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Efficacy of 5-aminolevulinic acid based photodynamic therapy in pituitary adenomas—experimental study on rat and human cell cultures

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ABSTRACT

Background: Incomplete resection of pituitary adenomas may result in recurrence. As adjuvant irradiation is not riskless, alternative treatment options should be investigated. 5-aminolevulinic acid based photodynamic therapy (5-ALA based PDT) showed promising results for malignant gliomas. The present study examined the efficacy of 5-ALA PDT *in vitro* on benign pituitary adenoma cell cultures.
Methods: In group I experiments were performed on immortalized rat pituitary adenoma cells (GH3). The cultured cells were treated with different 5-ALA concentrations ranging from 7.5–16.5 μg/ml. In Group II human pituitary adenoma cell cultures were obtained from surgically resected adenoma tissue ($n = 15$). These were incubated with 5-ALA concentrations from 12.5–100 μg/ml. The concentration ranges had been determined in preliminary dose-finding tests. For both groups incubation time was four hours and PDT was performed by exposition to laser light (635 nm, 625 s, 18.75 J/cm^2). Cell viability was examined by WST-1 assay.
Results: In both groups PDT showed a 5-ALA concentration-dependent effect on cell death. In group I lower 5-ALA concentrations were necessary to destroy all cells as compared to group II. Moreover, in group II, the different subtypes of human adenomas showed different sensitivities to 5-ALA-based PDT (secreting *vs.* non-secreting). Especially corticotroph adenomas were highly sensitive to 5-ALA PDT.
Conclusions: The GH3 cell line was an useful *in vitro* model to optimize different PDT parameters. Human pituitary adenoma cells could also be killed by 5-ALA PDT, however this required higher 5-ALA concentrations. Furthermore, the results suggested different 5-ALA sensitivities between different human adenoma cell types. More experiments are necessary to confirm these preliminary results.
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1. Introduction

Pituitary adenomas represent approximately 16% of all intracranial tumors [1]. Although pituitary adenomas are slow-growing benign tumors, they should be resected if symptomatic or growing in serial neuroimaging. Previous studies showed that complete resection may be hindered around the cavernous sinus and the optic nerve harboring a risk of recurrence [2] [3]. Adjuvant radiotherapy of incompletely resected adenomas may cause hypopituitarism and/or radionecrosis [4,5].

Therefore alternative adjuvant treatments should be investigated [6,7]. Photo-dynamic therapy (PDT) is a well-studied local cancer treatment for skin, bladder and GIT tumors [8–10]. For pituitary tumors experience is still limited [3,11–15]. Two former studies revealed that PDT with hypericin resulted in cell death of subcutaneous implanted human pituitary adenoma cells in mice [12,16]. Despite encouraging preliminary results PDT for pituitary adenoma in a clinical setting has not been further pursued [3].

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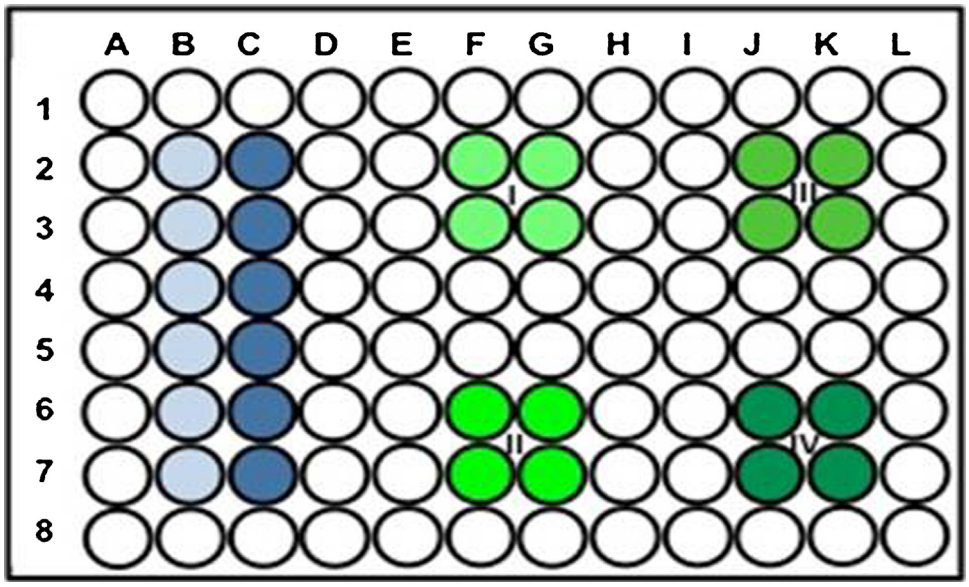

