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Gadolinium toxicity: Iron and ferroportin as central targets

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ABSTRACT

Gadolinium-based magnetic resonance (MR) contrast agents (GBCM) causes a devastating systemic fibrosing illness, nephrogenic systemic fibrosis (NSF), in patients with reduced kidney function. GBCM targets iron-recycling CD163- and ferroportin-expressing macrophages to release labile iron that mediates gadolinium toxicity and NSF. GBCA might similarly target iron-rich, ferroportin-expressing structures such as globus pallidus and cerebellar dentate nucleus in the brain to result in metal accumulation and potential toxicity.

1. Introduction

Gadolinium-based contrast agents (GBCM) are widely used in magnetic resonance imaging (MRI). GBCM were widely considered safe until the discovery of its link with the devastating systemic fibrosing illness, nephrogenic systemic fibrosis (NSF) in 2006, in patients with reduced kidney function [1,2]. Most cased were attributed to less stable linear GBCM such as gadodiamide (Omnisan™) [3,4]. This lead to a "black box" warning by the US Food and Drug Administration (FDA) and European regulatory authorities against using linear GBCM in patients with advanced chronic kidney disease (CKD) and end stage kidney disease (ESKD). Since these warnings were issued, the number of incident NSF cases have dramatically reduced confirming the link between GBCM and NSF [5]. More recently, gadolinium deposition, particularly in the brain, has been described in patients with normal renal function [6–8]. The mechanisms of gadolinium deposition in selective areas of the brain and its clinical consequences are unknown. In this review, we will focus on the pathogenesis of gadolinium toxicity with a special emphasis on its potential direct link to iron homeostasis.

The pathogenic mechanisms of gadolinium toxicity continue to be investigated although several clues have emerged. We will review: 1) the potential role of iron in transmetallation and gadolinium toxicity; 2) link between altered iron homeostasis, iron exporter-ferroportin and cellular mechanisms of fibrosis; 3) a potential link between metal homeostasis and the recently described selective gadolinium deposition in the brain of patients with intact renal function.

1.1. Transmetallation in gadolinium toxicity: role of iron

Linear GBCM such as Omniscan™ and Magnevist™ are the primary gadolinium-based contrast agents that have been implicated in the pathogenesis of gadolinium toxicity and NSF. With their linear gadolinium to chelate structure, thermodynamic stability is lower than cyclic GBCM such as ProHance™ [9]. One of the leading theories for gadolinium toxicity is the role of transmetallation where endogenous metals such as iron and zinc attract the ligand to release free gadolinium that deposits in the tissue as gadolinium phosphate [10–12]. Lower thermodynamic stability of the GBCM will facilitate easier transmetallation with endogenous metals such as iron or zinc [13,14].

In support of transmetallation, animal and human studies have demonstrated increased zincuria after linear GBCM administration, particularly at toxic doses. Further, animal models of NSF also demonstrate increased urinary zinc excretion [10,15]. Zinc-dependent transmetallation could not fully explain NSF pathogenesis as exogenous zinc supplementation did not exaggerate the severity of fibrosis in animal models of NSF [16].

Our studies and others have demonstrated iron mobilization in a subset of patients exposed to linear GBCM [13]. In our prospective observation of 2 CKD patients, we observed that GBCM triggered iron mobilization, transferrin oversaturation and induced substantial elevations in serum ferritin. One of these patients required hemodialysis that normalized the iron studies but the patient eventually developed NSF. In a retrospective analysis, we could also confirm that transferrin saturation and serum ferritin levels were higher in ESKD patients with established NSF than in control ESKD patients [13]. In an autopsy study of NSF patients, we further demonstrated that NSF is associated with tissue accumulation of not only gadolinium but also of significant

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amounts of iron [17]. Schroeder et al., using energy filtering transmission electron microscope, confirmed our observations by demonstrating juxtaposition of gadolinium and iron particles in the tissues of patients with NSF [18]. Collectively, these observations pointed to a role of iron mobilization and tissue iron accumulation in the pathogenesis of gadolinium chelate toxicity.

