Application of Atmospheric Microplasma for Nose to Brain Drug Delivery

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Introduction

Intranasal administration has been reported to be a potential pathway for nose-to-brain (N2B) delivery of drugs for the treatment of neurological diseases [1].

However, nasal physiology can hinder drug absorption and limit bioavailability. Studies of dielectric barrier discharge (DBD) microplasma has been shown to enhance transdermal drug delivery [2].

This novel study aimed to deliver galantamine hydrobromide into the brain of Sprague Dawley (SD) rat using the assistance of a non-thermal plasma (NTP). The type of NTP used in this study is DBD microplasma.

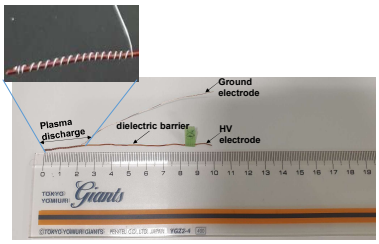
The effect of DBD microplasma discharge for N2B drug delivery was investigated using MALDI-IMS. The drug distribution to brain and kidney of plasma treated rat was compared to non-plasma treated rat.

Methods

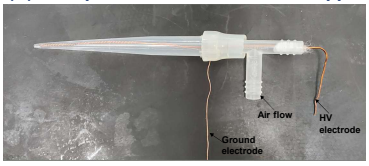
This study was performed at Hamamatsu University School of Medicine. It complied with the regulations for Care and Use of laboratory Animals. 8 weeks male SD rat were purchased from Japan SLC Inc.

The rats were anesthetized and kept in supine position. The plasma electrode is inserted into the rat left nose and energizes at discharge voltage of 1.4kV$_{(0\text{-}p)}$ for 4 min at room condition with 0.2L/min air flow rate. Immediately after plasma treatment, 10 µl of galantamine hydrobromide was intranasally administered to each nose in a drop of 2 µl simultaneously. The rat remained in supine position for 10 min before transferring to cage. The rat was sacrifice after 1 hour at the cage.

(A) DBD plasma electrode design structure



(B) DBD plasma electrode for N2B application



(C) Experimental conditions

Discharge voltage	1.2 kV $_{(0\text{-}p)}$
SINE frequency	5 kHz
Gas flow rate	0.2 L/min room air
Treatment time	4 min
Animal	8 weeks SD rat
Weight	280 g, and 275 g
Nose diameter	0.1 mm
Drug	Galantamine hydrobromide
Drug volume	10 µL/nostril

Experimental setup

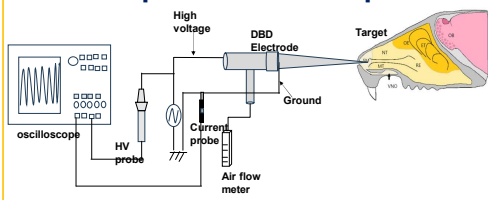


Fig 1a: Schematic diagram of the DBD microplasma set-up

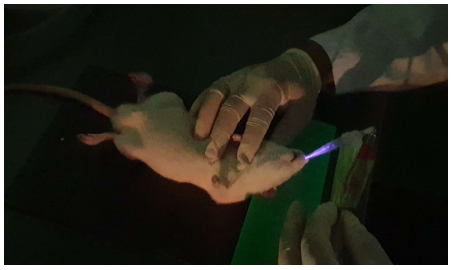


Fig 1b: DBD plasma electrode is energized in room air and the radiative state of plasma discharge is observed in a dark room during treatment of the nose.

Results

(A) Rat brain: Galantamine detection at *m/z* 288.16 [M+H]$^+$

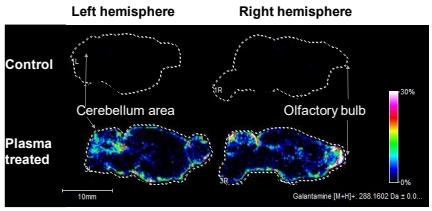


Fig 2a: MALDI ion images showing high galantamine detection in the left and right brain of plasma treated rat compared to control rat

