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MRI Assessment of Post-Ischemic Neuroinflammation in Stroke: Experimental and Clinical Studies

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1. Introduction

Stroke is a major healthcare issue in both industrialized and developing countries (Yach et al., 2004): it is the third leading cause of death, after myocardial infarction and cancer, the second leading cause of dementia, and the leading cause of permanent disability in Western countries (Pendlebury et al., 2009; Rothwell et al., 2011). Ischemic stroke accounts for up to 85% of total stroke events (Feigin et al., 2003). Cerebral ischemia is caused by blood-clot obstruction of a cerebral artery. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction. The resulting lesion comprises a central infarct core of irreversibly damaged brain tissue and a surrounding area of hypoperfused but still viable brain tissue (the ischemic penumbra), which can potentially be salvaged by rapid restoration of the blood flow. Intravenous thrombolysis with tissue plasminogen activator (tPA) within 4.5 hours of symptom onset can improve the clinical outcome (NINDS, 1995; Hacke et al., 2008). Endovascular strategies (e.g. thrombectomy) can enhance reperfusion rates in large artery occlusions, but remain to be validated in randomized clinical trials. Although approved by North American and European authorities, only a small proportion of patients receive acute revascularization therapies, mainly because of late diagnosis and limited access to specialized stroke units. Neuroprotective drugs aim at salvaging the ischemic brain by targeting multiple pathophysiological processes: prolonging the time window for reperfusion therapies, limiting reperfusion injury and the risk of hemorrhage, minimizing the deleterious effects of inflammation. Compounds regulating the inflammatory response are being evaluated by the pharmaceutical industry (Barone & Parsons, 2000). Indeed, stroke triggers a marked inflammatory reaction, involving several types of immune cells, including those of the mononuclear phagocyte system. There has been a longstanding controversy about the respective role of these cells, whether they are infiltrating blood-borne macrophages or resident microglia. On one hand, there is evidence that inflammation can contribute to secondary ischemic injury and worsening of neurological status (Iadecola & Alexander, 2001). On the other hand, inflammation under certain circumstances could promote functional recovery, by supporting neurogenesis and plasticity (Ekdahl et al., 2009). Therefore, targeted intervention to control specific aspects of post-ischemic neuro-

inflammation is a promising strategy in human stroke, with a potentially wide therapeutic window. A thorough understanding of these processes is required in order to develop safe and effective anti-inflammatory therapies for stroke patients.

Microglial cells are the main brain-resident population of the mononuclear phagocyte system. Microglial activation is considered a hallmark of central nervous system (CNS) inflammation. Activated microglial cells become immunohistochemically indistinguishable from infiltrating myeloid cells (monocytes/macrophages) (Raivich et al., 1999). In particular, activated cells of the monocytic lineage, whether resident microglia or blood-borne macrophages, overexpress an outer mitochondrial membrane protein formerly known as the peripheral benzodiazepine receptor (PBR), now renamed “translocator protein (18kDa)” (TSPO 18kDa) (Papadopoulos et al., 2006). Nearly 30 years ago, radiolabeling of the prototypic PBR/TSPO ligand PK11195 with carbon-11 enabled in vivo imaging of microglial activation using Positron Emission Tomography (PET scan) (Camsonne et al., 1984), and paved the road for neuroinflammation imaging. However, [¹¹C]PK11195 has shown limitations that until now slowed clinical application of neuroinflammation imaging by PET (Venneti et al., 2006). Although the field is still very active, as seen from the plethora of radioligands for PBR/TSPO that have been radiolabeled these last few years (Chauveau et al., 2008), large-scale clinical PET studies are difficult to set up in the context of emergency stroke management.

