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HYPONATRAEMIA

Unfolding osmotic demyelination

> urea might help to maintain adequate protein folding and act as a chemical chaperone

Abrupt correction of chronic hyponatraemia can cause osmotic demyelination syndrome (ODS) characterized by massive astrocytic death. New research shows that this astrocyte loss is caused by severe alterations of proteostasis including protein aggregation and ubiquitylation.

Fabrice Gankam-Kengne and colleagues had previously shown that astrocyte death is one of the first pathological events in ODS. "We also showed that activation of microglia or breakdown of the blood–brain barrier were not the initiating events, so the question of how and why do astrocytes die remained," says Gankam-Kengne.

Using a rat model of osmotic demyelination, the researchers showed that rapid correction of hyponatraemia induced perinuclear protein aggregates, high levels of ubiquitylated proteins, endoplasmic reticulum (ER) chaperones and markers of ER stress, increased autophagy, unfolded protein response (UPR) activation and DNA damage in astrocytes. Abrupt restoration of sodium levels also altered the balance of apoptotic proteins and led to cell-cycle arrest in astrocytes. All of these pathological changes were restricted to astrocytes in regions prone to demyelination in ODS.

Interestingly, correction of hyponatraemia with urea decreased the levels of ubiquitylated proteins, ER stress markers, UPR activation and autophagy, restored the balance of apoptotic proteins and prevented DNA damage. "These results confirm that in osmotic stress conditions, urea might help to maintain adequate protein folding and act as a chemical chaperone, much like organic osmolytes," says Gankam-Kengne.

In future studies, the researchers plan to investigate how the brain senses changes osmolality and if classic osmolytes such as myoinositol preserve proteostasis. "It will also be interesting to see if the changes that we saw in the rat brain are also present in human autopsy material," says Gankam-Kengne.

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ORIGINAL ARTICLE Gankam-Kengne, F. *et al.* Osmotic stress-induced defective glial proteostasis contributes to brain demyelination after hyponatremia treatment. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016050509 (2017)