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REVIEWS

Regulation of brain metabolism by peripheral nutritional signals: the role of blood-brain barrier in health and disease

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[Abstract] The blood-brain barrier (BBB) prevents unregulated substance exchange between the central nervous system and the blood, while providing highly regulated transport of nutrients and tonic factors essential to brain metabolism. A group of carriers, transporters, and receptors is utilized by endothelial cells of the BBB to aid the influx and efflux of nutrients and metabolic wastes, and their function is subject to changes during metabolic disorders such as diabetes mellitus and obesity. This regulated barrier function of BBB is essential for maintaining the normal metabolism of the brain and transduction of metabolic signals from the periphery. As such, disruption of the BBB nutrient/hormone transport system has been proposed to be major contributors of many neurological diseases.

[Key words] Blood-brain barrier; Metabolic disorders; Diabetes mellitus; Obesity

1 Introduction

The brain is the central organ of neuronal activities, and its proper function relies on a homeostatic environment. The blood-brain barrier is a specialized structure of the brain blood vessels, consisting of endothelial cells, pericytes, astrocytes, and basement membranes[1]. These cellular and non-cellular components act together to isolate the brain parenchyma from peripheral circulation, avoiding the uncontrolled entrance of neurotoxins, pathogens and immune cells while allowing strictly regulated transport of essential nutrition and hormones[2]. To achieve this function, the endothelial cells of the BBB have high expression levels of tight junction proteins, a low level of transcytosis, and low expressions of adhesion molecules, all of which minimize unspecialized transport of blood substances[2-3]. On the other hand, endothelial cells express a group of carrier proteins, membrane receptors, and influx and efflux transporters, providing highly regulated transport of nutrients and tonic factors essential to brain metabolism[4].

As an organ of extensive energy demand, the brain requires continuous nutrient transport from peripheral circulation. The presence of BBB blocks free penetration of nutrients and hormones, and thus has a major role in the regulation of brain function. Disruption of BBB nutrient/hormone transport, along with dysfunction of receptors and insufficient

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downstream signaling have been proposed to be major contributors of many neurological diseases[5].

In this review, we summarize the routes that essential nutrients and hormones utilize to enter the brain across the BBB, as well as the routes through which metabolic wastes efflux from the brain. Finally, we briefly discuss changes of the transport function of BBB in the most common metabolic diseases, diabetes mellitus and obesity.

2 Nutrients and hormones transport across the BBB during physiological condition

2.1 Glucose

The brain is an organ of high energy demand and consumes about 20% of total glucose in the body[6]. In periphery organs, glucose from the blood enters interstitial fluid from the ultrafiltrate produced in the capillary beds, and its entry to cells is insulin-dependent[7]. In contrast, direct glucose leakage from the capillary is eliminated by the tightly regulated barrier function of BBB. Instead, glucose is transported across the BBB via an insulin-independent glucose transporter expressed on brain endothelial cells, GLUT-1[8]. GLUT-1 transports glucose in a saturable, but not active fashion (energy independent), and transports 50 times more glucose to the central nervous system (CNS) than otherwise conveyed to meet the high energy demand from neuronal activity[9]. Similarly, the uptake of glucose by CNS cells is largely independent of insulin signaling. Insulin insensitive glucose transporters, including GLUT-1 (astrocytes), GLUT-3 (neurons), and GLUT-5 (microglia) direct the glucose transport to various types of CNS cells[10]. It should be noted that glucose transport mediated by the sodium-dependent glucose transporter 2 (SGLT2), have also been proposed[11-12], although it is expressed at a lower level on endothelial cells compared with GLUT-1, suggesting its relatively minor role in glucose transportation to the brain [13].

2.2 Lactate and ketone bodies

Lactate has been previously considered as a metabolic waste and the consequence of insufficient oxidation in skeletal muscles[14]. However, recent studies have set its role as an alternative energy source[15] and a signaling molecule in regulating complex neurological behaviors[16-17]. Lactate is transported to the brain via the monocarboxylate carrier 1 (MCT1) in a bi-directional fashion[18]. MCT1 is also capable of transporting ketone bodies into the brain, which can be used as an alternative energy source when glucose supply is limited in situations of prolonged fasting[19-20].

2.3 Nucleotides

The brain has little capacity of synthesizing purines and pyrimidines *de novo*, which gives great significance to nucleotide transport systems in the BBB[21-22]. The nucleotides in the brain are transported by two systems, that is the bidirectional processes driven by chemical gradients via the equilibrative nucleoside transporter (ENT) 1 and ENT2 transporters, and the unidirectional concentrative processes driven by sodium electrochemical gradients via the CNT2 transporter[22]. Because of a relatively high Km of ENT1 and ENT2 compared with CNT2, it is likely that CNT2 plays the major role in nucleotide transport in physiological conditions, and ENT1 and ENT2 are only more active when peripheral nucleotide is at a very high level, for example after an experimental supplementation[23-24].

