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Nonlinear optical effects in PDT

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Abstract

Use of near infrared instead of visible light would markedly improve tissue penetration, making larger tumors candidates for PDT. Since common photosensitizers exhibit virtually no absorption in this wavelength region, conditions are required where the simultaneous action of two photons is possible. Healthy tissue (rat ears), sensitized by hematoporphyrin derivative, sulfonated chloroaluminium phthalocyanine (CIBA-GEIGY) or pheophorbide a (PORPHYRIN PRODUCTS), was irradiated (1064 nm, 10 nsec) with power densities up to 200 MWcm⁻² and energy densities up to 200 kJcm⁻². No reproducible photodynamic lesions were observed, but there was a strong sensitizer fluorescence which depended quadratically on the excitation intensity. This may be useful to determine the tissue sensitizer concentration to an otherwise inaccessible depth.

Introduction

Poor tissue penetration of the activating light is one of the principal physical limitations of photochemotherapy, restricting its use to the treatment of superficial tumors. It is well known that the penetration depth depends on the nature of this light - grossly it increases with increasing wavelength throughout the visible and near infrared.

The possibility of exciting photosensitizers with infrared light due to a nonlinear mechanism has been suggested by the observation of two-photon induced fluorescence of hpd above 100 MWcm⁻² (1). The first attempt to implement this modality on biological objects (2) failed. More recently reduction of the survival rate of cultured cells (3,4) and tumor necrosis (4,5) were observed. According to the authors' claims this was the result of photodynamic action. Hyperthermia may, however, have contributed to produce positive results. The present in vivo study strives to exclude hyperthermal lesions and to employ high power densities which are expected to be the prerequisite of the occurrence of nonlinear effects.

Materials and methods

Wistar rats were used, the ears of which had been chosen as target for irradiation. This choice is determined by the ease of access for irradiation and for subsequent observation and, most importantly in this study, by the possibility of maintaining the tissue temperature at a convenient value (see below). The photosensitizers were hematoporphyrin derivative (21 to 42 mg/kg), sulfonated chloroaluminium phthalocyanine (CIBA-GEIGY) (45 to 58 mg/kg) or pheophorbide-a (PORPHYRIN PRODUCTS) (7.5 to 14 mg/kg).

Fig. 1

The set up used for irradiation is shown schematically in fig. 1. The rat is placed above the drawing plane with one ear *E* immersed in a water bath *W*. The ear is fixed to a frame on three points (not shown) so as to take a plane shape. In order to improve the definition of its temperature the ear is not only immersed but is constantly irrigated from both sides by a flow of water issuing from two tubes *T*. While it is desirable to maintain as high a temperature as possible to intensify photodynamic lesions (6) the temperature must obviously be low enough to prevent the generation of hyperthermal ones. It was found that above 40 °C huge blisters form after one or two hours. At 39 °C, however, no modification could be detected even after three hours. The water temperature was therefore always adjusted to this value.

The beam of the Q-switched Nd:YAG laser (10 nsec, 10 Hz) used to irradiate the ears was not homogeneous but exhibited a more or less regular structure. The thus locally enhanced power density was suspected to favour trivial lesions. To smooth out the power distribution a slightly frosted glass plate *F* was inserted in the beam path. The resulting loss of mean power density was partly compensated for by a lens *L1*.

Trivial lesions consisted of internal hemorrhage from major vessels. It was possible to avoid them by directing the laser beam to zones of the ear where

Fig. 2

Fig. 3

only small vessels were present and by not exceeding a threshold power density. Actually the maximal power densities were comprised between 100 and 200 MWcm^{-2} , the energy densities between 100 and 200 kJcm^{-2} .

The assembly on the right hand side of fig. 1 is used for fluorescence measurements: A filter K (KG 5; 2 mm), a lens L2 roughly imaging the irradiated spot onto the grating of a monochromator M, a photomultiplier P having a multialkali photocathode, and an oscilloscope O. The monochromator was equipped with very large slits (4 mm), giving a bandwidth of approximately 18 nm. K was necessary to avoid spurious signals produced by scattered IR light.

Results

Visual observation: The impact of the laser beam was visible on both sides of the rat ears due to a faint but easily perceptible emission of green light. Its narrow spectrum centered around 532 nm and its quadratic dependence on irradiation intensity reveal the presence of second harmonic generation.

Photodynamic response: Three out of the nine rats the survival time of which was sufficient to make a several days' observation possible exhibited a slight localized erythema that appeared 1 or 2 days after irradiation and persisted about 8 days.

Fluorescence: Fig. 2 represents results obtained with three rats which had received 21 mg/kg hematoporphyrin derivative (curve a), 50 mg/kg phthalocyanine (curve b) and 7.5 mg/kg pheophorbide-a (curve c) respectively. The spectra are normalized with regard to the green light mentioned above. The peak height depends nearly quadratically on IR intensity (fig.3). Given the high relative intensity of fluorescence its excitation cannot be produced by the green light but must be due to the action of two photons.

Conclusion

Photodynamic lesions were hardly detectable, even using very high light doses, and not reproducible. Thus their authenticity must be considered as questionable. Two-photon excited fluorescence, however, was unambiguously observed in all rats. It may be useful to determine the tissue sensitizer concentration to an otherwise inaccessible depth.

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