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DIFFERENT EFFECTS OF PENTOBARBITAL AND PENTYLENETETRAZOL ON NITRIC OXIDE LEVELS IN RAT FRONTAL CORTEX

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Levels of nitric oxide (NO) in the rat's frontal cortex were continuously monitored before and after intraperitoneal administration of an antiepileptic drug-pentobarbital (20 and 40 mg/kg) or convulsant drug – pentylenetetrazol (50 mg/kg). Pentobarbital decreased the levels of NO in a dose dependent manner. However, NO levels had a tendency to increase following the administration of pentylenetetrazol. It is suggested that central NO participates in the modulation of neuronal excitability, supporting the idea that NO is an important excitatory factor involved in the regulation of seizure susceptibility. Also, our results on anaesthetized rats suggests that endogenous NO may be involved in the mechanism of action of antiepileptic and analeptic drugs and this further suggest that NO levels in the human brain may decrease during antiepileptic therapy and increase during epileptic attacks or administration of excitatory drugs.

The aim of the present study was to determine the possible role of NO levels in the brain during neuronal excitability and seizures.

Key words: nitric oxide levels, pentobarbital, pentylenetetrazol, rat frontal cortex

INTRODUCTION

Epilepsy is a common and heterogeneous neurological disorder arising from biochemical and molecular events that are not completely understood. To effectively manage epilepsy, it is important to understand the mechanisms underlying both seizure-induced brain damage as well as seizure initiation (Patel *et al*., 2002).

Experimental data indicate that nitric oxide (NO) may play a role in the pathophysiology of epilepsy: it is also possible that NO-mediated events are involved in the expression of the anticonvulsant action of some antiepileptics (Wojtal *et al*., 2003). NO plays a key role in neurotransmission, acting as a mediator controlling neuronal signalling, cGMP levels and release of several neurotransmitters (Bredt *et al*., 1990; Garthwaite, 1991). Also, NO has been involved in the regulation of neuronal excitability and seizure threshold, thus

368   **Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.**
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

stimulating the release of three main excitatory neurotransmitters such as aspartate (Guevara-Guzman *et al*., 1994), glutamate (Guevara-Guzman *et al*., 1994; Montague *et al*., 1994) and noradrenaline (Montague *et al*., 1994).

The precise mechanisms of NO in the expression of seizure is unclear and controversial (Kirkby *et al*., 1996; Rundfelt *et al*. 1995; Van Leeuwen *et al*., 1995; De Sarro *et al*., 1991). However, levels of NO in the brain could be used as an important parameter to clarify the role of NO in epileptic phenomena. Therefore, we measured NO levels in the rats' frontal cortex following administration of pentobarbital and pentylenetetrazol, selected as representatives of anticonvulsant and proconvulsant drugs.

MATERIALS AND METHODS

Animals and surgery

The experiments were performed on adult male Wistar rats (340-360 g). Rats were bred and kept under ordinary laboratory conditions. The investigation conforms to the Guide for the care and use of laboratory animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1985). The experimental procedure was approved by the Regional Ethical Committee. Rats were divided in 4 equal groups and anaesthetized by intraperitoneal administration of 0.15 ml/kg solution of Hypnorm[R] (fentanyl citrate 0.315 mg/ml and fluanisone 10 mg/ml, *Janssen Pharmaceuticals, Beerse, Belgum)* (0.15 ml contains 0.0472 mg fentanyl citrate plus 0.15 mg fluanisone per kg) prior to pentobarbital treatment. In the case of pentylenetetrazol treatment, pentobarbital sodium (60 mg/kg) was used as the anaesthetic drug. The rats were artificially ventilated with a frequency of 70 /min, maintaining constant pO_2 and pCO_2. Experiments were performed in the laboratory at constant room temperature (21.0 $\pm$ 1.0 ^oC) and humidity (55%), while the rectal temperature of the animals was maintained at 37.0 $\pm$ 0.5 ^oC with a heating pad. The head of the animal was mounted in the stereotaxic head holder and a hole was drilled into the right frontal region of the skull. After slicing the dura, a sensor for the detection of NO was stereotaxically implanted perpendicular to the right cortex at coordinates: 2 mm lateral, 2 mm anterior to bregma and 2 mm below the dura. A ground electrode was placed subcutaneously in the animals' neck. In order to prevent convulsions, animals treated with pentylentetrazol were injected with d-tubocurarine (0.1 mg/kg, i.p.). Cortical levels of NO were continuously monitored before and after intraperitoneal administration of drugs.