Thermodynamic stability of iron with chelates such as DTPA-BMA is several orders of magnitude higher than of gadolinium [9,19]. Thus, free or excess iron (non-transferrin bound iron or NTBI or labile iron would favor dissociation of gadolinium from its chelate [14,20]. A recent *in vitro* study demonstrated that a solution that was spiked with iron preparations strongly induced transmetallation of linear GBCM [21]. Hope et al. have demonstrated in a murine model that intravenous iron exaggerates gadolinium-induced fibrosis [22].

While studies have suggested a prolonged tissue presence of chelated gadolinium, most studies have shown gadolinium to be deposited in tissues as an insoluble gadolinium phosphate. Collectively, these observations suggest that endogenous free iron-dependent GBCM transmetallation could potentially play a role in the pathogenesis of NSF.

1.2. Iron recycling macrophages as a target of gadolinium toxicity (Fig. 1)

While the above discussed studies demonstrate that GBCM induces iron mobilization, our subsequent studies seeking to examine the cellular source of iron identified an important role of $CD163^+$ iron recycling macrophages in gadolinium toxicity [23].

Body iron homeostasis and stores depends on dietary iron absorption and more importantly on erythrocyte and heme turnover mediated by the $CD163^+$ iron recycling macrophages. CD163 pathway serves to endocytose hemoglobin bound to haptoglobin [24,25]. Subsequently, this results in intracellular heme degradation by heme oxygenase-1 (HO-1) and release of ferrous iron, which gets exported out of the cell through the iron exporter, ferroportin [26]. Cellular iron export and ferroportin expression are strictly regulated by hepcidin, an endogenous peptide produced by the liver [27]. Thus, high hepcidin levels are associated with low ferroportin expression and high intracellular iron retention in macrophages.

Most of the body iron is processed and stored in these iron-recycling $CD163^+$ macrophages, and peripheral blood monocytes are the precursors to these macrophages [28]. In our studies, we examined if GBCM could induce differentiation of human peripheral blood mononuclear cells (PBMC) into $CD163^+$ macrophages *in vitro* [23]. Our studies demonstrated that GBCM (Omniscan™) facilitated the differentiation of PBMC into $CD163^+$ macrophages. These cells were pro-fibrotic (procollagen-1 expression) and expressed high levels of iron recycling and storage proteins: transferrin receptor (Tfr1), HO-1, H-ferritin and ferroportin. We examined the relevance of these observation *in vivo* in patients with NSF. We demonstrated that pro-fibrotic $CD163^+$ $ferroportin^+$ macrophages were shown to infiltrate the dermis, subcutaneous tissue, myocardium and vascular tissues of patients who died with NSF [23]. In a recent study, using bone marrow chimera animal models, a central role of procollagen-1-expressing CD163/HO-1+ myeloid cell infiltration in NSF was further confirmed [29].

Macrophage iron loading with heme (M_{heme} or MOX) were recently shown to have anti-inflammatory and pro-healing properties [30]. Our recent studies in a model of ischemic kidney injury have also demonstrated pro-healing effects of macrophage iron retention [31]. Collectively, these observations suggest that 1) gadolinium targets mononuclear phagocyte system to induce iron recycling $CD163^+$ macrophages; 2) targeting of iron recycling macrophages could explain systemic iron mobilization seen in some patients with gadolinium toxicity and NSF; and 3) $CD163^+$ $ferroportin^+$ macrophages are the likely sources of tissue iron accumulation seen in NSF patients. The latter observation is supported by a recent study that showed co-localization of Prussian-blue positive iron deposits with fibrocytes (procollagen-1 expressing myeloid cells) [32].