2.4 Lipids

2.4.1 Cholesterol

Cholesterol is the major component of CNS myeline, and the brain consists of around 25% of all cholesterol weight in the body[25]. Due to the prevention of lipoprotein uptake by the BBB, cholesterols cannot be transported from the peripheral but are mostly synthesized *de novo*,

insulated from circulating cholesterols[26-27]. Glia cells, especially oligodendrocytes and astrocytes, are the major sites of cholesterol synthesis[28]. An efflux of astrocytic cholesterol is mediated by the ATP-binding cassette transporter 1, and is shuttled to neurons as Apolipoprotein E (apoE) and cholesterol-containing lipoproteins[25].

2.4.2 Fatty acids

The exact mechanism for fatty acid transport through the BBB remains controversial. Two possible models of fatty acid transportation to the CNS have been proposed. The most straightforward method would be passive diffusion from the endothelial plasma membrane in a "flip-flop" way[29]. That is to say, fatty acids diffuse to the exofacial leaflet of the plasma membrane and are then flipped to the cytofacial leaflet, ultimately entering the cell for use[30]. The capacity of this transportation method is limited, possibly due to the thermodynamic challenge resulting from the negative charge carried by carboxylic acids[31-32]. A second model is through protein-mediated transport, such as fatty acid transport proteins (FATP) and fatty acid translocase/CD36[33]. FATPs, also known as the solute carrier family 27, contain the members FATP1-6, with the most abundant expression of FATP1 and FATP4 in brain microvascular endothelial cells[34]. Knockdown of either FATP1 or FATP4 significantly reduced transport of long-chain fatty acids across human brain microvascular endothelial cells (HBMEC) *in vitro*, suggesting a predominant role of carrier-mediated transport[33]. Knocking down of fatty acid translocase/CD36, on the other hand, decreased transport of short-chain, medium-chain, and long-chain saturated and unsaturated and very long-chain fatty acids, suggesting its more general role in fatty acid transport[33].

Docosahexaenoic acid (DHA), an omega-3 fatty acid essential for brain development and cognitive function, has a unique route for transport across the BBB. With the aid of major facilitator superfamily domain-containing protein 2A (Mfsd2a), a member of the major facilitator superfamily, DHA is transported in the form of lysophosphatidylcholine, but not unesterified fatty acid[35-36]. Deficiency of Mfsd2a results in a significant decrease in the level of DHA in the brain, in company with microcephaly, neural loss, cognitive deficits and abnormal behavior[35]. Mfsda2 is also critical for the formation and function of the BBB via regulating transcytosis[37-38], which could also affect the transport of other key nutrients to the CNS[39].

2.4.3 Amino acids

Amino acids are building blocks of protein synthesis and have a particular role in regulating neurotransmitter synthesis and release in the brain[40]. Amino acids are transported with the aid of a group of solute carrier family members (SLCs) with preferences[2]. CAT1 and CAT3 transport cationic L-amino acids, such as Lys and Arg, while the L amino acid transporters 1 (LAT1, or Slc7a5) and LAT2 (Slc7a8) transports large neutral amino acids such as Phe, Trp, Leu, and His[41-42]. Deficiency of LAT1 leads to an abnormal amino acid profile in the brain and its mutation is associated with an autism spectrum disorder in human patients[43]. Glutamine can be transported to the brain with the help of SNAT5.

2.5 Hormones

2.5.1 Leptin

Leptin is a peptide hormone produced by adipose tissues. Its target organ lies in specific leptin-receptor-expressing neurons in the arcuate nucleus of the hypothalamus, with the main functions of controlling appetite, body weight, neuroendocrine functions, and glycemia[44-45]. Leptin is transported to the CNS in a saturable and receptor-dependent process[5] and its entry path to the CNS include across the blood-brain barrier, the brain-cerebral spinal fluid (CSF) barrier, and tanycyte endocytosis in the

median eminence in the basal hypothalamus[46-49]. Because of the low diffusion rate of leptin in the brain tissue, leptin entered from different sites seems to have unique functions on specific regions of the brain[5]. Mice with selective deletion of leptin receptor (LepR) in brain microvascular endothelial and ventricular epithelial cells present aggravated obesity when fed with a high-fat diet compared with wild type controls because of high sensitivity in food reward[50]. Interestingly, an obesity phenotype is not observed when fed with a normal diet[50]. Leptin entered via the tanycytes endocytosis path, in contrast, controls homeostatic lipid metabolism and pancreas function[51]. In the physiological circumstance, the rate of transport of leptin to the CNS is affected by blood glucose, triglycerides, adrenaline and probably estrogens[52-53].