In contrast, magnetic resonance imaging (MRI) is being increasingly used in the diagnosis and management of acute ischemic stroke patients. Abnormalities observed on diffusion-weighted imaging (DWI) allow early identification of severely ischemic brain regions that typically evolve into infarction (i.e. the ischemic core). Perfusion-weighted imaging (PWI) provides information about the hemodynamic status of the cerebral tissue. PWI lesions are frequently larger than the corresponding DWI lesions during the first hours of stroke evolution. Subsequent infarct enlargement has been described in the region of DWI/PWI mismatch, supporting the hypothesis that this area represents the ischemic penumbra. Combined DWI and PWI imaging at the acute stage of stroke might thus help to identify patients with salvageable tissue, who may benefit from thrombolytic therapy. These MRI techniques are increasingly used for the evaluation of neuroprotectants, as PWI/DWI mismatch is considered a valuable estimate of penumbra in both animal models (Chauveau et al., 2011) and patients (Donnan et al., 2009). Given its pivotal role in the management of stroke patients, an additional MRI-based technique to image inflammation is thus particularly compelling. MRI has an unparalleled ability to image brain structure and function in both humans and small animals.

This chapter focuses on the MRI techniques that have been developed so far to image inflammation in stroke.

2. In vivo imaging of phagocytic cells using endogenous mechanisms

Magnetic Resonance Imaging of inflammation was first attempted in stroke models by taking advantage of endogenous contrast mechanisms. Schroeter et al. (Schroeter et al., 2001) thus used high resolution multimodal MRI to investigate inflammatory and glial response following focal cerebral ischemia. Images were acquired in rats, with transient occlusion of the middle cerebral artery 3, 7 and 14 days after stroke onset, and compared to immunostaining of phagocytic cells and astrocytes. This MRI approach, however, failed to visually discriminate inflammatory regions from healthy tissue, and highlighted the need to

develop new MRI techniques for specific detection of inflammatory cells. Two subsequent studies (Justicia et al., 2008; Weber et al., 2005) demonstrated the potential of 3D T2*-weighted sequences for detecting regions with phagocytic activity, due to cell accumulation of endogenous iron, which induces strong susceptibility artifacts. However, both studies were performed at late stages of stroke (starting 10 weeks post-injury), in a time-window that was less than optimal for therapeutic intervention.

3. In vivo labeling of phagocytic cells

Cellular imaging of inflammation using MRI coupled with the injection of iron oxide nanoparticles has recently emerged as a promising non-invasive technique for pre-clinical and clinical studies of several inflammatory diseases. Two distinct classes of iron oxide nanoparticles are currently used in MRI, depending on hydrodynamic particle size: superparamagnetic iron oxide (SPIO) particles, with a mean particle diameter of more than 50 nm, and ultrasmall superparamagnetic iron oxide (USPIO) particles with a smaller hydrodynamic diameter (Corot et al., 2006). When injected intravenously, both types of nanoparticles are phagocytosed by macrophages, whether within the blood-pool (circulating monocytes) or locally at the inflammation site (tissue macrophages/activated microglia). Macrophages can thus be labeled and monitored in vivo with exogenous magnetic contrast agents. Importantly, this technique can be applied in patients, as several (U)SPIOs are already being used in humans.

3.1 Pre-clinical studies

To date, few teams have monitored phagocytic cell trafficking after focal cerebral ischemia on MRI coupled with (U)SPIO injection. Investigations were mostly conducted in rats, using differing protocols (various stroke models, rat strains, contrast agents, magnetic field strengths and imaging protocols), which render inter-study comparisons difficult. Of note, an early study (Doerfler et al., 2000) showed no impact of USPIO injection on clinical scores and lesion size in a model of permanent focal cerebral ischemia in rats; the dose, however, was ten times as low as in the following studies, the aim being to use USPIO as a marker of perfusion, not inflammation.

