brain Regions

The characteristics of the saturable transport of hormones are markedly different from those of metabolic substances. Representative of metabolic substances, glucose is needed by every region of the brain and in large amounts, and a high rate of transport throughout the CNS reflects this need. In comparison, the transport rate for a hormone can vary greatly among brain regions. As examples: some regions of the brain do not have measurable rates of insulin transport (46); the transport rate for TNF-α varies among brain regions by 10-fold (47); transport of leptin occurs throughout the CNS but with a high concentration at the arcuate nucleus (48); IL-1 has a concentrated uptake at the posterior division of the septum (49) and marked differences in transport into brain vs. spinal cord (13). In essence then, the transport of regulatory substances is much more variable, assumedly reflecting a targeting to areas of hormone activity. For example, the high rate of uptake of IL-1 into the posterior division of the septum coordinates with its ability to modulate memory (50).

Many of the hormonal transporters are not static but are themselves regulated. This regulation is presumed to reflect responses of the BBB to the needs of the CNS and therefore are, on one level, physiological. In some cases, this regulation contributes to premorbid conditions and disease states (Table 1). For example, impaired transport of leptin in obesity contributes to the leptin resistance seen in that condition (51–53). Triglycerides, insulin, glucose, estrogen, and epinephrine are some of the modulators of leptin transport that likely contribute to the regulation of the leptin transporter (54–57). Lower CSF and CSF/serum ratios of insulin suggest a decrease in insulin transport in

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pregnancy and could underlie the insulin-remediable defect in baroreceptor response seen in pregnancy (58, 59).

The BBB as an Endocrine Tissue

The cells that form the BBB both respond to hormones in the circulation and also secrete substances into the circulation. Examples of the BBB responding to circulating hormones are numerous. Insulin affects several parameters of brain endothelial cell function including modulation of amino acid, leptin, and the p-glycoprotein transporters (56, 60–62) and affects alkaline phosphatase and glutamate cysteine ligase catalytic subunit, the latter important in maintaining intracellular levels of glutathione (63, 64). Estradiol alters the Na-K-Cl cotransporter at the BBB (65). Angiotensin II affects vesicular trafficking of brain endothelial cells (66). Circulating epinephrine enhances leptin and enzyme transport across the BBB (67, 68). TNF-α and endothelin modulate the brain-to-blood efflux transporter p-glycoprotein (69, 70).

The study of the BBB as secretor is less well explored. However, brain endothelial cells secrete cytokines, chemokines, nitric oxide, adrenomedullin, and prostaglandins both constitutively and in response to treatment with lipopolysaccharide, cytokines, and other substances (71–80).

A unique feature of the BBB that relies on it having cell membrane surfaces facing both into the blood stream and into the interstitial fluid of the CNS is that it can receive signals from one compartment and secret regulatory substances into the other. For example, lipopolysaccharide applied to the brain (abluminal) side of the brain endothelial cell (BEC) stimulates them to increase their release of IL-6 from the blood (luminal) side (81). Adiponectin applied to the luminal membrane of BECs inhibits IL-6 secretion from the abluminal membrane, providing a mechanism by which the adipogenic effects of adiponectin could be relayed into the brain (82).

These endocrine effects at the BBB likely also contribute to disease states. The effects of angiotensin II on vesicular trafficking across brain endothelial cells (66) may underpin BBB disruption in hypertensive encephalopathy (83) as mediated by the renin-angiotensin-aldosterone system (84). IL-1 induces the fever seen in sickness behavior by inducing the secretion of prostaglandins from brain endothelial cells (79, 85–87). Up-regulation of adrenergic receptors at BBB cells in Alzheimer’s patients could be a basis for, or in response to, the cerebrovascular abnormalities seen in that disease (88). Through its regulation of Na-K-Cl channels, estradiol reduces brain edema after middle cerebral artery occlusion, providing a mechanism that may underlie the effects of estrogens on stroke and stroke outcomes (65).

Unique Interactions: Counterregulatory and Potentiating Effects

Hormones transported across the BBB can act within the CNS to modulate their peripheral effects (Fig. 2). As appreciated for almost two decades, many peptides that are transported across the BBB have effects in the brain opposite to those produced at peripheral tissues (89). For example, CNS insulin has been associated with an increase in serum glucose and a decrease in feeding (90–93); administration of cholecystokinin-8 into the CNS is associated with an attenuation of passive avoidance behavior whereas peripheral administration is associated with facilitation (94); CNS calcitonin enhances whereas peripheral calcitonin inhibits glucose-stimulated insulin release (95); and CNS TRH simulates whereas peripheral TRH decreases locomotor activity (96–98). This suggests that these hormones may be acting as their own counterregulatory hormones, the main effect being induced at peripheral tissues and a secondary, counterregulatory effect be-
ing induced within the CNS by the small amount of hormone that crosses the BBB.

