EXPERIMENTAL STUDY

Effects of terguride treatment on glucose abnormalities induced by ischemic brain damage in SHR/N-cp lean Koletsky strain and in rats of Wistar strain

Kudlackova Z, Golda V

*Department of Biological and Medical Sciences Faculty of Pharmacy, Charles University in Prague, Hradec Králové, Czech Republic.***kudlacko@faf.cuni.cz**

Abstract

Background: **Severe head injury is associated with a stress response that includes hyperglycemia, which has been shown in both experimental and clinical studies to exacerbate the severity of brain injury during ischemic conditions.**
Objectives: **This study evaluated the possible protective effect of Terguride (trans-dihydrolisuride) on glucose metabolism against hyperglycemia.**
Methods: **The experiments were performed in male and female rats of Wistar and Koletsky strain. Glucose intolerance was induced in both strains by 4-hour-occlusion of both common carotid arteries followed by 44-hour reperfusion.**
Results: **Brain ischemia induced glucose intolerance in both rat strains. Basal glycemia was significantly increased by the brain ischemia in male and female Wistar rats, but not in Koletsky rats. The analysis of the effect of Terguride treatment of glucose abnormalities on the "area under the glucose tolerance curve" (AUC) has shown significant decrease of AUC in both sexes of Wistar strain and in females of Koletsky strain. Basal glycemia was significantly decreased only in males of Wistar strain.**
Conclusion: **Terguride (trans-dihydrolisuride) decreases hyperglycemia in rats with ischemic brain damage.** ***(Fig. 4, Ref. 29.)***
Key words: brain ischemia, hyperglycemia, glucose tolerance, terguride.

In this study we investigated glucose tolerance abnormalities induced by ischemic brain damage.

Since the time of Claude Bernard it has been known that the hypothalamic lesions cause hyperglycemia and glycosuria. On the other hand, it was reported (Pentelenyi, 1992) that hyperglycemia can be found in patients with brain lesions which do not affect the hypothalamus.

Hyperglycemia is only one variation in the sequence of biochemical changes which is ischemia of brain defined with. The incidence of brain ischemia in industrially advanced countries is 250 – 400/100 000; mortality is 30 % and brain ischemia is the third most frequent cause of death (Dirnagl et al, 1999).

The preclinical histological evaluations demonstrated that hyperglycemia impairs brain damage due to transient ischemia. Extensive lesions were found in the following regions: putamen, hippocampal CA 1 sector, substantia nigra pars reticularis, neocortex, thalamus, globus pallidus, cortex of lobus parietalis, cerebellum, nucleus caudatus, gyrus temporalis superior, and girus cinguli. Ischemic brain injury associated with hyperglycemia-increased incidence of seizures and mortality and impaired motor function were observed in the group of survived animals (Kudláčková and Hronek, 2001 a).

Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University in Prague, Hradec Králové, Czech Republic, and Institute of Experimental Neurosurgery, University Hospital of Faculty of Medicine, Charles University in Prague, Hradec Králové, Czech Republic

Address for correspondence: Z. Kudlackova, Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University in Prague, Heyrovskeho 1203, CZ-500 05 Hradec Kralove, Czech Republic. Phone: +420.49.5067253, Fax: +420.49.5210002

Dedication: I would like to thank my supervisor doc. MUDr. PhDr. Věroslav Golda, CSc. (+19.8. 1999) for leading of my dissertation and also commemorate his scientific effort which he devoted to experimental neurosurgery during all his life.

Acknowledgement: The authors wish to thank G.W.Ashe, Imperial Chemical Industry, Ltd., Pharmacological Division, Macclesfield, U.K., for providing normotensive rats of Wistar strain and Carl T. Hansen, Animal Genetics Division, National Institute of Health, Bethesda, USA, for providing genetically hypertensive rats of Koletsky type.

In clinical studies evaluating patients with serious craniocerebral injury after subarachnoidal hemorrhage, after acute head trauma, after surgical removal of intracranial hematoma, or after cerebral infarct of hemispherium it was observed that hyperglycemia during acute damage is associated with enhanced neuronal death. Hyperglycemia correlated with clinical outcome, early death and invalidism (Kudláčková and Hronek, 2001 b; Els et al, 2002; Yendamuri et al, 2003).

