Makarova *et al.: Intrinsic Activity*, 2017; **5**(Suppl.2):A2.21
doi:10.25006/IA.5.S2-A2.21
published online: 16 October 2017

INTRINSIC ACTIVITY

2nd International Conference in Pharmacology: From Cellular Processes to Drug Targets

Rīga, Latvia, 19–20 October 2017

MEETING ABSTRACT

A2.21

The comparative effects of carnitine and γ-butyrobetaine on elimination of meldonium: competition for OCTN2-mediated transport

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Background: The inhibition of organic cation transporter 2 (OCTN2) leads to a decrease in carnitine and acylcarnitine contents in tissues and energy metabolism optimization-related cardioprotective effects. The most potent clinically used inhibitor of OCTN2, the anti-ischemic drug meldonium, was recently included in the World Anti-Doping Agency List of Prohibited Substances and Methods due to possible enhancement of physical performance. In addition to the transport of endogenous carnitine, OCTN2 ensures the kidney reuptake of exogenous compounds, their transport to and accumulation in tissues and it could be responsible also for the observed unusually long elimination time of meldonium.

Objective: The aim of this study was to test the rate of meldonium washout after the end of the treatment and compare the effects on the washout duration of OCTN2 substrates, carnitine and γ-butyrobetaine (GBB), to evaluate the importance of competition for OCTN2 transport and pharmacokinetics of meldonium in mice.

Methods: Twenty-five male SW mice (6 weeks old, Tartu, Estonia) were divided into 5 groups. Twenty mice received meldonium (400 mg/kg) with drinking water for 2 weeks. One group was sacrificed after meldonium treatment; the other groups received water, GBB (200 mg/kg) and carnitine (200 mg/kg) with drinking water for one week to evaluate washout. Plasma, urine, and tissue samples were collected and stored at −20 °C. The concentrations of meldonium, carnitine and GBB were measured using the UPLC/MS/MS method.

Results: Administration of carnitine and GBB effectively stimulated the washout of meldonium. GBB had a more pronounced effect on meldonium elimination than carnitine due to the higher affinity of GBB for OCTN2.

Conclusions: The competition of meldonium, carnitine and GBB for OCTN2-mediated transport determines the pharmacokinetic properties of meldonium. The unusually long washout period of meldonium after long-term treatment is determined by OCTN2-mediated transport that ensures a high muscle content of meldonium, while tissue clearance depends on relatively slow diffusion.

Acknowledgements: This study was supported by the European Regional Development Fund project no. 1.1.1.2/VIAA/1/16/245.

Keywords: meldonium – carnitine – γ-butyrobetaine – pharmacokinetic

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