Other hormones have effects in the CNS that are consistent with their peripheral effects. Secretin was the first hormone to be discovered, stimulating pancreatic secretion when administered peripherally (99). Secretin also affects CNS function either when given peripherally (100) or directly into brain (101). Secretin is found in the brain (102, 103) in part because of CNS synthesis (104) and in part because it is transported into the CNS, possibly across the choroid plexus rather than at the vascular barrier (105), where it acts at its CNS receptors (106, 107), stimulating cAMP and facilitating γ-aminobutyric acid neurotransmission (108, 109). Interestingly, CNS secretin also stimulates pancreatic secretion, but at much lower doses than those required when administered peripherally (110). About half of the effect that systemic insulin exerts on hepatic glucose production may be derived from insulin crossing the BBB and activating the vagus through ATP-sensitive potassium channels in the hypothalamus (111). Some hormones cross the BBB to stimulate their own secretion from CNS sources. For example, TNF-α transported across the BBB stimulates release of TNF from CNS sources, increasing to levels that can be toxic to dopaminergic cells of the substantia nigra, thus promoting the development of Parkinson’s disease (112). In contrast to the paradoxical effect outlined above, this suggests that other hormones cross the BBB to reinforce or potentiate their peripheral effects through CNS mechanisms.

**Unique Interactions: The Question of Variable Hormone Resistance**

Hormone resistance syndromes have been appreciated since the description of pseudohypoparathyroidism (113, 114). The variable hormone resistance syndromes for thyroid hormones illustrate that the degree of resistance may not be the same at all of the sites of action for a hormone (115). The presence of a BBB, which first divides the body into central and peripheral compartments and then defines and regulates the interactions between these compartments, fosters the development of hormonal resistance arising at three sites: 1) the CNS compartment, 2) the peripheral tissue compartment, and 3) the BBB. The relative resistances of tissues within and among these compartments may play a role in various diseases, including obesity and Alzheimer’s disease.

In humans and animals who do not make leptin, its administration causes profound weight loss (116, 117). However, in humans and in animal models of diet-induced obesity, resistance to leptin limits its usefulness as an anorectic (118). Resistance to leptin’s anorectic effects arises at two levels: at the BBB and at brain receptors (119). Modeling based on CSF and serum levels of leptin suggests that, although resistance at both of these sites is progressive with increasing obesity, early in obesity the dominant site of resistance is at the BBB (120). Studies of the progressive resistance to leptin given by the CNS and peripheral routes to animals with diet-induced obesity further support this (52, 53).

Diabetes mellitus type III is a term that emphasizes that Alzheimer’s disease has been associated with a defect in insulin action within the CNS, either because of decreased levels of insulin in the brain or because of resistance at CNS insulin receptors (121–125). Several studies have shown that delivery of insulin to brain by way of peripheral or intranasal administration can improve cognition in normal subjects, persons with memory impairment, and in patients with Alzheimer’s disease (126–130). Although diabetes mellitus type 2 is a risk factor for Alzheimer’s disease, there are many patients with diabetes type 2 who do not have Alzheimer’s disease and many patients with Alzheimer’s disease who do not have diabetes. This would suggest that to the degree that Alzheimer’s disease relates to CNS insulin deficiency, that deficiency can be independent of peripheral insulin resistance.

A mismatch between the degree of CNS and peripheral resistances to insulin would illustrate an interesting dilemma in hormonal regulation. In the case of partial peripheral insulin resistance, the pancreas can compensate by increasing insulin secretion until glucose returns to a normal range. But CNS receptors, especially those not related to glucose sensing, are not involved in the negative feedback loop that exists in the periphery between glucose and insulin. Furthermore, at some point, elevations in serum insulin are not translated into equivalent elevations in CNS insulin because the insulin transporter at the BBB becomes saturated. As a result of these two phenomena, how or even if the CNS can compensate for an isolated partial resistance to insulin is unclear.

**Conclusions**

The BBB’s unique location that places it simultaneously in the peripheral circulation and in the CNS and its unique functions of first separating the CNS from the periphery and then regulating their humoral interactions gives the BBB unusual endocrine properties. The cells that compose the BBB themselves also qualify as endocrine tissues, both responding to and secreting circulating substances. Endocrine conditions and diseases such as diabetes mellitus and obesity lead to BBB dysfunction, and dysfunctions of the
endocrine BBB contribute to these states. These characteristics allow for unique interactions among the BBB, peripheral tissues, and CNS.

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