The mechanisms of brain damage, which are caused hyperglycemia during hypoxic-ischemic brain injury, are not completely known. Several reasons for brain damage associated with hyperglycemia have been indicated: lactate acidosis (Siesjö et al, 1996; Parsons et al, 2002), increase in intracellular pH of brain tissue (Li et al, 1995; Dempsey et al, 1996), increase in the recovery rate of ATP levels (Roh et al, 1992), retardation of NADH regeneration (Anderson et al, 1999), accelerating free radical production (1996, Lundgren et al, 1991), hydroxyl radical production (Li et al, 1999; Wei et al, 1997), slower recovery of Na+ homeostasis (Tyson et al, 1996), perturbing action of intracellular signal transduction pathway, leading to changes in gene expression or protein synthesis, or with activation of endonucleases which cause DNA fragmentation (Siesjö et al, 1996), changes in blood-brain barrier transport (Kawai et al, 1999), increase in extracellular glutamate levels. (Guyot et al, 2000; Li et al, 2000).

Results of experimental and clinical studies show that normalization of glucose level during a severe head injury is necessary as protection of hypoxic brain tissue (Kudláčková a Hronek, 2001 a).

On the basis of preclinical and clinical data, which revealed negative effect on hypoxic brain tissue, we determined the aim of our experiments. We evaluated changes of glucose tolerance abnormalities and the effect of Terguride on these abnormalities in rats of Wistar strain and in rats of Koletsky strain.

We can conclude that Terguride is not only a drug which is tested on animals with ischemic brain injury following hyperglycemia. From the facts given below we will see that in experimental studies only insulin and Terguride, used by us, are bent on decreasing hyperglycemia which arised during brain ischemia and other pharmacological procedures always solve only one of the consequences imposed by hyperglycemia. In his study Lanier et al (1996) attempted to find out whether infusion of insulin leads to recovery of normoglycemia by rats with neurological damage and also if neurological after effects of ischemia are comparable with the normoglycemic rats. He found that therapy with insulin led to metabolic profile which was comparable with non-diabetic rats. It is, however, well-know that therapy with insulin would not be sufficient by insulin-resistant rats. Other authors were not directly interested in treatment of hyperglycemia but they were concentrated on treatment of main after-effects that develop because of hyperglycemia e.g.: lactate acidosis, acceleration of free radical production, increase in the recovery rate of ATP levels, acceleration of NO production. Acidosis that arises as a consequence of brain ischemia worsens metabolic regeneration of damaged brain tissue. Kim et al (1996) found that application of Tirilazad showed increased regeneration of ATP, increase of pH, decrease of intracranial pressure, increase of the concentration of endogenous antioxidant gluthation. Dimlich and Nielsen (1992) found that dichloracetate facilitates a decrease in brain lactate during reperfusion after incomplete ischemia in rats. Quast et al (1995) were in their research interested in normalization of imported mediator which evokes postischemic damage in hyperglycemic rats. He proved that inhibitor of NO synthesis: NG-nitro-L-arginin metylester reduces production of edema and improves perfusion. Li et al (1997) found that immunosuppressant cyclosporin A dramatically ameliorates the selective neuronal necrosis which results from 10 min of forebrain in rats. The study of Pahlmark et al (1993) showed that dimethylthiourea (scavenger of free oxygen radicals) significantly reduced damages of neurons in hippocampus, caudoputamen and neocortex. Similar antioxidative effects were found by Watanabene et al (1994) in 3-methyl-1-phenyl-pyrazoli-5on in rats with hyperglycemia with total brain ischemia. All these therapeutic procedures are important, if there cane serious increasing of glycemia. The primary aim of the therapy appears to be the prevention of hyperglycemia development what we tried in our work.

Methods

All experiments performed on laboratory animals were approved by the Ethical Committee of the Faculty of Medicine, Charles University, Hradec Králové.

Animals

Experiments were carried out on the Han-Wistar rats (Imperial Chemistal Industry, Ltd., Pharmacological Division, Macclesfield, U.K.) as well as on lean rats of Koletsky strain (SHR/N-cp) of both sexes. Lean SHR/N-cp rats (Animal Genetics Division, National Institute of Health, Bethesda, U.S.A.) represent dominant non-obese homozygotes and heterozygotes whereas their obese siblings are recessive homozygotes (cp/cp). The abnormal animals were obtained by Koletsky when mating a female spontaneously hypertensive rat (Okamoto-Aoki strain) with normotensive Sprague-Dawley male rat. What considers of lean rats of Koletsky strain, there were proved, except others, there features: hypertension, disorder of glucose tolerance and higher concentration of plasmatic lipids (Koletsky, 1975).