NO measurement

NO measuring system was an Isolated Nitric Oxide Meter (ISO-NO Mark II made by World Precise Instrument, Inc. Sarasota, Florida, USA) with amperometric micro-sensor (tip diameter: 200 μm) - ISO-NOP 200 also made by World Precise Instrument, Inc. Sarasota, Florida USA. This electrochemical microprobe method using amperometric sensors has frequently been employed to detect quantitative changes of NO levels in different tissues *in vivo* (Zhang *et al*.,

Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.   369
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

2000; Stefano *et al.*, 2002, Foresti *et al.*, 2003; Badzynska *et al.*, 2004). ISO-NO Meter II is sufficiently sensitive and selective to detect the release of NO in the brain tissue (Shibuki, 1990) but without altering the electrophysiological recording of basal cell firing during *in vivo* experiments (Crespi *et al.*, 1994). Briefly, NO diffuses through a semipermeable membrane and is than oxidized on a working platinum electrode resulting in an electric current. This redox current is proportional to the level of NO at the membrane's surface. The output current of the probe correlates linearly with the NO level at the tip (Shibuki, 1990; Engelman *et al.*, 1995). The electrode calibration was done daily before each experiment and sensitivity was 1.1 pA/nM change in NO level. Calibration was obtained by measuring the current generated by the 10 μM NO in aqueous solution, prepared by adding saturated NO solution to 120 ml 0.9% saline under strict inert atmosphere and stored in an all-glass container with a small head space. The probe showed no sensitivity to oxygen or to oxidized derivatives of NO (Zhang *et al.*, 2000). The output of the amplifier was connected to a chart recorder. Due to significant interindividual variations in absolute NO levels, the data were expressed as percentage difference from relatively stable NO level before drug administration. After NO baseline level was reached, the animals were injected i.p. with the drug or vehicle. Recording of the current continued for the next 60 minutes. The NO levels for each experiment were calculated by comparing the current measured from experimental amperometric curve with the current obtained after calibration with NO solution. On completion of the experiments, animals were killed with a high dose of sodium pentobarbital.

Statistical evaluation

Statistical analysis was carried out using GraphPad Prism/Instat 1.1 (GraphPad Software, California, USA) using one-way analysis of variance (ANOVA) followed by Dunnett's post-significance testing. A P value of less than 0.05 was considered significant.

Drugs

The following drugs were used: Hypnorm[®] (fentanyl citrate 0.315 mg/ml plus fluanisone 10 mg/ml, *Janssen Pharmaceuticals, Beerse, Belgum*), Nembutal[®] (pentobarbital sodium, solution 60 mg/ml, *Eppendorf, Hamburg, Germany*), Pentylenetetrazol[®] (*Sigma-Aldrich Company Ltd., Poole, Dorset, UK*), d-tubocurarine chloride hydrate[®] (*Sigma-Aldrich Company Ltd., Poole, Dorset, UK*). All drugs were dissolved in non-pyrogenic saline (0.9 % NaCl; *Baxter Healthcare Ltd., Thetford, Norfolk, UK*). Drug solutions were prepared prior to application. The doses of pentylenetetrazol and pentobarbital used in this study are known to exert proconvulsant and anticonvulsant effects in rats, respectively. Pentylenetetrazol was administered in a convulsant dose of 50 mg/kg, which induced clonic-tonic convulsions in all animals. Pentobarbital in doses of 20 mg/kg and 40 mg/kg exerted known anticonvulsant or anaesthetic effects, respectively.

370 **Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.**
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

