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Nitrendipine and motor activity of spinal cord injured rabbits

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INTRODUCTION

Spinal cord injuries are not rare. They often result in profound motor and sensory deficit *(15)* and there is no effective drug therapy of the spinal cord traumatised persons *(9)*. Calcium accumulation in the nerve cells, caused by nerve tissue trauma, ischemia, hypoxia, epilepsy etc. might lead to nerve tissue damage and deterioration of neural functions *(2, 12, 20)*. Some investigations support the hypothesis that a common denominator of various cellular damages in the central nervous system is a massive influx of extracellular calcium ions (C^{2+}), dominantly through the L-type of voltage-sensitive calcium channels *(6, 10, 11, 16)*.

The search for effective drugs, competent to prevent or attenuate disturbances in a C^{2+} homeostasis and protect central nervous system against damage, has been of a great research interest. Pharmacological investigations are concentrated on voltage-sensitive calcium channel blockers, NMDA, non NMDA receptor blockers, and blockers of Ca^{2+} release from intracellular stores. This study has been meant to investigate the influence of 1,4 dihydropyridine calcium channel blocker nitrendipine on motor activity of spinal cord injured rabbits.

MATERIAL AND METHODS

The study was carried out on adult rabbits of both sex and 2.5 – 3.5 kg body weight. A dorsal medial L3 lumbal laminectomy was performed under pentobarbital anesthesia (30 mg/kg intravenously). Using the method of Albin et al. *(1)* and Osterholm *(18)*, a measurable spinal cord compact injury was applied. Spinal cord was contusioned by a strike of 50 or 150 p•cm. Penicillin G (400 000 i. u.) was given to each animal after the operation. The urinary bladder was emptied by manual compression twice a day.

Hind limbs motor activity was controlled daily in accordance with Tarlov's system *(24)* in the course of the next nine posttraumatic days. The ratings were as follows: 1 – complete paraplegy, 2 – minimal voluntary movements, 3 – animal able to stand up but unable to run, 4 – animal able to run with some spasticity and incoordination and 5 – normal motor activity. Rates between 1 and 5 were graded in subrates. Thus the rates were elevated or lowered for 0.2, 0.4, 0.6, 0.8, according to motor deficit severity.

All rabbits were randomly divided in 8 equal groups, 10 animals in each. Control group 1 was only laminectomised, control group 2 was contusioned by a strike of 50 p•cm, while all the other animals were traumatised by a strike of 150 p•cm. Control group 3 received no substance. Control group 4 received a vehicle solution containing propylene glycol 400 and ethanol (50 : 50), while other animals received nitrendipine.

Nitrendipine was given intravenously in doses of (0.1; 0.3 and 1.0 mg/kg) either once a day or in the dose of 0.5 mg/kg twice a day. The first dose was injected immediately after the trauma and the other doses during the eight subsequent days. The substance was injected in the total volume of 10 ml/kg (per one injection).

Nitrendipine and propylene glycol 400 were obtained from the Pharmaceutical and Chemical Industry "KRKA" (Novo Mesto, Slovenia).

The motor activity was monitored by two independent observers and a result asigned to each animal without knowledge of the experimental procedure. The results are presented as a value of the motor activity expressed in Tarlov's units (TU) per each day separately.

Statistical significance was calculated according to Analysis of variance, followed by Duncan's multiple range test ($p \leq 0.05$).

RESULTS

Laminectomy (control group 1) provoked a slight motor deficit that persisted during the first four posttraumatic days (motor activity was between 3.65 ± 0.1 and 4.96 ± 0.01 units of Tarlov) (Figure 1). After this period, the animals had completely normal motor activity (5.0 0 ± TU).

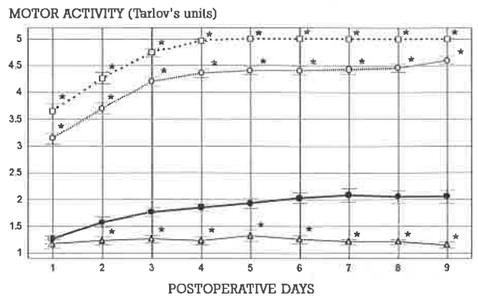

FIGURE 1. *Motor activity of laminectomised rabbits, control group 1 (□); in other animals spinal cord was injured. In the control group 2 (○) by a strike of 50 p•cm and by a strike of 150 pcm in all the other groups. The animals were receiving no substance, control group 3 (△) or a vehicle solution, control group 4 (●). Points represent mean S.E.M. (N = 10). *p ≤ 0.05: Statistically significant difference from control group 4.*