The experiments were carried out on 122 rats weighing 370–390 g (males), 220–250 g (females). Rats were housed at 23±1 °C, 55±10 % relatively humidity, air exchange 12–14 times per hour with a 12 h light-dark cycle. All animals received care according to the guidelines set by the Institutional Animal Use and Care Committee of the Faculty of Medicine, Charles University, Hradec Králové.

After weaning at the age of 30 days, the animals were kept in groups of four and supplied with water and standard pelleted diet ad libitum.

Drugs used

Terguride (trans-dihydrolisuride, Galena, Czech Republic) was used. The drug was applied twice a day at 7 a.m. and 2 p.m.

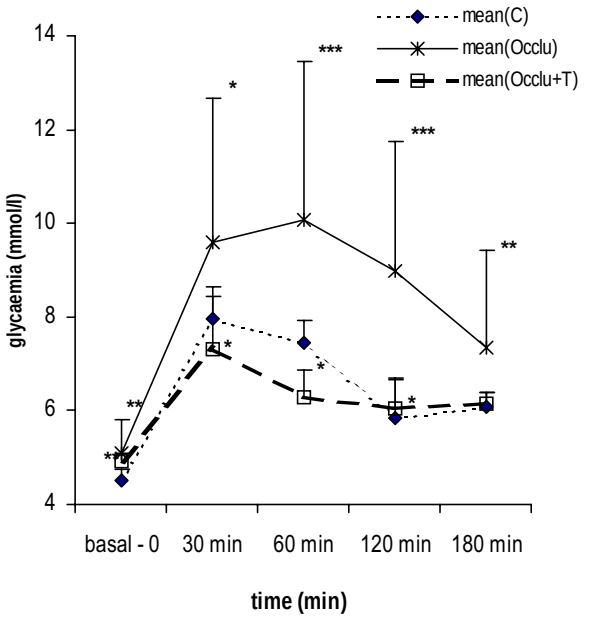

Fig. 1. Effect of Terguride treatment (T) on abnormalities of glucose tolerance curve in rats (males) of Wistar strain. Animals of the group Occlu (animals with bilateral occlusion of common carotid arteries) were compared with animals of the group C (control animals), animals of the group Occlu+T (animals with occlusion and with Terguride treatment) with animals of the group Occlu. n(C)=6, n(Occlu)=12, n(Occlu+T)=5, * p<0.05, ** p<0.01, *** p<0.001.

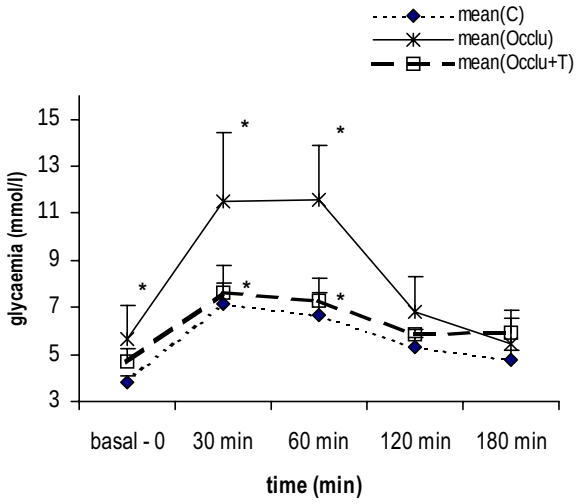

Fig. 2. Effect of Terguride treatment (T) on abnormalities of glucose tolerance curve in rats (females) of Wistar strain. Animals of the group Occlu (animals with bilateral occlusion of common carotid arteries) were compared with animals of the group C (control animals), animals of the group Occlu+T (animals with occlusion and with Terguride treatment) with animals of the group Occlu. n(C)=7, n(Occlu)=6, n(Occlu+T)=4, * p<0.05.

for four days before operation and for two days after operation. Terguride maleate was administered at a dose of 0.1 mg/kg i.p.. Pentobarbital sodium (Nembutal®, sodium solution, Abbott Laboratories, U.S.A.) was used for anesthesia at a dose 45 mg/kg i.p. Ether was applied for evoking light anesthesia, which was used during glucose tolerance test.