2.5.2 Insulin

Although the transport and usage of glucose is independent of insulin in the CNS, insulin still plays important roles in the CNS[8]. Brain insulin acts on the control of appetite, adipose tissue lipolysis, hepatic triglyceride secretion, and branched-chain amino acid metabolism[7]. Insulin crosses the BBB by a saturable mechanism. However, whether its transportation requires binding with its receptor remains controversial. In a mouse model genetically deficient in endothelial insulin receptor, the CNS level of insulin, the rate of transport of insulin, and the saturable fashion of its transportation is maintained, albeit a decrease in binding of insulin to endothelial cells[54]. However, in an *in vitro* model of BBB, pretreatment of monolayer of isolated brain endothelial cells by the insulin receptor blocker S-961 significantly decreased its uptake and transcytosis[55].

2.5.3 Thyroid hormones

The thyroid hormone, T3 and T4, are iodinated amino acid hormones produced and secreted by the thyroid gland. T3 is the major functional form of thyroid hormone and T4 can be transformed to T3 in periphery organs[56]. Upon binding with its nuclear receptors, T3 activates tissue-specific transcriptional changes, which is critical for normal development, growth and metabolism[57]. Thyroid hormone is especially important for the developing brain, as children who develop under the condition of severe thyroid hormone deprivation suffer from severe mental retardation, deaf-mutism, spastic diplegia and extrapyramidal rigidity after birth[58].

The transport of T3 across the BBB is mediated by the solute carrier MCT8[59-60]. Deficiency in MCT8 in a mouse model resulted in a selective defect in T3 uptake, while T4 accumulation is maintained, suggesting a different transport system of T4[61]. T4 is transported via the T4 transporter Oatp1c1 in rodents. In the presence of T3 deficiency, the activity of type 2 iodothyronine deiodinase, the enzyme which converts T4 to T3 in astrocytes in the brain, is enhanced to compensate for the lack of T3[62]. Oatp1c1, however, is expressed at a very low level in human and monkey brains, indicating that T4 transport and conversion in the brain might not be sufficient to compensate for MCT8 loss in human as in rodent models[63].

2.5.4 Insulin-like growth factor 1

Insulin-like growth factor 1 (IGF-1) is a peptide growth factor produced in the liver[64-65]. IGF-1 has been shown to have multiple effects on the brain, including brain vessel growth, adult neurogenesis and neuronal excitability. IGF-1 is also transported to the brain through multiple routes. IFG-1 can be uptaken to the CSF in a saturable fashion independent of its receptor[64]. Instead, this process is mediated by the endocytic receptor megalin/low-density lipoprotein receptor-related protein-2 (LRP2)[66]. IGF-1 can also be transported across the BBB, and this process is tightly related to neurovascular coupling[67]. Upon increased neuronal activity, glutamate released by neurons activates vasodilation resulting in increased availability of serum IGF-1, and increasing the activity of metalloprotease 9

to release IGF-1 from its serum binding protein, allowing its entrance to the CNS[67]. The brain microvascular endothelial cells express high levels of IGF-1 receptor IGF1R[68]. However, there is no direct evidence for receptor-mediated transcytosis of IGF-1 via IGF1R across the BBB.

3 Efflux of metabolic wastes from brain during physiological condition

3.1 Cholesterol

Because cholesterols are mainly synthesized in the brain *de novo*, an export mechanism must exist to remove excess cholesterol and achieve its active balance in the brain. A small amount of excessive cholesterol can be excreted from the BBB in the form of apoE-bound cholesterol via the CSF at the rate of 1 to 2 mg per day, or quantitively more significant, as the cholesterol metabolite 24*S*-hydroxycholesterol[69-70]. Unlike cholesterol, 24*S*-hydroxycholesterol can be excreted to the circulation via the solute carrier organic anion transporter family member 1B1 carrier expressed on endothelial cells[71]. 24*S*-hydroxycholesterol is an endogenous ligand for liver X receptors (LXRs) in the brain, whose activation increase cholesterol release from astrocytes, and loss of these receptors results in neurodegenerative diseases[72]. These results suggest a dual role of 24*S*-hydroxycholesterol in regulating brain cholesterol release and export.

