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Short communication

Trimetazidine increases [^{3}H]glucose uptake in rat brain

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Abstract:
Trimetazidine, a clinically effective antianginal agent with no negative inotropic or vascular properties, acts by optimizing cardiac energy metabolism through inhibition of free faty acid oxidation, shifting substrate utilization from fatty acids to glucose. Up to now there has been no study associating trimetazidine's effect on metabolic processes with glucose utilization in the mammalian brain. The objective of the present study was to determine if trimetazidine altered [^{3}H]glucose uptake in rat brain. Adult male Wistar rats were administered trimetazidine (Metazydyna, Polfa) either as a single dose (10.0 mg/kg *po*) or for 14 consecutive days (5.0 mg/kg *po* per day) or vehicle saline (2.0 ml/kg *po*). Sixty minutes after the single dose or 14th dose of trimetazidine, and 15 min before experiment termination and brain dissection, 6-[^{3}H]D-glucose (500 Ci/kg *ip*; Amersham) was administered. Using liquid scintillation counting, trimetazidine, either in a single or multiple dose regimen, was found to increase [^{3}H]glucose uptake (DPM/100 mg of wet tissue) in all dissected regions of the brain (i.e., striatum, hippocampus, frontal cortex, thalamus with hypothalamus, pons with medulla oblongata, and cerebellum). Therefore, central effects need to be taken into considereation as possibly adding to known beneficial cardiac effects of trimetazidine.

Key words:
trimetazidine, [^{3}H]glucose, brain, rats

Introduction

Optimizing energy metabolism in the heart is a novel approach for the management of ischemic heart disease, particularly in conjugation with optimizing or restoring coronary flow. In particular, promoting myocardial glucose metabolism can enhance heart function, limit injury to tissue, or both [3]. Several pharmacological agents that directly stimulate myocardial glucose oxidation secondary to inhibition of oxidation of fatty acids are now available. Trimetazidine is the first compound in the class of 3-ketoacyl-coenzyme A thiolase inhibitors to see widespread clinical use. It is a clinically effective antianginal agent with vasodilatatory properties [2]. Trimetazidine also increases glucose oxidation in the isolated working rat heart [2], and increases glucose metabolism in the resting heart by direct inhibition of fatty acid metabolism [4]. In our preliminary study, we partially confirmed that trimetazidine applied for 14 days at a dose of 5.0 mg/kg *po* in rats, increased exogenous [^{3}H]glucose uptake in the muscle of the right heart ventricle [8].

* A part of this study was presented during XL Congress of the Polish Biochemical Society, Lublin, September 19–23, 2005. Abstract P7.50.

The central nervous system (CNS) plays an important regulatory role in cardiac function. In order to assess whether the CNS might be directly affected by trimetazidine and thus potentially exert some influence on the supposed cardiac effects of trimetazidine, the influence of trimetazidine on [^{3}H]glucose uptake in the brain of adult rats was investigated.

Materials and Methods

Adult male Wistar rats, weighing approximately 250 g, were used for this study. Rats were housed singly in a room at 22 ± 1°C, with an alternating light/dark cycle of 12 h (lights on at 07.00). Rats had free access to water and standard food pellets (Labofeed, A. Morawski's Animal Food Works, Kcynia, Poland). All studies were approved by the Local Bioethics Committee for Experiments on Animals of the Medical University of Silesia (permission # 42/04 issued on 15.09.2004).

Rats were divided into 3 groups. The first group received trimetazidine (Metazydyna, Polfa, Poland) at a single dose of 10.0 mg/kg *po*. The second group received 14 consecutive daily treatments with trimetazidine 5.0 mg/kg *po*. Drugs were prepared from the tablets, suspended in 0.9% NaCl and applied by stomach tube (*po*) in a volume of 2.0 ml/kg. Control rats received vehicle (2.0 ml/kg *po*) once daily for 14 consecutive days.

