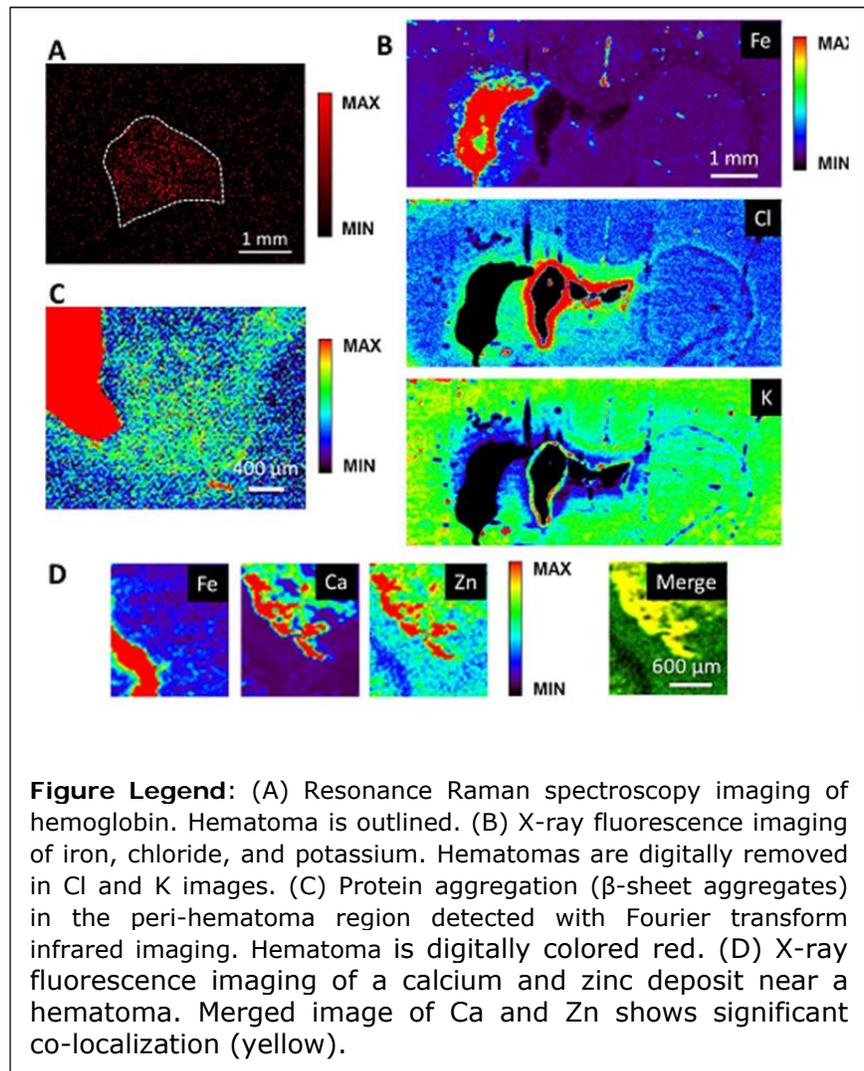


Multimodal Synchrotron-based Imaging Reveals Novel Effects of Rehabilitation after Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is a subtype of stroke characterized by bleeding within the brain. Rehabilitative therapy is key to alleviating the functional deficits suffered by ICH patients. A more thorough mechanistic understanding of ICH pathophysiology and rehabilitation-induced recovery will likely lead to improvements in existing therapies and the development of novel treatments.

After the initial bleed and brain injury, ongoing processes within the peri-hematoma zone cause progressive cellular injury and dysfunction. Notably, it is widely accepted that hematoma-derived redox-active iron, which catalyzes free radical production, contributes to this secondary damage by instigating non-discriminant oxidative injury. Preclinical studies have repeatedly shown that rehabilitation (e.g., training on reaching for food starting 1 week after ICH) reduces the extent of chronic injury and improves behavioral outcome; however, the underlying mechanisms have not been fully elucidated^{1,2}. Researchers from the University of Alberta and the University of Saskatchewan sought to clarify the effects of rehabilitation on Fe-mediated injury and other pathophysiological processes. To this end, multimodal imaging was done on brain sections from rehabilitated and untreated rats given ICH³.

Resonance Raman spectroscopy revealed that the amount of hemoglobin, the source of redox active iron, was decreased within the brains of animals given rehabilitation (Fig. A). This suggests that the therapy promotes removal of neurotoxic blood products. X-ray fluorescence imaging (XFI) at SSRL Beam Line 10-2 showed that iron concentration was increased (~ 3-fold) near the hematoma and decreased in areas further away (Fig. B). Moreover, XFI confirmed that, concomitant with the decreased amount of hemoglobin, the amount of iron in peri-hematoma tissue was diminished by rehabilitation. Also, β -sheet protein aggregate



content, a measure of oxidation, was determined using Fourier transform infrared imaging (Fig. C). Aggregate content was increased in tissue immediately surrounding the hematoma. These findings are consistent with the idea that iron slowly liberated from hemoglobin spreads into surrounding tissue to promote free radical production and cell damage. Importantly, rehabilitation normalized aggregate content in the peri-hematoma area. Cumulatively, these data indicate that long-term iron-mediated oxidative damage occurs after ICH and is attenuated by rehabilitation.

XFI also revealed novel aspects of ICH pathophysiology. Under normal conditions, Na^+ , K^+ , and Cl^- are tightly regulated to facilitate proper neuronal activity. After ICH, there was a marked dyshomeostasis of K^+ and Cl^- surrounding the injury (Fig. B, Na^+ was not assessed). Rehabilitation attenuated the dyshomeostasis of Cl^- but not K^+ . This finding is potentially of significant interest regarding activity-dependent plasticity processes, which are strongly implicated in recovery. In addition, calcium and zinc deposits were identified nearby the hematomas (Fig. D). These deposits may play a role in chronic injury. This study clarified the effects of rehabilitation after ICH and identified novel features of ICH pathophysiology.

References

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