PRACA ORYGINALNA

Effect of chlorpheniramine and cimetidine, a histamine H_1 and H_2 antagonist on (^{3}H)glucose uptake in the brain of adult rats lesioned with 5,7-dihydroxytryptamine as neonates

Wpływ chlorfeniraminy i cymetydyny, antagonistów receptorów histaminowych H_1 i H_2 na wychwyt (^{3}H)glukozy w mózgu dorosłych szczurów po podaniu noworodkom 5,7-dihydroksytryptaminy

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ABSTRACT

BACKGROUND

The aim of the study was to examine effect of chlorpheniramine (histamine H_1 receptor antagonist) and cimetidine (histamine H_2 receptor antagonist) on (^{3}H)glucose uptake in the brain of adult rats lesioned with 5,7-dihydroxytryptamine (neurotoxin for the central serotoninergic system) as neonates.

MATERIAL AND METHODS

Male 3-days old Wistar rats were injected with serotoninergic neurons neurotoxin 5,7-dihydroxytryptamine, 75 µg *icv*. Control rats were injected with saline 10 µg *icv*. At 8 weeks level of 5-HT and 5-HIAA was estimated in the striatum, frontal cortex and hippocampus of the brain. Other 8 weeks old animals of control and 5,7-DHT lesioned as neonates were injected with S(+)chlorpheniramine (H_1 receptor antagonist) 10.0 mg/kg *ip* or with cimetidine (H_2 receptor antagonist) 5.0 mg/kg *ip*. Control rats were injected with saline 1.0 ml/kg *ip*. 60 minutes later 6-(^{3}H)-D-glucose was applied in a dose of 500 µCi/kg *ip* and 15 minutes later all rats were decapitated and their brains were excised, placed on the ice and sample of frontal cortex, striatum, hippocampus, thalamus with hypothalamus, pons and cerebellum were separated and weighted. Then in the examined tissues radioactivity was measured in liquid scintillation counter and expressed in DPM/100 mg of wet tissue.

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RESULTS
5,7-DHT decreased significantly the level of 5-HT and 5-HIAA in all examined tissues in the brain of adult rats. In rats neonatally lesioned with 5,7-DHT radioactivity significantly increased as compare to the control. Chlorpheniramine prevent significantly that effect in the frontal cortex and cimetidine in the frontal cortex, hippocampus and cerebellum.

CONCLUSION
From above we conclude that in the brain of mammalians the metabolic link between histaminergic and serotoninergic system exist in regulation of energetic prcesses connected with glucose metabolism.

KEY WORDS
5,7-DHT, 5-HT, 5-HIAA, chlorpheniramine, cimetidine, 6-^{3}H-D-glucose, brain, rats

STRESZCZENIE

WSTĘP
Celem pracy było zbadanie wpływu chlorfeniraminy, antagonisty receptora histaminowego H_1 i cymetydyny, antagonisty receptora histaminowego H_2 na wychwyt (^{3}H)glukozy w mózgu dorosłych szczurów z lezją (zniszczenie) ośrodkowego układu serotoninergicznego wywołaną podaniem noworodkom neurotoksyny 5,7-dihydroksytryptaminy.

MATERIAŁ I METODY
Trzydniowe noworodki płci męskiej szczepu Wistar otrzymały do bocznej komory mózgu (*icv*) 75 µg 5,7-dihydroksytryptaminy (5,7-DHT), neurotoksynę układu serotoninergicznego. Zwierzęta kontrolne otrzymały *icv* 10 µl 0,9% roztworu NaCl. Po osiągnięciu 8 tygodni życia zwierzęta dekapitowano i w korze czołowej, prążkowiu oraz zakręcie hipokampa oznaczono zawartość 5-HT i 5-HIAA metodą HPLC/ED. Osobnej grupie badanej i kontrolnej podano S(+)chlorfeniraminę 10,0 mg/kg *ip* (antagonista receptora histaminowego H_1) lub cymetydynę 5,0 mg/kg *ip* (antagonista receptora histaminowego H_2). Zwierzęta kontrolne obu grup otrzymały 0,9% roztwór NaCl 1,0 ml/kg *ip*. Po 60 minutach wszystkie szczury otrzymały 6-(^{3}H)-D-glukozę 500 µCi/kg *ip*. Po dalszych 15 minutach zwierzęta dekapitowano, wyjmowano z czaszki mózg, separowano z niego korę czołową, prążkowie, hipokamp, wzgórze z podwzgórzem, most i móżdżek, w których oznaczono radioaktywność przy użyciu licznika scyntylacyjnego. Wyniki wyrażono w DPM (Desintegrations Per Minute) na 100 mg świeżej tkanki.

