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Review Article

Therapeutic potential of iron chelators in diseases associated with iron mismanagement

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Abstract

A considerable array of diseases are now recognized to be associated with misplacement of iron. Excessive deposits of the metal in sensitive tissue sites can result in formation of destructive hydroxyl radicals as well as in stimulation of growth of neoplastic and microbial cell invaders. To counteract potential iron damage, hosts employ the iron chelators, transferrin and lactoferrin. These proteins have been recently developed into pharmaceutical products. Additionally, a variety of low molecular mass iron chelators are being used/tested to treat whole body iron loading, and specific diseases for which the metal is a known or suspected risk factor.

Introduction

During the past half century, a considerable array of diseases has been recognized to be associated with mismanagement of iron. At the same time, awareness has developed of the existence of an innate iron withholding defence system, starting with the discovery of transferrin (Schade & Caroline 1946) and proceeding with the delineation of the system (Weinberg 1984). With the more recent recognition of the roles of specific cytokines and such key molecules as hepcidin and ferroportin, the system is now fairly well characterized (Cardoso et al 2005; Weinberg 2005).

Nevertheless, despite the vigilance of our iron withholding defence system, under some circumstances excessive iron accumulates and is deposited in various cells and tissues. Some of the conditions that can compromise the iron withholding defence system are listed in Table 1.

Examples of diseases for which misplaced iron can be a risk factor are contained in Table 2. Accumulation of the metal can result in illness in several ways. Non-protein bound ferric ions are reduced by superoxide, and the ferrous product is reoxidized by peroxide to regenerate ferric irons and yield hydroxyl radicals. The latter attack all classes of macromolecules. Hydroxyl radicals can initiate lipid peroxidation, inactivate enzymes, depolymerize polysaccharides, and cause DNA strand breaks (McCord 1998).

Moreover, such aspects of leucocyte defence as natural killer cell activity, phagocytic capacity of neutrophils and monocytes, and microbicidal action of the latter are depressed by excessive iron (Kontoghiorghes & Weinberg 1995). Furthermore, the metal can serve as an essential growth factor for invading bacterial, fungal and protozoan organisms as well as for neoplastic cells (Weinberg 1996a, 1998, 1999). Indeed, even viral synthesis can be increased in iron-loaded host cells (Weinberg 1996b; Drakesmith et al 2005). Additionally, some intracellular pathogens can compel their host cells to upregulate iron acquisitions (Weinberg 2000; Drakesmith et al 2005).

Protein iron chelators

Vertebrate hosts rely on the iron withholding defence system to prevent accumulation of nonprotein-bound iron in extracellular fluids. Essential components of the scavenging arm of the system are the powerful iron chelating proteins transferrin (Tf) and lactoferrin (Lf). These 80 kDa glycoproteins each can bind strongly two atoms of iron per molecule. Transferrin is responsible for removing free iron from serum, lymph and cerebrospinal fluid whereas Lf has an analogous function in exocrine secretions: milk, tears, nasal

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Table 1 Some conditions that compromise the iron withholding defence system

Genetic disorders
Aceruloplasminaemia
African siderosis
Haemochromatosis
Haemoglobinopathies
Sicklaemia
Thalassaemia
Behavioural factors
Ingestion of excessive amounts: haeme (in meat), iron supplements, ascorbic acid, ethanol, food that has been adulterated with iron
Inhalation of iron-containing items: asbestos, coal, other industrial sources of iron; tobacco smoke; urban air particulates
Injection of excessive amounts: iron saccharates; whole blood or erythrocytes
Pathological conditions
Release of body iron into plasma: efflux of erythrocyte iron in haemolytic conditions; efflux of hepatocyte iron in hepatitis; myeloablative conditioning before cell/tissue transplants

Table 2 Examples of diseases for which misplaced iron can be a risk factor

Cardiovascular
atherosclerosis
cardiomyopathy
Endocrine
diabetes
growth deficiency
hypogonadism
hypothyroidism
Hepatic
alpha-1-anti-trypsin deficiency
cirrhosis
porphyria cutanea tarda
steatohepatitis
viral hepatitis
Neoplastic and infectious
neoplasms of colon, liver, lung
bacterial, fungal, protozoan infections of all body systems
Neurologic
depression
Alzheimer's
Freidreich's ataxia
Parkinson's
Ophthalmic
macular degeneration
Pre- and post-natal
neonatal haemochromatosis
pre-eclampsia
sudden infant death
Skeletal
osteoarthritis
osteoporosis

exudate, saliva, bronchial mucus, gastrointestinal fluids, cervico-vaginal mucus and seminal fluid (Weinberg 2001).

