

Regulation of brain iron and copper homeostasis by brain barrier systems: Implication in neurodegenerative diseases

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Abstract

Iron (Fe) and copper (Cu) are essential to neuronal function; excess or deficiency of either is known to underlie the pathoetiology of several commonly known neurodegenerative disorders. This delicate balance of Fe and Cu in the central milieu is maintained by the brain barrier systems, i.e., the blood–brain barrier (BBB) between the blood and brain interstitial fluid and the blood–cerebrospinal fluid barrier (BCB) between the blood and cerebrospinal fluid (CSF). This review provides a concise description on the structural and functional characteristics of the brain barrier systems. Current understanding of Fe and Cu transport across the brain barriers is thoroughly examined, with major focuses on whether the BBB and BCB coordinate the direction of Fe and Cu fluxes between the blood and brain/CSF. In particular, the mechanism by which pertinent metal transporters in the barriers, such as the transferrin receptor (TfR), divalent metal transporter (DMT1), copper transporter (CTR1), ATP7A/B, and ferroportin (FPN), regulate metal movement across the barriers is explored. Finally, the detrimental consequences of dysfunctional metal transport by brain barriers, as a result of endogenous disorders or exogenous insults, are discussed. Understanding the regulation of Fe and Cu homeostasis in the central nervous system aids in the design of new drugs targeted on the regulatory proteins at the brain barriers for the treatment of metal's deficiency or overload-related neurological disease

Keywords: Iron, Copper, Blood–brain barrier, Blood–CSF barrier, Choroid plexus, Transferrin receptor or TfR, Divalent metal transporter or DMT1, Copper transporter or CTR1