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Photodynamic therapy within edematous brain tissue: Considerations on sensitizer dose and time point of laser irradiation

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Abstract

Photosensitizer is known to spread with vasogenic edema fluid arising from a cerebral lesion (Neurosurg 33:1075–1082, 1993), which may be essential for sensitizing malignant cells outside the main tumor mass. The present experiments seek to elucidate whether resultant necrosis of perifocal brain tissue after laser irradiation follows a corresponding time pattern and whether damage depends on the photosensitizer dose.

Male Wistar rats were anaesthetized with chloralhydrate for venous cannulation, craniotomy and focal cold lesion in order to induce vasogenic edema. Simultaneously, Photofrin II^{R} (PF II) was administered at a dose of 5 mg kg^{-1}. The animals were re-anaesthetized after either 4, 12 or 24 h for the irradiation of lesion and perifocal tissue with 200 J cm^{-2} of laser light (630 nm). The brains of other animals were irradiated 4 h after cold lesion with 200 J cm^{-2} after receiving either 0, 2.5 or 5 mg kg^{-1} PF II (all groups: n = 6). Resultant necrosis was assessed planimetrically in serial coronal cryosections of brains perfusion fixed 24 h after irradiation.

Necrosis was significantly enhanced with irradiation 4 h after cold lesion and photosensitizer (avg. area ± SD: 4.3 ± 0.7 mm^2) compared with lesion only (0.84 ± 0.2 mm^2). Maximal necrosis (6.3 ± 1.6 mm^2) occurred with irradiation 12 h after lesion, whereas necrosis was only slightly increased with irradiation at 24 h (2.8 ± 0.4 mm^2). Furthermore, the area of necrosis was dependent on the sensitizer dose (0 mg kg^{-1}: 0.7 ± 0.3 mm^2, 2.5 mg kg^{-1}: 2.09 ± 0.2 mm^2, 5 mg kg^{-1}: 4.3 ± 0.7 mm^2; all differences $p < 0.05$).

Therefore, to prevent unwanted side-effects such as necrosis of edematous but otherwise healthy, peritumoral tissue in the treatment of malignant cerebral tumors by PDT, tribute should be paid to the possibility of time and dose dependent sensitization of the perifocal tissue after i.v. administration of photosensitizer.

Keywords: Photodynamic therapy; Blood-brain barrier; Brain edema; Drug delivery

1. Introduction

Photodynamic therapy has been under investigation as an adjuvant for malignant brain tumor therapy after surgical debulking of the tumor mass [1,2]. This mode of treatment relies on the putative ability of intravenously or topically applied photosensitizer to be selectively taken up or retained by malignant tumors. Irradiation of the tumor with light of an appropriate wavelength activates photosensitizer and leads to tumor necrosis [3]. However, malignant glioma is accompanied by edema of the vasogenic type, which has been shown to transport significant amounts of intravenously administered photosensitizer into perifocal brain tissue [4]. While propagation of photosensitizer with edema fluid may be essential for sensitizing tumor cells outside the main tumor mass, time-dependent sensitization of perifocal tissue may occur. Therefore, to minimize side-effects resulting from unwanted sensitization of perifocal tissue, the present experiments were designed to assess the susceptibility of perifocal tissue to irradiation at various timepoints after the intravenous administration of sensitizer in a model of vasogenic edema, the cold injury model by Klatzo [5,6]. Furthermore, the influence of varying photosensitizer doses on the necrosis area resulting from irradiation of perifocal tissue was determined.

2. Materials and methods

Male Wistar rats were anaesthetized with 3.6% chloralhydrate. After cannulation of the right external jugular vein, the rats were fixed in a stereotactic holder for craniotomy in the left parietal region. Cold injury was induced as previously described [4] by applying a copper stamp cooled to −68°C by a mixture of dry ice and acetone to the exposed dura for

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