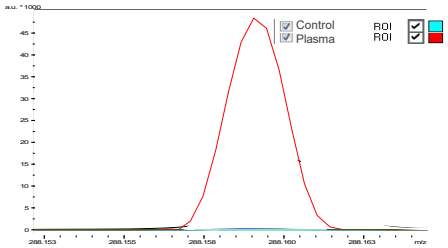


Fig 2b: MALDI expanded spectra images showing high galantamine detection in the brain of plasma treated rat compared to control rat

(B) Rat kidney: Galantamine detection at *m/z* 288.16 [M+H]$^+$

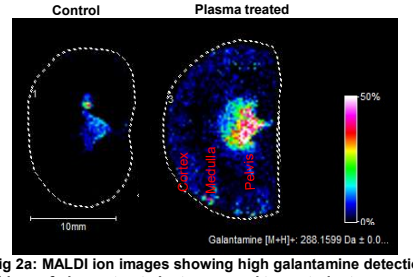


Fig 2a: MALDI ion images showing high galantamine detection in the kidney of plasma treated rat compared to control rat

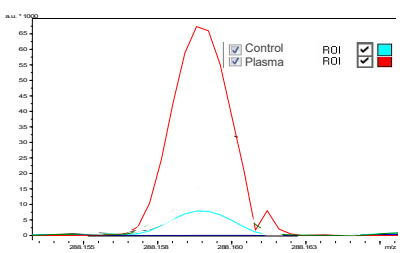


Fig 2b: MALDI expanded spectra images showing high galantamine detection in the brain of plasma treated rat compared to control rat

Discussion

To observe the efficiency of the thin DBD microplasma electrode for N2B drug delivery, Matrix-Assisted Laser Desorption Ionization-Imaging Mass Spectrometry (MALDI-IMS) was used to evaluate the distribution of galantamine in brain section. The result showed higher distribution of galantamine in both left and right brain hemisphere of plasma treated rat when compared to non-plasma treated rat. When the kidney tissue was evaluated, a similar trend was observed.

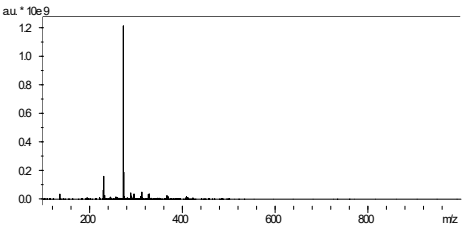


Fig 3a: MALDI-IMS full mass spectra for detection of galantamine in rat brain and kidney section

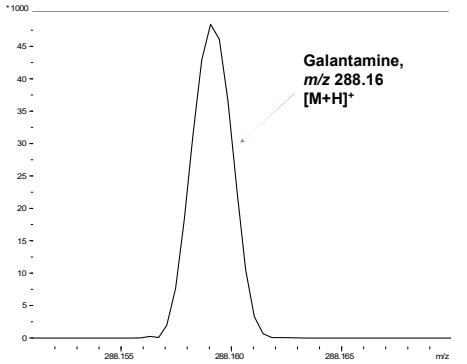


Fig 3b: MALDI-IMS expanded mass spectra of galantamine detected at m/z of 288 [M+H]$^+$ in the rat brain and kidney section.

Conclusion

❑ In brain;

Though plasma discharge was in the left nostril, drug distribution was observed in both left and right brain. The distributions was most prominent in the olfactory bulb and cerebellum areas of plasma assisted intranasal drug delivery.

❑ In kidney;

Galantamine distribution was observe in renal pelvis of both plasma and non-plasma treated rat. Most prominent distributions was observed in the renal pelvis areas of plasma treated rat and exclusively observed in the renal cortex of plasma treated rat only.

Reference

1. Flamm J., Hartung S., Gänger S., Maigler F., Pitzer C., Schindowski K. (2022). Establishment of an olfactory region-specific intranasal delivery technique in mice. Front. Pharmacol., 12:789780. https://doi.org/10.3389/fphar.2021.789780
2. Shimizu K., Hayashida K., Blajan M. (2015). Improving transdermal drug delivery by atmospheric microplasma irradiation. Biointerphases, 10(2):029517. https://doi.org/10.1116/1.4919708