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Regulatory Peptides: Exchange across the Blood-Brain Barrier

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Abstract

Regulatory peptides produced by endocrine cells of the digestive tract and other peripheral organs affect the brain and thereby elicit multiple CNS-dependent effects. For example, more than two dozen of gut peptide hormones are involved in the transmission of satiety signals, opening up alluring prospects of creating anorexigenic drugs. Nevertheless, these agents, known for almost four decades, have not so far received wide application in clinical medicine. Such a protracted delay in application suggests a need for a better understanding of the theoretical conceptualizations underlying peptide regulation. Our mini review attempts to bridge the gap between theory and practice.

Keywords: Blood-brain barrier; Regulatory peptides; Transport; Appetite suppressants

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Introduction

Regulatory peptides produced by endocrine cells of the digestive tract and other peripheral organs affect the brain and thereby elicit multiple CNS-dependent effects. For example, more than two dozen of gut peptide hormones are involved in the transmission of satiety signals, opening up alluring prospects of creating anorexigenic drugs. As potential medicinal agents, regulatory peptides have important advantages: (a) eventually, they all break down to amino acids, making overdose impossible, (b) short regulatory peptides can be taken perorally.

Nevertheless, these agents, known for almost four decades, have not so far received wide application in clinical medicine. Such an inconsistency suggests a need for a better understanding of the theoretical conceptualizations underlying peptide regulation.

The same regulatory peptides -gastrin, secretin, cholecystokinine and many others— are produced both by endocrine cells of the gut mucosa and neurons of the brain. These peptides are implicated in humoral regulation in the digestive organs and the brain, respectively. However, the relationship between central and peripheral regulatory peptides, such as intestinal and cerebral cholecystokinines, or peripheral and cerebral secretins, is still unclear. Is there a synergistic relationship between these 'peripheral' and 'central' peptides, or do they represent two distinct and independent regulatory systems? If a cooperative relationship does exist, how is it realized if the brain is separated from the periphery by a peptide-impermeable (or poorly permeable) blood-brain barrier (BBB)? Answering these questions can better inform the choice of strategies used in developing new medicines.

The passability of peptides across the BBB

The passability of peptides across the BBB, i.e. their ability to pass through the BBB, depends on such properties as the size, flexibility, conformation, biochemical properties of constituent amino acids and spatial arrangement of the molecules. Peptide structure determines to some extent such properties of the molecule as the degree of binding it to plasma proteins, peptidase resistance, absorption by nontarget

tissues, excretion rate, and affinity for transporters [1]. By a very rough estimate [2], the passability of peptides across the BBB is two-three orders of magnitude lower than for glucose and two orders higher than for albumin.

Passive influx of peptides

Substances with low (but not zero) lipophilicity can penetrate from the blood to the brain in small amounts via simple diffusion

(Figure 1). Pathways of penetration of hydrophilic substances from the periphery into the brain parenchyma. Proven pathways: 1) simple diffusion to the brain parenchyma, directly or via the choroid plexus and cerebrospinal fluid; 2) active transport; 3) intra-axonal transport along afferent fibers. Putative pathways: 4) via the circumventricular organs and then (a) by intra-axonal transport, (b) across the ependyma into the cerebrospinal fluid, or (c) by bulk flow to the regions not protected by the ependyma. (BBB: blood-brain barrier; CP: Choroid Plexus; CVO: Circumventricular Organ; CSF: Cerebrospinal Fluid).

A variant of such penetration is the pathway: blood → choroid plexus → ependymal of the cerebral ventricles → cerebrospinal fluid. "Theoretically, there is also what is termed as the "functional leak", where the ependymal cells are linked by tight junctions around the circumventricular organs and the permeable ependymal lining the ventricles join [3].

Dipeptides, glycylphenylalanine (Gly-Phe) and glycylleucin (Gly-Leu), are absorbed by the brain at about the same rate as sucrose, i.e. insignificantly and slower than their constituent amino acids, singly. Dipeptides do not suppress the absorption of their constituent amino acids [4], indicative of the mechanism of passive influx.