RESULTS

Levels of NO in the frontal cerebral cortex of anaesthetized rats were continuously monitored during the baseline period of 1-2 h (period of stabilisation). During this period, NO levels were 2.2±1.3 μM (mean±S.E.M.) (range 0.5-4.6 μM). In control animals (n=5), treated only with the vehicle solution i.e. non-pyrogenic saline (0.9 % NaCl), a slow but not significant decline in brain level of NO during the first hour of the experiment was registered. However, the decline of NO level continued in the following hours of the experiment until the animals died. Therefore, the comparison between brain NO levels in control animals (treated with vehicle solution) and drug treated animals was in our experiment limited to the first 60 minutes after drug injection. Administration of pentobarbital (20 and 40 mg/kg) induced a significant and dose-dependent decrease of the brain NO level compared to the control group. In contrast, administration of a convulsant dose of pentylenetetrazol (50 mg/kg) significantly increased frontal cortex level of NO (P<0.05) in comparison with the control group, 30 minutes after administration of the drug (Figure 1).
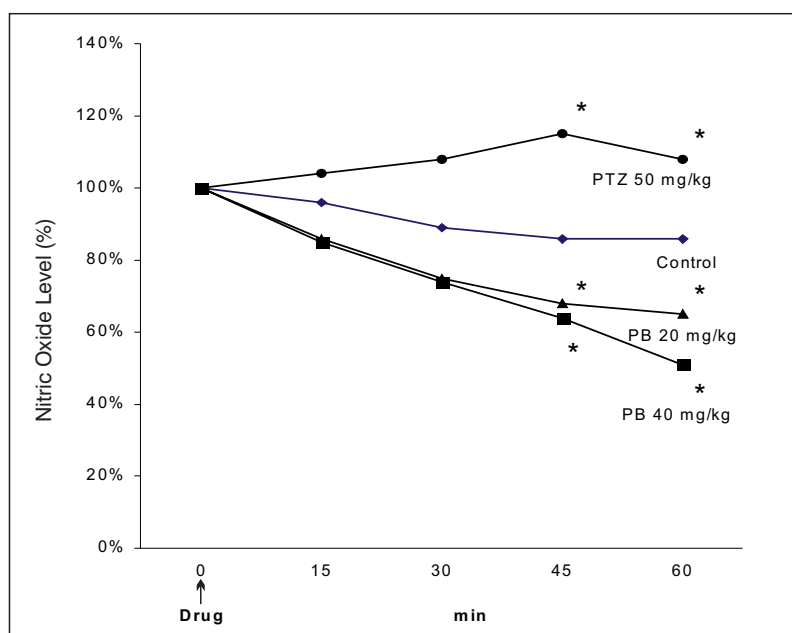
Legend: -♦-: Control; -•-: PTZ (50 mg/kg); -▲-: PB (20 mg/kg); -■-: PB (40 mg/kg);
Figure 1. Nitric oxide (NO) levels in rat frontal cortex, measured by electrochemical microprobe (ISO-NO II), before and after intraperitoneal administration of pentobarbital (PB, 20 and 40 mg/kg, n=5), pentylenetetrazol (PTZ, 50 mg/kg, n=5) or vehicle-control (0.5 ml, n=5). Levels of NO were expressed as percentage difference to relatively stable NO level when the drug was administered (t=0; denoted as ↑). Asterisk (*) represents a significant difference in comparison with control (*P*<0.05; ANOVA followed by Dunnet' test).

Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.   371
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

DISCUSSION

Baseline levels of NO registered in rat frontal cortex in this study ($\sim 10^{-6}$ M) correlate with NO levels found in the rat frontal cortex throughout the sleep-waking cycle (Burlet *et al*., 1995) and in the rat parietal cortex during middle cerebral artery occlusion (Zhang *et al*., 1995). These two studies report that baseline NO levels are lower ($\sim 10^{-8}$ M) compared with the baseline NO levels found in our study. This may be due to different experimental conditions, such as different anaesthetics used (fentanyl citrate plus fluanisone in our study vs. ketamine and xylazine), different levels of anaesthesia with corresponding difference in cerebral blood flow (which affects NOS activity) and/or different locations of the working electrodes (frontal cortex in our study vs. parietal cortex). Spontaneous, but not statistically significant decrease of brain NO levels in the first hour in control animals is probably due to the applied anaesthesia (Allimoff and Miller, 1993; Tobin *et al*., 1994). Also, it is probably a result of the decline in vital functions and central blood flow in experimental animals.

The main finding in our study is that anticonvulsant and proconvulsant drugs affect the NO levels in rat frontal cortex *in vivo* in opposite ways: anticonvulsant pentobarbital decreases and proconvulsant PTZ increases the NO levels. Many studies show that pentobarbital and other antiepileptics decrease levels of NO in the cerebral cortex and it is also possible that NO is involved in the anticonvulsant action of antiepileptics (Wojtal *et al.*, 2003; Borowicz *et al*., 1997). Borowicz *et al.* (1997) have shown that 7-nitroindazole decreased NO level in brain. Such effect may be responsible for the anticonvulsive action of 7-nitroindazole in certain models of epilepsy and for the protective activity of pentobarbital against electroshock-induced convulsions in mice. At the same time, 7-nitroindazole did not affect anticonvulsive activity of other antiepileptic drugs, such as carbamazepine, diphenylhydantoin and valproate. Anticonvulsive properties of pentobarbital are mainly due to the potentiation of GABA$_A$ receptor mediated effects and inhibition of glutamate activity (Haefely, 1980). It is known that barbiturates also decrease cGMP formation in many brain regions (Kant *et al*., 1980). This may explain a decrease of NO levels following administration of pentobarbital. Many studies have shown that NOS inhibitors exert anticonvulsant activity (Mollace *et al*., 1991; De Sarro *et al*., 1991; Zhang *et al*., 1993; Osonoe *et al*., 1994; Przewlocka *et al*., 1994; Mülsch *et al*., 1994; Nakamura *et al*., 1995; Becker *et al*., 1995; Van Leeuwen *et al*., 1995; Kirkby *et al*., 1996; Dzoljic *et al*., 1996). This study indicates that a decrease of neuronal excitability following barbiturates may be due, at least partially, to low levels of endogenous NO. Evidently, the decrease of neuroexcitability and corresponding increase of seizure threshold following administration of pentobarbital is due to activation of GABA inhibitory pathways and reduction of NO transmission, in conjunction with a decrease in the release of excitatory amino acids and NO production. Therefore, involvement of decreased brain NO levels in the mechanism of action of barbiturates (or other anticonvulsant) drugs deserves serious consideration.

