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Review

Porphyrins and related macrocycles: Combining photosensitization with radio- or optical-imaging for next generation theranostic agents

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ABSTRACT

This review summarises recent research into combining the photosensitizing properties of porphyrins with imaging techniques such as PET and NIR fluorescence for so called "theranostic" applications, which combine biomedical imaging and therapeutic potential into a single administered substance. The photophysical mechanisms of both the therapeutic and diagnostic properties of porphyrins are discussed, as well as key characteristics that are required in order to deliver the most effective treatment.

1. Introduction

Herein this review intends to address several important questions, such as the nature of electromagnetic radiation and its use in photodynamic therapy, as well as the physical processes of photodynamic behaviour. A photosensitizer, for the purposes of this review, is a photoactive molecule that can serve as a therapeutic agent upon light activation, but can also be used as an imaging agent for diagnostics, thus combination of both these properties yields a theranostic agent [1]. The imaging component of these molecules can be obtained through optical properties or *via* radiolabelling of the photosensitizer [2]. This review focuses on porphyrins, which are arguably some of the most important molecules responsible for life; haem in haemoglobin binds the oxygen required for cellular respiration in red blood cells and a related macrocycle, chlorophyll, is the light absorbing pigment in photosynthesis [3]. The related corrin, found in vitamin B12, contains the only Co – C bond found in nature [4].

Cancer therapy includes modalities such as surgery, chemotherapy, immunotherapy and radiotherapy [5–7]. Photodynamic therapy (PDT) is becoming an alternative method in cancer treatment [2,8,12], and porphyrin based photodynamic sensitisers have become more accessible since the synthetic advancements by Adler and Lindsey [9,10]. PDT is typically used for small localised tumours close to the surface of tissue, such as skin, neck and throat cancers [11,12] but has also shown potential for lung [13,14] and breast cancers [15]. The simplicity of light activated drugs has brought PDT to the forefront of cutaneous curative cancer therapy [16]. PDT can be used as the sole source of therapy or in combination with surgery and other cancer therapies [17]. Almost 500 000 new cases and more than 400 000 deaths from head and neck cancer occurred in 2008 [18], while data on skin cancer indicates rates increasing by 5% annually, placing an increasing burden on health services, and making PDT especially relevant [19].

1.1. Personalized medicine

As of January 2015 the UK government pledged an investment of approximately £14 million for research into personalised medicine [20]. Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology have suggested that the future of cancer treatment is personalised medicine. The main principle of personalised medicine is to treat the individual and the individual's needs, as opposed to the commonly employed concept of the same drug and treatment for all patients [21]. Personalised medicine involves an individualised approach to the needs of the patient at all stages from diagnosis, treatment and prognosis [22]. This is important clinically as not all patients respond in the same manner, and understanding the disease and how to combat it improves the efficacy of the treatment regime [22]. Only recently has PDT emerged as a viable therapy technique in the clinic [19]. The value and potential of theranostic systems can be outlined herein, where the imaging and therapy plays an increasingly important role in personalized cancer treatment [22]. Imaging modalities offer non-invasive detection and characterization,

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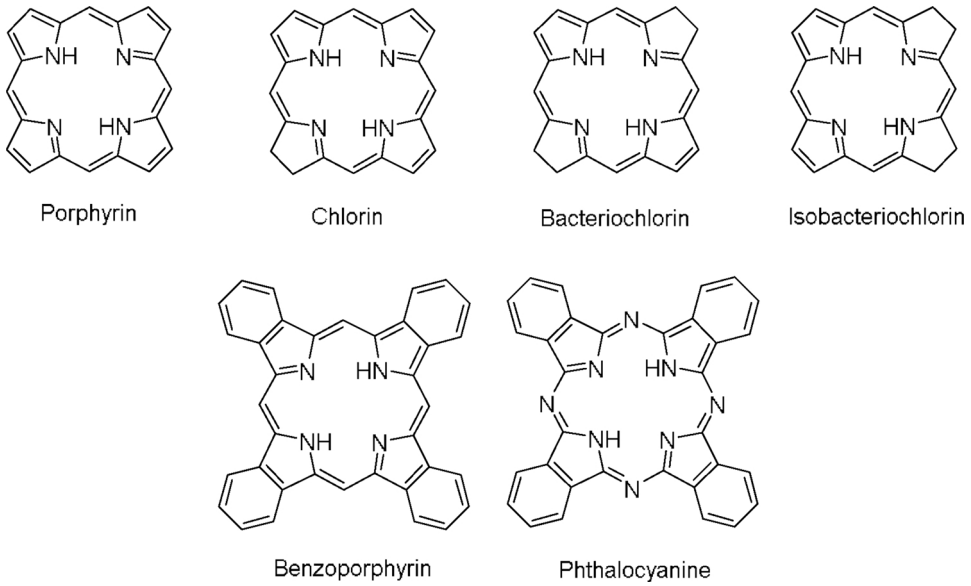

Fig. 1. Molecular structure of porphyrin and related macrocycles.

as well as quantification of the tumour, and delivers the therapeutic system to the tumour [22]. Multimodal imaging offers complementary information pertaining to the strengths of individual modalities to better elucidate disease from morphological behaviours to physiological mechanisms [22].

