METALLOPORPHYRINS - APPLICATIONS AND CLINICAL SIGNIFICANCE

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ABSTRACT

The fascinating structures of naturally occurring porphyrins and metalloporphyrins have been perfected by nature to give functional dyes par excellence. The important roles these tetrapyrrolic macrocycles play in vital biological processes, in particular photosynthesis (chlorophyll), oxygen transport (hemoglobin), oxygen activation (cytochrome), have led to their characterization as 'pigments of life'. Because porphyrins possess extended π -electron systems and exhibit stability, they are finding use, to an increasing extent, in advanced materials, as components in organic metals, molecular wires, and other devices. In medicine, porphyrins are experiencing a renaissance due to the advent of photodynamic therapy of great promise in the treatment of cancer and dermatological diseases. The interdisciplinary interest porphyrins thus generate has provided the impetus to develop Novel- porphyrin like molecules anticipated to exhibit special properties, by structural variation of the tetrapyrrolic macrocycle, while maintaining a $(4n+2)\pi$ main conjugation pathway.

In addition to their esoteric application in science, porphyrins have been shown to have profound implications for therapeutic purposes. Their photosensitizing properties have led to their utilization in photodynamic therapy. Certain metalloporphyrins such as SnPP are being tested as drugs for the treatment of neonatal jaundice. Metalloporphyrins are serving as SOD mimetics to combat oxidative stress and a range of metalloporphyrin complexes have been proposed as contrast agents for magnetic resonance imaging

KEY WORDS Metalloporphyrin, Photodynamic Therapy, Photosensitization, Radiosensitizers.

INTRODUCTION

Porphyrins are macrocyclic tetra pyrroles of profound importance in biology. They are found at the heart of the oxygen carrying proteins such as hemoglobin and in variety of vital enzymes, especially those involved in biological oxidation and

reduction. Modified porphyrins power all green plants through their role as light harvesting and energy transfer centers for photosynthesis.

The parent structure of all porphyrins (Fig.1) consists of four pyrrole units linked by four methine bridges. Two of the four-ring nitrogen carry protons and there are eight positions at which substitution can occur with side groups; these are numbered 1-8 and are referred to as β -substituents. The porphyrin nucleus obeys Huckel's rule of aromaticity $[(4n+2)\pi$ electrons where $n=2$] and has been shown by x-ray crystallography to be planar.

In the uv-visible absorption spectrum the highly conjugated porphyrin macrocycle shows an

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intense absorption (extinction coefficient $>200,000$) at around 400nm (the Soret band), followed by several weaker absorptions (two bands) at higher wavelength 450-700nm

Fig. 1. Porphyrin

Variations of the peripheral substituents on the porphyrin ring often cause minor changes to the intensity and wavelength of these absorptions. Protonation of two of the inner nitrogen atoms or insertion of a metal into the porphyrin cavity also changes the visible absorption spectrum.

The porphyrin ring is very stable to concentrated acids such as sulphuric acid and it itself can act both as an acid and a base. Strong bases such as alkoxides can remove the two protons (pK_a-16) on the inner nitrogen atoms of a porphyrin nucleus to form a dianion.

On the other hand, the two free pyrrolidine nitrogen atoms (pK_b-9) can be protonated easily with acids such as trifluoroacetic acid (TFA).

Porphyrins have a strong ability to absorb visible light, which causes their intense colors. As porphyrins possess an extended π system and exhibit high stability, they are finding use, to an increasing extent, in advanced materials, as components in organic metals, molecular wires and other devices. Owing to their ready accessibility large molecular size and rigid planar geometry as well as their electronic properties and their ability to complex almost any kind of metal ions, porphyrins

are irreplaceable building blocks, for the synthesis of both straight chain and branched extended molecular systems, designed to perform a great variety of functions. These include enzyme mimetic catalysis, optical switches, molecular photonic wires, molecular opto-electronic gates and light harvesting arrays.

Procedures for the synthesis and functionalization of monomeric porphyrin molecules have advanced to the stage that almost any porphyrin can be obtained using available methodology. Many research groups have now moved to the development of the synthesis of porphyrin analogues and to the construction of multiporphyrin arrays which can mimic the vital functions of photosynthetic reaction centers and antenna systems. In order to develop new functions and properties of porphyrins, variously substituted porphyrins have been extensively studied, for example, electron withdrawing groups, electron donating groups and sterically hindered groups have been introduced into the porphyrin periphery to control the redox, spectroscopic and catalytic properties of metalloporphyrins. However, porphyrin rings are flexible enough to adopt various distorted conformations such as saddle, wave, ruffle and dome conformations depending on the size of periphery substituents and the central metal. Furthermore, π -stacking of porphyrin rings also affects their conformations and electronic properties.

Porphyrin arrays are potential precursors in building electron and energy-transfer molecular devices; they are also robust and efficient catalysts for the multielectron redox transformations of small molecules and for the oxidation of organic substrates. For all of the uses mentioned above, it is important that the individual molecules within an array communicate with each other, otherwise the whole will be no better than the sum of the components and the array cannot behave with enhanced effectiveness. For effective electronic communication between adjacent porphyrins, the geometry, distance, and orientation between components of rigid porphyrin arrays are usually to be considered, though, in the area of molecular recognition, such rigidity is not essential. The nature

of the bridges between porphyrin components, the extent of steric interactions (if any), and the connectivity of the porphyrin components directly affect the photophysical properties of covalently linked systems.

