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ANTIOXIDATIVE EFFECT OF NERVE GROWTH FACTOR (NGF) IN RAT THALAMUS AFTER QUINOLINIC ACID-INDUCED NEUROTOXICITY

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Quinolinic acid (QA) produces a pattern of selective cell loss in the striatum, that closely mimics that of Huntington's disease (HD). The aim of this study was to investigate the antioxidative status in the thalamus after intrastriatal application of QA and the influence of nerve growth factor (NGF) on such neurotoxicity. Wistar rats were treated intrastriatally (coordinates: 8.4A, 2.6L, 4.8V), using a stereotaxic instrument. The first group was treated with QA (150 nmol/l). The second group was treated with QA, followed by NGF (4.5 μg/kg b.w.). The control group was treated with 0.9 % saline solution. Seven days after the treatment, we found decreased superoxide dismutase (SOD) activity in mitochondrial fractions of the striatum of both groups. In the thalamus, SOD activity showed no differences. The content of superoxide anion increased in the striatum of QA- treated animals. It was decreased in both structures in the group that was treated with QA and NGF. In the QA+ NGF-treated group, we found increased glutathione peroxidase (GSHPx) and GSH, compared to the group that was treated with QA only, but these values were lower than in the controls. Thus, NGF showed beneficial effects on the oxido-reduction status in the striatum, and also in the thalamus, a structure that is separated from but tightly connected with the striatum.

Key words: oxidative stress, NGF, rat, striatum, thalamus, quinolinic acid

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss and psychiatric manifestations. HD gene mutation seems to be widely expressed both in peripheral tissues and in the central nervous system, but the fundamental biochemical mechanism, which leads to neuronal degeneration, is unknown (Beal, 1995). Several techniques have demonstrated abnormal metabolism in HD brain (Martin *et al*., 1992).

There is a severe deficiency of respiratory chain enzyme system - complex II/ III and a milder defect of complex IV (Harding, 1995).

The excitotoxic hypothesis of pathogenesis in Huntington's disease suggests that selective striatal neuronal loss results from excessive activation of striatal excitatory amino acid receptors. The neurotoxicity of 2,3 pyridinedicarboxylic acid (quinolinic acid- QA) contributes to the pathogenesis of neuronal injury, such as HD. QA is an endogenous excitotoxic metabolite of L-tryptophan, and it mediates neuronal injury through N-methyl-D-aspartate (NMDA) receptor activation, and subsequent elevation of intracellular calcium, oxidative stress and lipid peroxidation (Schwarcz *et al*., 1982). The predominant neuropathological feature of HD is degeneration of the γ-aminobutyric acid (GABA)ergic, medium-sized spiny neurons, which innervate the globus pallidus and substantia nigra pars reticulata (Albin, 1995). These are critical parts of basal ganglia loop circuitry. The thalamus is a structure which connects basal ganglia with appropriate parts of the neocortex, and it has an important role in the motor and associative loops. The majority of projections of striatum and *nuclei,* closely connected with it, converge through the globus pallidus and thalamus to precentral parts of the cortex (area 4 and 6) (Otake and Nakamura, 1998).

Besides its neurotrophic role in development, survival and recovery from injury (Levi-Montalcini and Angeleti, 1968; Donald, 1995), it has been reported that nerve growth factor (NGF) may be important in the detoxification of reactive oxygen species (Park *et al*., 1998). It has been shown that intrastriatal implants of immortalized central nervous system (CNS)- derived progenitor cells, that had been genetically modified to secrete NGF, could prevent the neural degeneration in a rodent model of HD (Kume *et al*., 1998).

NGF prevents degeneration of striatal neurons destined to die from excitotoxic insult or mitochondrial dysfunction, so we decided to investigate the QA induced changes in the antioxidative defence, as a consequence of its neurotoxicity, in some parts of the basal ganglia loop (striatum and thalamus), and the influence of NGF on these effects of QA.

