Photosensitive Substances

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Photodynamic therapy (PDT) is part of photochemotherapy and requires the presence of a photosensitive substance (drug, PS), oxygen, and a powerful light source in the area of absorption of the PS used.

Photosensitive Substance Photodynamic therapy photochemotherapy

1. Introduction

The main requirements for activating the properties of a PS are its selective accumulation in tumor tissue, high intensity of absorption in the visible and near-infrared region of the spectrum, low level of dark toxicity, and absence of side-effects [1][2]. Selective accumulation and retention of PS in tumor tissues rather than in the surrounding healthy tissue lead to selective destruction of the tumor in PDT, while the surrounding healthy tissue remains intact. Such selectivity is one of the biggest advantages of this method, which may be substituted in some cases for chemotherapy, radiotherapy, or surgery in the treatment of cancer. Due to drug excretion [3] and redistribution, the effective therapeutic dose entering tumor cells is only a fraction of the administered PS. Administration of increased amounts of therapeutics is not possible because they have cytotoxic effects, which could cause significant toxicity in healthy cells. It is very important therefore to find alternative approaches, which increase the efficacy of the drug dose in the tumor and decrease the dose in healthy tissue [4]. Higher selectivity of PSs for tumor cells can be achieved by combining them with transport agents, which preferentially interact with tumor cells, ensure the selective accumulation of the drug within the diseased tissue, and deliver the desired therapeutic drug concentration to a targeted site in the patient's body. Transport systems commonly used for photosensitizers are polymers, liposomes, oil emulsions, certain metals, some proteins, and carbon-based nanoparticles [5][6][7][8][9][10]. Stable and biocompatible transport systems with a long half-life in the blood are ideal. Selective drug delivery to tumor tissue, transport of nanoparticles containing a PS, and a tumor cell with a receptor is the objectives for achieving high selectivity and low drug concentration [11]. Several research groups have confirmed the hypothesis that one possible approach to achieving these goals is to prepare low-density lipoprotein (LDL)-based particles [12][13][14][15][16][17].

Physicochemical Mechanism of PDT

The photodynamic effect can be induced by two mechanisms called Type I and Type II (Figure 1—Step 4). After photon absorption, the PS molecule goes from the ground state (S_0) to the singlet excited state (S_1). From this excited state, the PS can be returned to the ground state by energy emission through non-radiative and/or radiant processes (fluorescence). In its excited state, the PS can also spontaneously move from the singlet state S_1 to the

excited triplet state (T_1) by means of the intersystem conversion process. In this state, the transition to the ground state through a phosphorescence process can occur [18].

The type I mechanism involves electron transfer reactions between the PS molecule in the excited states of S_1 and T_1 and the substrate. This process results in the formation of ionic radicals, which tend to react immediately with oxygen to form a mixture of highly reactive oxygen radicals, such as superoxide radical ($\cdot O_2$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\cdot OH$), which oxidize a wide range of biomacromolecules [2].

The type II mechanism is characterized by energy transfer reactions between PS in the excited triplet state T_1 and molecular oxygen, which is also in the triplet ground state (T_0). These reactions cause the formation of singlet oxygen ($^1O_2$), which is able to rapidly oxidize cellular structures such as proteins, lipids, nucleic acids [19][20], and organelles leading to tumor cell death [21][22]. This also means that PDT may be a useful alternative treatment for cancer cells resistant to chemotherapy [23][24].

The reaction mechanism depends on the following conditions. First, the location of the PS is crucial because most of the ROS are highly reactive and cannot move far from the point of origin before disappearing. Second, the relative number of target biomolecules is important [25]. Davies (2003) calculated the percentage of $^1O_2$ responses in leukocytes: protein 68.5%, ascorbate 16.5%, RNA 6.9%, DNA 5.5%, beta-carotene 0.9%, NADH/NADPH 0.69%, tocopherols 0.5%, reduced glutathione 0.4%, lipids 0.2%, and cholesterol 0.1% [26]. This means that the distribution of $^1O_2$ may vary in different cell targets.

Both mechanisms can occur simultaneously. Their proportional representation is significantly influenced by the PS, the substrate, the oxygen concentration, and the binding of PS to the substrate. In addition, the type II mechanism appears to be more efficient as it has a higher rate constant than electron transfer reactions (type I mechanism). As a result, energy transfer to other compounds that can compete with oxygen is less important, so type II is more often dominant [21][27].