The rate of passive penetration of a peptide from the blood into the brain is directly proportional to such its properties as: (a) lipophilicity (being quite low); (b) arterial blood concentration (in a free state); and (c) resistance to enzymatic degradation. It is also inversely proportional [5] to the: (a) polarity of a molecule (e.g., in the presence of -COOH, -OH or -NH_2 groups — the surface of the molecule is very important in terms of how the molecule passes through the BBB, since there is an interaction between the molecule surface charge and the cells of the BBB) and (b) binding to plasma proteins.

The surface of the molecule is very important in terms of how the molecular passes through the BBB since there is an interaction between the charge of the surface molecule and the cells of the BBB. In general, major restrictors for molecules of hydrophilic substances, such as peptides, for passing through the BBB are the number and strength of intermolecular bonds that hold water molecules [6]. Therefore, the factors that reduce the passability are: (a) dipolarity; (b) polarizability; and (c) hydrogen bonding potential. The passability is promoted by (a) small size of a molecule and (b) molar refraction. Importantly, the role of lipophilicity far exceeds that of all other factors. Yet, August Krogh (winner of the Nobel Prize in Physiology or Medicine in 1920) maintained that creating new pharmaceutical preparations which are able to penetrate into the brain should be guided, not by the charge of a molecule, but by its solubility in lipids [5]. Simple diffusion was shown to drive into the brain the following regulatory peptides:(a) dipeptide cyclohistidylproline cyclo(His-Pro) [7] and tripeptide thyrotropinreleasing hormone [8]; (b) some opioid peptides [9]; and (c) amylin (number of amino acids, n=37) [7] and nesfatin-1 (n=82) [10].

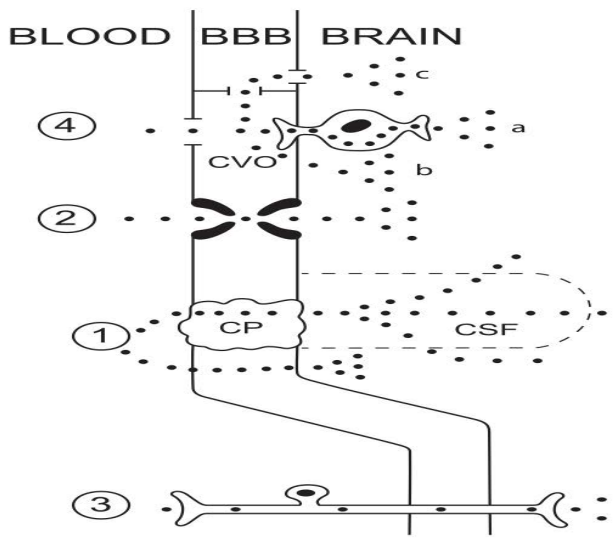

Figure 1 Pathways of penetration of hydrophilic substances from the periphery into the brain parenchyma.

Active influx of peptides

Peptide transporter-2 (PEPT2) mediates the influx of di- and tri- peptides [11]. A peptide transport system is not identical to a peptide-specific receptor. Thus, Tyrmelanotropin release-inhibiting factor-1 and met-enkephalin are transported by the same peptide transporter system (PTS-1) but have different receptors [12].

The systems for active transport from the blood to the brain have been described for various regulatory peptides, including: (a) ghrelin [13]; (b) urocortin I [14,15]; (c) corticotropin-releasing hormone [16]; (d) leptin [17]; (e) pituitary adenylate cyclaseactivating polypeptide [18,19]; (f) thyrotropin-releasing hormone [20,21]; (g) insulin [7,22]; and (h) opioid peptides. Nevertheless, as exemplified by ghrelin, the role of peptides penetrating across the BBB via active transport is dubious: the ghrelin penetration rate is too small to create a peptide concentration in the brain that is sufficient for its binding to specific receptors GHS-R [23-25].