Additionally, Tf conveys nutritional amounts of iron to and from cells throughout the body. Quantities of the metal that are not immediately required for metabolic use are deposited in the intracellular iron-sequestering arm of the system, ferritin. This 450 kDa protein can amass up to 4500 atoms of iron per molecule.

Lactoferrin has a second indispensable function: the removal of iron from tissue sites that are being damaged by infection, neoplasia, ischaemia and reperfusion. The protein, contained in granules of circulating polymorphonuclear neutrophils (PMNs), is released upon degranulation at the invasion sites. In such locations, the pH value is lowered by catabolic acids released from metabolically active invading cells as well as from PMNs. Fortunately, Lf is an effective iron scavenger at pH values as low as 3.5.

During the past decade, Tf and Lf with very low iron saturation (apo compounds) began to be considered as potential pharmaceutical agents. A research team of the Finnish Red Cross Transfusion Service has developed a procedure for extracting and purifying Tf from human plasma (von Bonsdorff et al 2001). The starting protein normally is 24–30% saturated with iron; the final apo product has an iron content of 0.3%.

The purified agent could be useful not only in hypo- and atransferrinaemic persons but also in conditions in which iron saturation of the patient's Tf has become highly elevated. For instance, recipients of bone marrow are myeloablatively conditioned with a week of cytotoxic chemotherapy before the transplantation. The procedure temporarily halts erythrocyte production as well as damages hepatocytes with release of iron deposits. In these patients, 100% iron saturation can occur (Durken et al 2000).

Intravenous injection of the apo-Tf product has been well tolerated in such patients and was effective in temporarily lowering Tf iron saturation (Sahlstedt et al 2002). In a subsequent study (von Bonsdorff et al 2003), *Staphylococcus epidermidis* grew in serum samples from stem cell recipient patients when Tf iron saturation exceeded 80%. Repeated doses of the apo-Tf product restored the growth inhibiting effect of the patients' sera. Those persons who received repeated doses had significantly fewer days of fever and elevated C-reactive protein than did the controls.

Similarly, apo-Tf could benefit those haemodialysed patients who have highly elevated Tf iron saturation due to parenteral administration of iron dextran (Parkkinen et al 2002). Moreover, in pre-term infants, oxidation radical injury such as retinopathy and bronchopulmonary dysplasia also might be alleviated by injection of Tf with low iron saturation (Sullivan 1988).

In some bacterial infections, the pathogens have differentiated from vegetative forms into sessile cells that become irreversibly attached to the body tissue linings or to indwelling prostheses. These biofilms resist killing by antibiotics or immunoglobulins. Apo-Tf markedly lowers Gram-positive and Gram-negative bacterial adhesion to synthetic or protein-coated surfaces (Ardehali et al 2003). Likewise, apo-Lf as well as specific low molecular mass iron chelators similarly suppress biofilm formation (Weinberg 2004).

The development of apo-Lf as a potential therapeutic agent has exceeded that of apo-Tf (Weinberg 2006).

Recombinant human apo-Lf is produced in microorganisms, as well as in cells of plants and animals. The remarkable diversity of present and projected uses of the recombinant product is illustrated in Table 3. In most, but not all, of the examples, the mechanism of action is considered to be that of iron chelation.

Possible side effects of apo-Tf and apo-Lf

Inasmuch as the apo-Tf and apo-Lf agents are natural products rather than synthetic chemicals or microbial secondary metabolites, side effects should be minimal. Nevertheless, it could be anticipated that those recipients of the proteins who form variants might develop antibodies to the agents.

Of 38 known variants of human Tf, four occur with a frequency greater than 1% (de Jong et al 1990). Moreover, antibodies to endogenous Lf have been observed in some patients who have autoimmune disorders such as systemic lupus erythematosus (Caccavo et al 2005) or type 1 diabetes (Taniguchi et al 2003).