Table 1 synthesizes the studies published so far, using a permanent model of focal cerebral ischemia (pMCAO). Administration of iron oxide nanoparticles was performed at different times after ischemia. T2/T2*-weighted imaging was used in all studies to detect MR signal changes following (U)SPIO injection, typically showing decreasing signal intensity. The most relevant protocol in terms of T2/T2* effects involved injection at day 5 post-injury with a dose of 300 $\mu\text{mol Fe/kg}$, and follow-up at day 6, whether with USPIO (Ferumoxtran-10) or with SPIO (Ferucarbotran) (Engberink et al., 2008; Kleinschnitz et al., 2003; Saleh et al., 2004b; Schroeter et al., 2004). This 24-hour interval between injection and imaging is necessary in order for the iron oxide particles to wash out from the vascular compartment (the half-life of Ferumoxtran 10 in plasma is 5 hours in rat). T2/T2* hypointense signals were usually observed at day 6 in the perilesional area (Saleh et al., 2004b; Schroeter et al., 2004). At later time-points, these hyposignals were detected in the lesion core (Kleinschnitz et al., 2003). The hypothesis of passive diffusion of iron oxide nanoparticles through a disrupted blood brain barrier (BBB) was rejected, because post-gadolinium and post-(U)SPIO MR signal changes did not superimpose, suggesting an active mechanism of brain entry, via (U)SPIO-laden infiltrating macrophages (Engberink et al., 2008; Kleinschnitz et al., 2003).

Animal model		Contrast Agent			MRI			Ref.
Species	Stroke model	Name	Dose (μmol/kg)	Injection time	Imaging times	Field strength	Sequences	
Rat	EC	Ferumoxtran-10	100	T0+5h	D0, D1, D2, D4, D7	4.7T	T2 map	(Rausch et al., 2001)
Rat	PT	Ferucarbotran	200	MRI-24h	D1-9, D11, D12, D14	1.5T	T2, 3D CISS, Gd-T1	(Kleinschnitz et al., 2003)
Rat	PT	Ferumoxtran-10	300	MRI-24h	D6	7T	3D T2*	(Schroeter et al., 2004)
Rat	PT	Ferumoxtran-10	300	MRI-24h	D6	7T	T2*, 3D T2*	(Saleh et al., 2004b)
Rat	PT	Ferucarbotran	300	T0, T0+2h, T0+24h	D1, D2, D5, D7, D14	1.5T	T2, 3D CISS	(Kleinschnitz et al., 2005)
Rat	PT	Ferumoxtran-10	300	MRI-24h	D6, D8, D11	4.7T	T2 map, T2, Gd-T1	(Engberink et al., 2008)
Mouse	EC	Ferumoxtran-10	2000	T0+5h,	D0, D1,D2, D3	7T	T2, T1, Gd-T1	(Wiert et al., 2007)
Mouse	EC	Ferumoxtran-10	2000	T0+5h,	D0, D1	7T	T2, T1, Gd-T1	(Desestret et al., 2009)

Table 1. Literature review of USPIO-enhanced MRI in the permanent middle cerebral artery occlusion (pMCAO) model. EC- Electrocoagulation; PT- Photothrombosis; T0 = Occlusion time; T0+5h = 5h after occlusion; MRI-24h = 24h before MRI; Gd-T1: T1-weighted MRI with gadolinium chelate injection (to assess BBB integrity).

Despite the number of post-ischemia time points investigated (between D0 and D14), few animals were followed longitudinally, because most were usually sacrificed after MRI for comparison with immunohistochemistry. Post-mortem analysis typically comprised immunostaining of phagocytic cells (ED1) and Prussian Blue (PB) staining to detect iron. Spatial co-location between macrophages, iron and MR hypointense signals was well documented at the periphery of the lesion in a photothrombosis model at D6 (Saleh et al., 2004b). Double immunostaining on the same histological slices confirmed internalization of iron inside macrophages in this set-up (Kleinschnitz et al., 2003). Co-location was also suggested in an electrocoagulation model (Rausch et al., 2001). It should be noted, however, that in all cases ED1 immunostaining exceeded iron staining, suggesting that only part of the inflammatory response was revealed by (U)SPIO-enhanced MRI.

