Brain Iron

The accumulation of iron in the brain is a common physiological process. However, alterations in the deposition of iron or other paramagnetic substances are associated with various diseases.

Regulation

The brain requires iron for a number of processes, including energy production. Inadequate or excessive amounts of iron can be detrimental and lead to a number of neurological disorders. As such, regulation of brain iron uptake is required for proper functioning. Understanding both the movement of iron into the brain and how this process is regulated is crucial to both addressing dysfunctions with brain iron uptake in disease and successfully using the transferrin receptor uptake system for drug delivery.

Using in vivo steady-state infusions of apo- and holo-transferrin into the lateral ventricle, Baringer et al. demonstrated the regulatory effects of brain apo- and holo-transferrin ratios on the delivery of radioactive 55Fe bound to transferrin or H-ferritin in male and female mice. In discovering sex differences in the response to apo- and holo-transferrin infusions, ovariectomies were performed on female mice to interrogate the influence of circulating estrogen on the regulation of iron uptake.

The model reveals that apo- and holo-transferrin significantly regulate iron uptake into the microvasculature and subsequent release into the brain parenchyma and their ability to regulate iron uptake is significantly influenced by both sex and type of iron delivery protein. Furthermore, they showed that cells of the microvasculature act as reservoirs of iron and release the iron in response to cues from the interstitial fluid of the brain.

These findings extend the previous work to demonstrate that the regulation of brain iron uptake is influenced by both the mode in which iron is delivered and sex. These findings further emphasize the role of the microvasculature in regulating brain iron uptake and the importance of cues regarding iron status in the extracellular fluid [1)].

Dysregulation

Iron is a tightly regulated micronutrient with no physiologic means of elimination and is necessary for cell division in normal tissue.

Evidence suggests that dysregulation of iron regulatory proteins may play a role in cancer pathophysiology.

Weston et al used public data from The Cancer Genome Atlas (TCGA) to study the association between survival and expression levels of 61 genes coding for iron regulatory proteins in patients with World Health Organization Grade II-III gliomas. Using a feature selection algorithm they identified a novel, optimized subset of eight iron regulatory genes (STEAP3, HFE, TMPRSS6, SFXN1, TFRC, UROS, SLC11A2, and STEAP4) whose differential expression defines two phenotypic groups with median survival differences of 52.3 months for patients with grade II gliomas (25.9 vs. 78.2 months, $p< 10-3$), 43.5 months for patients with grade III gliomas (43.9 vs. 87.4 months, $p = 0.025$), and 54.0 months

when considering both grade II and III gliomas (79.9 vs. 25.9 months, p < 10-5) [2)]

Iron in intracerebral hemorrhage

see Iron in intracerebral hemorrhage.

Subarachnoid hemorrhage

Previous studies have shown that iron accumulation is involved in the pathogenesis of brain injury following subarachnoid hemorrhage (SAH) and chelation of iron reduced mortality and oxidative DNA damage.

Germinal matrix hemorrhage

Brain iron overload has a key role in brain injury after intracerebral hemorrhage (ICH).

Iron plays a role in brain injury following GMH and minocycline reduces iron overload after germinal matrix hemorrhage (GMH) and iron-induced brain injury [3)].

Posttraumatic hydrocephalus

The role of iron in the development of posttraumatic hydrocephalus is still unclear.

TBI was induced by lateral fluid-percussion in male Sprague-Dawley rats. Some rats had intraventricular injection of iron. Acute hydrocephalus was measured by magnetic resonance T2-weighted imaging and brain hemorrhage was determined by T2* gradient-echo sequence imaging and brain hemoglobin levels. The effect of deferoxamine on TBI-induced hydrocephalus was examined. TBI resulted in acute hydrocephalus at 24 h (lateral ventricle volume: 24.1 ± 3.0 vs. 9.9 ± 0.2 mm3 in sham group). Intraventricular injection of iron also caused hydrocephalus (25.7 ± 3.4 vs. 9.0 ± 0.6 mm3 in saline group). Deferoxamine treatment attenuated TBI-induced hydrocephalus and heme oxygenase-1 upregulation.

Iron may contribute to acute hydrocephalus after TBI [4)].