Quantitative assessment of peptide influx

The degree of peptide passability is positively associated with the quantitative assessment of the peptide lipophilicity (octanol coefficient or octanol water partition coefficient, Kow) and negatively correlated with the molecular weight, percentage of unbound peptide, and various kinds of charges of a molecule Oldendorf technique. William Oldendorf (1925–1992) was the first to announce in 1961 the possibility of neurovisualization. His lesser known contribution to neurology was the proposition in 1970 of the method for quantitative assessment of BBB permeability, based on determining the brain uptake index (BUI). To do this, the substance tagged with a radioactive label was injected by bolus dosing into the carotid artery with animal decapitated the label concentration was then measured in brain tissue and compared to the reference level, the super-heavy water ($3H_2O$) passability [2,26], using 14C-antipyrine with a zero passability as a reference substance. Oldendorf and his colleagues adapted this method to assess the transport of amino acids [27] and peptides [28] to the brain.

In assessing the peptide influx, the Oldendorf's method theoretically has a drawback typical for similar methods: the passage of the radioactive label to the brain does not necessarily mean the passage of the whole molecule; peptide molecule can undergo peptidase-induced degradation, after which the label, alone or coupled to a peptide fragment, penetrates into the brain. Nevertheless, the Oldendorf method has been widely used until very recently [29].

The attempts to experimentally establish the percentage of peptide absorbed by the brain from the blood yielded quite high values: 2-3% for enkephalins and 1% for the thyrotropin-releasing hormone [30]. It is more likely that penetration of peptides from the blood to the brain parenchyma via simple diffusion is evaluated in fractions of a percentage. For example, 0.18% of peptide YY injected intravenously [31] and about 0.40 % of natriuretic peptide A injected into the carotid artery [32] pass through the BBB in this way. A whole-molecule penetration? Results of experiments with intracarotid injections of delta sleep-inducing peptide (DSIP), conducted in the late 1970s by researchers in the lab of Andrew Schally (winner of the Nobel Prize in Medicine in 1977) at Tulane University indicated that small amounts of regulatory peptides can penetrate across the BBB as whole molecules. Initial evidence was only indirect [33] and included findings that: (a) the brain/blood ratio of radioactive label concentrations was higher for labeled DSIP than for labeled insulin and (b) the brain DSIP concentration rises too fast (within first seconds after peripheral peptide injection) and lasts too short (about 1 min) to be explained by activation of the intracerebral synthesis of DSIP.

Shortly after that, more reliable evidence appeared. The use of highly specific antibodies to DSIP, targeted at the sequence fragment of no less than eight amino acids, showed that DSIP passes to the brain as a whole molecule [34]. Later, it was demonstrated that this is true not only for oligopeptides, but also for polypeptides with a molecular weight of 16–18 kD, specifically for interleukins IL-1alpha, IL-1beta, IL-6, tumor necrosis factor-alpha and leptin [35].

Efflux of peptides

Release of peptides in and through the hypophysis — are classic pathways of releasing peptide hormones from the brain (hypothalamus) into the blood via: (a) the hypophyseal portal system to the adenohypophysis, apart from the well-known releasing (corticotropin-releasing hormone, luteinizing hormone-releasing hormone, growth hormone-releasing hormone, thyrotropin-releasing hormone, prolactinreleasing peptide) and inhibitory (somatostatin, melanotropin release-inhibiting factor-1) hormones, as well as pituitary adenylate cyclase-activating polypeptide, which is also discharged into the bloodstream [36,37] and (b) the axons of hypothalamic neurons from which two cyclic nonapeptides, vasopressin and oxytocin, are released anterogradely into the neurohypophysis. Nonselective release of peptides with excessive liquid. Vascular plexuses produce and secrete into the ventricles of the human brain roughly 500 ml of cerebrospinal fluid per day, while the total volume of the ventricular system is about 3.5 times smaller (~140 ml). Excessive liquid is periodically flushed down a hydrostatic pressure gradient into the dural venous sinuses through the arachnoid villi, which serve as valves. This provides a continuous "flushing" of brain tissues by cerebrospinal fluid [5].