Occlusion of common carotid arteries

Occlusion was performed under general anesthesia. The animals were fixed in supine posture, skin was incised in the ventrolateral neck region and the common carotid arteries were separated from surrounding tissue bilaterally. Both arteries were occluded for four hours by Yasargil Standard aneurysm clip (Aesculap, Germany). Subsequently reperfusion period (44 hours) was started.

Glucose tolerance test

After finishing the reperfusion period, glucose tolerance test was performed. Blood was sampled to heparinized capillaries (from retro bulbar plexus under light ether anesthesia) before glucose loading (basal glycemia), as well as 30, 60, 120 and 180 minute after glucose loading. Glucose (3 g/kg b.w. in 30 % solution, Lachema, Czech Republic) was applied intragastrically after 14 hours of starvation. Glycemia was estimated enzymatically (Oxochrom glucose, Lachema, Czech Republic).

Results

Basal glycemia

In the control animals, the occlusion of common carotid arteries showed significant elevation of basal glycemia in male and female rats of Wistar strain (Figs 1 and 2). Occlusion was without effect on basal glycemia in males and females of Koletsky strain (Figs 3 and 4). In occluded animals with treatment of Terguride showed decreasing effect on basal glycemia in males of Wistar strain (Fig. 1). Terguride treatment did not show any effect on basal glycemia in females of Wistar strain and male and female rats of Koletsky strain (Figs 2, 3 and 4).

Glucose tolerance

In control animals, occlusion of common carotid arteries showed elevation of glucose tolerance in both strains. Occlusion showed significant increase 30, 60, 120 and 180 min after glucose loading in males of Wistar strain (Fig. 1). Area under curve of glucose tolerance curve (AUC) was significantly increased ($p<0.01$). Females of Wistar strain (Fig. 2) and males of Koletsky strain (Fig. 3) showed significant increase in 30 and 60 min of glucose tolerance test. AUC was significantly increased ($p<0.01$) in female of Wistar strain. In males of Koletsky strain was AUC as well significantly increased $p<0.05$. Hypertensive females showed significant increase in glycemia

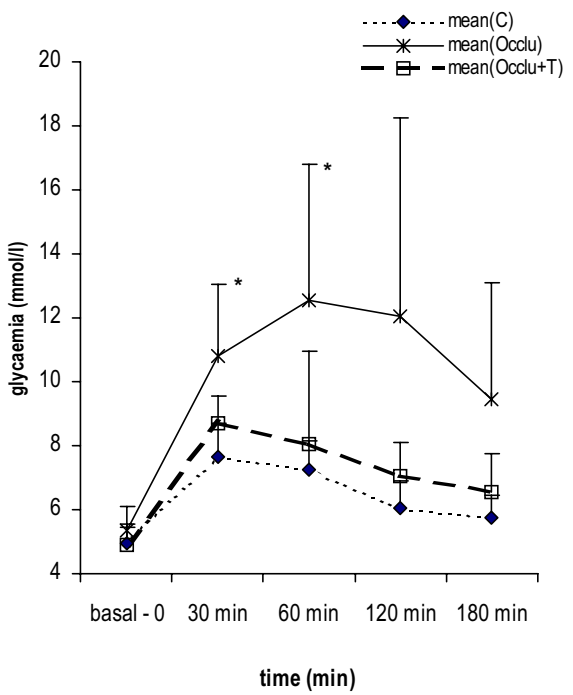

Fig. 3. Effect of Terguride treatment (T) on abnormalities of glucose tolerance curve in rats (males) of Koletsky strain. Animals of the group Occlu (animals with bilateral occlusion of common carotid arteries) were compared with animals of the group C (control animals), animals of the group Occlu+T (animals with occlusion and with Terguride treatment) with animals of the group Occlu. n(C)=11, n(Occlu)=6, n(Occlu+T)=4, * p<0.05.

