DYNAMICS OF USPIO CONTRAST IN THE CENTRAL NERVOUS SYSTEM UNRAVELED IN AN ANIMAL MODEL OF MULTIPLE SCLEROSIS

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Introduction

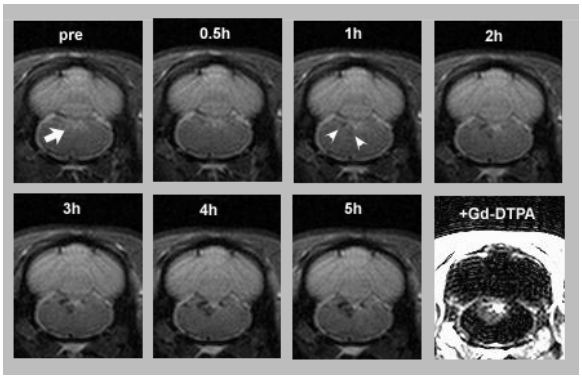
Contrast effects observed after magnetic resonance imaging (MRI) of the central nervous system (CNS) following intravenous administration of ultra small superparamagnetic iron oxide (USPIO) have been correlated with macrophage activity in lesions [1]. To date the mechanism of USPIO uptake in vivo is unclear. USPIO may leak over an impaired blood brain barrier (BBB) or specifically travel to inflammatory sites in the CNS by cellular uptake. The purpose of this study was to monitor USPIO enhancement longitudinally in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. Gaining insight in the timing that USPIO enter and persist in the CNS will contribute to accurate interpretation of post-USPIO MR images.

Material and Methods

Acute EAE was induced in Lewis Hannover rats as previously described [2] and USPIO (Sinerem®, 300 µmol Fe/kg) was intravenously injected at onset of the disease (day 10 post immunization) and at the peak of the disease (day 13 post immunization). To monitor USPIO presence in brain, spinal cord and cervical lymph nodes (CLN), repetitive T_2-weighted MRI (4.7T, Varian, Palo Alto, USA, FOV=3.2x3.2cm, matrix= 128x128, 21x 1mm) was performed before and directly after USPIO injection every 30 minutes up to 6h (n=4). In a subset of animals (n=7) scans were performed 24h and 72h later. Tissue sections were processed for histology to detect the presence of USPIO (Prussian blue; PB), infiltrated monocytes (ED1) and damage to the BBB (IgG).

Results

USPIO were detected in the brain parenchyma within 1h after intravenous injection (Fig 1). A similar area was enhanced by Gd-DTPA, a marker for BBB damage. Histological analysis of corresponding sections showed extra-cellular iron clusters that were present in the vicinity of both ED1+ and ED1- areas (Fig 2). Injections at disease onset resulted at 24h in hypointense areas in the cerebellum that were less pronounced as compared to the 6h scan. In contrast, USPIO injections at the disease peak resulted in an increased number of hypointense areas in which signal intensity had further decreased at 24h. Contrast effects in the CNS were no longer apparent 72h post injection indicating breakdown or efflux of USPIO. MR images of CLN showed that at disease onset USPIO accumulation was maximal 72h after injection. In contrast, injection at disease peak resulted in signal loss in CLN that was maximal after 24h. Histological analysis showed the presence of USPIO in the CLN.



▲**Figure 1**: Time course of contrast effects following USPIO injection at disease onset. In the pre-injection image the lesion is hyperintense (arrow). Contrast effects are observed within 1h (arrowheads). The Gd-DTPA difference image is obtained at 6h.

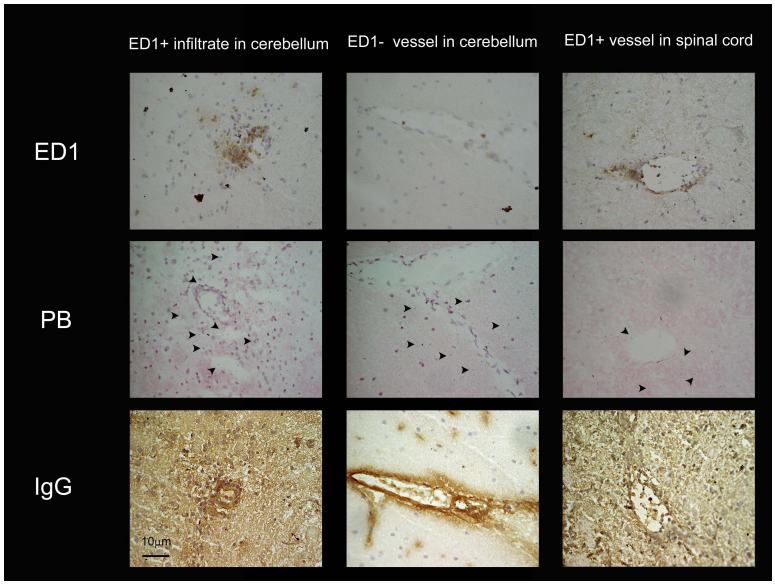


Figure 2: Extra-cellular iron clusters (arrowheads) are detected distant ► from ED1+ (brown) infiltrates. The presence of IgG (brown) indicates breakdown of BBB.

Discussion

Our findings suggest that BBB leakage is one of the most important physiological mechanisms responsible for USPIO entrance in the inflammatory CNS. This early entrance of USPIO will contribute to the contrast effects frequently observed after 24h. In addition, longitudinal MRI analysis suggested that a possible mechanism for particle efflux from the inflammatory CNS is via drainage by CLN. These data shed a new light on the use of USPIO in neuroinflammatory diseases identifying USPIO as marker for BBB damage in an early time frame.

References: [1] Floris et al., 2004: Brain
[2] Schreibelt et al., 2006: Journal of Immunology