WYNIKI
5,7-DHT podany noworodkom znamiennie obniżył zawartość 5-HT i 5-HIAA w badanych fragmentach mózgu dorosłych szczurów. U zwierząt z lezją ośrodkowego układu serotoninergicznego we wszystkich badanych częściach mózgu wykazano znamienny wzrost wychwytu (^{3}H)glukozy. Badani antagoniści receptorów histaminowych nie wpływali na wychwyt (^{3}H)glukozy w mózgu zwierząt grupy kontrolnej, natomiast chlorfeniramina zapobiegała wychwytowi glukozy tylko w korze mózgowej, a cymetydyna w korze mózgowej, hipokampie i móżdżku zwierząt z lezją ośrodkowego układu serotoninergicznego wywołaną podaniem noworodkom 5,7-DHT.

WNIOSKI
Wyniki wskazują na metaboliczne powiązania w mózgu ssaków między układem serotoninergicznym i histaminergicznym.

SŁOWA KLUCZOWE
5,7-DHT, 5-HT, 5-HIAA, chlorfeniramina, cymetydyna, 6-(^{3}H)-D-glukoza, mózg, szczury

INTRODUCTION

Glucose is the main energy source in mammalian brain. Many factors and agents can influence and modify glucose uptake in brain. We showed that 6-hydroxydopamine (6-OHDA), a neurotoxin for the central dopaminergic system [1] applied to newborn rats in a dose of 134 µg icv reduced [^{3}H]glucose uptake in the brain of adult rats [2]. In those animals an increase of serotoninergic and histaminergic activity was observed in brain [3–5]. Beside we founded that in 5,7-dihydroxytryptamine (5,7-DHT) lesioned rats as neonates increase of (^{3}H)glucose uptake in the brain of adult rats, and thioperamide, a central histamine H_3 receptor antagonist prevents this effect [6]. Therefore, the aim of the present study was to examine the effect of 5,7-DHT, a neurotoxin for the central serotoninergic system applied to newborn rats on (^{3}H)glucose uptake in the brain of adult rats, and effect of chlorpheniramine and cimetidine a histamine receptor H_1 and H_2 antagonist on it.

MATERIALS AND METHODS

At 3rd day after birth male Wistar rat pups were pretreated with 5,7-DHT 75 µg introcerebroventricularly (*icv)*, (base form, half on each side with 0.1% ascorbic acid – Sigma MO, USA) or saline with 0.1% ascorbic acid vehicle (5 µl on each side). For details see Brus et al. [4]. Rat's pups remained with their mothers until 21st day, then were separated to individual cages. All rats were kept under a 12 h light: 12 h dark cycle in a well ventilated room, at 22 ± 1°C, with free access to food and tap water. This study was approved and controlled by the Local Ethics Committee for Animals at the Medical University of Silesia (permission no 4/2008 issued on 08.01.2008).

When rats attained of 8 weeks biochemical studies were performed. Rats of both groups were scarified by decapitation and the brains were immediately excised and placed on the ice. The corpus striatum, frontal cortex and gyrus hippocampus were separated at temperature of 0°C, placed on dry ice, weighed and stored at -70°C pending of analysis of 5-hydroxytryptamine (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) by an HPLC/ED technique [7]. Results were expressed as ng/g of wet tissue.