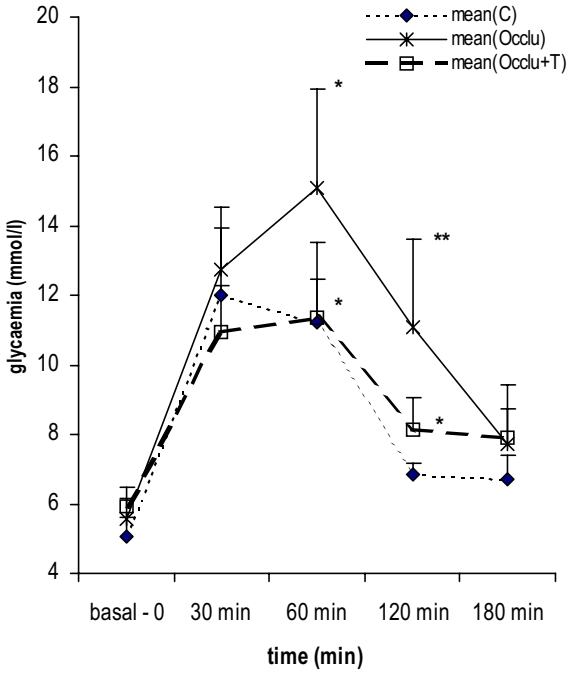

Fig. 4. Effect of Terguride treatment (T) on abnormalities of glucose tolerance curve in rats (females) of Koletsky strain. Animals of the group Occlu (animals with bilateral occlusion of common carotid arteries) were compared with animals of the group C (control animals), animals of the group Occlu+T (animals with occlusion and with Terguride treatment) with animals of the group Occlu. n(C)=4, n(Occlu)=7, n(Occlu+T)=6, * p<0.05, ** p<0.01.

60 and 120 min after glucose loading (Fig. 4). AUC was significantly increased $p<0.01$.

Considering occluded animals with drug, Terguride showed significant decrease in glucose intolerance ($p<0.05$) in both strains, except for males of Koletsky strain.

Discussion

In treatment of the later phase of brain ischemia (after 8th–10th hour since the beginning) following drugs are important: drugs which defended the development of brain edema (e.g. dexamethazon), nootropic drugs, pentoxifylin, scavengers of free oxygen radicals (e.g. tirilazad mesylat), teofylin, vinpocetin and others. The group of nootropic drugs in the therapy of this phase of brain ischemia includes, except others, also ergot alkaloid nicergolin which is used in activation of metabolic processes in the nerve cells (Kalvach et al, 1997). In this indication we were interested in the effects of another ergot alkaloid drug Terguride, namely it's influence on the changes of glucose metabolism.

Terguride is a common dopaminergic agonist. It's main effect, the influence on postsynaptic receptors in striatum, was developed during the research of dopaminergic agonists, potentials drugs or parkinsonism. Terguride decreases secretion of PRL and pathologically increases secretion of STH. In clinical practice it is used in the treatment of pathological hyperprolactinemia, e.g. disorders of menstruation and infertility caused by hyperprolactinemia, galactorrhea, adenoma of hypophysis with secretion of prolactin, disorders of libido, fertility in men connected with hyperprolactinemia. There belongs acromegaly to another indication (Pertz and Eich 1999).

In experimental conditions methods of global ischemia and methods of local ischemia are used. For our experimental arrangement we did not use local brain lesion but we induced brain ischemia affecting the whole brain. Our model (occlusion of both a. carotis communis) is only one of the models of global ischemia, which is used in gerbils and rats (Lin et al, 1998; Usuda et al, 1996).

The duration of brain ischemia in experimental models of ischemia used by many scientist is very different. We selected 4-hour-bilateral occlusion of a. carotis communis followed by 44-hour reperfusion, because this model affects intolerance of glucose with a level higher than 11.1 mM/l. In patients with serious craniocerebral injury this level of glycemia is associated with enhanced neurological prognosis (Kawai et al, 1999; Rovlias et al, 2000).

