# Iron in intracerebral hemorrhage

Iron, an important metabolic product that accumulates in the brain parenchyma, has a detrimental effect on secondary injury following ICH. Because the damage mechanism of iron during ICH-induced secondary injury is clear, iron removal therapy research on animal models is effective. Although many animal and clinical studies have been conducted, the exact metabolic pathways of iron and the mechanisms of iron removal treatments are still not clear. This review summarizes recent progress concerning the iron metabolism mechanisms underlying ICH-induced injury. We focus on iron, brain iron metabolism, the role of iron in oxidative injury, and iron removal therapy following ICH, and we suggest that further studies focus on brain iron metabolism after ICH and the mechanism for iron removal therapy [1)].

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Iron overload plays a key role in secondary bleeding after intracerebral hemorrhage in Angiotensin II-induced hypertensive mice. Iron chelation during the process of Ang II-induced hypertension suppresses secondary bleeding after ICH [2)]

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Brain iron overload is involved in brain injury after intracerebral hemorrhage (ICH). There is evidence that systemic administration of minocycline reduces brain iron level and improves neurological outcome in experimental models of hemorrhagic and ischemic stroke. However, there is evidence in cerebral ischemia that minocycline is not protective in aged female animals. Since most ICH research has used male models, this study was designed to provide an overall view of ICH-induced iron deposits at different time points (1 to 28 days) in aged (18-month old) female Fischer 344 rat ICH model and to investigate the neuroprotective effects of minocycline in those rats. According to our previous studies, we used the following dosing regimen (20 mg/kg, i.p. at 2 and 12 h after ICH onset followed by 10 mg/kg, i.p., twice a day up to 7 days). T2-, T2$*$-weighted and T2$*$ array MRI was performed at 1, 3, 7 and 28 days to measure brain iron content, ventricle volume, lesion volume and brain swelling. Immunohistochemistry was used to examine changes in iron handling proteins, neuronal loss and microglial activation. Behavioral testing was used to assess neurological deficits. In aged female rats, ICH induced long-term perihematomal iron overload with upregulated iron handling proteins, neuroinflammation, brain atrophy, neuronal loss and neurological deficits. Minocycline significantly reduced ICH-induced perihematomal iron overload and iron handling proteins. It further reduced brain swelling, neuroinflammation, neuronal loss, delayed brain atrophy and neurological deficits. These effects may be linked to the role of minocycline as an iron chelator as well as an inhibitor of neuroinflammation [3)].

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Studies mainly in animal (rodent and porcine) ICH models have shown the role of bound and unbound iron in causing neurotoxicity following an ICH. There is currently no noninvasive method for assessing iron levels in the cerebral tissue following ICH.

A study intends to explore the role of magnetic resonance imaging (MRI) in establishing iron levels in cerebral tissue at the periphery of the hematoma following an ICH. Initially, an MRI phantom was constructed with varying concentrations of liquid iron preparation in a water bath container. Susceptibility weighted imaging sequences were utilized to scan this phantom to generate T2* signal

magnitude measurements corresponding to the iron concentration in the phantom. Encouraged by the reliability of the measurements on the phantom, patients with ICH were then recruited into this experimental study once the inclusion criteria were met. One control and two human subjects had their brains scanned in a 3 T MRI scanner utilizing the same susceptibility weighted sequence.

They found that ICH perihematomal brain tissue iron susceptibility signal measurements were 4 times higher than those of the baseline control and normal contralateral brain tissue. Three different baseline measurements (one control and two contralateral normal brain) revealed a level of 0.1 mg/ml of iron concentration in the contralateral brain tissue in the identical anatomical location as the hematoma, typically in the basal ganglia region. T2 * signal measurements in the brain tissue at the periphery of the basal ganglia hematoma at day 7 following hemorrhage revealed iron concentration of 0.4 mg/ml (approximately 4 times the baseline/control) in two human subjects included in the study. These measurements mimic those obtained in published animal ICH model studies [4].

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