Regulatory Functions: The Blood–Brain Barrier

In the brain, so-called “tight junctions” between the endothelial cells of blood capillaries represent the blood–brain barrier. Lipophilic substances can pass this barrier, moving through the endothelial lipid bilayer. Also, $O_2$–$CO_2$ diffusion occurs along their partial pressure gradient. Water can diffuse through the tight junctions because of its small molecular size. All other polar substances need special transport systems to pass the blood–brain barrier (A). For this, appropriate carriers have to be present on the luminal as well as on the brain side of the membrane. Such carriers exist for glucose, ions (as active pumps and channels), and for various groups of amino acids (AA). The transport mechanisms permit selective enrichment of specific substances inside the brain, rendering it theoretically independent of plasma concentrations.

However, this system has limits. On the one hand, carrier capacity becomes insufficient when concentrations of the transported substance drop below certain plasma levels (e.g., with hypoglycemia). On the other hand, when several substances use the same transport system, they compete for the carrier. This makes the system indirectly dependent on substrate supply in the plasma. This situation applies, for instance, to large, neutral AA.

Competition for the carrier is particularly significant between tryptophan (Trp) and long-chain neutral amino acids (LNAA). Trp is converted to 5-hydroxytryptamine (5HT) better known as serotonin in serotonergic neurons. The latter is stored in intraneuronal vesicles and released after neuron depolarization. A classic neurotransmitter, it binds to a specific postsynaptic receptor (5HT receptor) with subsequent active reuptake into the neuron.

The following model was developed based on animal experiments and it might explain seasonal affective disorder (SAD), which causes increased carbohydrate cravings during winter, among others. Rising insulin levels (B) after carbohydrate consumption trigger increased AA absorption into muscles. Trp levels are not affected by this since it easily binds to albumin and thereby escapes the effects of insulin. Consequently, the Trp/LNAA ratio is increased, causing Trp to be transported preferentially across the blood–brain barrier. The subsequent increase in neuronal 5HT synthesis has a negative feedback effect on carbohydrate cravings.

When insulin production is insufficient, particularly in the case of peripheral insulin resistance (type 2 diabetes, obesity), this satiety mechanism does not work (C). 5HT effects remain below normal even after pure protein meals since, due to the lacking insulin release, the Trp/LNAA ratio is not changed in favor of Trp.

5HT neurons have significant carbohydrate consumption-limiting effects. For example, the effect of pharmaceutical drugs that increase 5HT concentrations in the synaptic gap shows that 5HT plays a role in regulating feeding behavior. Weight reduction—albeit transitory—can be achieved mainly through reduction of meal sizes.
A. Transport Systems

- Brain
- Capillary
- Endothelial cell
- Membrane on brain side
- Membrane on blood side
- Capillary lumen
- Large neutral amino acids
- D-Glucose
- Glycine
- Na+
- K+
- Ion channel
- Unknown channel
- Neuron
- Blood-brain barrier
- Insulin

B. Physiological Satiety Control

- Proteins
- Carbohydrates
- LNAA
- TRP
- TRP/LNAA
- Insulin
- Plasma
- Blood-brain barrier
- Neuron
- 5HT-Receptor

C. Pathological Satiety Control

- Proteins
- Carbohydrates
- LNAA
- TRP
- TRP/LNAA
- Insulin
- Plasma
- Blood-brain barrier
- Neuron
- 5HT-Receptor