1.3. Cellular iron import in gadolinium toxicity

Transitional polyvalent cationic metals and gadolinium have been shown to perturb cellular iron metabolism and induce increased cellular iron acquisition by myeloid phagocytic cells through transferrin receptor [33]. This would result in increased macrophage iron content. Ghio et al. have recently confirmed these observations. In their study, addition of linear GBCM disrupted cellular iron homeostasis and dramatically increased transferrin-dependent cellular iron uptake and induced an increase in H-ferritin content [34]. These observations along with the findings of our studies indicate that both heme- and non-heme iron import, storage and export pathways are activated by GBCM.

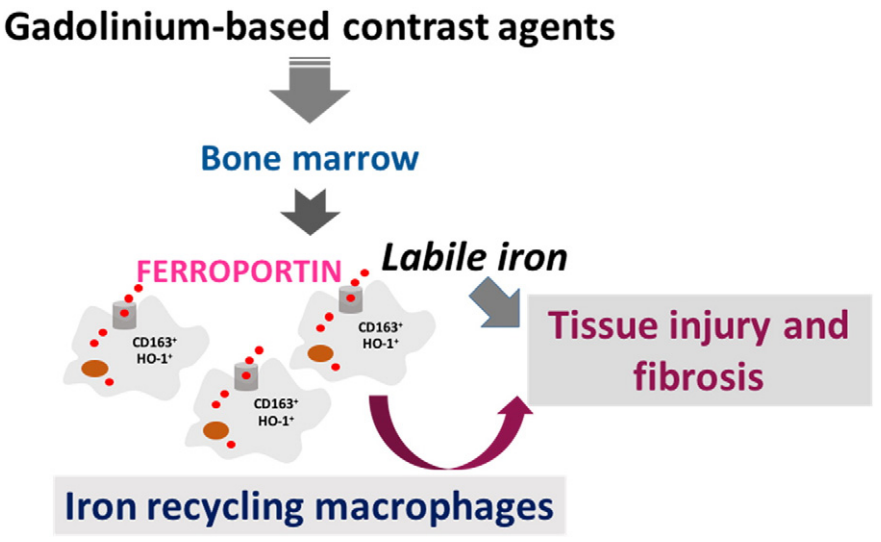

Fig. 1. Gadolinium-based contrast agents target CD163/ferroportin-expressing iron-recycling macrophages, perturbs macrophage iron homeostasis, and triggers labile iron release. Iron-induced transmetallation of GBCA leads to gadolinium and labile iron toxicity and a pro-fibrotic milieu.

1.4. Labile iron, macrophages and tissue injury in gadolinium toxicity

In our earlier studies, we have implicated a potential role of labile iron or NTBI in GBCM transmetallation [13,14]. Labile iron is defined as free, non-transferrin bound ferrous iron species that is capable of participating in Fenton reaction to induce oxidative stress, lipid peroxidation and tissue injury [35,36]. Labile iron levels are increased in ESKD [37], in patients with tissue iron overload, in those with low transferrin levels, in tissue injury and in patients with hepcidin deficiency. In our studies, we have demonstrated that GBCM not only induces differentiation of $CD163^+$ macrophages but also triggers labile iron release by these cells [38]. Thus, it is likely that a combination of ESKD status, malnutrition with hypotransferrinemia and $CD163^+$ macrophage induction and infiltration in NSF is accompanied by labile iron-mediated tissue injury. Of note, labile iron is known to be pro-fibrotic and has been implicated in the pathogenesis of variety of systemic fibrotic conditions [39,40]. Our recent studies confirm a pathogenic role of labile iron in NSF. We first demonstrated that iron chelator, deferiprone, significantly inhibited GBCM-induced *in vitro* differentiation of human PBMC into $CD163^+$ macrophages, and reduced their labile iron release. Further, deferiprone substantially reduced $CD163^+$ ferroportin$^+$ macrophage infiltration and dermal fibrosis in a murine model of GBCM-induced fibrosis [38].