2. Plant-Derived Photosensitive Substances

Photoactive compounds occurring in medicinal plants with potential utilization in PDT have been found to be less toxic than synthetic agents. The reduction of side effects using natural PSs in cancer treatment is another advantage of this therapeutic approach. However, their clinical applications have been limited by several imperfections such as accumulation in tissues, a lack of chemical purity, or low penetration [28]. Muniyandi et al. [29] have published a comprehensive review article about the role of photoactive phytocompounds in PDT. Phototoxic effects, potential applications in the PDT of cancer of the main natural PSs groups (furanocoumarins, thiophenes, alkaloids, curcumins, polyacetylenes, and anthraquinones) have been described [29]. Our paper focuses on the four anthraquinones, of which hypericin is the most promising PS in the PDT of cancer. With regard to the hydrophobicity of studied anthraquinones, which is important for their penetration through membranes, the following types of PSs have been distinguished.

Types of Photosensitive Substances by Hydrophobicity

PDT either uses chemotherapeutics commonly applied in chemotherapy, which must also be photosensitive, or new PSs are proposed. All photosensitizers (except uroporphyrin and photophrin), which have been proposed as drugs for use in PDT, interact more or less with serum proteins after intravenous administration. From the point of view of PDT, however, the interaction of the drugs with DNA is also quite important, as it is necessary to disrupt and stop the division of tumor cells, and this can be achieved only through their interaction with DNA [26][30]. In some cases, this interaction is not very significant (as these drugs have a greater affinity for proteins), so it is necessary to find a transporter that will help deliver the drug to the cell nucleus, thereby mediating the drug–DNA interaction [31][32]. Success in the treatment of cancer requires sufficiently hydrophobic drugs to cross the lipid membrane. For this reason, the hydrophobicity of drugs plays an important role in their distribution, metabolism, and excretion from the patient´s body. Due to these facts, we distinguish four groups of drugs with the ability to localize and accumulate in the tumor. Moreover, there are no rigid boundaries between these groups of drugs, and there is some overlapping between them, in some cases a continuous transition.

- Hydrophobic PSs—compounds requiring the presence of transporters, such as liposomes or Cremophor EL, or Tween 80. They have the ability to localize in the inner lipid part of lipoproteins, mainly in LDL and high-density lipoproteins (HDLs), but also in very-low-density lipoproteins (VLDLs). This group includes phthalocyanines (ZnPC, C1A1PC), naphthalocyanines (isoBOSINC), tin-etiopurpurine (SnET2) [32], and hypericin [33].

- Amphiphilic PSs—asymmetric compounds, which can be incorporated into the outer phospholipid and apoprotein layer of lipoprotein particles, e.g., disulfonates ($TPPS_{2a}$, $C1A1PCS_{2a}$), lutetium teraphyrin (LuTex), and monoaspartyl chlorine (MACE), which forms a barrier between albumin and HDL [32]. Emodin can be included in this group [34].

- Hydrophilic PSs—drugs that predominantly bind to albumins and globulins, e.g., tetra-sulfone derivates of tetraphenylporfin ($TPPS_3$ and $TPPS_4$) and chloroaluminum phthalocyanine ($C1A1PCS_3$ and $C1A1PCS_4$) [32].

- Intercalators—drugs that are used mainly in chemotherapy, which intercalate into DNA and are also photoactive, e.g., doxorubicin [35], daunorubicin [36], adriamycin [37], quinizarin [38], and danthron [39].

In this work, we focused in more detail on a very prospective PS in PDT of cancer hypericin. During a study of hypericin molecule incorporation into biomacromolecules (we focused on DNA) model compounds are using for simplification of the problem. Anthraquinones emodin, quinizarin, and danthron represent a significantly smaller part of the larger hypericin molecule with the same chemical groups. This fact facilitates the creation of a proper model for interaction between hypericin and biomacromolecules. Moreover, chosen hypericin derivatives themselves originate from medicinal plants, as the PS can be utilized in PDT and their anticancer effects are known. With respect to the above-mentioned sorting of PSs into groups, they can be representatives of highly hydrophobic (hypericin), mildly hydrophobic (emodin), and intercalating molecules (quinizarin and danthron).

Scientists and physicians are currently working on how to increase the effectiveness of cancer treatment. One option that has been shown to be very effective is a combination of therapies (PDT and chemotherapy), which involve the direct or mediated interaction of anticancer drugs with DNA and other bioactive macromolecules (serum albumins, lipoproteins) [40][41][42]. Hypericin, emodin, quinizarin, and danthron are examples of anticancer drugs which are chemotherapeutics synthesized by medicinal plants and PSs, and which can be used, in PDT. The discovery of new natural drugs is very important because they have many benefits for the patients. Drugs derived from medicinal plants are less toxic to the body, their use poses less risk of adverse side effects, does not depends on them, they are suitable for all age groups of patients, and can be easily combined with conventional drugs, i.e., do not show contraindications.

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