A second potential hazard of the use of Tf or Lf in therapy is the ability of a small but dangerous group of pathogenic microorganisms to employ these proteins as nutritional iron carriers. Of concern especially are bacteria in the family Neisseriaceae such as *Neisseria meningitidis* and *Haemophilus influenzae* (Wong & Schryvers 2003). Other examples include *Helicobacter pylori*, a risk factor for gastritis and possibly gastric cancer, and also *Trichomonas vaginalis*, a protozoan cause of vaginitis. Before administration of Tf or Lf, patients should be evaluated for possible carriage of these and related pathogens.

Low molecular mass iron chelators

In the twentieth century, several classes of low molecular mass compounds with iron binding substituents became sources of

Table 3 Potential applications of lactoferrin*

Product	Purpose	Reference
Nutraceuticals		
Rice expressing Lf + lysozyme; fed to chicks	Improvement in feed efficiency; replacement of antibiotics	Humphrey et al (2002)
Rice expressing Lf + lysozyme; fed to man	Prevention of acute diarrhoea	Bethell & Huang (2004)
rhLf + probiotic; fed to pre-term infants	Prevention of necrotizing enterocolitis	Sherman et al (2004)
rhLf added to formula; fed to infants	Prevention of iron-induced oxidation in stored formula	Raghuveer et al (2002)
Pear expression of bLf	Prevention of bacterial fire blight	Malnoy et al (2003)
Rice expression of hLf	Prevention of bacterial seedling blight	Takase et al (2005)
Preservatives		
bLf added to food-and drink-stored items; e.g. soy powder	Prevention of iron-induced oxidation during storage	Steijns & van Hooijdonk (2000)
bLf sprayed on meat products	Prevention of bacterial growth during storage	Taylor et al (2004)
Pharmaceuticals		
Topical rhLf	Enhancement of wound healing	Engelmayer & Varadhachary (2003)
Topical bLf	Promotion of bone repair	Cornish et al (2004)
Topical bLf	Suppression of oral candidiasis	Masci (2000)
Topical pH-buffered Lf	Suppression of oral candidiasis	Kuipers et al (2002)
Topical bLf	Suppression of feline stomatitis	Sato et al (1996)
Oral rhLf	Enhancement of IL-18 in gut cells; suppression of tumour cell growth	Varadhachary et al (2004)
Oral rhLf	Enhancement of circulating IL-18; suppression of tumour cell growth	Hayes et al (2005)
Oral rhLf + i.p. cisplatinum	Additive enhanced suppression of tumour cell growth	Varadhachary et al (2004)
Oral apo-Lf	Suppression of gut cell release of pro-inflammatory cytokines in ulcerative colitis	Amati et al (2003)
Oral apo-Lf + probiotic	Suppression of overgrowth of enteric pathogens	Griffiths et al (2004)
Oral apo-Lf + antibiotics	Enhancement of antibiotic efficacy	Aguila et al (2001)
Intra-articular hLf entrapped in liposomes	Suppression of joint inflammation	Guillen et al (2001)
Cervical rhLf	Suppression of infection-induced pre-term delivery	Hasegawa et al (2005)
Vaginal activated Lf + fluconazole	Suppression of candidal growth	Naidu et al (2004)

*Modified from Weinberg 2006 (Table 7).

useful drugs. Examples include anti-inflammatory salicylates; anti-infectives such as tetracyclines, aminoglycosides, vancomycin, rifampicin, and isoniazid; antineoplastics such as bleomycin, anthracyclines, and mitoxantrone; and adrenergics such as isoprenaline and ephedrine. However, pharmaceutical development of these compounds occurred without emphasis on their possible ability to alter iron mismanagement.

Various classes of compounds with iron chelating ability have been screened for possible therapeutic use in patients who have iron loading disorders (group I), or cancer, infection or chronic disorders associated with iron-induced oxidative damage (group II). A compound safe and effective for one of the two groups might not be acceptable for the other group. Thus a drug useful in therapy of group I generally would be required throughout life. For group II, briefer periods of administration could suffice. Moreover, a chelator useful in treatment of whole body iron loading might lack the required specificity for withdrawal of the metal from an iron-contaminated site while simultaneously abstaining from causing iron deficiency in normal tissues.