Collectively, these observations demonstrate that GBCM targets iron recycling $CD163^+$ macrophages, induces cellular iron import and export, and labile iron release, which participates in systemic fibrosis.

1.5. Brain gadolinium accumulation: potential link to iron homeostasis (Fig. 2)

Several recent studies have revealed that even in patients with apparently normal renal function, repeated administration of linear GBCM are associated with significant quantities of residual gadolinium in brain tissues [6,8,41]. Several recent radiologic and autopsy studies have demonstrated that multiple GBCA doses induce increased T1 signal intensity in the globus pallidus, thalamus, caudate nucleus, and dentate nucleus of brain. Some of these studies have confirmed tissue gadolinium deposition in these brain areas [7]. It is of interest that these brain gray matter structures are intrinsically iron-rich and are specifically affected by neurodegenerative disorders with brain iron and manganese accumulation [42]. As an example, in Friedreich's ataxia due to mutation in mitochondrial iron metabolism gene, Frataxin, iron accumulates in cerebellar dentate nucleus and globus pallidus [43]. In certain neurodegenerative disorders such as those associated with hepatic encephalopathy, there is significant accumulation of manganese in the basal ganglia [44]. Manganese is neurotoxic and has been implicated in parkinsonism. Neuronal manganese export is again regulated the divalent metal exporter, ferroportin [45]. Induction of ferroportin limits neurotoxicity of manganese. Thus, gadolinium could target ferroportin-rich areas of neuronal tissue that are involved in active regulation of iron and manganese metabolism to result in metal accumulation and toxicity. Whether neuronal metal accumulation would predispose patients to future neurodegenerative disorders and parkinsonism-like syndromes is currently unknown. However, our unpublished clinical observations indicate that there are several patients with normal renal function and significant residual gadolinium who manifest new-onset unexplained extremity pain (neuralgic type) and stiffness without any definitive evidence of NSF after exposure to GBCA.

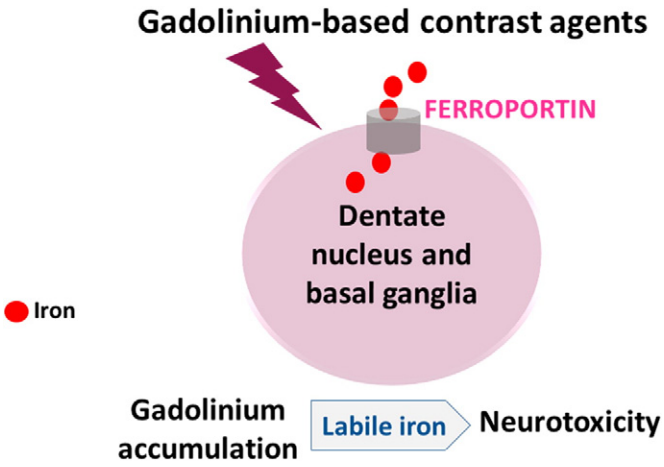

Fig. 2. Gadolinium-based contrast agents target ferroportin-expressing iron-recycling brain structures (such as cerebellar dentate nucleus and globus pallidus). Local iron-induced transmetallation of GBCA would facilitate tissue gadolinium accumulation and possible toxicity.

2. Conclusions

Iron plays an important role in cellular homeostasis and macrophage function, and seems to be a major target of gadolinium toxicity. Iron-recycling macrophages and labile iron are mediators of gadolinium toxicity. $CD163^+$ pro-fibrotic macrophages (or fibrocytes) and labile iron are novel targets to prevent and treat gadolinium toxicity and NSF. Iron-recycling ferroportin-rich cells in structures such as globus pallidus, cerebellar dentate nucleus, thalamus, retina and dorsal root ganglia may similarly be the targets of GBCA in the brain. Further studies are required to understand the role of neuronal iron transport and ferroportin in gadolinium toxicity.

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