We sought to investigate the feasibility of macrophage imaging in mice using MRI. USPIOs were injected into mice 5h after pMCAO (Wiert et al., 2007). The timing of injection and imaging (from D0 to D3) was early compared to previous studies, because we aimed at assessing the early, potentially pathological role of macrophages, anticipating future studies

of anti-inflammatory drugs at the acute stage. Hypointense MR signals were detected in the perilesional area at 48h and 72h post-injury, in accordance with published data obtained in rats with a similar protocol (Rausch et al., 2001). More surprisingly, USPIO-enhanced MRI kinetic analysis disclosed a hypointense MR signal in the contralateral hemisphere: this hyposignal spread along to the corpus callosum (ipsilateral to contralateral) from D0 to D3. Imaging data correlated with histochemical analysis at 48h and 72h post-injury, showing macrophage activation remote from the lesion, and macrophage ingestion of USPIO (Figure 1). Remote inflammatory response to brain injury was previously reported in animal models of focal cerebral ischemia using invasive techniques (Dubois et al., 1988; Schroeter et al., 1999) and in stroke patients using PET-scan (Gerhard et al., 2005; Pappata et al., 2000), but to our knowledge the present study provided the first evidence obtained in living animals.

Whereas the accumulation of (U)SPIOs in cells is well explained by phagocytosis activity of macrophages, their route of transport to brain macrophages is not yet well described. Three hypotheses have been put forward to explain the MR signal changes observed after (U)SPIO injection: (i) intravascular trapping of iron particles (Bendszus et al., 2007; Kleinschnitz et al., 2005); (ii) (U)SPIO uptake by phagocytes, on the assumption that (U)SPIOs are primarily taken up by circulating phagocytes (Kleinschnitz et al., 2003); and (iii) interstitial iron particle diffusion into damaged tissue after nonspecific leakage through a disrupted blood-brain barrier (Engberink et al., 2008). To assess the early brain distribution of iron particles, MRI signal changes after intravenous USPIO injection were then compared with the histological iron and macrophage distribution from 6h to 24h, using the same experimental set-up as before (Desestret et al., 2009). In this electrocoagulation model of stroke, USPIO-related MR signal changes were indisputably paralleled by phagocyte-associated iron deposits detected on histology after 24h post-ischemia, but the pattern of results suggested that early USPIO-related MR signal changes were mainly caused by passive diffusion of free USPIOs after BBB leakage or by intravascular trapping, rather than by peripheral phagocyte infiltration. Indeed, at early time-points after USPIO injection, BBB disruption matches the spatiotemporal pattern of MR signal change. These results were in accordance with a previous study investigating both early and delayed time-points after SPIO injection in a photothrombosis model in rats (Kleinschnitz et al., 2005). Intravascular trapping was found to be the main mechanism of particle entry into peripheral areas and lesion core. These findings highlight the fact that several mechanisms of (U)SPIO entry into the brain may co-exist, so that MR data interpretation should take account of the experimental set-up used (post-ischemia time-points, model characteristics, and nature of the contrast agent used).

Table 2 synthesizes the studies published so far, to our knowledge, using a transient model of focal cerebral ischemia (tMCAO). Transient ischemia was in all cases performed using the suture model, which allows mechanical reperfusion by withdrawing the suture from the artery. This model is thought to be more representative of the clinical situation than permanent ischemia models. Results of these studies are contradictory and all the more difficult to interpret since protocols differed on many points (in particular in terms of the type of iron oxide nanoparticles used, and timing of injection). The first study (Rausch et al., 2002) presented the most unexpected results, with the observation of a transient T1 hyperintense signal inside the lesion, without corresponding T2 hypointense signal, although the study was performed at high field (4.7T). Furthermore, while macrophages (ED1) were detected in the lesion from day 1 to day 7, Prussian Blue immunostaining was positive only at day 7, i.e. 5 days after the onset of the hyperintense signal. The authors

Fig. 1. Correlation of gradient echo (GRE) MR signals with immunohistology (Bregma 0mm according to Franklin and Paxinos's atlas). A- GRE MRI 72h post-pMCAO and i.v. injection

of USPIO. Note the hypointense signal around the lesion, the contralateral corpus callosum and the ipsilateral peri-ventricular area. B- Double staining with Prussian Blue and F4/80 of the right (ipsilateral) ventricle. Iron-stained microglia/macrophages are clearly visible along the lateral wall, in correlation with the hypointense signal observed in GRE images (A). C- Prussian Blue staining for iron in the contralateral corpus callosum of the corresponding slice. Positive staining was observed around cell nuclei, which suggests cytoplasm uptake (insert). D- F4/80 immunostaining for mouse microglia/macrophages in the contralateral corpus callosum. Note the F4/80+ brown cells, in spatial agreement with iron+ cells (B) and MRI hypointense signal (A). E- F4/80 immunostaining of a non-operated control mouse in the left corpus callosum, with no positive staining. F- Double staining with Prussian Blue and F4/80: magnification of B. Microglia/macrophages, as identified by their brown color and typical ramified shape, were also blue-stained, suggesting USPIO intra-cellularity. From (Wiart et al., 2007).