MATERIALS AND METHODS

Wistar rats of both sexes, weighing between 200 and 250 g, were used in the experiments. The animals were housed inside a climate-controlled facility. Food and water were available *ad libitum*. All animals received care in strict agreement with good laboratory practice and in accordance with guidelines for the humane care of animals, ethical principals of the Military Medical Academy and other federal statutes (Sl. list, 1998). The animals were anaesthetized with pentobarbital sodium i. p. in a dose of 40.5 mg/kg b.w. We used a stereotaxic instrument for small animals for the administration of the substances in to the striatum (coordinates: 8.4A, 2.6L, 4.8V) (Paxinos and Watson, 1982). The substances were administered using a Hamilton needle, and all of them were given in a volume of 10 μl.

The animals were randomized into three groups. There were 8 animals in each group. The first group of animals was treated with QA (Aldrich Chemical Company, Inc, Milwaukee, USA), in the single dose of 250.7 μg (150 nmol/l). The

animals of the second group were treated with QA in the same dose, and after it, they were treated with NGF (NGF-β - Sigma, Aldrich Chemie, Germany), in a dose of 4.5 μg/ kg b.w. The control group was treated with 0.9 % sterile saline solution.

The animals were decapitated 7 days after the treatment and heads were frozen immediately (-80°C). Prepared mitochondrial fractions of the striatum and thalamus were used for the appropriate biochemical analyses (Lowry and Passonneau, 1974).

Superoxide dismutase (EC 1.15.1.1. SOD) activity was measured spectrophotometrically, as inhibition of epinephrine autooxidation at 480 nm. The kinetics were followed in sodium carbonate buffer (50 mM, pH -10.2; Serva, Feinbiochemica, Heidelberg, New York) containing 0.1 mM EDTA (Sigma, St. Louis, USA), after addition of 10 mM epinephrine (Sigma, St. Louis, USA) (Suna and Zigman, 1978).

Superoxide anion content was determined through the reduction of nitroblue-tetrazolium (Merck, Darmstadt, Germany), in alkaline, nitrogen saturated medium. Analysis was performed at 515 nm (Auclair and Voisin, 1985).

Glutathione peroxidase activity (EC 1.11.1.9; GSH-Px) was measured indirectly, as oxidation of glutathione (GSH) to its oxidized form (GSSH), in the presence of a glutathione reductase (E.C. 1.6.4.2., Sigma, St. Louis, USA), at 340 nm. The reaction was followed in potassium-phosphate buffer (50 mM pH-7.0; Serva, Feinbiochemica, Heidelberg, New York), containing 1 mM EDTA (Sigma, St. Louis, USA) (Maral *et al*., 1987).

The content of total glutathione (GSH + 1/2 GSSH) was determined with a DTNB-GSSH reductase recycling assay. The rate of formation of 5-thio-2-nitrobenzoic acid (TNBA), which is proportional to the total glutathione concentration, was monitored spectrophotometrically at 412 nm (Anderson, 1986).

Descriptive data were expressed as the mean ± standard error (SE). Statistical analysis was performed on a pentium PC, using a statistical software program (Statistica 5.0 for Windows). Groups were compared by analysis of variance and Students t-test. Differences were considered statistically significant at $p<0.05$.

RESULTS

After awakening, all rats from the group treated with QA, showed signs of hyperreactivity and convulsions. Neither animals of the second group (QA and NGF), nor from the control one, showed any of these signs. Six hours after the operation, the animals showed no behavioral differences, from the control ones.

We found decreased SOD activity in the ipsi and contralateral striatum in both groups, compared to the control group. In the thalamus, we found no changes in the SOD activity compared to the control group (Table 1).

Table 1. Activity of SOD in the striatum and the thalamus in Wistar rats after an intrastriatal, single dose of quinolinic acid (QA), given alone or in combination with nerve growth factor (NGF). Values are given in U/mg protein. Mean ± SE.*- Significant difference in comparison to corresponding values of the control group ($p<0.05$)

Group / Structure	Control	QA	QA + NGF
Ipsilateral striatum	800.24 ± 127.67	625.44 ± 73.63*	711.82 ± 76.84*
Contralateral striatum	726.30 ± 43.28	615.33 ± 36.03*	612.66 ± 37.05*
Ipsilateral thalamus	865.53 ± 10.22	890.89 ± 61.07	829.38 ± 98.59
Contralateral thalamus	835.14 ± 63.61	850.13 ± 34.73	833.18 ± 43.77

The superoxide anion content was increased in the striatum, but was unchanged in the thalamus, after QA administration, compared to the controls. It was decreased after application of QA+NGF, compared to the QA - treated or control group of animals (Figure 1).

