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Accumulation of exogenous sensitizers in rat brain

Vytautas Kulvietis[1],

Eugenijus Zakarevičius[1],

Juozas Lapienis[1],

Gražina Graželienė[1],

Violeta Žalgevičienė[2],

Ričardas Rotomskis[1, 3]

[1] *Laboratory of Biomedical Physics, Institute of Oncology, Vilnius University, Lithuania*

[2] *Faculty of Medicine, Vilnius University, Lithuania*

[3] *Laser Research Center, Vilnius University, Lithuania*

Background. Nowadays fluorescence diagnostics can be applied for tumour boundary delineation. One of the most important sensitizer's characteristics in fluorescence diagnostics is accumulation and distribution in biological tissue. However, the blood-brain barrier protects the brain, and, as a consequence, the accumulation of sensitizers in the brain should be restricted. Unfortunately, there are not enough comparative studies about the possible accumulation of different contrasting agents – sensitizers – suitable for brain tumours identification. Therefore, the accumulation and distribution of two sensitizers in the healthy rat brain were investigated by means of the fluorescence spectroscopy.

Materials and methods. Sensitizers – Photogem® and aluminum phthalocyanine tetrasulfonate ($AlPcS_4$) – were administered intravenously (by equal doses – 5 mg/kg) to Wistar rats, and after the appropriate incubation time the animals were sacrificed. Fluorescence spectra of the brain white and grey matter, cerebellum and other tissues were measured. Accumulation of sensitizers was evaluated according to the fluorescence intensity at the sensitizers' main fluorescence peak.

Results. Fluorescence of Photogem® was not observed in the brain tissues but was registered in other rat organs. $AlPcS_4$ fluorescence intensity was higher in all the organs in comparison with Photogem®. Fluorescence intensity of $AlPcS_4$ in the brain structures, which is about 7 times lower than that in other tissues, seems to be sufficient for tumour delineation. The formation of endogenous porphyrins in the healthy rat brain white matter was observed. Fluorescence of endogenous porphyrins could disturb the identification of Photogem® in both healthy and tumour tissue.

Conclusion. Photogem® poorly accumulates in rat brain, and its fluorescence is masked by the formation of the endogenous porphyrins. $AlPcS_4$ accumulates in rat brain much better and, therefore, $AlPcS_4$ would be a more effective sensitizer for the brain tumour margins delineation.

Key words: blood brain barrier, fluorescence spectroscopy, brain tumour diagnostics, sensitizer, Photogem®, $AlPcS_4$

BACKGROUND

Surgical removal of brain tumours is the most common form of treatment. However, many brain tumours do not have any distinct boundary, making complete resection difficult or even impossible. Visual brain tumour inspection by a neurosurgeon and conventional intra-operative diagnostic techniques – magnetic resonance imaging, computer tomography or ultrasonography – are not effective enough for the delineation of tumour margins (1, 2). Fluorescence diagnostics is a new, harmless and highly promising method which enables to distinguish neoplastic tissue from a healthy one during the operation. It is reasoned by selective accumulation of the fluorescent agent – sensitizer – in the tumour. Limited success in the fluorescence diagnostics of tumours in the brain is generally attributed to two factors: low selective accumulation of sensitizers in tumour cells, and delivery impediment related to the blood-brain barrier. Moreover, there are not enough studies indicating which sensitizer is the most suitable for the brain tumours fluorescence diagnostics.

Our investigated sensitizers – Photogem® and $AlPcS_4$ – are localized in tissue primarily where collagenous proteins are normally found, i. e. basal lamina, collagenous connective tissue, and in keratinized epithelium, mononuclear phagocyte system and on the membrane of muscular cells (3, 4). However, Photogem® constitutive porphyrins are more lipophylic than $AlPcS_4$ and therefore they penetrate through cell membrane better and accumulate in bigger quantities in intracellular structures, while $AlPcS_4$ is more inclinable to localize in blood vessels and extra cellular matrix (5, 6). These sensitizers differ also in their pharmacokinetical properties: $AlPcS_4$ faster reaches its maximum concentration in the tissues and has a shorter clearance period from the organism than Photogem®. Therefore, the organism remains photosensitive for a shorter time after the $AlPcS_4$ sensitized diagnostic procedure (5–7).