Fig. 1. Graphic illustration of the 96-well microplate: row of medium-filled blank (light blue), row of negative control with untreated cells (dark blue), four blocks with cells and different 5-ALA concentrations for PDT (different green colors).

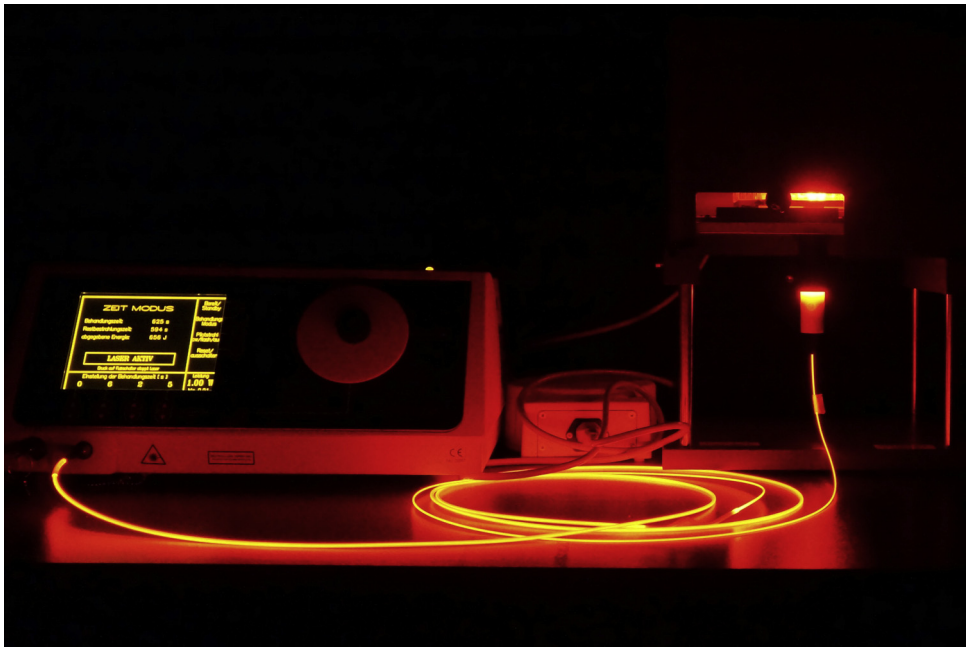

Fig. 2. Irradiation setup during PDT: Laser (left), fiberglass probe (middle), 96-well plate in the irraditation chamber (right).

More clinical experience exists for 5-ALA based photodiagnosis and photodynamic therapy of gliomas [17–24]. Meanwhile 5-aminolevulinic acid has proven safe and effective in daily neurosurgical routine of glioma surgery. It was authorized in the European Community for fluorescence-guided resection of malignant gliomas [23].

Therefore we proposed to investigate 5-ALA based PDT in pituitary adenomas. We screened the efficacy of 5-ALA PDT in rat pituitary adenoma cells (GH3 cell line). Furthermore, we studied 5-ALA PDT of pituitary adenoma cells which were obtained from operated patients.

2. Material and methods

2.1. Ethical

The study was approved by the local ethic committee (study 4290, 11th June 2013). Informed and written consent was obtained pre-operatively from each patient.

2.2. Materials

Collagenase solution and HDB buffer were obtained from the central hospital pharmacy. 5-Aminolevulinic acid (5-ALA) was delivered from Merck, Darmstadt, Germany. Dulbecco's modified

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