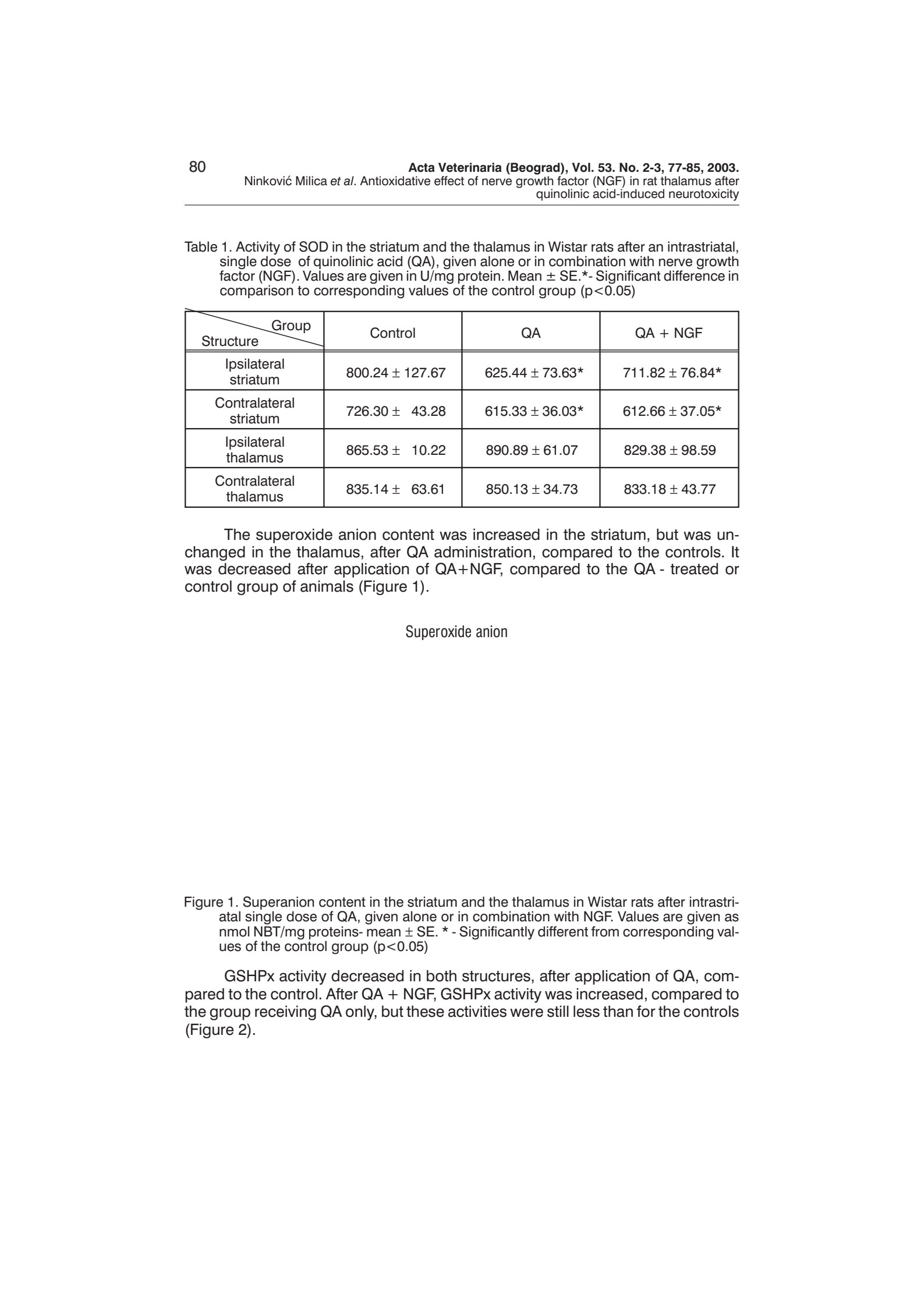

Figure 1. Superanion content in the striatum and the thalamus in Wistar rats after intrastriatal single dose of QA, given alone or in combination with NGF. Values are given as nmol NBT/mg proteins- mean ± SE. * - Significantly different from corresponding values of the control group ($p<0.05$)

GSHPx activity decreased in both structures, after application of QA, compared to the control. After QA + NGF, GSHPx activity was increased, compared to the group receiving QA only, but these activities were still less than for the controls (Figure 2).

