

Metals in the brain

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Metal ions in the brain are a necessity as well as a poison. The presence of metal ions in the active sites of biological catalysts or metalloproteins and in the biological functioning of nucleic acids is very well documented and they are required for brain activity. On the other hand, metals are very effective in generating oxidative stress which not only plays an important role in our immunology but also is the root of practically all neurodegenerative disorders by inducing disease via the death of neurons.

The brain (2% of the body weight) is a major consumer of oxygen in the human body (20% of total oxygen), so production of reactive oxygen species (ROS) is believed to be inherent to the progression of many disorders. Because metals are involved in both ROS production and as the active centres in antioxidant enzymatic systems, the proper distribution and homeostasis of metal ions is critical for brain function. Indeed, metal ions that are highly concentrated in some regions of the brain are also able to promote protein aggregation and thus aid the formation of protein aggregates, e.g. fibrils, which are toxic for neurons. Therefore, managing metal ions in the brain could be an important strategy in the search for therapeutic agents to be used in the treatment of neurodegenerative diseases.

The actual biological function of many proteins involved in neurodegenerative disorders is not yet known although biochemical and biological data suggest that they could be metalloproteins. Metal ions such as Cu(II) bound to protein can act either as an antioxidant enzyme (e.g. when bound to prion protein) or as a Fenton-type catalyst producing ROS (when bound to beta-amyloid peptide). It can therefore be seen that much remains to be learnt about the chemistry and biology of these proteins and the metals bound to them before convincing mechanisms of neurological pathologies can be understood.

There are also two other enigmatic functional structures closely related to the brain, the blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier. These unusual structures formed by endothelial cells protect the brain from chemical species which could otherwise be potentially harmful. Both barriers are rather effective and also metal ion transport is strictly controlled; thus, entry into the brain is already a difficult challenge for metals. Therefore, as well as learning the basic biology and various pathological disorders within the brain areas, we must learn how to design a drug molecule to let it pass these barriers.

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