Correspondence to: R. Rotomskis, Laser Research Center, Vilnius University, Saulėtekio 9, LT-10222 Vilnius, Lithuania. E-mail: ricardas.rotomskis@ff.vu.lt

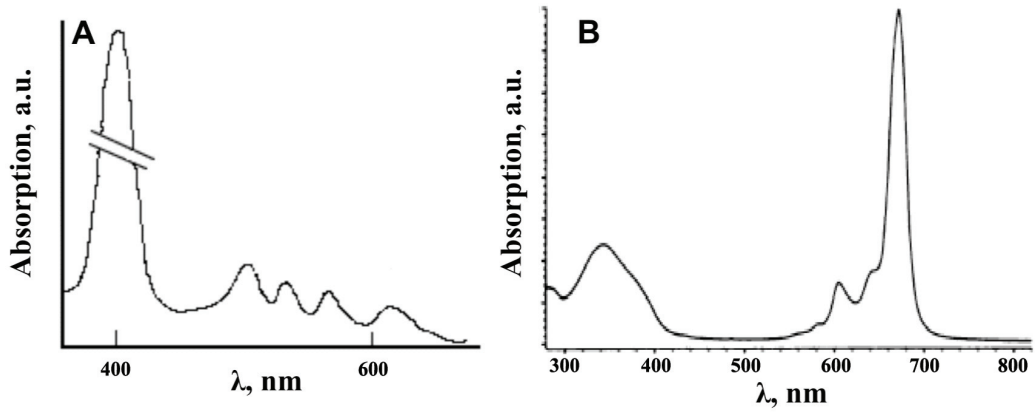

Fig. 1. Absorption spectra of Photogem® (A) – 2 mM in aqueous solution (13) and $AlPcS_4$ (B) – 10 mM in 0.1 M NaOH aqueous solution (6)

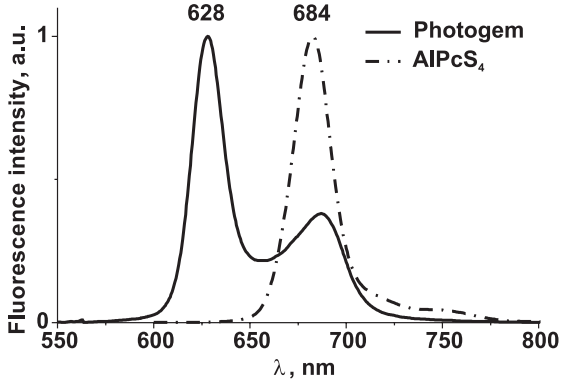

Fig. 2. Fluorescence spectra of Photogem® ($\lambda_{ex} = 405$ nm) and $AlPcS_4$ ($\lambda_{ex} = 351$ nm) at 10^{-5} M concentration in aqueous solution

Usually, accumulation of the sensitizers is investigated in experimental animals with implanted brain tumours. Whelan et al (3) report that the concentration of the Photofrin II® (sensitizer analogous to Photogem®) was higher in healthy brain tissue than in the muscle and blood, but lower than in other organs of rat and canine with inoculated gliomas. The highest quantities of the sensitizer were observed in the liver and spleen. Hematoporphyrin type sensitizers in the healthy brain tissue of tumour bearing rats were also observed by other authors (4, 8–10). On the other hand, the concentration of sensitizer in the healthy brain tissue is from 2 to 7 times lower than that in the tumour tissue. Efficient sensitizer's accumulation in gliomas is reasoned mainly by disturbed blood-brain barrier of the tumour.

Moreover, it is proved that sensitizer can pass through disturbed tumour blood-brain barrier into cerebral fluid and healthy tissue (2, 8–11). The bulk of this flow depends on histological structure of the tumour and physiological state of the organism. So, experimental models with inoculated tumours do not reflect accumulation of exogenous sensitizer in healthy brain impartially. In addition, experiments are done with a wide diversity of implanted tumours, and it impedes the summary of forthcoming results by different laboratories.

All in all, different experiments with implanted brain tumours are not impartial enough to evaluate and compare the accumulation of different sensitizers. There is a need for more objective studies which would describe and compare the accumulation of different sensitizers in brain tissue and evaluate their potential application in fluorescence diagnostics.

