Sonodynamic Therapy with 5-Aminolevulinic Acid and Focused Ultrasound for Deep-seated Intracranial Glioma in Rat

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Abstract. *Background: 5-Aminolevulinic acid (5-ALA) has already been applied clinically as a photosensitizer. In this study, sonodynamically induced selective antitumour effect of 5-ALA for deep-seated lesions was evaluated. Materials and Methods: First, normal rat brains were sonicated via a transducer placed on the dural surface to confirm safe acoustic conditions for normal rat brains. One week after inoculation of brains with C6 rat glioma cells, brains with/without administration of 5-ALA (100 mg/kg body weight) were sonicated. Results: Sonodynamic therapy (SDT) with 5-ALA and focused ultrasound (10 W/cm^2, 1.04 MHz, 5 min) achieved selective antitumour effect against deep-seated experimental glioma. Mean tumour sizes in the largest coronal section in sham-operated rats and rats receiving ultrasound with/without 5-ALA were 29.94±10.39, 18.32±5.69 and 30.81±9.65 mm^2, respectively. Tumour size was significantly smaller in the SDT group than in other groups ($p<0.05$). Conclusion: This experimental rat model showed that SDT appears to be useful in the treatment of deep-seated malignant glioma.*

Human malignant glial tumours, particularly glioblastomas, strongly invade neighbouring tissue and cannot be completely resected surgically, even with up-to-date technologies, such as the neuronavigator or photodynamic diagnosis (PDD). Fewer than half of such patients survive more than 1 year, and 5-year survival is only 5 to 8%, even when all treatment modalities, including radio-chemo-immunotherapy are applied (1). More aggressive therapy is required to eradicate unresectable nests of tumour cells invading adjacent normal brain tissue.

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5-Aminolevulinic acid (5-ALA) is a natural porphyrin precursor that has already been used in PDD and photodynamic therapy (PDT) for human glioma. Therefore, it is easy to apply to the treatment of human brain tumours, unlike other materials. PDT has been extensively investigated as a treatment for various brain tumours and has been applied in clinical trials (2). The selective antitumour effect of PDT is based on selective uptake of a photosensitizer by neoplastic tissue (3-5). However, it is quite difficult to focus PDT on deep-seated tumours and selectively kill the tumour cells without placing indwelling optical fibers directly into tumours (6). In contrast, the energy of focused ultrasound can be delivered into deep-seated lesions and can be focused into a small volume (7-9). Furthermore, Fry *et al.* reported that they were able to create focused ultrasound-induced lesions in brains of craniectomized cat through a formaldehyde-fixed human skull (10). Hynynen *et al.* also created focal lesions in rabbit brains through a piece of human skull (11). By adjusting the acoustic intensity of the ultrasound, hazardous effects to surrounding tissues can be minimized (12). In addition, the photosensiting haematoporphyrin derivative and antitumour drugs (13, 14) have been found to localise selectively in some tumour cells and to be activated by ultrasound, resulting in a significant antitumour effect. Sonodynamic therapy (SDT) has the potential to be very a useful and noninvasive treatment in the future if it can destroy deep-seated brain tumour by sonication through the human skull while avoiding destruction of surrounding normal brain tissue.

We investigated the antitumour effect of SDT in experimental rat glioma by using focused ultrasound in combination with 5-ALA.

Materials and Methods

Preparation of the sonodynamically active agent. The natural porphyrin precursor 5-aminolevulinic acid hydrochloride was purchased from Cosmo Biochemical Company (Tokyo, Japan). The material was supplied as a powder and was mixed in a sterile solution of distilled water (20 mg/ml).