GSHPx

Figure 2. GSHPx in the striatum and the thalamus in Wistar rats after application of QA and in animals that were treated with NGF after QA. Values are given as mU/mg proteins-mean ± SE.
* - Significantly different from corresponding values of control group ($p<0.05$)

The content of total glutathione decreased in both structures and in both groups, compared to the controls (Figure 3).

GSH

Figure 3. GSH in the striatum and the thalamus in Wistar rats after intrastriatal single dose of QA, given alone or in combination with NGF. Values are given as nmol/mg protein, mean ± SE.
* - Significantly different from corresponding values of control group ($p<0.05$)

DISCUSSION

Excessive activation of glutamate receptors is known to induce an influx of calcium ions into neurons, which entrains a destructive sequence of events within the cell, leading to the generation of reactive oxygen species (Cohen, 1995; Mc Donald and Johnston, 1990). These events initiate lipid peroxidation and disruption of membrane integrity, entry of calcium and a cellular energy crisis, that leads to cell death (Flint Beal, 1994; Kehrer, 1993). Although the biochemical basis of HD pathogenesis is not understood, several lines of evidence suggest that an abnormality of energy metabolism and compromised function of mitochondria can be critical for the energy status (Richter and Kass, 1991). The proposed mehanism of destruction in our experiment, could be due to the excitotoxicity of QA, and subsequent elevation of nitric oxide (NO) (Jelenkovic *et al*. 2002). It is well known that NO has higher affinity for the superoxide anion than SOD for the dismutation of this anion (Bredt and Snyder, 1994). Inability of a cell to maintain an appropriate level of ATP, as the result of excitotoxicity, could activate metabolic pathways involving arachidonic acid, which, besides well-known deleterious effects, could inhibit the return of glutamate from the synaptic space, and subsequently prolong action on the receptors (Murphy *et al*., 1989). The high potency of QA in producing damage is the result of synergism between the activation of NMDA receptors and the formation of free radicals.

The deficiency of glutathione that we have found, with resulting failure of detoxification of free radicals could increase the neurotoxic effects of glutamate (Reed, 1990). Therefore, a low glutathione content might contribute to the excitotoxic effects of glutamate in the striatum in HD. It was shown that soluble guanylat cyclase activity is required for nerve cell death caused by glutathione depletion. Cellular glutathione can be depleted by the release of the oxidized form, a process which is accelerated under conditions of oxidative stress. Novel actions of GSH in the nervous system have also been described, suggesting that GSH may serve additionally both as a neuromodulator and as a neurotransmitter. GSH binds via its gamma- glutamyl moiety to ionotropic receptor. At micromolar concentrations GSH displaces excitatory agonists, acting to halt their physiological actions on target neurons. At millimolar concentrations, GSH, acting through its cysteinyl thiol group, modulates the redox site of NMDA receptors. As such modulation has been shown to increase NMDA receptor channel currents, this action may play a significant role in normal and abnormal synaptic activity. GSH in the nanomolar to micromolar range binds to at least two populations of binding sites that appear to be distinct from all known excitatory amino acid receptor subtypes. GSH bound to these sites is not displaceable by glutamatergic agonists and antagonists. These binding sites, which are distinct receptor populations, appear to recognize the cysteinyl moiety of the GSH molecule. Like NMDA receptors, the binding sites possess a coagonist site(s) for allosteric modulation. GSH may be involved both directly or indirectly in synaptic transmission (Janaky *et al*, 1999). Methods to increase endogenous glutathione levels in neurodegenerative diseases associated with oxidative stress may be promising.