Therefore, the aim of this study was to evaluate accumulation of two sensitizers – Photogem® and $AlPcS_4$ – in healthy rat brain by means of fluorescence spectroscopy. To implement this, a few tasks were set: to evaluate fluorescence intensity of each sensitizer in different brain structures, to evaluate fluorescence of endogenous fluorophores in the brain structures and to compare potential effectiveness of Photogem® and $AlPcS_4$ in the brain tumours fluorescence diagnostics.

MATERIALS AND METHODS

Sensitizers

Two sensitizers: Photogem® (from "Биолек", Russia) and aluminum phthalocyanine tetrasulfonate – $AlPcS_4$ (from Frontier Scientific, USA) were used for experiments. Photogem is not a chemically pure compound but a mixture of purified fraction of hematoporphyrin derivate, oligomeric and monomeric porphyrins. Meanwhile, $AlPcS_4$ is a pure compound.

In order to get the most intense fluorescence, we irradiated the samples with the light of wavelength, which is best absorbed by each sensitizer: Photogem® – 405 nm and $AlPcS_4$ – 351 nm (Fig. 1). The sensitizers were identified in the samples according to the shape of their fluorescence spectra, and fluorescence intensity was evaluated at the main fluorescence peak: Photogem® – 628 nm, $AlPcS_4$ – 684 nm (Fig. 2).

Experimental procedure

In total, 12 Wistar albino rats (weight 200–350 g) were used for the experiments. 3 animals received Photogem® injections, while the other 3 were made $AlPcS_4$ injections. 6 rats constituted the control group. Animals received sensitizers by slow intravenous injections of 5 mg/kg in 0.5 ml saline. The incubation period was chosen according to the pharmacokinetics of the drug: for Photogem® it was 24 hours (3–5), and for $AlPcS_4$, 4 hours (6, 7, 14). Rats were kept in the dark until they were sacrificed by lethal ketamine dose (0.4–0.5 ml). The organs were removed and kept in the dark at –3 °C.

Parenchymous organs (liver, spleen, lungs, muscle, kidneys, Harderian gland) were prepared for fluorescence spectroscopy by

making their cross-sections (thickness ~1 mm). Tubular organs (oesophagus, stomach, duodenum, small intestine, bladder, uterus) were prepared by cutting their walls along the organ axis. The brain grey matter was separated from the surface of the brain. The white matter was collected from deeper layers. Cerebellum was prepared by making cross-sections. Totally, 16 samples from each animal were prepared for fluorescence spectroscopy.

The animal husbandry and experiments on animals were carried out according to the national and European regulations and were approved by the Lithuanian Animal Care and Use Committee.

Fluorescence analysis

Fluorescence spectra were registered by Perkin Elmer LS50B luminescence spectrophotometer. Excitation wavelength for specimens sensitized with Photogem® was 405 nm, and for sensitized with $AlPcS_4$ – 351 nm. Fluorescence emission spectra were measured in the range of 550–800 nm. Fluorescence spectra were measured for each sample at three different positions. Spectra obtained from all the samples of the same tissue were averaged. To eliminate the autofluorescence of the tissue and to evaluate the fluorescence of the sensitizer, all spectra were normalized at 600 nm. This wavelength was chosen according to two factors: firstly, tissue fluorescence of shorter wavelength is reabsorbed by blood (main absorption peak of oxyhemoglobin is at 580 nm) and, secondly, fluorescence of sensitizers was observed at longer wavelengths (Fig. 2).

On purpose to evaluate the accumulation of sensitizer in each tissue, the normalized autofluorescence spectra of control samples were subtracted from the normalized fluorescence spectra of the samples incubated with the sensitizer. The accumulation of sensitizers was evaluated by the difference at the main sensitizer's peak: for Photogem at 628 nm and for $AlPcS_4$, at 684 nm.

For the additional comparison of the fluorescence intensities of the control and sensitized samples, Mann-Whitney test was used. P values lower than 0.05 were considered statistically significant.