In any case, an acceptable iron chelating drug must comply with several requirements among which are: high specificity for iron, low specificity for such other physiologically important metals as zinc, copper, manganese; ability to deplete iron-loaded but not iron-normal sites; abstention from redistribution of iron to such iron-sensitive organs as heart and brain; abstention from donation of iron to neoplastic or microbial cells that might be latent in the patient; and efficient excretion of the iron chelate in urine and/or bile.

In addition, useful compounds should be readily administered (by oral route if possible), compatible with other drugs, and available at reasonable cost.

Various aspects of design and discovery of low molecular mass iron chelator drugs have been discussed in recent excellent reviews (Liu & Hider 2002; Chaston & Richardson 2003; Tam et al 2003).

Large numbers of children with such haemoglobinopathies as thalassaemia and sicklaemia are born each year. In the absence of red blood cell transfusions and iron chelation therapy, their quality of life and longevity are severely dimished. Features of the three iron chelators that have been most commonly employed and/or tested in iron-loaded subjects are contained in Table 4; formulae are shown in Figure 1. Recently, some thalassaemic patients have been treated with sequential desferrioxamine (deferoxamine) and deferiprone. This protocol permitted improved compliance because fewer painful subcutaneous prolonged injections of desferrioxamine were needed each week (Origa et al 2005; Rund & Rachmilewitz 2005).

Antineoplastic activity

During the past fifteen years, desferrioxamine has been reported to have antineoplastic activity in in-vitro systems, in rodents, and in man. Unfortunately, although the chelator inhibits sarcoma cells in-vitro, it has stimulated their growth when given to a patient by intralesional injection (Simonart et al 2002). Nevertheless, the drug might find utility as an adjunct in some clinical situations. In a recent study, desferrioxamine suppressed growth of xenografts of human breast cancer cells in nude mice, apparently by iron depletion (Hoke et al 2005).

As with desferrioxamine, iron depletion by deferiprone has resulted in inhibition of in-vitro growth of human leukaemic and squamous cell carcinoma cells (Yasumoto

Table 4 Selected features of iron chelators for transfusional iron loading

Feature	Desferrioxamine	Deferiprone	Deferasirox
Molecular weight	560	139	383
Source	Bacterial siderophore	Synthetic drug	Synthetic drug
Fe^{3+} affinity (pM)	26.5	19.5	22.5
Ligand formation	Hexadentate	Bidentate	Tridentate
Compound:iron ratio	1:1	3:1	2:1
Iron removal			
from Tf, Lf	No	Yes	
intracellular	No	Yes	Yes
Zinc depletion	No	Diabetics: slow release	No
Daily dose	40 mg kg^{-1}	75–100 mg kg^{-1}	20 mg kg^{-1}
Administration	Subcutaneous	Oral	Oral
Plasma half-life	1 h	1.5 h	12–16 h
Elimination in man	Urine and faeces	Urine	Faeces
Occasional side effects	Oto- and ophthalmic toxicity; bone dysplasia	Agranulocytosis Arthralgia	Urticaria Nephrotoxicity
Stimulation of latent infection; neoplasia	Yes	No	No
Decades of clinical experience	Four	Two	One-half
Geographic availability	Worldwide	Europe, India, Asia	In clinical trials
Cost per gram ($ US)	5–10	0.4 India	

References: Boelaert et al (1994); Galanello et al (2003); Kontoghiorghes et al (2003); Hoffbrand et al (2003); Cappelini (2005); Cunningham & Nathan (2005); Porter (2005).