Adult rats of both groups (control and neonatally lesioned with 5,7-DHT) were injected with saline vehicle or S(+)chlorpheniramine (histamine H_1 receptor antagonist) 10.0 mg/kg *ip* (Sigma MO, USA) or with cimetidine (histamine H_2 receptor antagonist) 5.0 mg/kg *ip* (Polfa, Poland). Then 60 minutes later all rats were injected with 6-(^{3}H)-D-glucose (Amersham Radiochemicals, Pittsburg, PA, USA) in a dose of 500 µCi/kg *ip*. 15 minutes later rats were decapitated without anaesthesia. Their brains were immediately excised and placed on ice, for dissection of samples (50–100 mg) of frontal cortex, striatum, hippocampus, thalamus with hypothalamus, pons, and cerebellum. Individual tissues were weighed and placed in 20 ml scintillation vials containing 1 ml of Soluene-350 (Packard Inc., Downers Grove, IL, USA). Each vial was then tightly sealed and incubated at 37°C for 48 h, for solubilization of tissue. Scintillation cocktail Dimilune-30 (Packard Inc., Downers Grove, IL, USA) 10 ml then added and vials were briefly vortexed and placed in a scintillation counter (DSA 14091, Wallac, Finland). Measurement of radioactivity was performed twice for two minutes and the mean was taken. Finally, the mean ± SEM DPM (desintegrations per minute) per 100 mg of wet tissue was calculated for each tissue and group.

Data were analyzed by two-way ANOVA and the post-ANOVA test of Neuman-Kuels. Differences in p values of < 0.05 were considered significant.

RESULTS

5,7-DHT injected to newborn rats decreased 5-HT and 5-HIAA level in significant way in all examined parts of the brain of adult rats (tab. I).

5,7-DHT applied to newborn rats significantly increased (^{3}H)glucose uptake in all examined parts of the brain of adult rats as compare to the control group (fig. 1, 2). Chlorpheniramine 10.0 mg/kg *ip* and cimetidine 5.0 mgkg *ip* did not change (^{3}H)glucose uptake in the intact group of rats versus respective control and prevented (^{3}H)glucose uptake in the frontal cortex of 5,7-DHT neonatally lesioned adult rats (fig. 1). Cimetidine prevented (^{3}H)glucose uptake in the frontal cortex, hippocampus and cerebellum versus respective control (5,7-DHT lesioned rats) (fig. 2).

Table I. Effect of 5,7-dihydroxytryptamine 75 µg icv applied to newborn rats on 5-HT and 5-HIAA level in brain of adult rats (X ± SEM; n = 5–8)

Tabela I. Wpływ podania dokomorowo 75 µ 5,7-dihydroksytryptaminy noworodkom szczurzym na stężenie 5-HT i 5-HIAA w mózgu dorosłych szczurów (X ± SEM; n = 5–8)

Part of the brain	5-hydroxytryptamine ng/g of wet tissue		5-hydroxyindoleacetic acid ng/g of wet tissue	
	saline 10 µl icv	5,7-dht 75 µg icv	saline 10 µl icv	5,7-dht 75 µg icv
Striatum	562 ± 42	62* ± 21	307 ± 55	96* ± 22
Frontal cortex	244 ± 19	22* ± 9	202 ± 19	35* ± 13
Hippocampus	255 ± 21	43* ± 14	221 ± 16	42* ± 13