The distribution of endogenous porphyrins in rat organism was evaluated by analyzing the fluorescence spectra of the control group with 405 nm excitation wavelength. Porphyrins were identified according to the shape of the fluorescence spectra and the position of the main peak.

RESULTS

The main fluorescence peak of Photogem® at 628 nm was detected in specimens of various organs after the injection of sensitizer (Fig. 3). The fluorescence peak of $AlPcS_4$ was seen at 684 nm.

The distribution of sensitizers in rat organism according to the fluorescence intensity at the sensitizers' main peak is represented in Fig. 4.

The fluorescence of $AlPcS_4$ was detected in all the specimens of sensitized tissues. The least concentrations of $AlPcS_4$ were registered in the brain structures: cerebellum, white matter and grey matter because of the limited passage through the blood-brain barrier. The largest quantities were found in bladder and uterus. The concentration ratio of other samples to brain structures varied from 2.5 for the spleen to 13.7 for the bladder. Moderately, $AlPcS_4$ accumulates in the brain tissues 7 times worse than in other organs.

Different spectroscopic picture was detected when Photogem® was injected to the experimental animals. The fluorescence peak at 628 nm (characteristic for Photogem®) was not detected in fluorescence spectra of sensitized brain tissues. The fluorescence spectra of brain samples after Photogem® administration did not differ significantly from the control group (Fig. 5). Mann-Whitney test showed that p values for the brain structures were greater than 0.05 (white matter – 0.51, grey matter – 0.83, cerebellum – 0.57).

The fluorescence peak in the brain white matter and cerebellum samples was observed at 625 nm. Another smaller peak was seen at 685 nm. These fluorescence peaks were assigned to endogenous coproporphyrin (11, 15, 16). They were not expressed in the brain grey matter or any other sample.

In some control samples of 405 nm excitation light, fluorescence peaks at 620 nm (in kidney) or 635 nm (in Harderian gland, skin, liver, oesophagus, stomach, duodenum and small intestine) were observed. These peaks were assigned to uroporphyrin and protoporphyrin IX, respectively (11, 15–17).

In some of these samples the main fluorescence peak after Photogem® administration was red shifted: from 628 nm to 630–633 nm, because of the overlap of Photogem® and endogenous porphyrins. After subtracting the appropriate control autofluorescence spectra from these spectra, the fluorescence peak of Photogem® at 628 could be identified, and the accumulation of the sensitizer could be evaluated. The highest concentrations of the accumulated Photogem® were observed in the liver and skin (Fig. 4).

The fluorescence of endogenous porphyrins was not expressed while analyzing the accumulation of $AlPcS_4$. Since endogenous porphyrins poorly absorb at 351 nm, only the fluorescence of $AlPcS_4$ was detected, when 351 nm excitation light was applied (Fig. 6).

Therefore, it was easier to analyse fluorescence spectra of the tissue sensitized with $AlPcS_4$ and to evaluate the accumulation more accurately.

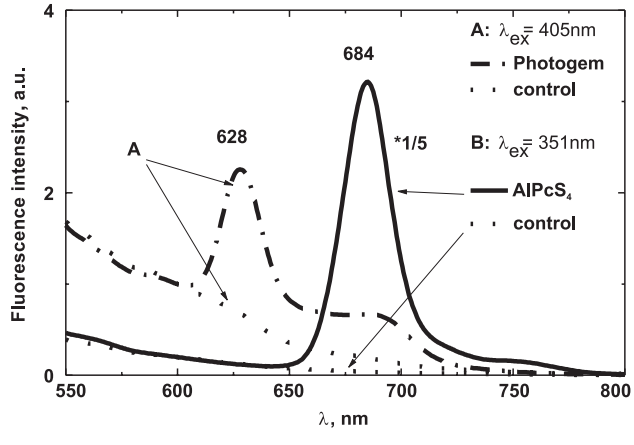

Fig. 3. Fluorescence spectra of rat uterus after i.v. administration of sensitizers at 5 mg/kg: A) Photogem® (λ_{ex} = 405 nm) and B) $AlPcS_4$ (λ_{ex} = 351 nm). $AlPcS_4$ and its control fluorescence spectra intensities are reduced 5 times