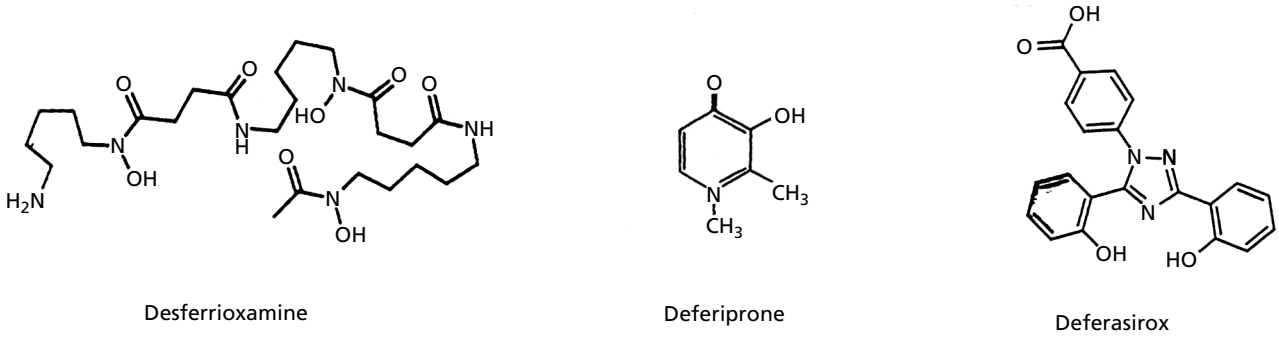

Figure 1 Formulae of selected iron chelators.

et al 2004). Mitoxantrone, an anthrecenedione, is used to treat various malignant disorders in man (Hartung et al 2002). As indicated in Table 5, its immunosuppressant property can suppress progressive multiple sclerosis in man and animal models. The role of iron chelation by the drug in its antineoplastic and immunosuppressive activities has not yet been clarified.

Anti-infective activity

Nearly all protozoan, fungal and bacterial invaders require host iron for growth. Thus compounds that can assist the host to withhold the metal from the invaders are potential candidates for anti-infective drug development. In a series of clinical trials, desferrioxamine has been observed to have activity in both uncomplicated and severe malaria in man (Mabeza et al 1999). In an in-vitro system, deferasirox suppressed malarial protozoan growth more strongly than did desferrioxamine (Goudeau et al 2001).

Fungal pathogens, also, are susceptible to iron chelating drugs. Candidal infections in man can be treated with ciclopirox (Niewirth et al 2003). In rodents, *Pneumocystis carinii* infections can be inhibited by desferrioxamine; in in-vitro models, deferiprone is active in concentrations achievable in human plasma (Weinberg 1994). Such bacterial pathogens as *Mycobacterium avium* (Douvas et al 2002) and *M. tuberculosis* (Cronje et al 2005) are susceptible to deferiprone and desferrioxamine, respectively.

Table 5 Examples of iron chelators with various biological activity

Compound	Chemical designation	Activity	System	References
Carvedilol	(±)-1-[Carbazoloyl-(4) oxyl]-3-(2-methoxy-phenoxy)-ethylamino-2-propanol	Anti-hypertensive	In-vitro	Oettl et al (2001)
Ciclopirox	6-Cyclohexyl-1-OH-4-methyl 2 (1H)-pyridone	Anti-fungal	Human candidiasis	Niewirth et al (2003)
		Angiogenic	In-vitro	Linden & Wenger (2003)
Dp44MT	Di-2-pyridyl thiosemicarbazone	Antineoplastic	Rodent	Yuan et al (2004)
Feralex	2-Deoxy-2-[N-carbamoylmethyl-(N′-2′-3′-OH-pyrid-4′-one)]-D-glucopyranose	Iron detoxication	In-vitro	Kruck & Burrow (2002)
		Aluminum detoxication	In-vitro	Kruck et al (2004)
HBED	N,N′-bis (O-hydroxybenzyl) ethylene diamine-N,N′-diacetic acid	Iron detoxication	Monkey	Bergeron et al (2002)
Hydrazones	2-OH-1-naphthylaldehyde isonicotinoyl	Anti-malarial; antineoplastic	In-vitro	Walcourt et al (2004)
	2-OH-1-naphthylaldehyde isonicotinoyl	Immunosuppressive	In-vitro	Leung et al (2005)
	Salicylaldehyde isonicotinoyl	Cyto-protective	In-vitro	Simunek et al (2005a)
Mimosine	3-OH-4-oxo-1 (4H)-pyridinealanine	Radiation sensitizer	In-vitro	Samuni et al (2001)
Mitoxantrone	1,4-Dihydroxy-5, 8-bis [2-OH-ethyl) aminoethylaminol]-9, 10-anthracenedione	Antineoplastic	Man	
		Immunosuppressive	Man	Hartung et al (2002)
Phytate	Inositol hexaphosphate	Suppression of lipid peroxidation in colonic mucosa	Pig	Porres et al (1999)
Tachpyridine	N, N′, N″-tris (2-pyridylmethyl)-cis, cis-1,3,5-triaminocyclohexane	Antineoplastic	In-vitro	Zhao et al (2004)
Triapine	3-Aminopyridine-2-carboxaldehyde thiosemicarbazone	Antineoplastic	Man	Murren et al (2003)
VK28	5-[4-(2-hydroxethyl)piperazine-1-y1-methyl] quinoline-8-o1	Neuroprotective	Rodent	Shachar et al (2004)