proposed the following explanations: (i) that USPIOs might be leaked by the infiltrating macrophages before being re-ingested by secondarily recruited macrophages, and (ii) that Prussian Blue might become sensitive to iron oxide nanoparticles only after degradation of their dextran coating, an enzymatic process that could take several days. The second study (Kim et al., 2008) presented results more in line with those obtained in the permanent model, with an hypointense signal appearing relatively late (day 3-4) after stroke onset. Macrophages (ED1) and focal iron deposition were detected in the lesion at these time-points, in agreement with T2/T2* hypointense areas. However, these results obtained with SPIO injection failed to be reproduced with USPIO in a recent study : Farr and colleagues did not observe T1, T2, nor T2* signal changes, despite a three-dose assay and extensive ED-1-positive macrophage accumulation at the sub-acute stage (Farr et al., 2011). In line with this negative results, the single study performed with a mouse model of transient ischemia reported no detectable MRI changes in the first 72h following stroke onset (Denes et al., 2007). It should be noted, however, that the dose used in that study was particularly low (160 $\mu\text{mol/kg}$) and perhaps not optimal for MRI detection. Besides, this study confirmed the predominance of microglial response, demonstrated by a paucity of immunohistological markers, at acute and subacute stages, compared to monocytic infiltration (Denes et al., 2007).

Henning and colleagues (Henning et al., 2009) used an original strategy of “in vivo pre-labeling”. The methodology is based (i) on the fact that iron oxide nanoparticles injected intravenously target, amongst other phagocytic cells, those from bone marrow (Denes et al., 2007; Simon et al., 2005); and (ii) on the hypothesis of resident macrophage turnover from bone-marrow progenitor cells (Priller et al., 2001). SPIO injection was performed 7 days before tMCAO, in order to pre-label bone marrow-derived macrophages. A T2/T2* hypointense signal was observed in the lesion periphery with a peak at D4 post-reperfusion in pre-loaded rats, and remained constant until D7 in the perilesional area. Conversely, post-loaded animals (which received the same SPIO injection 5 minutes after occlusion) showed no significant signal changes. Another interesting result of the study concerned the nature of the subpopulation of labeled macrophages, which were confined to three distinct locations: the perivascular regions, the meninges and the choroid plexus. In these areas, Prussian blue co-located with differentiated macrophages staining (ED2 marker) rather than with the non-specific staining of macrophages (ED1 marker) and activated microglia staining (IBA). In line with previous studies, Prussian Blue staining was found in only a small proportion of

cells. Although the exact mechanisms of cell labeling by SPIOs and migration of these labeled cells into the central nervous system were not elucidated in this study, the proposed approach is elegant in the sense that it solves the question of passive diffusion of SPIOs (since they are washed out from the plasma before stroke onset). Other independent studies are nevertheless mandatory to confirm these results.

Animal model		Contrast Agent			MRI			Ref.
Species	Extent (min)	Name	Dose (μmol/kg)	Injection time	Imaging times	Field strength	Sequences	
Rat	30	Ferumoxtran-10	300	T0+5h	D0, D1, D2, D3, D4, D7	4.7T	T2, T1	(Rausch et al., 2002)
Mouse	30/60	Ferumoxtran-10	160	MRI-2h	D0, D1, D2, D3	7T	T2, Gd-T1	(Denes et al., 2007)
Rat	60	Ferucarbotran	200	MRI-24h	D1-6, D8, D10, D14	3T	T2, 3D T2*, Gd-T1	(Kim et al., 2008)
Rat	30	Ferumoxide	286	T0-7days	D1-4, D7	7T	T2 map, 3D T2*	(Henning et al., 2009)
Rat	60	Ferumoxtran-10	300 / 600 / 1000	T0+3days T0+6days	D3-4, D6-7	4.7T	T2, T2*, T1	(Farr et al., 2011)