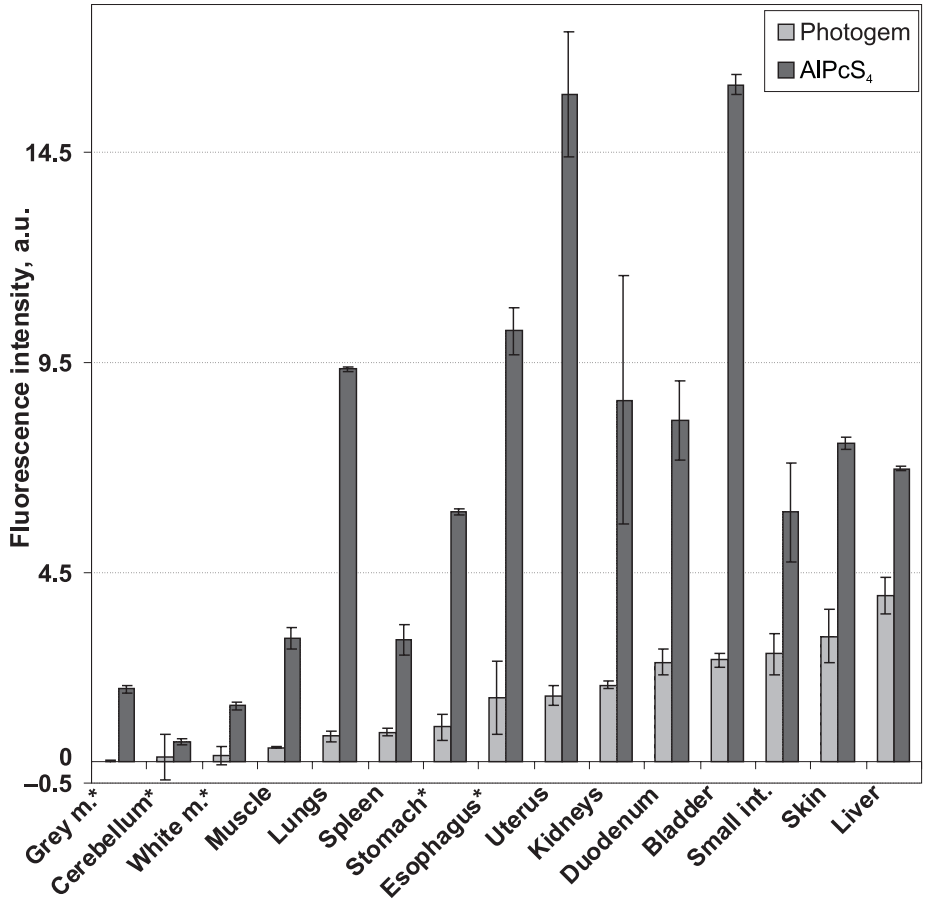

Fig. 4. Distribution of Photogem® (λ_{ex} = 405 nm, λ_{fl} = 628 nm) and $AlPcS_4$ (λ_{ex} = 351 nm, λ_{fl} = 684 nm) in rat brain structures and other organs. Sensitizers' dose 5 mg/kg, incubation time 24 h for Photogem® and 4 h for $AlPcS_4$. Intervals indicate standard errors
* p > 0.05 for Photogem®

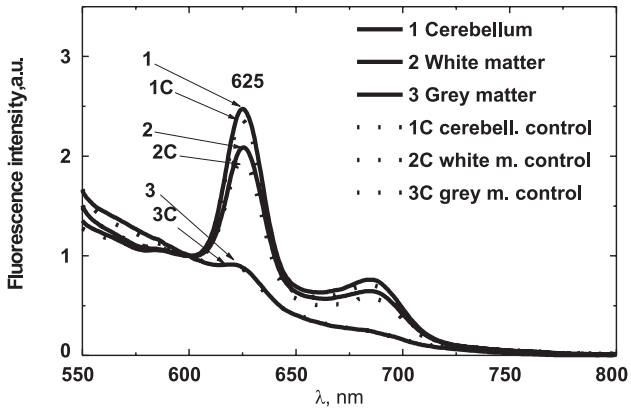

Fig 5. The fluorescence spectra of the brain structures after Photogem® administration (solid lines) and control samples (dotted lines), λ_{ex} = 405 nm