*p < 0.05 versus: saline

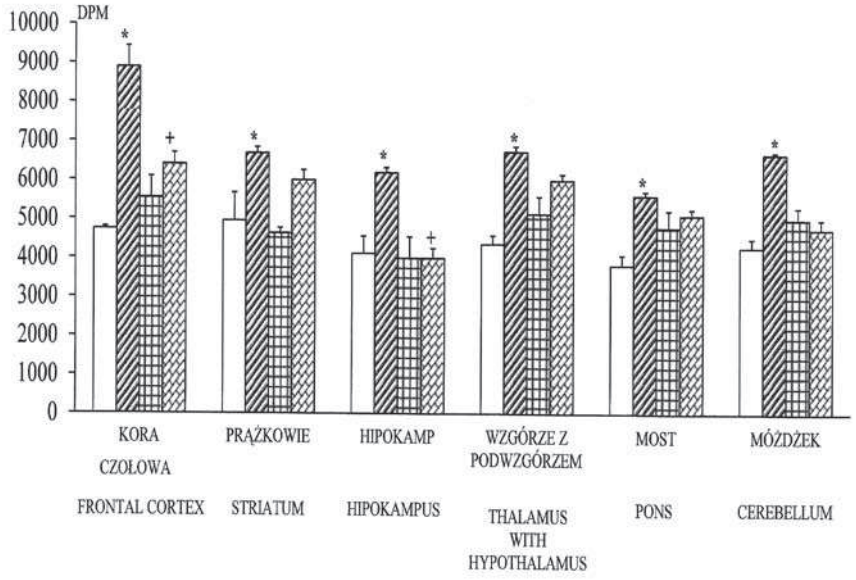

Fig. 1. Effect of S(+)chlorpheniramine on (^{3}H)glucose uptake in the brain of adult rats lesioned with 5,7-dihydroxytyramine as neonates (x ± SEM; n = 5).

- 0.9% NaCl 10 ml *icv* as neonates; 0.9% NaCl 1,0 ml/kg *ip* as adult; (^{3}H)glucose 500 µg/kg *icv*
- 5.7-Dihydroxytryptamine 75 µg *icv* as neonates; 0.9% NaCl 1.0 ml/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult
- 0.9% NaCl 10 µl *icv* as neonates; S(+)Chlorpheniramine 10.0 mg/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult
- 5.7-Dihydroxytryptamine 75 µg *icv* as neonates; 0.9% NaCl 1.0 ml/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult

Explanation:
* p < 0.05 versus to the 0.9% NaCl *ip*
+ p < 0.05 versus to the 5,7-DHT *icv*

Ryc. 1. Wpływ S(+)chlorfeniraminy na wychwyt (^{3}H)glukozy w mózgu dorosłych szczurów, u których w okresie noworodkowym dokonano uszkodzenia mózgu 5,7-dihydroksytyraminą (X ± SEM; n = 5).

- 10 ml 0,9% NaCl podane dokomorowo noworodkom; 1,0 ml/kg 0,9% NaCl podane dootrzewnowo dorosły; 500 µg/kg (^{3}H)glukozy podane dokomorowo
- 75 µg 5,7-Dihydroxytryptaminy podane dokomorowo noworodkom; 1,0 ml/kg 0,9% NaCl podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym
- 10 µl 0,9% NaCl podane dokomorowo noworodkom; 10,0 mg/kg S(+)Chlorfeniraminy podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym
- 75 µg 5,7-Dihydroxytryptaminy podane dokomorowo noworodkom; 1,0 ml/kg 0,9% NaCl podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym

Objaśnienie:
* p < 0,05 w porównaniu do 0,9% NaCl podanego dootrzewnowo
+ p < 0,05 w porównaniu do 5,7-DHTpodanego dokomorowo