Table 2. Literature review of USPIO-enhanced MRI in the transient middle cerebral artery occlusion (tMCAO) model. All transient models were performed with the intraluminal thread model. T0 = Reperfusion time; T0+5h = 5h after reperfusion; MRI-24h = 24h before MRI; Gd-T1: T1-weighted MRI with gadolinium chelate injection (to assess BBB integrity); PB- Prussian Blue

3.2 Clinical studies

The first clinical study was published in 2004 by Saleh et al. (Saleh et al., 2004a). USPIOs (Ferumoxtran-10) were injected in 10 stroke patients at the end of the first week after symptom onset (6 to 9 days). MRI was performed at 1.5T before injection, then between 24h and 36h and again between 48h and 72h post-injection. Parenchymal enhancement was observed on T1-weighted imaging in most cases (8 out of 10). However, T2/T2* effects were not systematically observed and seemed to be associated with vessels. As in experimental studies, there was a mismatch between regions showing BBB disruption (as assessed by post-gadolinium T1 enhancement) and regions showing USPIO enhancement. The authors suggested that USPIO enhancement was due to the infiltration of magnetically-labeled macrophages. We conducted a similar study, in which USPIOs were injected at D6 after stroke onset and MRI was performed 72h post-injection (Nighoghossian et al., 2007). In the 10 included patients, USPIO response was heterogeneous and not related to subacute lesion volume. As in the study by Saleh et al. (Saleh et al., 2004a), T1 enhancement was observed in most cases (9 out of 10), while T2/T2* effects were not systematically observed (5 patients out of 10) (Figure 2). No obvious relationship was observed between regions with BBB disruption and those showing USPIO-induced signal changes: for example, 3 patients without BBB disruption

showed enhancement following USPIO administration, whereas one patient with severe BBB disruption showed no USPIO-induced signal change.

Fig. 2. A 55-year-old woman, with a past history of transient confusional state 2 months before admission, which was likely related to a right posterior middle cerebral artery (MCA) stroke, was admitted for acute left MCA stroke with nonfluent aphasia and severe right hemiplegia. From left to right: (1) Day 6 diffusion-weighted imaging (DWI) without contrast; (2) Day 9 T2*-weighted imaging; and (3) Day 9 T1-weighted imaging 72 hours after USPIO infusion. Right, old posterior superficial MCA ischemic infarction and recent left superficial MCA stroke with a large USPIO enhancement (arrow) compared with DWI lesion volume. From (Nighoghossian et al., 2007).

In their second study, Saleh et al. (Saleh et al., 2007) investigated an earlier time window: USPIOs were injected 2 to 3 days following symptom onset and MRI was performed at different post-injection time points (24h-36h, 48h-72h, 10-11 days). Only 3 of the 9 patients included in the analysis showed signal change on post-injection MRI. None of these patients showed T1 enhancement following gadolinium chelate administration. As in the previous study, signal changes consisted in enhancement on T1-weighted images, with an increase in enhancement between the first two post-injection examinations, and a decrease between the last two. A subsequent study involving the same earlier time-window (2 days after stroke onset with MRI performed 48h after) confirmed these findings (Cho et al., 2007). T1 enhancement was observed inside the lesion in only 1 of the 5 included patients. In this patient, post-gadolinium enhancement was more extensive than post-USPIO enhancement. The heterogeneity of USPIO-labeling was thought to reflect inter-individual variability of post-ischemic inflammation (Saleh et al., 2007). Accordingly, MRI may be of use in selecting patients for targeted anti-inflammatory therapies.