Pentylenetetrazol (PTZ), a GABA$_A$ receptor antagonist has been extensively utilized in animal models of seizures. Several classes of compounds can modulate the PTZ discriminative stimulus including 5-HT (1A), 5-HT(3), NMDA, glycine, and L-type calcium channel ligands (Jung *et al*., 2002). It has been shown

372

Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

that PTZ proconvulsant activity is mediated by activation of NMDA receptors, leading to increase of cGMP levels in the brain. Also, PTZ induces oxidative damage in brain tissue by increasing the production of reactive oxygen species (Ilhan *et al*., 2004). These effects were considered as important factors for seizure onset and propagation (Ferrendely *et al*., 1980; Jiang *et al*., 2004). Because NMDA receptor activation stimulates NO (Garthwaite *et al*., 1989; East and Garthwaite, 1991), it seems that increased neuroexcitability following pentylenetetrazol administration is, at least partially, due to the activation of glutaminergic transmission and increase of NO levels. Itoh *et al*. (2004) studied the role of NO in the development of PTZ-kindling as an animal model of primary generalized epilepsy. They found that a daily administration of PTZ is associated with an increase in the amount of neuronal nitric oxide synthase (nNOS). NO generation was measured directly by *in vivo* and *ex vivo* electron paramagnetic resonance on rodents undergoing progressive convulsions. They found that primary generalized epilepsy is caused by NO induction during the persistent up-regulation of nNOS expression. Severe generalized seizures following PTZ withdrawal are not associated with NO production. Also, they reported that cerebellum volume for kindled rats decreased 20%, but not in rats treated with the nNOS inhibitor, 3Br-7-nitroindazole, suggesting that generation of NO in the cerebellum is related to decrease in cerebellum volume following PTZ-kindling.

However, increase in NO levels by pentylenetetrazol in our study is not as high as would be expected probably due to prior administration of pentobarbital in anaesthetic dose (60 mg/kg), known to block glutaminergic transmission and release excitatory amino acids (Alifimoff and Miller, 1993). It seems that future experiments with unanaesthetized animals could clarify the positive interactions between excitatory drugs and brain NO levels.

In conclusion, these results indicate that NO levels in the frontal cortex of the central nervous system in anaesthetized rats are decreased by pentobarbital and increased following administration of pentylenetetrazol. This study shows that NO levels in the brain are related to neuronal excitability, indicating an important modulatory role of NO in the regulation of seizure susceptibility.

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Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.   373
Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

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374

Acta Veterinaria (Beograd), Vol. 55. No. 5-6, 367-374, 2005.

Džoljić Eleonora *et al.* Different effects of pentobarbital and pentylenetetrazol
on nitric oxide levels in rat frontal cortex

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UTICAJ PENTOBARBITALA I PENTILENETETRAZOLA NA NIVO AZOT OKSIDA U FRONTALNOM KORTEKSU PACOVA

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SADRŽAJ

Nivo azot oksida (NO) u frontalnom korteksu pacova meren je kontinuirano kako pre, tako i nakon intraperitonealne primene antiepileptika pentobarbitala (u dozi od 20 i 40 mg/kg) ili konvulzivnog agensa pentilenetetrazola (u dozi od 50 mg/kg). Rezultati ovih eksperimenta su ukazali da pentobarbital smanjuje nivo NO u frontalnom korteksu pacova, dok koncentracija NO ima tendeciju rasta nakon primene pentilenetetrazola. Osim toga, dokazano je da endogeni NO ima važnu ekscitatornu ulogu u centralnim mehanizmima nastanka epilepsije. Takođe, naši rezultati su ukazali da kod anestetisanih životinja endogeni nivo NO ima uticaja na dejstvo kako antikonvulzivnih, tako i prokonvulzivnih lekova. Nivo NO u mozgu pacova je bio snižen tokom terapije antiepilepticima, a povišen tokom epileptičkih napada ili primene lekova iz grupe centralnih stimulansa.