More recently attention has been focused on specific biomedical applications of pyrrolic based macrocycles as a result of their physical properties. One such field is photodynamic therapy (PDT) a new modality for the treatment of diseased tissue, wherein a combination of visible light and a photosensitizing drug are used to bring about a therapeutic response. The efficacy of such photosensitizers depends among other factors on the absorption of light at wavelengths greater than 630nm, since at these wavelengths the natural chromophores in human tissue and blood become relatively transparent, thereby allowing a greater depth of light penetration.

Certain porphyrins e.g., hematoporphyrin derivative [HpD] and its clinical relative Photofrin, were found to concentrate in malignant tissue to a greater extent than in normal tissue. However, such porphyrins have weak absorptions in the desired red region of the visible spectrum. Fortunately, modification of the porphyrin periphery for e.g., as in bacteriochlorin and chlorin-like systems, or increasing the degree of conjugation, results in a bathochromic shift in wavelength of the desired Q band, farther into the red region of the electromagnetic spectrum. Consequently, this and the need for infrared absorbing chromophores in area such as digital data storage has stimulated research toward the synthesis of what are now generically termed the expanded porphyrins. These compounds have similar physical properties to their porphyrin congeners, but contain an increased number of π -electrons, additional co-ordinating heteroatoms, and/or central binding core.

In addition, the introduction of other co-ordinating atoms and heterocycles other than pyrrole yields new classes of molecules containing novel chelating properties. For e.g. they may exhibit an affinity for binding larger metal cations such as lanthanides and actinides, and have ability to

stabilize a range of unusual oxidation states and/or co-ordination geometries. This can be especially important with ligands which can form stable 1:1 adducts with highly paramagnetic gadolinium (III) cations in aqueous medium.

Such complexes have significant potential as contrast agents in magnetic resonance imaging (MRI), another rapidly developing biomedical diagnostic technique. Here, the contrast agent, which ideally should show a greater affinity for the tissue under investigation due, to its paramagnetism, will decrease the relaxation times of the nearby nuclei, usually the water protons, thereby enhancing the difference between normal and abnormal tissue.

Another biomedical application of metalloporphyrins is in the treatment of hyperbilirubinemia, a common problem, affecting 45-60 percent of term infants and up to 80 percent of premature neonates. Phototherapy, the standard treatment for neonatal hyperbilirubinemia, is effective but has the potential for adverse effects. Prevention of bilirubin formation, rather than dependence on therapeutic measures to remove excess bile pigment, is a logical alternative. Metalloporphyrins- specifically tin- protoporphyrin (SnPP) and tin mesoporphyrin (SnMP)- are being used experimentally to prevent and treat neonatal hyperbilirubinemia.

It is well known that reactive oxygen (ROS) species are implicated in a number of pathological processes including tissue injury, inflammatory disorders, cardiovascular, pulmonary and neurodegenerative diseases. Catalytic antioxidant superoxide dismutase (SOD) and catalases are metalloproteins that employ dismutation reaction which detoxify ROS. Several metalloporphyrin such as tetrakis- (N-ethyl-2-pyridyl) porphyrin (MnTE-2-pyridyl porphyrin) and tetrakis-(-4-benzoic acid) porphyrin (MnTBAP) can substitute for these native antioxidant enzymes by facilitating the aerobic growth and preventing nutritional auxotropies and paraquat hypersensitivity of null SOD E.coli. In this the postulated role of ROS, as common context mediators of tissue damage in diseases of diverse etiologies, emphasizes the wide range of possible therapeutic applications of metalloporphyrin.

CLINICAL SIGNIFICANCE

PHOTODYNAMIC THERAPY

Photosensitizers

Light can interact with biological systems and thereby cause both beneficial and undesirable effects. Examples of the first are processes like vision, photosynthesis, photomorphogenesis and photomovement, which are essential for life on this planet. In all these examples light is absorbed by highly specialised pigments. The interaction can also cause damage to biological systems; this can be undesirable e.g. when it leads to mutagenesis or carcinogenesis, but it is also used in several therapies. Damage can be brought about by two different pathways (1).

Pathway 1: Biological molecules like proteins and nucleic acids absorb light themselves and as a result are chemically changed.

Pathway 2: certain molecules absorb light, so-called photosensitizers' (PS) that can transfer the absorbed light energy to other molecules (substrates or targets). The targets are chemically altered in the process.

A pre-requisite for a dye to be a sensitizer is that the molecule can undergo intersystem crossing from the initially excited singlet state to the triplet state. The sensitizer undergoes two main types of reactions;

Type-1 Pathway- The sensitizer in the Triplet State can either transfer electrons to an acceptor or accept electrons itself from a suitable substrate.

Type-2 Pathway- The sensitizer can transfer its energy to other molecules like ground state oxygen, thus reactive singlet oxygen is formed, which can oxidize most biological molecules (Fig.2)

Certain common properties are;

The ability to efficiently absorb photons (a high extinction co-efficient).

- 1) A high triplet quantum yield and
- 2) A long triplet lifetime, which markedly increases the probability to interact with other molecules.
- 3) A good type-1 sensitizer can, in the Triplet State, easily donate or accept electrons and a good type-2 sensitizer has a high singlet oxygen yield.