3.2 Amino Acids

Amino acids in the brain are 10 to 20 times lower than in the plasma, with the exception of a similar concentration of glutamine[73]. Thus, the brain-to-blood transport of amino acid against concentration gradient depends on Na^+-dependent systems expressed on the abluminal side of endothelial cells[73]. These transporters include the system LNAA for large neutral amino acids (Leu), system A for small non-essential neutral amino acids (Pro, Gln, Ser, Asn, His, and Ala), system ASC for transport of Ala, Ser and Cys, system N for nitrogen-enriched amino acid transport (His, Gln and Asn), and the excitatory amino acids transporters(EAATs) that transports Asp and Glu[74]. Among these transporters, the EAAT1, 2, and 3 transporters for glutamate is especially important, which function to maintain the glutamate levels and avoid excessive neuronal excitation and neurotoxicity[19,75]. Excessive accumulation of glutamate in the brain has been implicated in several neurodegenerative disorders, including Alzheimer's disease (AD), Huntington's disease, and amyotrophic lateral sclerosis[76].

3.3 Amyloid *β*-peptide

Amyloid β-peptide (Aβ) is a group of 36-43 amino acid peptides produced from the heterogeneous cleavage of the amyloid precursor protein (APP)[77]. Aggregation and deposition of Aβ in amyloid plaque in the brain is a hallmark of AD[78]. In physiological conditions, Aβ is transported bi-directionally across the BBB via various transporters. Advanced glycosylation end product-specific receptor (RAGE) has been reported to be an influx transporter of Aβ from the periphery, while the transporters LRP1, LRP2 and ABC subfamily B member 1 (ABCB1) mediates its efflux[79-81]. Aging significantly reduces the expression of LRP1 and ABCB1 on brain endothelial cells[82], which could potentially perturb Aβ efflux and ultimately cause Aβ deposition in the brain and AD.

4 BBB changes during metabolic disorders

4.1 Diabetes mellitus (DM)

Diabetes mellitus has a profound effect on brain vascular function. Patients with DM have a 2.5-fold more risk of developing ischemic stroke, and a 1.5-fold more risk of developing vascular dementia, indicating potential deficits in microvascular function[83-85]. An increase in BBB permeability has been observed in both patients with type 2 diabetes and in rodent

models, as indicated by postcontrast enhancement of the brain parenchyma and increased ratio of CSF to serum albumin level[86-87]. This dysfunction in BBB integrity has been associated with pericyte glucotoxicity. The increased glucose uptake by pericytes induces overproduction of reactive oxygen species, and therefore leading to pericyte degradation and BBB disruption[88]. Chronic hyperglycemia also includes accumulation of advanced glycation end products (AGE) and the upregulation of its receptor (RAGE) on microvascular endothelial cells, pericytes and astrocytes[84]. RAGE activated the NF-κB pathway, inducing neuroinflammation and further impairs BBB function[89]. Hyperglycemia also directly acts on endothelial cells by downregulating the tight junction protein ZO-1 and occludin, and upregulating the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), which potentially facilitates the infiltration of immune cells[90-91] (Fig. 1).

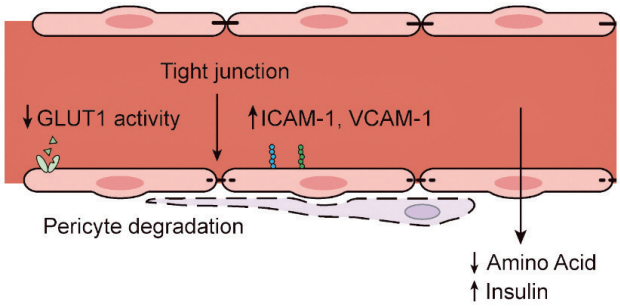

Fig. 1 BBB change in diabetes mellitus

Diabetes mellitus significantly impairs the barrier function of the BBB by inducing pericyte degradation and downregulating the expression of tight junctions on endothelial cells. In the meantime, the endothelial cells express higher levels of adhesion molecules ICAM-1 and VCAM-1, and decrease the activity of the glucose transporter GLUT-1. The BBB also transports less amino acid and more insulin to the brain.

DM also interferes with the metabolic condition of the brain. Upon hyperglycemia, the glucose transporter activity on BBB is downregulated, in association with a parallel decrease in cerebral blood flow[92]. Correspondent with the increased level of insulin in the circulation in T2DM, DM animals also have an increased transport of insulin to the brain. However, the capability of insulin to promote leptin transportation is impaired[52]. Disruption of amino acid metabolism in DM has also been reported and associated with the development of diabetic neuropathic pain[93]. The level of amino acids which are the precursors of neurotransmitters, including L-tryptophan, L-histidine and L-tyrosine, are downregulated[93]. Whether these changes are related to altered transporter function remains unknown.