In all preparations of a. carotis communis basic condition of a successful experiment is regardful isolation of vessel. Arteria carotis communis lies with n. vagus in common connective tis-

sue, however injury of nervus vagus increases mortality, which is already high itself. Our experiments in males of Wistar strain showed zero mortality in control group, 60 % in the group with bilateral occlusion of a. carotis communis and 38 % in animals with Terguride treatment. In females of Wistar strain we found the following values of mortality: zero in control group, 25 % in the group with bilateral occlusion of a. carotis communis and 43 % in animals with Terguride treatment. Control males group of Koletsky strain showed 0 % mortality, the group with bilateral occlusion of a. carotis communis 54 % and in animals with Terguride treatment 67 %. Control group females of Koletsky strain showed 0 % mortality, the group with bilateral occlusion of a. carotis communis 38 % and in animals with Terguride treatment 25 %.

Brain ischemia induced glucose intolerance in both strains of rats. When we evaluated the effect of brain ischemia on "area under the curve of the glucose tolerance curve" (AUC), we found statistically significant increase of AUC in both sexes of both strains. Brain ischemia increased the level of glycemia in males of Wistar strain by 27 % ($p=0.01$) and in females of Wistar strain by 32 % ($p=0.01$). Statistically significant increase of the level of glycemia was found also in animals of Koletsky strain. Brain ischemia induced increases of the level of glycemia in males by 40 % ($p=0.05$) and in females by 24 % ($p=0.01$).

Basal glycemia was changed by the brain ischemia in males and females of both strains. The basal glycemia was increased in males of Wistar strain by 12 % and in females of this strain by 33 % through the brain ischemia; in males of Koletsky strain by 7 % and in females by 8 %. This increase was statistically significant only in animals of Wistar strain.

In our previous paper we documented that terguride treatment showed alleviation of glucose intolerance of hereditary origin in SHR/N-cp obese rats of Koletsky strain and in their lean siblings (Golda, 1994).

In this paper terguride treatment shows ambivalent effects on glucose metabolic abnormalities, which are caused by oligemic brain hypoxia. Differences in effects of Terguride were found between sexes and between strains. Terguride decreased statistically significantly AUC in males of Wistar strain by 30 % ($p=0.05$) and in females this strain decreased glycemia by 24 % ($p=0.05$). Glycemia was decreased in males of Koletsky strain by 33 % and in females of this strain by 19 % ($p=0.05$), but this decrease was significant only in females of Koletsky strain.

The basal glycemia was decreased in males of Wistar strain by 3 % and in females of this strain by 17 %; in males of Koletsky strain by 9 % and in females was increased by 7 %. This data were statistically significant only in males of Wistar strain.

In males of Koletsky strain we observed the highest level of glycemia induced by brain ischemia and the highest decrease of glycemia by terguride treatment as well.

The above mentioned ambivalent effects of terguride treatment when individual groups of animals are considered can be explained by strain and/or substrain effect. There is apparent sex dependence of ambivalent effect, which is more expressed in males when glucose tolerance is considered.

Decreasing glycemia is an important contributor to better prognosis in mortality and morbidity of craniocerebral injury after ischemia/reperfusion in hyperglycemic patients. Our data show that Terguride decreased hyperglycemia in rats with ischemia-damaged brain.

References

1. Dempsey RJ, Baskaya MK, Combs DJ, Donaldson D, Rao AM, Prasad MR. Effect of hyperglycemia on reperfusion-associated recovery of intracellular pH and high energy phosphates after cerebral ischemia in gerbils. Neuronal Res 1996; 18: 546—52.

2. Dimlich RV, Nielsen MM. Facilitating postischemic reduction of cerebral lactate in rats. Stroke 1992; 8: 1145—1153.

3. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999; 22: 391—397.

4. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, Lucking CH. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc Dis 2002; 13: 89—94.

5. Golda V, Cvak L. Terguride but not bromocriptine alleviated glucose tolerance abnormalities and hyperglykemia in obese and lean genetically hypertensive Koletsky rats. Physiol Res 1994; 43: 299—305.

6. Guyot LL, Diaz FG, Oregan MH, Song D, Phillis JW. The effect of topical insulin on the release of excitotoxic and other amino acids from the rat cerebral cortex during streptozotocin-induced hyperglycemic ischemia. Brain Res 2000; 28: 29—36.

7. Kalvach P. Medikamentózní léčba cévních mozkových příhod. In: Mozkové ischemie a hemoragie. 2rd Ed, Prag, Grada Publishing, 1997: 301—320.

8. Kawai N, Stummer W, Ennis SR, Betz AL, Keep RF. Blood-brain barrier glutamine transport during normoglycemic and hyperglycemic focal cerebral ischemia. Ecological Modell 1999; 116: 79—86.