Fig. 2. Physio-chemical processes underlying biomolecular lesions induced by photosensitization

METALLOPORPHYRINS AS PHOTSENSITIZERS

Therapeutic uses of photosensitizers

PDT of cancer

Perhaps the most well known application of photodynamic sensitizers today is their use in the treatment of cancer. Porphyrins and Porphyrin like compounds are sensitizers with the most suitable properties for this purpose. Irrespective of the mode of administration, i.v, i.p, and thereafter they appear to be present in tumours at a higher concentrations than in the surrounding tissues (2).

Fig. 3. Hematoporphyrin Derivative

Porphyrin	$R_3 = R_5$	R
HP	CHOHCH ₃	H
DP	H	H
HPDME	CHOHCH ₃	CH ₃
DPDME	H	CH ₃

PDT using haematoporphyrin derivative

During last 15 years, thousands of patients suffering from various kinds of tumors have been treated worldwide with PDT using haematoporphyrin (HPd) derivative (Fig. 3) which is retained to a greater extent in the neoplastic tissues (3) and produces cytotoxicity upon photoirradiation with light of appropriate wavelength.

HPd has 5 absorption peaks in the visible region with a major absorption band around

400nm(Soret band). However, due to higher penetration in tissues, red light (620-630nm) is usually used in clinical work, although the light absorption of Hpd in this region is small. Advances in laser coupled with fibre-optic light delivery systems have made photo-irradiation of even deep-seated tumors possible. HPd-PDT has provided encouraging results in-patients suffering from various types of tumor particularly in the lung, breast, bladder, skin and eye (4,5). Dougherty (4) have shown that a mixture of porphyrins, known as haematoporphyrin derivative(HPd) can be used for the detection and treatment of a number of tumors. HRd is a complex mixture of several porphyrins including hematoporphyrin (HP), hydroxy ethyl vinyl-deutroporphyrin(HUD), protoporphyrin(PP), and a hydrophobic factor which is supposed to be responsible for tumor localisation and photosensitization in vivo (6).

The hydrophobic fraction, isolated and purified to certain extent, and marketed under the commercial name Photofrin (II). PF(II) has been shown to contain haematoporphyrin ether or ester linked porphyrin units, whose degree of polymerization may range from 2(DHE) to 6-oligomers (7).

It is generally accepted that the mode of action of porphyrins as photosensitizers involves the formation of porphyrin triplet states, which react by any one of the two pathways.

New generation of PDT-photosensitizers the Phthalocyanines (Fig. 4) possess strong absorption intensity in the red region of the electromagnetic spectrum (where the light penetration in the bio-tissues is greater). Photofrin -2(di-hematoporphyrin ether or ester) acts both through Type-1 and Type-2 photoreactions. Probably the predominance of one of these two photoreaction pathway depends on the local photosensitizer environment as medium polarity, microheterogeneity, etc.(8,9).

Palladium (II)-corprotoporphyrin I is a good PS for singlet oxygen generation. The complex has been used as a photoactivable group in sequence-specific modifications of nucleic acids in oligonucleotides(10).Meso-Tetraphenylporphyrin (TPP)-substituted with hydroxyphenyl groups have

also been prepared, and in particular, a chlorin analogue showed good photodynamic activity and is currently in clinical PDT trials.

Fig. 4. Phthalocyanine

Platinum(II) complexes of TPP like the diamine dicarboxylato-Pt(II) complexes showed the highest antitumor activity, reflecting the combined effect of the cytotoxicity of the Pt complex and the photodynamic activity of the porphyrin moiety.

Expanded metalloporphyrin and expanded porphyrins have similar physical properties to their porphyrin congeners, but contain an increased number of π electrons, additional coordinating heteroatoms and/or a larger central binding core. Scientists have designed and synthesized a ring shaped, planar, expanded porphyrin molecule called Texaphyrin. It may be envisaged as a 22π benannulene with both 18π and 22π electron delocalization pathways (11). The photophysical properties of metalotexaphyrins ($M = \text{Zn, Cd, Mn, Sm, Eu}$) parallel to those of the corresponding metalloporphyrins. The diamagnetic texaphyrin Zn and Cd complexes show strong red-shifted optical absorptions in the 730-770 nm range, as well as high triplet quantum yield, and act as efficient PS for the production of singlet oxygen ($\phi > 0.6$). Thus in particular, the diamagnetic texaphyrin complexes are highly efficient photosensitizers for singlet oxygen production of interest for PDT applications. Compound in its bis-acetate are being evaluated in a phase I clinical study for PDT of pigmented melanoma, breast cancer, AIDS-related Kaposi's sarcoma, and basal cell carcinoma (2).

Phthalocyanines (Pc), the first biomedical application of Pc relates to the 3 experimental murine brain tumors. With recent development of clinical PDT, Pc was advanced as second-generation PS for PDT and an extensive literature on their biological properties as photodynamic drugs evolved.