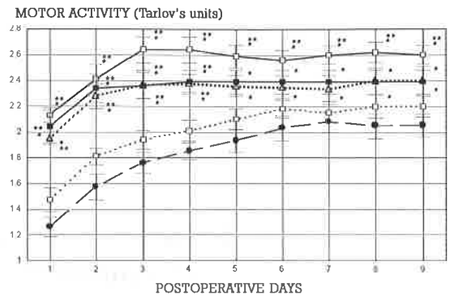

FIGURE 2. *Motor activity of rabbits traumatised by a strike of 150 p•cm. Animals were receiving a vehicle solution, control group 4 (●) or nitrendipine, in the doses of 0.1(□); 0.3 (△) or 1.0 mg/kg (▲) once per day, or 2•0.5 mg/kg twice a day (■). Points represent mean S.E.M. (N = 10). *p ≤ 0.05: Statistically significant difference from control group 4; **p ≤ 0.05: Statistically significant difference from nitren-dipine 0.1 mg/kg.*

Spinal cord trauma of 50 p•cm (control group 2) (Figure 1) produced a spontaneously reversible paraplegy with slightly expresed motor deficit that persisted during the whole experimental period (motor activity was between 3.12 ± 0.08 TU and 4.60 ± 0.06 TU). There was no statistically significant difference between control group 1 and control group 2.

Spinal cord contusion provoked by a strike of 150 p•cm (control group 3) caused significant motor deficit that persisted during the whole experimental period. Motor activity was between 1.17 + 0.08 TU and 1.29 ± 0.07 TU in the course of the whole experiment (Figure 1).

Motor activity of control group 4, which received a vehicle solution, was between 1.26 + 0.08 and 2.08 + 0.12 TU. (Figure 1). These animals had almost complete paraplegy which persisted during the whole experimental period. There was statistically significant difference between control group 4 and control groups 1, 2 and 3.

Nitrendipine in all tested doses improved the motor deficit that had been caused by spinal cord contusion of 150 p•cm (Figure 2). Analysis of variance, followed by Duncan's multiple range test, revealed that tested doses of nitrendipine (0.3; 1.0 and 2•0.5 mg/kg) produced a statistically significant improvement of motor activity in relation to the rabbits of control group 4 (Figure 2) during the whole course of the experiment.

There is staistically significant difference between the the activity of nitrendipine 0.1 mg/kg and nitrendipine in doses of 0.3 mg/kg and 2•0.5 mg/kg during the first half of the experiment, while the statistically significant diference between doses 0.1 and 1.0 mg/kg persisted during the whole experiment.

DISCUSSION

The results of the present experiment confirm that the spinal cord trauma caused by a strike of 50 p•cm produced a spontaneously reversible, and by strike of 150 p•cm produced a spontaneously irreversible paraplegy in the rabbit *(21, 22)*. These results are in agreement with other data in literature *(4, 5, 18)*.

Nitrendipine is dihydropyridine calcium channel blocker which is for its outstanding peripheral vasodilatatory effects predominantly used in essential hypertension therapy *(7, 8, 17, 23)*. In comparison to nimodipine which central effects are proved in a row of experimental studies, the data about the effect of nitrendipine on central nervous system are very poor. Since it has been proved that nitrendipine has a tendency towards attaching, among other, to the central nervous system, and in the dosage of 1.0 mg/kg it accelerates perfusion of the central nervous system *(8, 10, 11, 20)*, it has been considered interesting to investigate the effects of the mentioned drug in animals with spinal cord trauma.

The results of our experiments indicate that nitrendipine improves motor deficit of the spinal cord injured rabbits. This confirms the idea that by preventing of calcium overload in the spinal cord neurons we could diminish consecutive neuronal cell damage and the motor deficit caused by a spinal cord contusion.

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ABSTRACT

Nitrendipine and motor activity of spinal cord injured rabbits

Background and purpose: Spinal cord injuries are often followed by profound motor and sensory deficit. They are a great medical and social problem because there is no effective drug therapy. It is well known that disturbances in Ca2+ accumulation into the nerve cells might contribute to nerve cells damage. So the purpose of the study was to investigate the influence of calcium channel blocker, nitrendipine on motor activity of spinal cord injured rabbits.

Material and methods: The study was carried out on adult rabbits of 2.5 - 3.5 kg body weight. Medial dorsal lumbal laminectomy was performed under pentobarbital anesthesia. Experimental, lumbal spinal cord injury provoked by a strike of 50 p•cm caused a spontaneously reversible paraplegy, while by 150 p•cm caused a spontaneously irreversible paraplegy. Hind limbs motor activity was controlled daily in accordance with Tarlov's system during the whole course of the experiment. Nitrendipine was injected intravenously immediately after the trauma and during the eight subsequent days in various doses.

Results: Tested drug diminished motor deficit in the animals with spontaneously irreversible paraplegy. Doses of 0.3; 1.0 mg/kg daily and 20.5 mg/kg daily significantly improved motor deficit during all nine posttraumatic days.

Conclusion: Spinal cord injury in rabbits, provoked by a strike of 150 p•cm resulted in a spontaneously irreversible paraplegy. Nitrendipine in dose related manner diminished motor deficit. The results support the opinion that calcium channel blockers can be used in the treatment of spinal cord injured persons.

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