In a study, the deposition of paramagnetic substances in patients with brain tumours was evaluated using T2 relaxometry. A total of 23 patients with untreated tumours or with recurrent tumours following treatment, together with a group of 19 age-matched healthy controls, were examined using T2 relaxometry at 3T. The relaxation times in the basal ganglia, thalamus and white matter were evaluated. Significantly lower T2 relaxation times were identified in the basal ganglia and thalamus of the patients with tumours, as compared with those of the controls (P<0.05). No statistically significant difference was identified between patients with untreated or recurrent brain tumours. The reduction in T2 relaxation times in the brain tumour patients was possibly caused by the accumulation of iron, since iron homeostasis is known to be altered in patients with tumours. Increased iron deposition is a consequence of a higher risk of oxidative stress caused by an increased iron concentration in the plasma or cerebrospinal fluid [5)].

Traumatic brain injury

Female LCR rats had less iron-induced brain swelling, smaller lesion volumes, and reduced BBB disruption and HO-1 upregulation compared with male LCR rats. This may contribute to the reduced ICH-induced brain injury found in females [6].

Iron induced less brain edema in female mice than in males. estrogen receptor (ER) modification can affect iron-induced brain edema [7].

Stroke

The available findings on the association between iron status and risk of stroke remain controversial. Xu et al. used multivariable logistic regression and restricted cubic spline models to explore the association between iron exposures and risk of stroke in the US National Health and Nutrition Examination Survey (NHANES 2007-2016, n = 24,627). A total of 941 (3.82%) stroke cases were identified in this study. In women, the ORs with 95% CIs of prevalence of stroke were 0.92 (0.65-1.28), 0.66 (0.44-0.98) and 0.72 (0.49-1.08) across quartiles 2-4 compared with quartile 1 of iron intake, respectively. An inverse and L-shaped association between iron intake and risk of stroke in women was observed, and the curve plateaued at 20 mg/day. However, neither serum iron concentrations nor iron intake were significantly associated with risk of stroke in men. Our study found that iron intake was inversely associated with risk of stroke in a sex-dependent fashion [8].

1)
Baringer SL, Neely EB, Palsa K, Simpson IA, Connor JR. Regulation of brain iron uptake by apo- and holo-transferrin is dependent on sex and delivery protein. Fluids Barriers CNS. 2022 Jun 10;19(1):49. doi: 10.1186/s12987-022-00345-9. PMID: 35689283.
2)
Weston C, Klobusicky J, Weston J, Connor J, Toms SA, Marko NF. Aberrations in the Iron Regulatory Gene Signature Are Associated with Decreased Survival in Diffuse Infiltrating Gliomas. PLoS One. 2016 Nov 29;11(11):e0166593. doi: 10.1371/journal.pone.0166593. PubMed PMID: 27898674.
3)
Guo J, Chen Q, Tang J, Zhang J, Tao Y, Li L, Zhu G, Feng H, Chen Z. Minocycline-induced attenuation of iron overload and brain injury after experimental germinal matrix hemorrhage. Brain Res. 2015 Jan 12;1594:115-24. doi: 10.1016/j.brainres.2014.10.046. Epub 2014 Oct 31. PubMed PMID: 25451129.
4)
Zhao J, Chen Z, Xi G, Keep RF, Hua Y. Deferoxamine Attenuates Acute Hydrocephalus After Traumatic Brain Injury in Rats. Transl Stroke Res. 2014 Jun 17. [Epub ahead of print] PubMed PMID: 24935175.
5)
Herynek V, Wagnerová D, Malucelli A, Vymazal J, Sameš M, Hájek M. Alterations in the basal ganglia in patients with brain tumours may be due to excessive iron deposition. Oncol Lett. 2015 Jan;9(1):43-46. Epub 2014 Oct 24. PubMed PMID: 25435931; PubMed Central PMCID: PMC4246608.
6)
Zheng M, Du H, Gao F, Koch LG, Britton SL, Keep RF, Xi G, Hua Y. Effect of Gender on Iron-induced Brain Injury in Low Aerobic Capacity Rats. Acta Neurochir Suppl. 2016;121:367-71. doi: 10.1007/978-3-319-18497-5_63. PubMed PMID: 26463976.
7)
Xie Q, Xi G, Keep RF, Hua Y. Effects of Gender and Estrogen Receptors on Iron-Induced Brain Edema Formation. Acta Neurochir Suppl. 2016;121:341-5. doi: 10.1007/978-3-319-18497-5_59. PubMed PMID: 26463972.
8)
Xu J, Xu G, Fang J. Association between iron exposures and stroke in adults: Results from National

Health and Nutrition Examination Survey during 2007-2016 in United States. Int J Environ Health Res. 2021 May 18:1-10. doi: 10.1080/09603123.2021.1926440. Epub ahead of print. PMID: 34003723.