PORPHYRINS AND NEONATAL JAUNDICE

Hyperbilirubinemia is common in neonates and a significant number of infants require clinical intervention for this condition because bilirubin is potentially neurotoxic (12). At present an effective clinical management of neonatal hyperbilirubinemia is limited to phototherapy and to exchange transfusion. Both the treatment modalities are associated with possible side effects, and in the case of exchange transfusion, there is a significant rate of mortality. Furthermore these therapies are designed to remove preformed bilirubin at a time when blood levels of this toxic bile pigment are either already at high levels or increasing rapidly in new infants. An alternate methods of treatment, which is designed to diminish the production of bilirubin rather than to dispose of the bile pigment after its formation and tissue distribution, has been proposed using the heme oxygenase inhibitor, SnPP. SnPP, because of its ability to bind more actively to the heme binding site of heme oxygenase, then to heme itself, inhibits heme degradation and often the production of bilirubin and there by suppresses hyperbilirubinemia, thus offering a new and potentially useful therapy for the clinical management of the hyperbilirubinemia in the new born (13,14). This action of metalloporphyrin has been confirmed in non human primate including the rhesus neonate (15). CrPP, also has the capacity to suppress hyperbilirubinemia in rat neonate (16,17). SnPP is also a photosensitizer that could cause serious and unknown side effects when administered to newborn. The findings demonstrate that halogenation of a suitable porphyrin macrocycle can substantially diminish photoactive properties of the compound where as retaining its ability to act as a heme oxygenase inhibitor.

Incorporation of heme-oxygenase inhibitor into phosphatidylcholine liposomes markedly

enhanced localization of these agents with in a spleen. These studies suggest that heme-oxygenase inhibitors administered within liposomes may so effectively block bilirubin production in the human new born that ancillary methods for treatment. Among nine metal-protoporphyrin chelates (i.e. metal –hemes) studied, Sn-heme, Mn-heme and Zn-heme substantially diminished heme-oxygenase activity in vivo in the rat. These metalloporphyrins act as competitive inhibitors of hemeoxygenase but are themselves not oxidatively degraded (18-21). This demonstrates that a synthetic metalloporphyrin, when administered to the new born, also prevent the hyperbilirubinemia that occurs post natally (22).

A range of investigations have been carried out in our laboratory utilizing metalloporphyrins. In one particular study an attempt was made to examine the hepatic, splenic and renal HMOX activity in response to gossypol and gossypol in conjunction with ZnPP. High levels of HMOX activity were detected in the liver & kidney of male wistar rats on gossypol administration (50µmol/Kg bw), whereas gossypol & ZnPP treatment effectively blocked the gossypol induced HMOX activity and substantially suppressed the elevated serum bilirubin levels. The findings underscored the toxic effect of gossypol in eliciting increased heme degradation by stimulating HMOX activity in the liver & kidney and the potential usefulness of ZnPP in

experimental and perhaps clinical conditions in which hyperbilirubinemia occurs (23,24). In another investigation the features of the combined action of retinoic acid & tin metalloporphyrin in vivo led to a substantial suppression of bilirubin formation and many chemicals can attest the enhancement. The effect of Cr(III) & Mn(II) complexes of macrocyclic ligand derived from carbohydrazide, thiocarbohydrazide & 5-furandihydrazide and 2,6 diacetyl pyridine, on heme metabolism and biosynthesis along with mitochondrial membrane stability were studied in wistar rats, defined novel properties of these synthetic heme analogues.

The results of these studies (25) have defined novel properties of these synthetic heme analogues which make the examination of the biological properties of such compounds on heme metabolism of considerable biochemical and clinical interest. The physiochemical characteristics of individual metal chelates are unique and, thus, influence the action of metal complexes in vivo. However, other factors also influence the metal complexes in vivo action: the biological variables related to pharmacokinetics, tissue distribution, dispositions, and subcellular localization of these compounds.

In the heme metabolic pathway, heme is converted to biliverdin, which is then reduced by the cytoplasmic enzyme biliverdin reductase in the

Table 1. Macrocyclic Ligands and their metal Complexes.

Name/Symbol	Formula
Ligands	
2,5 Furandihydrazide	FaHh
2,6 Diacetylpyridine-bis-(carbohydrazide)	DAPCh ₂
2,6 diacetylpyridine-bis-(thiocarbohydrazide)	DAPTh ₂
Cr(III) and Mn(II) Complexes of FaHh	
Cr ₁	[Cr(FaHh-DAP)Cl ₃
Mn ₁	[Mn(FaHh-DAP)Cl ₂
Mn ₄	[Mn(FaHh-DAP)(OAc) ₂]
Cr(III) and Mn(II) Complexes of DAPCh₂	
Cr ₂	[Cr(DAP-Ch ₂ -DAP.H ₂ O)]Cl ₃
Mn ₂	[Mn(DAP-Ch ₂ -DAP.H ₂ O)]Cl ₂
Mn ₅	[Mn(DAP-Ch ₂ -DAP.H ₂ O)](OAc) ₂
Cr(III) and Mn(II) Complexes of DAPTh₂	
Cr ₃	[Cr(DAP-Th ₂ -DAP.H ₂ O)]Cl ₃
Mn ₃	[Mn(DAP-Th ₂ -DAP.H ₂ O)]Cl ₂
Mn ₆	[Mn(DAP-Th ₂ -DAP.H ₂ O)](OAc) ₂

presence of NADPH to bilirubin. In the liver, bilirubin is conjugated with glucuronic acid to form bilirubin diglucuronide, which is water-soluble and is readily excreted by means of the bile into the intestines. Administration of organic macrocyclic ligands (Table1) (1 mmol/Kg body wt) to rats decreased biliverdin reductase activity in the order $\text{DAPTh}_2 > \text{FaHh} > \text{DAPCh}_2$. Administration of these ligands also decreased the biliverdin reductase activity in the order $\text{Mn}_2 > \text{Cr}_2 > \text{Mn}_5 > \text{Mn}_3$. However, other metal complexes induced the activity of the enzyme in the order $\text{Mn}_4 > \text{Cr}_1 > \text{Mn}_1 > \text{Mn}_6 > \text{Cr}_3$. In view of the above, the metal complexes (Cr_2 , Mn_2 , Mn_3 , Mn_5) which decreases biliverdin reductase activity can be used as antihyperbilirubinemic agents (25).