As a result of induced inversions of the hydrostatic pressure gradient (to −20 cm H_2O), central injections of regulatory peptides (specifically, gastrin-17 and somatostatin-14) does not cause an elevation of their blood concentrations, even at high doses [38]. Under normal (positive) hydrostatic pressure gradient, central injections of regulatory peptides, as a rule, also does not lead to increases in their blood level concentrations. For example, this was shown in experiments with gastrin, calcitonin, corticotropin-releasing hormone and calcitonin gene-related peptide [39].

It has been hypothesized that some peptides injected into the brain are excreted to the blood so quickly that they have no time to exert the peripheral effects [40]. We consider this mechanism unlikely, asthe blood level of any regulatory peptide, independent of its concentration in cerebrospinal fluid, of which approximately 500 ml is produced per day, which is the same amount that is discharged to the blood. The half-life of regulatory peptides in the blood and other body fluids never exceeds 10 min [41].

Therefore, during 5 min (a rough half-life of most regulatory peptides) a little more than 1.5 ml of liquid dissolves in 3 L of circulating plasma, meaning a 2,000-fold dilution. Moreover, the liquid concentration of regulatory peptides is initially low. It is not without reason that there is a special vascular system providing the effect of releasing hormones on the adenohypophysis: its microscopic volume allows retaining their concentration at a quite high level. Active efflux of peptides. The efflux transport system has been described for brain ghrelin [42], while brain beta-endorphin gets into the blood via a more general-purpose system, involving P-glycoprotein [43]. It appears that the function of this mechanism consists of removing the excess regulatory peptides from the CNS. It is unlikely that the amount of a peptide, actively eliminated from the brain into the blood, would be sufficient for inducing any peripheral effects, although there is an opposite opinion that corticotropin-releasing hormone may be actively excreted into the blood and accumulated in the spleen, inducing its specific effects there [29]. Regulatory peptides are well known to penetrate, if at all, from the blood into the brain only in very small amounts. All the longstanding attempts to boost the passability of regulatory peptides across the BBB have not gained much success. Instead, it seems more productive to focus not so much on boosting the passability of regulatory peptides across the BBB as on increasing the efficacy of their binding to peptide receptors outside the brain — in the circumventricular organs and/or vagal afferents. The adoption of this paradigm prompts yet another practical approach—designing more stable, peptidase-resistant, forms of regulatory peptides.

Practical Consequences

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Conclusion

In human, the morphological substrate of a BBB is a layer of brain microvessel endothelial cells interconnected by tight and adherens junctions. Permeability of the BBB to any substance including peptide is determined primarily by its lipophilicity.By separating the blood and brain parenchyma, the BBB maintains homeostasis of the brain and provides neurons with a unique extracellular milieu optimal for humoral transmission. Simultaneously, the BBB is an interface between peripheral tissues and brain. Humoral communication between the periphery and the brain can be realized without any penetration of a substance into the brain parenchyma. Hydrophilic substances (including regulatory peptides) circulating in the blood can transmit information to the brain by binding to specific receptors on vagal afferents and/or in the circumventricular organs (ie outside the BBB). In the circumventricular organs (small areas of brain tissue scattered along the perimeter of the ventricles), not capillary endothelium, but the ependyma of ventricles performs barrier function (the blood-cerebrospinal fluid barrier). The BBB selectively transports some regulatory peptides in the blood-to-brain or the brain-to-blood direction. Efflux transporters protect the brain by clearing it from numerous potentially harmful exogenous and CNS-borne compounds. To understand the mechanism of central effect of any (endogenous or exogenous) substance, we have to find out wheter the substance penetrates through the BBB or affects the brain without penetrating into it.

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