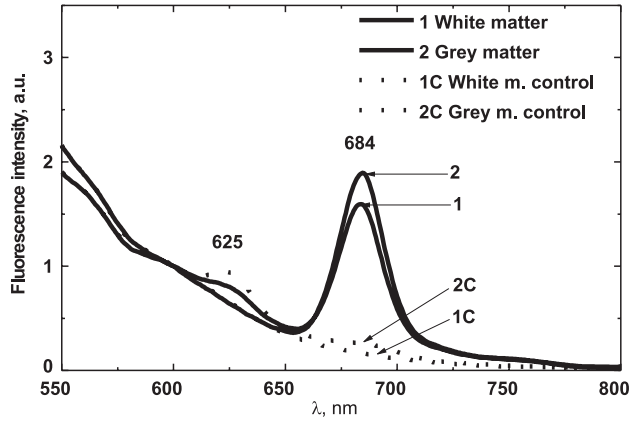

Fig 6. The fluorescence spectra of brain structures after $AlPcS_4$ administration (solid lines) and control samples (dotted lines), λ_{ex} = 351 nm

DISCUSSION

Our findings show that using therapeutic dose (5 mg/kg) of Photogem®, it was not detected in the healthy rat brain by fluorescence spectroscopy, while it was observed in all other organs. This result is in disagreement with the authors, who detected hematoporphyrin derivate in the brain tissue of brain tumour bearing experimental animals (4, 8–10). It is proved that sensitizer can pass through the intact tumour blood-brain barrier into cerebral fluid and healthy tissue (2, 8–11). The bulk of this flow depends on the histological structure of the tumour and on the physiological state of the organism. So, experimental models with inoculated tumours do not reflect the accumulation of exogenous sensitizer in healthy brain impartially. However, our results and those in the literature show that blood-brain barrier has low permeability for Photogem®.

$AlPcS_4$ was detected in all the investigated samples. The least concentrations were observed in the brain structures. $AlPcS_4$ accumulates in the brain at a 7 times lower concentration than in other organs. This result is in agreement with the other authors, who detected $AlPcS_4$ in the brain 8–50 fewer times than in other organs (4, 7). The fluorescence intensity of $AlPcS_4$ in all our investigated samples was about 4.8 times higher than the one of Photogem®.

During our study it was found out that endogenous porphyrins accumulate in some rat tissues. They were identified considering the main tissue autofluorescence peak position (with λ_{ex} = 405 nm): protoporphyrin IX (fluorescence peak at 635 nm), uroporphyrin (620 nm) and coproporphyrin (625 nm) (11, 15–17). The biggest quantities of protoporphyrin IX were observed in Harderian gland. It also appears in lower concentrations in digestive tract, skin and liver. Protoporphyrin IX is thought to pass from the Harderian gland with tears through nasal duct into nasal cavity, pharynx, and oesophagus and further on to the digestive tract. This way of passage was also observed by other authors (18, 19).

There can be many reasons for the origin of endogenous porphyrins in other organs. In our study uroporphyrin was observed in the kidney, whereas coproporphyrin in the brain white matter and cerebellum. The level of porphyrins in the organism may increase because of various disturbances of heme biosynthesis. The activities of heme biosynthesis enzymes change in the case of inherited diseases (porphyrias), inflammatory processes, pathological conditions or other physiological stresses (17, 20).

The accumulation of endogenous porphyrins in the brain white matter was also observed by other authors (2, 21). It was reported that porphyrins in the grey matter occur at lower concentrations than in myelinated tissue structures. This phenomenon is explained by the fact that heme biosynthesis in oligodendrocytes and Schwann cells, which form the myelin sheaths, is more intense than in other nervous tissue cells (2, 22).