GSHPx is a critical intracellular enzyme involved in detoxification of hydrogen peroxide (H_2O_2) to water. In our experiment, decreased GSHPx activity after application of NGF could be due to decreased superoxide anion content, and subsequent decreased production of H_2O_2. It has been found that knock- out of GSHPx may be adequately compensated under nonstressed conditions, but, after administration of mitochondrial toxins, GSHPx plays an important role in detoxifying oxygen radicals (Smith *et al*, 1996). GSHPx coupled to reduce nicotine adenine diphosphate regenerating systems via glutathione reductase is virtually able to guarantee effective protection of biological structures against oxidative attack (Kliveny *et al*., 2000).

There are many contradictory references about the influence of neurotrophins on the mechanism of excitotoxicity (Shen *et al*., 1997). It is known that NGF has some influence on some components of the antioxidant system, particularly the metabolism of glutathione. There is some evidence for a stimulative effect of NGF on the activity of γ-glutamyl-cysteine-sythetase (γ-GC-S), GSHPx and glucose-6-phosphate dehydrogenase (Pan and Perez-Polo, 1993; Pan and Perez-Polo 1996). NGF-tg mice showed a better response to oxidative stress, because of increased basal activity of Cu-Zn SOD and glutathione transferase (Guegan *et al*., 1999). Besides the changes in oxido-reduction status, NGF can alter the expression of glutamatergic receptors and that might be the beginning of the "dark side" of neurotrophic action (Behrens, 1999). There is some evidence for synergistic action of NGF and NO, which can partly explain the protective efect of this neurotrophin in our experiment. It has been found that NGF may operate via NO activity. It is known that NGF in PC12 and cultured *basal forebrain* cells increases the expression of neural NOS gene (Holzman *et al*., 1996) Also, NO can modulate the release of neurotransmitters and has an influence on nerve growth (Phung *et al*., 1999).

There is some evidence for connected metabolic pathways of tryptophan and its metabolites and NGF. Thus, L-Kynurenine, markedly increases the level of mRNAs for NGF. Other tryptophan metabolites, such as QA, kynurenic acid and serotonin had little effect on the levels of NGF mRNA (Dong- Rual *et al*., 1998).

The beneficial effect of NGF in the thalamus could be caused by retrograde axonal transport (Hendry and Hill, 1980). Despite the beneficial behavioral effect of NGF in our investigations, we have found partly damaged antioxidative defence in the striatum, and also, in the thalamus, which was distinct from the place of application. The thalamus is very tightly anatomico - functionally connected to the striatum, so the excitotoxic effect of QA probably spread. Decreased GSHPx and total glutathione content, could be indicators for some other mechanism of NGF protection, not only antioxidative.

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EFEKAT NGF NA ANTIOKSIDATIVNU ODBRANU U TALAMUSU PACOVA NAKON NEUROTOKSIČNOG DELOVANJA HINOLINSKE KISELINE

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SADRŽAJ

Hinolinska kiselina (HK) prouzrokuje takav selektivni gubitak ćelija u strijatumu, koji veoma dobro imitira onaj kod Huntingtonove bolesti. Cilj ovog istraživanja bio je da se ispita antioksidativni status u talamusu nakon aplikacije HK u strijatum i uticaj NGF na takvu neurotoksičnost. Wistar pacovi su tretirani intrastrijatno, pomoću stereotaksičnog instrumenta (koordinate: 8,4A, 2,6L, 4,8V). Prva grupa je bila tretirana HK (150 nmol/l). Druga grupa je bila tretirana HK, a nakon toga je dobila NGF (4.5 μg/ kg b.w.). Kontrolna grupa je bila tretirana fiziološkim rastvorom. Sedam dana nakon tretmana, u mitohondrijskim frakcijama strijatuma, našli smo smanjenu aktivnost SOD u obema grupama. U talamusu, aktivnost SOD se nije promenila. Sadržaj superoksidnog anjona se povećao u strijatumu životinja koje su bile tretirane HK, a smanjio se u obema strukturama, u grupi koja je bila tretirana sa HK i NGF. U HK+ NGF-tretiranoj grupi, našli smo povećanu aktivnost GSHPx i GSH u odnosu na grupu koja je bila tretirana samo sa HK, ali su te vrednosti bile manje u odnosu na kontrolne. NGF je pokazao povoljne efekte na oksido-reduktivni status u strijatumu, ali takođe i u talamusu, strukturi koja je odvojena, ali veoma blisko povezana sa strijatumom.