Metalloporphyrin class of therapeutic catalytic antioxidants

Aerobic organisms generate reactive oxygen species (ROS) by partial reduction of molecular oxygen yielding superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH). The bulk of cellular O_2^- is formed endogenously in the mitochondria during respiration (26). O_2^- is formed in the endoplasmic reticulum by cytochrome P450 (27) and in the cytoplasm by enzymes such as xanthine oxidase (28). The plasma membrane of many cell types can also produce O_2^- by the activation of enzymes such as phospholipase A_2 and NADPH oxidases. H_2O_2 is formed wherever O_2^- is generated by its rapid spontaneous conversion to H_2O_2 . It is also formed enzymatically as a by-product of lipid metabolism in peroxisomes. O_2^- can oxidize some iron-sulphur (Fe-S) proteins, such as aconitase, and release free iron. It can also reduce transitional metals such as iron or copper that can readily react with H_2O_2 to generate the very reactive OH. In the metal catalysed Haber-Weiss reaction ROS are implicated in a number of pathological processes including tissue injury (29), inflammatory disorders, cardiovascular disease, pulmonary disease and neurodegenerative diseases. Catalytic antioxidants SOD and catalase are metalloproteins that employ efficient dismutation reactions in their mechanisms to detoxify ROS. A dismutation reaction involves a series of one- or two-electron transfer where the electrons are accepted from one O_2^- or H_2O_2 and then donated to another. These efficient

reactions do not require reducing equivalents and thus do not require energy from the cell to operate. The overexpression of these enzymes in cell culture and in whole animals has provided protection against the deleterious effects of a wide range of oxidative stress paradigms. The use of superoxide dismutase (SOD) and catalase as therapeutic agents to attenuate ROS-induced injury responses have had mixed success (30). The main limitation of these natural products are their large size, which limits cell permeability, short circulating half-life, antigenicity and expense. An increasing number of low molecular weight SOD mimetics have been developed to overcome some limitations.

Development of SOD mimetics

Most catalytic SOD mimetics are designed with a redox-active metal centre that catalyses the dismutation reaction with O_2^- in a manner similar to the active site metals of the mammalian (Cu or Mn) SOD. An ideal SOD mimetic should be stable, with high specificity for interaction with O_2^- and with a high specificity for interaction with O_2^- and with a high rate constant. It should also be non-toxic, much like the native SODs. Additionally, their size and charge can be exploited for targeting crucial cellular sites of oxidative stress.

Simple metal chelates could react with O_2^- . These include Mn-desferal, copper complexes of amino acids or anti-inflammatory drugs like indomethacin, salicylates, manganese complexes of lactate, citrate or succinate, manganese complexes of lactate and citrate of metal-containing SOD mimetics. These include the salen, macrocyclic and metalloporphyrin SOD mimetics (31).

SOD-null Escherichia coli

Mutant *E.coli* lacking MnSOD (sodA) or FeSOD (sodB), or both provide a simple and elegant model exploring the function of synthetic SODs. The sodA-sodB-null strain of *E.coli* is indistinguishable from its SOD competent parental strain under anaerobic condition it shows oxygen-dependent nutritional auxotrophies, retarded growth, hypersensitivity to O_2^- generating agents (such as Paraquat) and increased mutagenesis.

Fig. 5. The structure of manganese meso-porphyrins commonly used as superoxide dismutase (SOD) mimics that include tetrakis-(4-benzoic acid) porphyrin(TBAP), tetrakis-(N-methyl-4-pyridyl)porphyrin(TM-4-PyP), b-octabromo-tetrakis-(N-methyl-4-pyridyl)porphyrin(OBTM-4-PyP) and Tetrakis-(N-methyl-2-pyridyl)porphyrin(TM-2-PyP). The manganese moiety of the SOD mimetics functions in the dismutation reaction with O₂ by changing its valence between Mn (III) and Mn (II).

The O₂⁻ dependent auxotrophes in sodAsodB-null *E.coli* are thought to be due, in part, to O₂⁻ mediated inactivation of Fe-S enzymes such as aconitase, whereas increased mutagenesis probably reflects oxidative DNA damage. These deficits can be overcome by complementation of functional SOD genes. Several metalloporphyrins such as tetrakis-(N-ethyl-2-pyridyl)porphyrin (MnTE-2-PyP) and tetrakis-(4-benzoic acid) porphyrin (MnTBAP) (Fig. 5) can substitute for these native antioxidant enzymes by facilitating the aerobic growth and preventing nutritional auxotrophies and paraquat hypersensitivity of sodAsodB-null *E.coli* (31).

MAGNETIC RESONANCE IMAGING CONTRAST AGENTS

Magnetic Resonance Imaging involves the variable absorption of a radiofrequency pulse by the body when placed in a magnetic field. This technology has become a leading diagnostic imaging method for numerous medical conditions, enabling greater accuracy and safety than

conventional X-ray and computerized tomography (CT) techniques. The contrast media are often used during X-ray and CT procedures to enhance the image quality. Its basic principle involves, when protons (tissue protons) are placed in a magnetic field, they become capable of receiving and then transmitting electromagnetic energy.