9. Kim H, Koehler RC, Hurn PD, Hall ED, Traystman RJ. Amelioration of impaired cerebral metabolism after severe acidotic ischemia by tirilazad posttreatment in dogs. Stroke 1996; 1: 114—121.

10. Koletsky S. Pathologic findings and laboratory data in a new strain of obese hypertensive rats. Amer J Pathol 1975; 80: 129—140.

11. Kudláčková Z, Hronek M. A level of glycemia — an indicator of severity of ischemic brain damage. I. Preclinical studies. DMEV 2001 a; 4: 287—292.

12. Kudláčková Z, Hronek M. A level of glycemia — an indicator of severity of ischemic brain damage. II. Clinical studies and hypotheses of mechanism the effect of hyperglycemia on brain damage during hypoxic/ischemic injury. DMEV 2001 b; 4: 293—298.

13. Lanier WL, Hofer RE, Gallagher WJ. Metabolism of glucose, glycogen and high energy phosphates during transient forebrain ischemia in diabetic rats: effect of insulin treatment. Anesthesiology 1996; 4: 917—925.

14. Li PA, Shamloo M, Katsura KI, Smith ML, Siesjö BK. Critical values for plasma glucose in aggravating ischaemic brain damage: correlation to extracellular pH. Neurobiol Dis 1995; 2: 97—108.

15. Li PA, Liu GJ, He QP, Floyd RA, Siesjö BK. Production of hydroxyl free radical by brain tissues in hyperglycemic rats subjected to transient forebrain ischemia. Free Radic Biol Med 1999; 27: 1033—1040.

16. Li PA, He QP, Miyashita HW, Siesjö BK, Shuiab A. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. Stroke 2000; 31: 183—191.

17. Li PA, Uchino H, Elmér E, Siesjö BK. Amelioration by cyclosporin A of brain damage following 5 or 10 min of ischemia in rats subjected to preischemic hyperglycemia. Brain Res 1997; 1: 133—140.

18. Lundgren J, Zhang H, Agardh CD, Smith ML, Evans PJ, Halliwell B, Siesjö BK. Acidosis-induced ischemic brain damage: are free radicals involved? J Cereb Blood Flow Metab 1991; 11: 587—594.

19. Pahlmark K, Folbergová J, Smith ML, Siesjö BK. Effect of dimethylthiourea on selective neuronal vulnerability in forebrain ischemia in rats. Stroke 1993; 5: 731—737.

20. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 2002; 52: 20—28.

21. Pentelenyi T. Significance of endocrine studies in the general assessment and prediction of fatal outcome in head injury. Acta Neurochir Suppl Wien 1992; 55: 21—24.

22. Pertz H, Eich E. Ergot alkaloids and their derivatives as ligands for serotoninergic, dopaminergic and adrenergic receptors. In: Ergot — The Genus Claviceps. 1rd Ed. Amsterdam; Hardwood Academic Publishers, 1999: 411—431.

23. Quast MJ, Wei J, Huang NC. Nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester decreases ischemic damage in reversibile focal cerebral ischemia in hyperglycemic rats. Brain Res 1995; 2: 204—212.

24. Roh JK, Hong SB, Yoon BW, Kim MS, Myung H. The effect of hyperglycemia on lipid peroxidation in the global cerebral ischemia of the rat. J Korean Med Sci 1992; 7: 40—46.

25. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery 2000; 46: 335—342.

26. Siesjö BK, Katsura KI, Kristián T, Li PA, Siesjö P. Molecular mechanisms of acidosis-mediated damage. Acta Neurochir Suppl (Wien) 1996; 66: 8—14.

27. Tyson RL, Sutherland GR, Peeling J. 23Na nuclear magnetic resonance spectral changes during and after forebrain ischemia in hypoglycemic, normoglycemic, and hyperglycemic rats. Stroke 1996; 27: 59—64.

28. Watanabene T, Yuki S, Egawa M, Nishi H. Protective effect of MCI-186 on cerebral ischemia: possible involment of free radical scavenging and antioxidant. Pharmacol Exp Ther 1994; 3: 1597—1604.

29. Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003; 55: 33—38.

Received May 30, 2004.
Accepted September 3, 2004.