Whereas the fluorescence spectra of endogenous porphyrins and Photogem® overlap, the use of this sensitizer in the brain tumour fluorescence diagnostics would be complicated: it would be difficult to distinguish fluorescence of the accumulated Photogem® in neoplastic tissue from the surrounding healthy areas with very similar optical properties. On the other hand, a part of excitation light for Photogem® (405 nm) is also absorbed by endogenous porphyrins, and less sensitizer's molecules are excited. These disadvantages are not characteristic of $AlPcS_4$. The excitation light, which would be used in $AlPcS_4$ sustained diagnostics, would not be absorbed by endogenous porphyrins, and more intense fluorescence signal could be detected. Moreover, $AlPcS_4$ fluorescence spectrum does not overlap with the spectra of endogenous porphyrins. Using $AlPcS_4$ in fluorescence diagnostics, more intense fluorescence signal and higher accuracy could be achieved. Therefore, $AlPcS_4$ would be a more effective marker in the brain tumours fluorescence diagnostics.

CONCLUSIONS

Our study shows that Photogem® poorly accumulates in healthy rat brain and it is not detectable by fluorescence spectroscopy, while fluorescence of $AlPcS_4$ is observed in all the brain structures. The fluorescence of Photogem® during intra-operative tumour delineation could be mistaken for fluorescence of endogenous porphyrins which occur naturally in the healthy brain tissue. The fluorescence of $AlPcS_4$ is more intense and it does not overlap with the fluorescence of endogenous porphyrins, therefore, $AlPcS_4$ would be more suitable for the brain tumour fluorescence diagnostics.

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Vytautas Kulvietis, Eugenijus Zakarevičius, Juozas Lapienis, Gražina Graželienė, Violeta Žalgevičienė, Ričardas Rotomskis

EGZOGENINIŲ SENSIBILIZATORIŲ KAUPIMASIS ŽIURKĖS GALVOS SMEGENYSE

S a n t r a u k a

Galvos smegenų navikų ribas galima nustatyti fluorescencine diagnostika, kurios metu į organizmą suleidžiamos kontrastinės medžiagos – sensibilizatoriai, kurie susikaupia ir pasiskirsto organizme. Vis dėlto hematoencefalinis barjeras riboja šių medžiagų patekimą ir kaupimąsi smegenų audiniuose. Deja, šiuo metu nėra atlikta pakankamai palyginamųjų studijų apie skirtingų sensibilizatorių tinkamumą galvos smegenų navikų diagnostikai. Todėl šio darbo tikslas buvo fluorescenciniu metodu palyginti dviejų sensibilizatorių susikaupimą ir pasiskirstymą sveikų žiurkių galvos smegenyse.

Sensbilizatoriai – Fotohemas (Photogem®) ir aliuminio ftalocianino tetrasulfonatas ($AlPcS_4$) – buvo lygiomis dozėmis (5 mg/kg) suleidžiami į Wistar baltųjų žiurkių uodegos veną. Po atitinkamo inkubacinio laikotarpio gyvūnai buvo numarinami. Fluorescenciniam tyrimui buvo ruošiami smegenėlių, baltosios ir pilkosios didžiųjų smegenų pusrutulių medžiagos bei kitų audinių bandiniai. Sensibilizatorių susikaupimas buvo vertintas pagal pagrindinės sensibilizatoriaus fluorescencijos smailės intensyvumą.

Mūsų duomenimis, Fotohemo fluorescencija galvos smegenų audiniuose nebuvo stebima, tačiau ji užfiksuota kituose organuose. $AlPcS_4$ fluorescencija buvo daug intensyvesnė, tik galvos smegenyse tas intensyvumas buvo vidutiniškai 7 kartus mažesnis negu kituose organuose. Taip pat nustatyta, jog sveikų žiurkių galvos smegenų baltojoje medžiagoje natūraliai kaupiasi endogeniniai porfirinai, kurių fluorescencija galėtų trukdyti Fotohemo identifikavimui tiek sveikame, tiek navikiniame audinyje.

Taigi Fotohemas prastai kaupiasi žiurkės galvos smegenų struktūrose, o jo fluorescenciją maskuoja endogeniniai fluoroforai. Tuo tarpu $AlPcS_4$ aptinkamas galvos smegenyse ir jo fluorescencija aiškiai identifikuojama. $AlPcS_4$ yra potencialiai tinkamesnis sensibilizatorius galvos smegenų navikų fluorescencinei diagnostikai.

Raktažodžiai: hematoencefalinis barjeras, fluorescencinė spektroskopija, galvos smegenų navikų diagnostika, sensibilizatorius, Photogem, $AlPcS_4$