The strength of the transmitted energy is proportional to the number of protons in the tissue. Properties of each proton's microenvironment, such as its mobility and the local homogeneity of the magnetic field modify signal strength.

MRI contrast agents require the use of certain metals that can affect radiofrequency pulses. The ability of the bound metal ion to interact freely with adjacent molecules, in particular water molecules, is an important parameter in effectuating contrast enhancement and forms the basis for the MRI contrast agents. Currently the contrast agents fall into two categories: paramagnetic materials, which have diagnostic properties similar to iodinated radiographic

contrast agents, and even more potent supramagnetic materials, which have a wide area of effect (32).

METALLOPORPHYRINS AS CONTRAST AGENTS

A variety of metalloporphyrin complexes have been proposed as tumor enhancing contrast agents for MRI. Mn (III) is an interesting metal ion for medical application due to its good contrast enhancing properties for MRI. Synthetic tetraarylporphyrins incorporate the Mn ions tightly; they are not readily metabolized and therefore ideal for MRI. A visual contrast required at least 1g/g of manganese in selected tissues. To achieve this, the use of an oligopeptide carrier, such as polylysine, which is capable of chelating 100-200 metalloporphyrin molecules, has been suggested. To date, one of the most extensively studied agent is the Mn (III) complex of sulfonated tetraphenyl porphyrins (32,2).

EXPANDED METALLOPORPHYRINS AS CONTRAST AGENTS

Scientists have designed and synthesized ring shaped, planar, expanded porphyrin molecule called texaphyrins, to perform specific functions in a number of medical applications. Texaphyrins accumulate in those areas of the body where substantial energy usage or metabolism occurs, such as in cancer cells and the tissues of atherosclerotic plaque. This selectivity for particular cell type provides the basis for the scientist's treatment approaches for certain cancers and atherosclerotic cardiovascular diseases. Texaphyrin have the ability to bind large metal ions. In contrast to naturally occurring porphyrins, texaphyrins have a larger (Texas=sized) central binding ring, which makes possible incorporation of a variety of lanthanide metals such as gadolinium, lutetium, europium and dysprosium. The binding of metal ions by Texaphyrin is unique in that the metal is held near or within the plane of the molecule. This allows the metal to interact freely with adjacent molecules while still being retained within the texaphyrin structure.

Since gadolinium (III) is used as a contrast - enhancing metal ion for MRI, it was anticipated that Gd (III)texaphyrins also could function as MRI

contrast agents (32). Administration of the Gd-Tex²⁺ complex (40umol/Kg) to SMT-M tumour- bearing Balb/c mice indeed revealed contrast enhancement of the tumour (94% at 10min to 7%at 24h p.i). Gadolinium (Gd) DTPA, diethylenetriamine pentaacetate) appear safer than iodinated contrast media.

RADIOLABELLED PHTHALOCYANINES AS IMAGING AGENTS

Like porphyrins, selected phthalocyanines derivatives exhibit tumor retention in animal models, which led to their evaluation as carrier of clinically accepted radioisotopes. Therefore, a series of mono-, di-, and tetra-DTPA- substituted znpc derivatives were prepared and complexed with in these negatively charged complexes revealed significant liver and spleen retention in an animal model, but uptake was marginal.

METALLOPORPHYRINS AS RADIOSENSITIZERS

Radiotherapy is an important curative and palliative modality in the treatment of cancer. Radiosensitizer is an agent that increases the sensitivity of cells to radiation. Serious thoughts on the use of radiosensitizers in tumour therapy were initiated with the observation of Bridges that N-ethyl maleimide (NEM) sensitized bacterial cells under hypoxia as well as euoxia and that its radiosensitizing effect could be ascribed to its reactivity with radioprotective intracellular sulfhydryls. A true sensitizer should significantly increase cell killing if present during irradiation but should be completely non toxic when acting alone.

To be of sufficient therapeutic interest for the treatment of tumours, a sensitizer should enhance the radiation response of the tumour without reducing the tolerance of the relevant normal tissues and without causing any toxicity to other tissue.

Several conflicting reports on the radio-sensitizing activities of porohyrins have appeared, and a clear understanding of structural features that could explain such does not exist. Both cationic and anionic metalloporphyrins do, however, exhibit radiosensitizing activity. A series of complexes featuring

various metal ions, i.e., Co(III), Zn(II), Fe(III), Cu(II), Pd(II), Rh(III), Sn(IV), or Mn(III), were tested at 100 μ M concentration against V79 cells. This included the following cationic ligands tetrakis(4-N-methylpyridyl)porphyrin(TMPyP), tetrakis(4-N-trimethylaminophenyl)porphyrin (TMAP), tetrakis(4-N-butylpyridyl)porphyrin(TMPyP) and tetrakis(3-N-methylpyridyl)porphyrin(3-TMPyP) and anionic ligands tetrakis(4-sulfonatophenyl) porphyrin(TPPS), tetrakis(4-carboxyphenyl)porphyrin(TCPP), and tetrakis(bi-phenyl)porphyrin sulfonate(TBPS). The largest increase in radiation-induced cell kill was observed with (M = Co) with sensitize enhancement ratios(SER) of 2.4. The overall charge on the molecule did not correlate to the biological activities. The introduction of a nitro and positively charged groups on the porphyrin moiety was expected to further increase the radiosensitization activities. The cationic Co(II) complexes showed highest SER values although none of the complexes showed SER > 1.2. The well known radiosensitizing effect of nitroimidazole prompted the evaluation of covalently linked nitroimidazole-metalloporphyrins. At 1.5 μ M concentration, this complex gave SER of 1.39 in cell culture, while in vivo assays in EMT-6 tumor-bearing Balb/c mice showed substantially improved tumor response to radiotherapy (2).