Positron emission tomography, PET, is a radio tracer based imaging technique which offers high sensitivity and rapid imaging times, but poor spatial resolution [23]. If the theranostic agent was photosensitizing PET agent however, then the patient's tumour could be monitored and diagnosed by PET, and the maximum uptake of the drug recorded, then the optimised curative therapy could be given to the patient. This would dramatically reduce the time from diagnosis to treatment. Furthermore, by tracking the maximum uptake of the drug into the tumour, the therapy could be delivered at the ideal time to confer maximum therapeutic effect for the patient. Finally, *in vivo* tracking of the drug molecules allows for the confirmation of drug localisation in the tumour, so that clinicians could be certain that PDT is taking place. It is clear that the research efforts of scientists are moving towards multimodal theranostic systems for enhanced patient care [24].

The development of combined PET-MRI imaging agents would present a novel combination of two powerful imaging modalities [25]. If a drug could be created that contained PET imaging modalities with a photosensitizing capability then a new generation of highly multimodal theranostic agents could be fostered. The apotheosis of all drugs for use in oncology utilizing multimodal imaging and therapeutic capabilities are now not far beyond the realms of modern science. Achieving the synthesis of such molecules would offer enhanced patient diagnosis and treatment, and pave the way for a new era of personalised medicine.

1.2. Theranostic porphyrins and related macrocycles

Photofrin® is the most widely known PS that is currently used in the treatment of cancer *via* PDT, such that it has been approved by the FDA for use against some cancers [24]. Photofrin is not limited to use in the US, other regulatory bodies in Japan, Canada and Europe have approved it as a PS [26]. However recent developments into theranostic agents are overshadowing single mode treatments such as Photofrin® for PDT alone. The term theranostic is a portmanteau of the words therapy and diagnostic and was first coined in 2002 [27]. Since then, a number of theranostic porphyrins have been developed and are reviewed by Lovell et al. [28]

Medical imaging in oncology is used to determine the morphology, physiology, location, metabolism and function of tumours [29]. These diagnostic modalities and therapeutic techniques are often applied synergistically, but this review also aims to highlight where this is not possible and the limitations. It is possible to combine two modalities of diagnostic techniques such as PET-MRI. Commonly, porphyrin theranostic agents are traditionally used for PDT and they can have positron emitters attached, as either ^{68}Ga or ^{18}F to yield a PET-PDT theranostic agent. For a comprehensive review on the generation of P block and D block radioisotopes and radiochemistry see Miller et al. and Waghorn et al. respectively [30,31].

As discussed above, porphyrins are known for their propensity to interact with light, both as PDT therapeutic agents and for their luminescent properties. Several extensive reviews have been issued, which discuss individual single mode porphyrins and metalloporphyrins in detail (see Pandey et al. and Bryden and Boyle) [2,32], but this review herein focuses on single theranostic constructs.

1.3. Nature of light

Electromagnetic (EM) radiation plays a central role in photodynamic therapy, since it provides the energy which is ultimately used to produce the reactive oxygen species that cause cellular damage to the tumour [33]. Light can be physically described by two main theories in physics, either by the classical theory as waves, and by the quantum mechanical approach as photons [34,35]. Planck reformulated blackbody radiation based upon the idea of light being discretely quantised. Einstein extended this idea such that light quanta were particles of light; photons. Spectroscopy is the study of the interaction of electromagnetic radiation with matter which uses the quantum approaches to explain photophysical processes of atoms. Photodynamic therapy can be understood by considering how the photosensitizer interacts with electromagnetic radiation.

1.4. Photophysics of PDT

One can consider the quantum mechanical approach to light when discussing the interaction between porphyrins and EM radiation. Light consists of quanta of electromagnetic energy defined by Planck's constant, wavelength and the speed of light in *vacuo*. Upon the irradiation of porphyrins (Fig. 1) with light, a specific photophysical mechanism occurs which is central to PDT. The process can be described