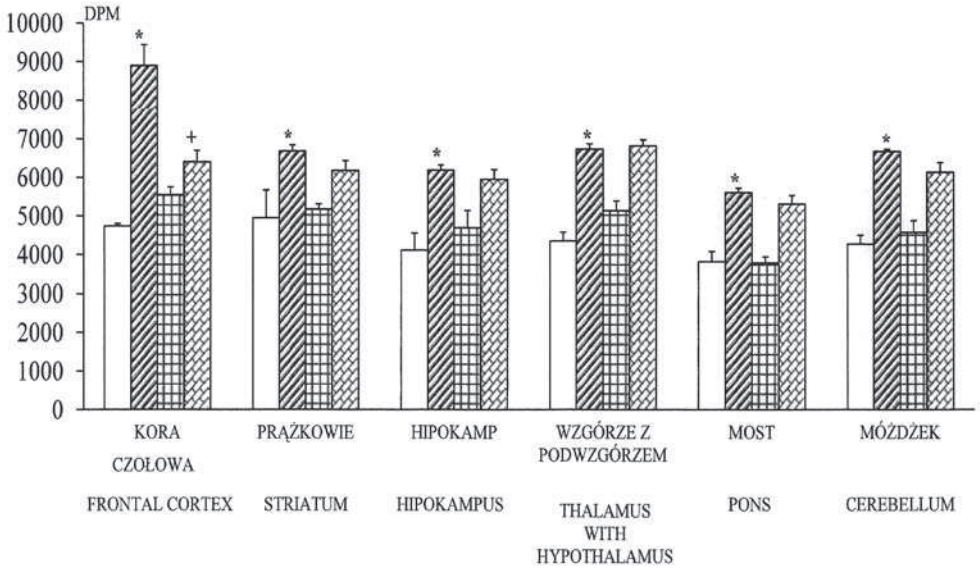

Fig. 2. Effect of cimetidine on (^{3}H)glucose uptake in the brain of adult rats lesioned with 5,7-dihydroxytyramine as neonates (x ± SEM; n = 5).
- 0.9% NaCl 10 ml *icv* as neonates; 0.9% NaCl 1.0 ml/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult
- 5.7-Dihydroxytryptamine 75 µg *icv* as neonates, 0.9% NaCl 1.0 ml/kg *ip* as adult, (^{3}H)glucose 500 µCi/kg *ip* as adult
- 0.9% NaCl 10 µl *icv* as neonates; Cimetidine 5.0 mg/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult
- 5.7-Dihydroxytryptamine 75 µg *icv* as neonates; Cimetidine 5.0 mg/kg *ip* as adult; (^{3}H)glucose 500 µCi/kg *ip* as adult

Explanation:
* $p < 0.05$ versus to the 0.9% NaCl *ip*
+ $p < 0.05$ versus to the 5,7-DHT *icv*

Ryc. 2. Wpływ cymetydyny na wychwyt (^{3}H)glukozy w mózgu dorosłych szczurów, u których w okresie noworodkowym dokonano uszkodzenia mózgu 5,7-dihydroksytyraminą (X ± SEM; n = 5).

- 10 ml 0,9% NaCl podane dokomorowo noworodkom; 1,0 ml/kg 0,9% NaCl podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dokomorowo
- 75 µg 5,7-Dihydroksytryptaminy podane dokomorowo noworodkom; 1,0 ml/kg 0,9% NaCl podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym
- 10 µl 0,9% NaCl podane dokomorowo noworodkom; 5,0 mg/kg Cymetydyny podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym
- 75 µg 5,7-Dihydroksytryptaminy podane dokomorowo noworodkom; 5,0 mg/kg Cymetydyny podane dootrzewnowo dorosłym; 500 µCi/kg (^{3}H)glukozy podane dootrzewnowo dorosłym

Objaśnienie:
* $p < 0,05$ w porównaniu do 0,9% NaCl podanego dootrzewnowo
+ $p < 0,05$ w porównaniu do 5,7-DHTpodanego dokomorowo

DISCUSSION

5,7-DHT is a selective neurotoxin for the central serotoninergic system. Applied to newborn rats in a dose of 75 µg *icv* decreased 5-HT and its metabolite – 5-HIAA content in the brain permanently, for whole life of animals. 5,7-DHT after applying to the brain (*icv*) is uptake via active transport like original neurotransmitter (5-HT) to the serotoninergic neurons where is metabolized to the very active neurotoxic derivatives induced neurons damage [8]. Damage central serotoninergic system with 5,7-DHT caused changes activity of the other systems, mostly dopaminergic one [4,9].