Table 1 Transporters for various nutritions on the BBB

Substrate	Transporter
Influx	
Glucose	GLUT-1
	SGLT2
Lactate	MCT1
Ketone bodies	MCT1
Nucleotide	ENT1, ENT2
	CNT2
Lipids	
Cholesterol	*de novo* synthesis
Fatty acids	FATP1, FATP4
	fatty acid translocase/CD36
	MFSD2A (DHA)
Amino acid	CAT1, CAT3 (System y+)
	LAT1, LAT2 (System LNAA)
	SNAT5 (System N)
Hormones	
Leptin	LepR
Insulin	IR (can occur independent of its receptor)
Thyroid Hormones	
T3	MCT8
T4	Oatp1c1
Insulin like Growth factor 1	LRP2
Efflux	
Cholesterol	Oatp2(24*S*-hydroxycholesterol)
Amino Acids	LAT1, LAT2 (System LNAA)
	SNAT1, SNAT2 (System A)
	SNAT3, SNAT5 (System N)
	ASCT1, ASCT2 (System ASC)
	EAAT1, EAAT2 (System EAAT)
Amyloid β-peptide	Abcb1(P-gp)
	LRP1
	LRP2

4.2 Obesity

The BBB participates in the pathogenesis of obesity through mediating resistance to peripheral leptin. Leptin enters the brain in a saturable fashion, and thus the relationship between serum and CNS leptin levels forms a hyperbolic curve[94]. In the linear range of this curve, an increase of serum leptin induces a proportional increase in CNS leptin. However, in conditions where serum leptin level is so high that has surpassed the linear range, transport of leptin to the CNS is saturated and cannot respond to the further increase in the serum, resulting in a relative hypo-leptin level in the brain. In fact, obese individuals have a more than 3-fold increase of leptin in serum, and a lowered CSF/serum ratio compared with lean individuals, further supporting the idea of transport deficiency of leptin in obesity[95-96]. Administration of leptin directly to the CNS, rather than injection to the peripheral circulation, has a profound dose-dependent decrease in food intake and body weight[97]. Increased level of triglycerides, which appears in both starvation and obesity, also inhibits leptin transport to the brain[98].

Obesity also alters nutrition transport to the brain. A transient high-fat feeding induced a reversible downregulation of GLUT-1 in BBB endothelial cells, reduced brain glucose uptake, but could be restored during prolonged high-fat diet feeding[99]. Obesity also decreases the transport of insulin to the brain, but increases the transport of free fatty acids[100]. A high-fat diet induced obesity model revealed a downregulation in cerebral microvessels relating to cell cycle regulation, cell metabolism and cytoskeleton associated protein[101]. The expression of a group of transport proteins, including clathrin light chain B, voltage-dependent anion-selective channel protein 3, dihydropyrimidinase-related protein 1 and 2, EF-hand domain-containing protein D2, and far upstream element-binding protein 2 is also decreased[101].

5 Conclusion and outlook

The BBB constitutes an interface between the peripheral circulation and CNS environment. The barrier function of BBB isolates the brain from direct peripheral nutritional signals. By highly selective transport of nutrients and hormones, the BBB plays an essential role in maintaining the normal metabolism of the brain and transduction of metabolic signals from the periphery. The BBB itself is susceptible to injury in metabolic diseases such as diabetic mellitus, and is an active participant in the pathogenesis of other metabolic disorders such as obesity. The specific changes of the transport function of BBB in metabolic diseases have not been fully understood, and warrant further studies.

Several questions remain to be answered in this field. When the internal environment is altered in metabolic disorders, is the presence of BBB sufficient to maintain the CNS homeostasis as in normal conditions? If not, how is the function of the BBB compromised and what can we do to reverse this dysfunction? In metabolic disorders, whether and how BBB dysfunction affects the metabolism and thus the functions of the cells in the brain tissue, including neurons, astrocytes, microglia, oligodendrocytes, etc.?

In the future development of novel therapeutic approaches towards obesity and diabetes, the maintenance of BBB function could be a potential target to avoid CNS complications. In diseases such as obesity, the transport capability of certain hormones across the BBB plays a major role in their pathogenesis. Targeted brain delivery of certain substrates, which can be modified to increase their passage across the BBB, constitutes a potential therapeutic approach for metabolic diseases.

6 Conflicts of Interest

These authors have no conflict of interest to declare.

7 Acknowledgements

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