Interpretation of clinical data is mainly based on experimental studies. Since (U)SPIOs have been found in macrophages following ischemic stroke, signal changes observed in patients are thought to reflect the phagocytic response. There are, however, several obstacles for direct translation from small animals to humans. Firstly, the animal model may not properly represent the clinical situation, so that the route of (U)SPIO transport to brain macrophages might not be the same. Secondly, there are some differences in the time-windows investigated: in the perspective of therapy, it is more attractive to treat in the very first days or even hours after symptom onset; experimental and clinical protocols performed during

the early stage failed to produce consistent signal changes. Thirdly, the dose used in humans (2.6 mg iron/kg body weight) is far less than in animals. Finally, the interpretation of MR signal changes may differ according to the field strength at which they were acquired. Animal experiments are usually performed at very high field compared to clinical studies, which obviously influences relaxation properties. The latter two elements (high dose/high field in pre-clinical studies and small dose/low field in clinical studies) could partly explain why T1 effects were mostly observed in clinical studies, whereas T2/T2* effects were always observed in experimental studies. Besides, though compartmentalization of USPIO inside cells is thought to induce magnetic susceptibility gradients leading to T2* effects, it seems that SPIO-labeled macrophages could produce T1 effects at 1.5T (Daldrup-Link et al., 2003). This shows the importance of performing quantitative studies in order to characterize the effects of compartmentalization and concentration on MR signal, at different field strengths for each contrast agent (Brisset et al., 2010a). In the future, the development of MR sequences specifically dedicated to detection and quantification of (U)SPIO-labeled macrophages, such as positive contrast techniques (Brisset et al., 2010b; Mani et al., 2008), may help data interpretation and analysis of longitudinal studies.

4. Ex vivo labeling of phagocytic cells

MRI techniques using intravenously injected SPIO/USPIO fail to distinguish between non-specific diffusion of free particles and magnetically labeled phagocytes. Thus, signal changes might be wrongly attributed to inflammatory processes. This limitation could be overcome in part by magnetically labeling macrophages before their injection (ex vivo labeling). To date, the majority of studies using ex vivo labeling in stroke models addressed cellular therapy, using subventricular zone progenitor cells (Athiraman et al., 2009; Cicchetti et al., 2007; Jiang et al., 2005; Zhang et al., 2003), embryonic neural stem cells (Hoehn et al., 2002; Modo et al., 2004) mesenchymal stem cells (Lee et al., 2009; Walczak et al., 2008), spleen-derived mononuclear cells (Stroh et al., 2006) or adipose-derived stem cells (Rice et al., 2007). To our knowledge, only one study was published using ex vivo labeling of macrophages in a rat stroke model (Engberink et al., 2008): 4 rats were intravenously injected with 5 million SPIO-labeled monocytes after induction of cerebral ischemia by photothrombosis. MRI was performed at 4.7T pre- and 24h, 72h and 120h post-injection. Although visual examination of T2*-weighted images and Prussian Blue staining were not conclusive, quantitative analysis (percentage of hypointense voxels compared to baseline) showed significant differences in MR signal changes compared to control animals (non-injected or injected with free USPIOs). According to the authors, the differences observed between groups are suggestive of an active monocytic infiltration into the lesion. One limitation of this method is that injected monocytes may not reflect the actual behavior of endogenous monocytes.

5. Conclusion

Despite abundant evidence for an inflammatory response after stroke, anti-inflammatory treatments have so far failed in clinical trials (Savitz & Fisher, 2007). In this context, non-invasive detection of inflammatory cells after brain ischemia could be helpful (i) to select patients who may benefit from anti-inflammatory treatment; (ii) to identify the optimal therapeutic time window; (iii) to develop therapies targeting specific pathophysiological processes. MRI coupled with (U)SPIO, a contrast agent taken up by macrophages ex vivo

and in vivo, appears to be a promising tool for this purpose. Current limitations of this approach include the difficulty in identifying non-specific signal changes. Additional studies on long-term monitoring of (U)SPIO-related signal changes are required. This will be of crucial importance for clinical trials aiming to assess immunomodulatory drugs. Multiple factors are likely to account for post-treatment modifications of MR signal: modulation of inflammation, changes in the iron microenvironment and biotransformation. Well-designed pre-clinical studies including dedicated quantitative MR sequences are still warranted before application of the technique in larger patient cohorts.

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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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