At 60 min after the last administration of trimetazidine or vehicle, all rats from each group were injected intraperitoneally (*ip*) with [^{3}H]glucose (6-[^{3}H]D-glucose; Amersham Radiochemicals, Pittsburg, PA, USA; 41 Ci/mmol), at a dose 500 μCi/kg. After 15 min, rats were sacrificed and their brains were immediately excised and placed on ice, while the striatum, hippocampus, frontal cortex, hypothalamus with thalamus, pons with medulla oblongata, and cerebellum were removed, weighed, and placed in 20-ml scintillation vials. Soluene-350 (Pacard Inc., Downers Grove, Ill. USA; 1 ml) was added to each vial, and the tightly-closed vials were incubated at 37°C for 48 h, by which time the tissues were completely solubilized. Then, 10 ml of scintillation cocktail (Dimilume-350, Pacard Inc.) was added and the vials were briefly vortexed and placed in a scintillation counter (Liquid Scintilation Counter: DSA 14091, Wallac, Finland). Radioactivity was assessed twice for 2 min each time, and the mean ± SEM of DPM (disintegrations per minute) per 100 mg of tissue wet weight was calculated for each group 9. Each group consisted of 5 rats (tissues).

Statistical analysis

Analysis of variance (ANOVA) and the post-ANOVA test of Newman-Keuls were used to compare the differences between groups for significance. A "p" value of 0.05 or less was considered as a significant difference between groups.

Results and Discussion

Trimetazidine administered as a single and multiple dose (14 days) increased [^{3}H]glucose levels, as assessed by DPM per 100 mg of wet tissue, in all examined regions of the brain, *vs.* control (Fig. 1). Tritium levels were somewhat higher after multiple dosing, but not significantly different from levels in the group treated with a single dose of trimetazidine.

To the best of our knowledge, following an appropriate literature search, there have been no prior data on trimetazidine and glucose uptake and utilization in the brain. There is scant information about other effects of trimetazidine on the CNS. For example, trimetazidine exerted potent neuroprotective effects against stroke in the gerbil model of transient forebrain global ischemia [1]. Trimetazidine prevented formation of free radicals, reduced lipid peroxidation, prevented a decrease in activity of antioxidant sys-

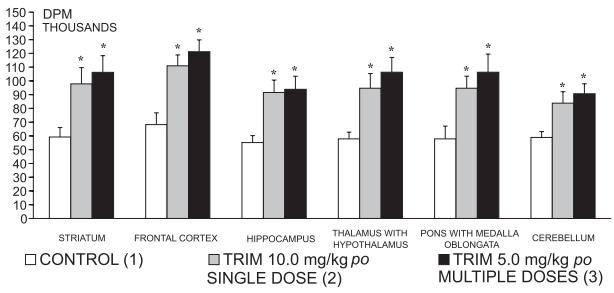

Fig. 1. Effect of trimetazidine on [^{3}H]glucose uptake in rat brain regions. Glucose level is expressed as radioactivity (DPM, per 100 mg of tissue, wet weight) (x ± SEM, n = 5). TRIM = trimetazidine; * $p < 0.05$ *vs.* the control group

tems [6, 7], and also reduced the number of damaged cells in cerebral tissue during the period of ischemia-reperfusion injury [5]. In the brain, trimetazidine appeared to restore ATP synthesis in the mitochondria of rat brain exposed to cyclosporins [10]. It is difficult to directly address the question of whether there are similar CNS energetic effects as in cardiac muscle after trimetazidine. It must be stressed that glucose, not fatty acids is the single source of energy in the brain [10]. Mechanisms by which trimetazidine exerts its central effect on [^{3}H]glucose uptake in the brain are difficult to explain and need further study in details.

Our findings appear to be novel, showing that trimetazidine exerts central beneficial effects by increasing glucose utilization in the brain, thereby supporting its beneficial central and peripheral action on the circulatory system.

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