There are some scarce data concern central serotoninergic activity on glucose metabolism in the mammalians brains. Darves and Gudelski [10] presented that activation of the central serotonin 5-HT_2 receptor using respective agonist (DOI) induces glycogenolysis in rat brain. Others presented that quipazine, a 5- HT_3 receptor agonist increased glucose metabolism in the rat's brain measured by quantitative autoradiographic (^{14}C)deoxyglucose technique

[11]. Also m-chlorphenylpiperazine (mCPP), a 5-HT_{2C} central receptor agonist increased glucose utilization in the brains of healthy volunteers examined by 2-(^{18}F)-2-deoxy-D-glucose positron emission tomography [12]. Presented finding that lesion of the central serotoninergic system as neonates increased glucose uptake in the adult rats' brain seems to be the first one.

Histamine (H) is a neurotransmitter with wide distribution in human and mammalian's brain [13]. The cell bodies of histaminergic neurons are located mostly in the *tubero- and mamilary nucleus* of poster hypothalamus [14]. Neurons provide histaminergic fibres to the all areas of the mammalian's brain. Since the time when it was recognized that classic H_1 receptor antagonists used as antiallergic drugs exert significant sedative effect, three types of H receptors were discovered in the brain of mammalians that is H_1, H_2 and H_3 [14,15]. The first two are postsynaptic and H_3 seems to be presynaptic one [16,17]. All of them, but mostly H_3 modulate H release from histaminergic neurons in the brain. Thioperamide is an agent which blocks central H_3 receptor and intensified H release from histaminergic neurons to synaptic cleft [14,18,19]. The H_3 central receptors seem to be a main target in alternative treatment of motor dysfunction in Parkinson's disease.

There are few data only concern effect of the central histaminergic system activity on glucose metabolism in the mammalian brains. Injection of H *icv* to the brain of rats induced hyperglycemic response [20]. Ohters founded that pyrilamine and ranitidine, a H_1 and H_2 receptor antagonists respectively, induced hyperglycemia in anesthetized rats [21]. In the next studies it was founded that metaprine a histamine N-methyltransferase inhibitor, elevated plasma glucose concentration in rats [22]. Others presented that 2-deoxy-D-glucose applied to the brain (*icv*) increased glucose plasma level and pretreatment of animals with cimetidine attenuate observed effect [23]. In our previous study we presented that thioperamide, a histamine H_3 receptor antagonist prevented (^{3}H)glucose uptake in all examined parts of the brain of rats neonatally lesioned rats with 5,7-dihydrxytryptamine as neonates [6].

It is difficult to explain inhibitory effect chlorpheniramine and cimetidine a H_1 and H_2 receptor antagonists on the increased (^{3}H)glucose uptake in the brain of rats with lesioned central serotoninergic system as neonates. Previously we founded that the changed activity of the central dopaminergic system by injection of the neurotoxin 6-hydroxydopamine (6-OHDA) *icv* or a dopamine receptor agonists such as SKF 38393 (D_1 receptor agonist) or quinpirole (D_2/D_3 receptor agonist) influenced (^{3}H)glucose uptake in rats as compare to the control [2,24].

It must be added that 6-OHDA , a neurotoxin of the central dopaminergic system, injected *icv* on the 3rd day of life of newborn rats increased histamine level in the brain of adult animals [6]. On the other hand neonatal lesion of the central serotoninergic system with 5,7-DHT decreased histamine level in the brain of adult rats [6]. Beside, thioperamide histamine H_3 receptor antagonist diminished reactivity of the central dopamine receptors in 6-OHDA neonatally lesioned rats and in opposite intensified it in 5,7-DHT lesioned as neonates adult rats [25,26]. From above we concluded and confirmed that in the brain of mammalians the functional link between histaminergic and serotoninergic system exist.

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