Antiviral activity

Although viruses do not use iron, host cells require the metal to synthesize new viral particles. Studies of iron chelators in viral infections have yielded mixed results (Weinberg 1996b). In some cases, concentrations of the test compounds could be identified that would prevent viral synthesis without damaging host cells. For instance, in human fibroblast cultures, 15 μM desferrioxamine suppressed replication of human cytomegalovirus, but not of herpes simplex virus, without affecting host cell viability (Cinatl et al 1994). In contrast, in human peripheral blood lymphocytes, deferiprone and other members of the 3-hydroxypyridine-one family inhibited replication of human immunodeficiency virus I by preventing proliferation of the infected host cells (Georgiou et al 2002).

Other activity

The oxidant action of misplaced iron as a risk factor for neurodegenerative, atherosclerotic, and other inflammatory conditions is becoming well recognized. Accordingly, iron chelators should become useful in therapy. Neuroprotection in Parkinson's disease animal models has been observed for clioquinol (Kaur et al 2003), VK28 (Shachar et al 2004), and desferrioxamine (Zhang et al 2005). However, clioquinol has been reported to be toxic to cell cultures of murine cortical neurons (Benvenisti-Zarom et al 2005).

In Alzheimer's disease (AD), haeme synthesis in temporal lobe tissue is elevated. Clioquinol, employed in clinical trials in AD patients, decreased haeme synthesis in a tissue culture model (Atamna & Frey 2004). In a two-year study of 48 AD patients, half were given two intramuscular injections per day of $\sim 2\,\mathrm{mg\,kg^{-1}}$ desferrioxamine (McLachlan et al 1991). As compared with the control patients, the treated subjects showed a reduction in the rate of decline of daily living skills ($P = 0.03$).

In a study of 6558 US adults followed from 1971 to 1992, the risk of developing Alzheimer's disease was much greater in people who had both elevated iron and high cholesterol than in those who had either raised factor alone (Mainous et al 2005). Likewise, in a set of 9252 US adults observed from 1980 to 1992, a significant increase in cardiovascular disease mortality occurred in people with both excess iron and elevated low density lipoprotein as compared with people who had an increase in only one of the two factors (Wells et al 2004). Similarly, rabbits with both hypercholesterolaemia and high iron had significantly more aortic atherosclerosis than rabbits with only one of the two factors increased above normal (Araujo et al 1995).

Thus, not surprisingly, in cholesterol-fed rabbits, desferrioxamine has been reported to inhibit significantly the development of atherosclerotic lesions (Minqin et al 2005). Moreover, deferiprone, as well, suppressed atherosclerotic progression in hypercholesterolaemic rabbits (Matthews et al 1997).

Drugs that require iron for an activity

Quinone antibiotics such as streptonigrin require iron to effect hydroxyl radical-mediated damage of bacterial cell membranes (Cohen et al 1987). Aminoglycoside antibiotics require iron not for antibacterial activity but rather for host toxicity (Forge & Schacht 2000). Hydroxyl radical catalysis by the 1:1 iron:aminoglycoside complex can result in damage to the proximal tubules of the kidney and the hair cells of the inner ear.

The sesquiterpene lactone artemisinin and its derivatives contain an endoperoxide that combines with iron to form cytotoxic carbon-based radicals that damage cell membranes (Meshnick et al 1996). The artemisinin compounds are highly selective against growing cells that are accumulating high levels of iron; for example, malarial protozoa (White 2005) and cancer cells (Efferth et al 2004; Singh & Lai 2004). Conjugation of artemisinin with human holotransferrin increases the selective toxicity of artemisinin for cancer cells (Lai et al 2005).