EXPANDED METALLOPORPHYRINS AS RADIOSENSITIZER

Texaphyrins are large planar porphyrin like macrocycles capable of co-ordinating a range of relatively large cations, including Gd (III) and other members of the trivalent lanthanide series. Complexes Gd - Tex²⁺ were tested in vitro against L1210 and HT 29 cell line at 10⁻⁵- 10⁻³. Both preparations are effective

with complex featuring a SER = 1.92 against the HT 29 cell line. In vivo treatment at a dose of 40 mmol/Kg (i.v.) prior to a single radiation dose of 30-Gy induced a significant growth delay of SMT-F tumors in DMA/ 2N mice(2,32).

OTHER APPLICATIONS OF PORPHYRINS MOLECULAR PHOTONIC WIRE

A wire is a device that conveys a signal or permits the flow of energy. As such, in addition to its transmission capabilities, a wire must include provisions for connection to an input device on one end and an output device on the other (33). The increasing interest in molecular scale devices has focused attention on the synthesis of molecular wires. The wires have been envisaged as carriers of electrons (or holes). With molecular electronic wires the 'connection problem' of attaching macroscopic input and output devices remains a major challenge. The light harvesting complexes in photosynthesis inspires our approach to molecular wires, which comprise hundreds of pigments in a solid state array. The excited state resulting from light absorption by one pigment migrates among the array of pigments, ultimately reaching a reaction Center. It was felt that an appropriate synthetic array of pigments could function as a molecular photonic wire. A molecular photonic wire is distinguished from a molecular electronic wire by supporting excited state energy transfer rather than electron (-or hole) transfer processes. The use of light to produce the excited state, as occurs in photosynthesis, provides a natural means of inputting a signal to a molecular wire. A fluorescent dye can be used to output an optical signal. The design of molecular photonic wires has much in common with the design of synthetic light harvesting system (Fig. 6).

Fig. 6. Molecular photonic wire

PORPHYRIN LIGHT-HARVESTING ARRAYS

Photosynthetic organisms employ light harvesting complexes to capture dilute sunlight and funnel energy to the reaction centers. Light-harvesting complexes are remarkable in achieving efficient energy migration among hundreds of pigments with avoidance of non-energy transfer quenching processes. Understanding light harvesting phenomena at the molecular level is a major objective of photosynthesis research and might also provide the foundation for the design of synthetic molecular devices. Synthetic porphyrin-based light harvesting arrays are essential for probing the effects of molecular organization on energy migration processes. Covalent arrays of five or more porphyrins have been prepared, but the combination of desired attributes in a light-harvesting model system, i.e. architectural rigidity, organic solubility, and incorporation of numerous porphyrins in controlled metallation states, including metalloporphyrins and free base porphyrins, has therefore not been met. The scientists reported a convergent strategy for preparing rigid, soluble arrays of covalently-linked porphyrins in various metallation states.

The strategy employed was to use readily available tetraaryl porphyrins as modular building

blocks. The porphyrins bore peripheral iodo or ethynyl groups and were facially encumbered to suppress aggregation. The free base or metalloporphyrins were then joined via homogeneous Pd-mediated coupling reactions under basic conditions to yield the desired assembly (34). This building block approach would provide an ideal pathway to larger arrays resembling those found in the natural photosynthetic system.

Photoresponsive Silicon Radical Within a Porphyrin π Cloud

Photochemical properties of porphyrin complexes have attracted continuing attention not only in connection with biological photosynthetic reactions, but also with the molecular design of other photo-responsive devices. Although extensive studies have been made on photoexcited metalloporphyrins with a variety of transition and nontransition metals (35), the photochemical behaviour of porphyrin complexes of non-metal elements are much less explored to date. Silicon porphyrin is a representative of non-metal porphyrin complexes, which accommodates a hexa coordinate silicon atom (Fig. 7). Very recently the scientists Aida et al. succeeded in the synthesis of a series of organosilicon porphyrins and have found by crystallographic studies that their two axial ligands are in a trans configuration to each other.

Fig. 7

Although the porphyrin rings in silicon porphyrins are highly non-planar, when the axial ligands are of electron -withdrawing character such as fluoride and triflate, these organosilicon porphyrins have a strong tendency to adopt a planar conformation for the porphyrin ring, indicating an electronic interaction between the axial ligands and the porphyrin ring via the central silicon atom. In the course of this study, it was noticed that some organosilicon compounds were labile under illumination with room light, prompting them to investigate the photochemical properties of organosilicon porphyrins. In a continuation of the above study, by the same group of scientists, photochemical reactions was carried on a series of organosilicon porphyrins with radical scavengers, such as nitroxy compounds which highlight the formation of a long -lived silicon diradical with a unique photoswitchable reactivity. Silylenes, including silicon diradicals with unpaired electrons have attracted considerable attention, not only from a fundamental interest in relation to carbenes, but also as new potential intermediates in organic synthesis and materials science. The new study demonstrated that dialkylsilicon porphyrins, upon excitation of the porphyrin ring with visible light, undergo homolytic cleavage of the axial Si-C bonds to generate a highly stable silicon diradical at the ground state, which can be activated by visible light, to react with nitroxy compounds. Furthermore it was shown that the axial Si-O bonds in the resulting dinitroxysilicon porphyrins are cleaved homolytically, to afford free radicals upon irradiation with visible light. These results indicated an interesting possibility that the silicon diradical within a porphyrin π cloud serves as a photoswitchable radical, whose reactivity can be controlled by visible light. Studies on reactivities of dialkyl and dinitroxysilicon porphyrins with unsaturated compounds may thus be a worthy area of further study.