In some systems, an iron chelator drug might have a dual antineoplastic effect (Chaston et al 2004). Thus the compound could suppress proliferation by iron deprivation followed by stimulation of iron-mediated free radical generation by the drug–iron complex.

Such anthracyclines as doxorubicin have been used as antineoplastic drugs for several decades. However, their continued use in individual patients is limited by the cardiomyopathy that may develop because of the formation of free radicals by drug–iron complexes (Minotti et al 2004). Inasmuch as the antineoplastic action does not require iron, it is possible to suppress heart damage by administering an iron chelator shortly in advance of the drug.

A variety of iron chelators have been tested for this purpose. In iron loaded, but not in iron normal, mice, desferrioxamine showed activity (Hershko et al 1996). In rat cardiac myocytes, protection occurred with deferiprone (Barnabe et al 2002) but not with deferasirox (Hasinoff et al 2003). Protection from doxorubicin by chlorogenic acid also has been reported in this system (Chlopcikova et al 2004). In rabbits, protection from doxorubicin toxicity has been observed by use of pyridyl isonicotinoyl hydrazone (Simunek et al 2005b).

A piperazine, dexrazoxane, can be administered to cancer patients who have received up to $300\,\mathrm{mg\,m^{-2}}$ and who may benefit from additional treatment with doxorubicin (Minotti et al 2004). Apparently, dexrazoxane and other iron chelators are more active in lowering cardiotoxicity of anthracyclines than in suppressing the antineoplastic action of the drugs. Moreover, in in-vitro studies of human leukaemic myeloid cell lines, combinations of anthracyclines with dexrazoxane showed increased antineoplastic action (Pearlman et al 2003).

The antitumour drug bleomycin requires iron for production of hydroxyl- and possibly carbon-based radicals that cause DNA strand breaks (Dabrowiak 1980). However, use of the drug is limited by pulmonary toxicity. In a recent study, dexrazoxane was observed to reduce bleomycin toxicity without adversely altering the antitumour action of the drug (Wu et al 2004).

As noted earlier, the anthracycline-derived drug mitoxanthrone is approved for treatment of progressive multiple sclerosis. However, its prolonged use is limited because of cardiotoxicity. In a rat model of autoimmune

encephalomyelitis, dexrazoxane abstained from suppressing the therapeutic action of mitoxanthrone while additively enhancing curative activity (Weilbach et al 2004).

Perspectives

In addition to chelation, other methods for suppressing deleterious effects of misplaced iron are becoming available. Gallium, for example, is both microbicidal (Olakanmi et al 2002) and antineoplastic (Chitambar 2004). The metal shares chemical properties with iron and blocks cellular acquisition of the latter. Gallium nitrate is being developed for therapy of non-Hodgkin's lymphoma (Chitambar 2004).

Another method of inhibiting cellular acquisition of iron is that of raising endosomal pH value. This action prevents intracellular unloading of iron by transferrin. Drugs that might function by this mechanism include chloroquine and hydroxychloroquine (Savarino et al 2003). For many decades, chloroquine has been used to treat malarial patients who are infected with susceptible strains of the intracellular protozoan. With recent recognition that host cells need iron to synthesize viral pathogens, chloroquine and hydroxychloroquine are being examined for possible use in such diseases as HIV/AIDS and SARS (Savarino et al 2003).

Chloroquine and hydroxychloroquine are useful also in patients with such autoimmune conditions as rheumatoid arthritis, lupus erythematosus, and sarcoidosis. In mice, autoimmune encephalomyelitis was prevented by iron deficiency (Grant et al 2003). Cytokine pathways in Thl cells can be markedly dampened by such iron chelators as 2-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone and desferrioxamine (Leung et al 2005). Pathways in Th2 cells are much more resistant to iron chelation. The authors have suggested that "a deeper understanding of macrophage and T lymphocyte-specific pathways that are subject to iron regulation might lead to better and cell specific therapeutic targets".

Conclusions

Our iron withholding defence system can be compromised in numerous ways; a considerable array of diseases for which misplaced iron is a risk factor can ensue. Potential applications of pharmaceutical transferrin and lactoferrin now are becoming available. Present and future therapeutic niches for low molecular mass iron chelators are increasingly being recognized.

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