POLYPORPHYRIN THIN FILMS

In pursuit of an appropriate material for studying the properties of porphyrins such as their catalytic activity, a film of function specific porphyrin is usually deposited or adsorbed on a support. Porphyrins have been incorporated into polymers as pendant groups, in the backbone of networks

(36) and linear polymers and as coordination polymers. Thin films for catalysis studies have been prepared on electrodes by electropolymerization (37,38). Free-floating films, synthesized by interfacial condensation, can be supported on polymer membranes. Wen et. al. (1997) reported the synthesis of free -standing films of porphyrin homopolymer, for the first time, using disulfide bridges to cross-link monomers into a three-dimensional network. The highly efficient polymerization is carried out at the liquid-liquid interface by oxidation of p-mercapto-porphyrins. Drying of films with supercritical carbon dioxide yields flexible material with thickness in the range 10-10000 nm. Polymers are made by interfacial polymerization between a chloroform solution of the appropriate p-mercapto porphyrins and a layer of aqueous oxidant, such as copper acetate.

The highly absorbing, shiny, purple polymer films are amorphous and retain their ability to be metalated, a valuable property for select catalytic applications. Such polyporphyrin films have been employed in the photosensitized oxidation of a cyclic thioether(Fig.8).

FULLERENE -PORPHYRIN COMPLEXES

The unique photophysical properties of C_{60} have generated significant research focused on its use as the acceptor in covalently bound donor-acceptor pairs. In particular, photophysical properties of porphyrin -linked C_{60} hybrids have received considerable attention (39). It has been shown that intramolecular electron transfer from the porphyrin to C_{60} to generate ion pairs occurs extremely rapidly with zinc porphyrins and with free base dyads in polar solvents; in non-polar solvents, efficient formation of $C_{60}^{\cdot-}$ was seen. The extent of such interactions in the ground state has been attributed to the rigid conformation enforced by the linker (40). Baran et al (1997) reported the efficient synthesis as well as computational and photophysical studies of two novel classes of porphyrin- C_{60} hybrids. These hybrids (i.e. dyads) are unique in that (i) their synthesis utilizes a convergent strategy, providing access to a rich array of new structures, including the first aza-linked porphyrin-fullerene hybrid (ii)

Fig. 8

despite the fact that the porphyrin moiety is not rigidly connected to C₆₀, electronic interactions still occur in the ground state, and (iii) cations induce formation of a complex with open-chain crown-ether mimics, in which there is a dynamic equilibrium between complexed and uncomplexed states. In the complexed state, the two chromophores are brought together, significantly increasing intramolecular interactions. These scientists developed new synthetic methodology which could be efficaciously exploited in the construction of structurally unique conformationally flexible porphyrin- fullerene hybrids in which intramolecular interactions are enhanced as a result of complexation with metal cations (41).

PEROXY FERRIC PORPHYRIN COMPLEXES

Peroxy ferric heme complexes, generated by one-electron reduction of oxy heme intermediates analogous to oxy myoglobin, are implicated as key intermediates in oxidation reactions catalyzed by the cytochrome P450 family of enzymes. However,

the details of the reaction mechanisms occurring after formation of these peroxy ferric heme intermediates are not known well. In fact, three distinctly different modes of reaction of this intermediate have been postulated to account for the type of reactivity observed for different enzymes. Assuming that these three modes of reaction of the peroxy ferric heme intermediate do all occur in the different cytochrome P-450 type enzymes, it is of considerable interest to elucidate the factors that determine which mode will be dominant in each oxidative process. The scientists had studied the analogs of the peroxy ferric heme intermediate. These complexes are prepared by oxidative addition of superoxide to synthetic ferrous porphyrin complexes to form high spin ferric porphyrin peroxo complexes. The reactivity of these ferric porphyrin peroxo complexes is of great interest in the ongoing attempts to mimic the three different modes of reaction proposed for different members of the Cytochrome P450 family. Earlier studies of the ferric porphyrin peroxo complexes have established that

these complexes are not themselves electrophilic i.e. they do not oxidise typical olefins such as cyclohexene or styrene and they do not hydroxylate hydrocarbons. Instead nucleophilic reactivity has been found to be most characteristic of these complexes, and the scientists Saka et. al. have recently discovered that this reactivity can be applied

to the direct oxygenation of a substrate with the finding that $[\text{Fe(III)(TMP)(O}_2)]$ -epoxidises electron poor olefins such as cyclohexenone (42). This nucleophilic oxygen transfer thus mimics the direct nucleophilic attack on enzyme-bound substrate proposed for certain types of the P 450 enzymes.

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