# Effects of NMDA Receptor Antagonists MK-801 and CPPene on Experimental Spinal Cord Injury

## NMDA Reseptör Antagonistleri MK-801 ve CPPene'in Deneysel Omurilik Travması Üzerine Etkisi

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**Abstract**: N-methyl-D-aspartate(NMDA)receptor-mediated events have been implicated in the pathophysiology of spinal cord injury. This study examines the effects of two NMDA receptor antagonists, CPPene (3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid) and MK-801 (dizocilpine maleate) after 50 gm-cm weight dropping spinal cord injury of white rats. Somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) were recorded before and in different intervals for 4 hours after injury. Lower extremity motor scales were observed on inclined table for 1 week after injury. MK-801 (n=15) were given intraperitoneally first at 1 mg/kg doses 30 minutes after injury and 3 rapel doses of 0.5 mg/kg at 75 minutes intervals. CPPene (n=10) were given at 4.5 mg/kg doses 15 minutes after injury and it was repeated 3 hours after wards. Control group (n=12) had saline injections. MK-801 group consisted of 15 animals and CPPene group 10 animals. Motor scale and evoked potential analysis were done by the second observer not knowing the groups. There were no differences on motor scales and MEPs between three groups; however, SEPs significantly recovered in CPPene group. These results show that CPPene has a positive effect in dorsal column function on this experimental spinal cord injury.

**Key Words:** Evoked potential monitoring, CPPene, MK-801, NMDA receptor antagonists, Somatosensory evoked potentials, Spinal cord injury

**Özet:** N-methyl-D-aspartate (NMDA) reseptör kökenli olayların omurilik yaralanmasının patofizyolojisinde rol aldığı bildirilmiştir. Bu çalışma, iki NMDA reseptör antagonistinin, CPPene (3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonicacid) ve MK-801 (dizocilpine maleate) beyaz sıçanlarda 50 gm-cm ağırlık düşürme omurilik travmasından sonraki etkilerini incelemektedir. Somatosensoriyel evoked potansiyeller (SEP) ve motor evoked potansiyeller (MEP) yaralanmadan hemen önce ve yaralanma sonrası 4 saat boyunca kayıtlanmıştır. Alt ekstremite motor skalaları travmadan sonraki 1 hafta boyunca eğimli tablada incelenmiştir. MK-801 (n=15) travmadan 30 dakika sonra 1 mg/kg dozda intraperitoneal olarak verilmiş, daha sonra da 75 dakika aralıklarla 0,5 mg/kglık 3 rapel doz yapılmıştır. CPPene (n=10) travmadan 15 dakika sonra 4,5 mg/kg dozda verilmiş ve 3 saat sonra bu tekrarlanmıştır. Kontrol grup (n=12) salin enjeksiyonları almıştır. MK-801 grubu 15 hayvandan, CPPene grubu 10 hayvandan, kontrol grubu 12 hayvandan oluşmaktadır. Motor skala ve evoked potansiyel analizi grupları bilmeyen ikinci bir gözlemci tarafından yapılmıştır. Üç grup arasında motor skalalar ve MEP lerde bir fark bulunamamıştır. Ancak SEPler CPPene grubunda belirgin şekilde düzelmiştir. Bu sonuçlar CPPene in bu deneysel omurilik yaralanması modelinde dorsal kolon fonksiyonuna olumlu bir etkisi olduğunu göstermektedir.

**Anahtar Sözcükler**: CPPene, MK-801, NMDA reseptör antagonistleri, omurilik yaralanması, somatosensoryel uyarılmış potensiyeller, uyarılmış potensiyel monitörlemesi

## INTRODUCTION

Spinal cord injury is still a disease with significant morbidity and mortality. The delayed autodestructive response, often referred to as "secondary injury", is found to be responsible for the irreversible tissue damage after primary injury. Different factors play a role in secondary injury such as blood flow alterations, lipid peroxidation, release of opioids, eicosanoids and free radical reactions (4,12,20,33).

The discovery of excitatory amino acits in central nervous system (26) and understanding their roles in trauma through some receptors aroused new hopes in the treatment of spinal cord injuries (8,12,23,25). It was urged that NMDA receptor antagonists play an important role in secondary injury phenomenon after central nervous system traumas (1,8-12,17,23). For that reason, any agent blocking these receptors would probably prohibit the secondary injury and as a result, neurological morbidity.

There are a cumulative literature intensified to determine the effects of NMDA receptors and their competitive and non-competitive antagonists on vascular and traumatic lesions of central nervous system (1,5-11,13,14,21,24,26,27,29).

This study is designed to examine the potential role of the N-methyl-D-aspartate (NMDA) receptor antagonists; one being a non-competitive antagonist MK-801 and the other a competitive antagonist 3-(+/-)-2-carboxypiperazin-4-yl-)-1-propenyl-1-phosphonic acid (CPPene) on the behavioral and electrophysiological consequences of impact trauma to the rat spinal cord.

## MATERIAL AND METHODS

Experimental Model: Thirty-seven white rats (Sprague Dawley) with weights ranging between 150-250 gm were used. They were anesthetized with 30 mg/kg intraperitoneal sodium pentobarbital (nembutal) injection. When necessary, 2-3 mg rapel doses were given throughout the experiment. After a thoracic midline incision and muscle seperation, a T8 and T9 laminectomy was performed using a high speed drill. Afterwards, a midline parieto-occipital skin incision was done. Two burr-holes on both parietal bones 2 mm lateral from the midline and 2 mm behind the coronal suture were opened. Two screws with 1.5 mm diameters and 4 mm length were inserted into the burr holes epidurally. Recording wires were secured on the heads of the screws.

Vital functions were monitored and kept in normal ranges with ECG and a rectal temperature probe. They were warmed with an infrared lamp keeping the rectal temperature between 35.5-37.5 °C.

Electrophysiology: Somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) were recorded before and after injury. The wires secured to the cranial screws were used both for SEP recording and MEP stimulation.

For SEP stimulation, subcutaneous needle electrodes were inserted nearby the left sciatic nerve. Two-channel recordings were done, first from rostral epidural spinal cord and right parietal epidural screws. The reference electrode for spinal epidural electrode was a paraspinal needle. Sciatic nerve was stimulated at 3.2 Hz frequency with 100 μsec square waves above the motor threshold (10-25 mA). Two hundred traces were averaged with 50 ms analysis time and 30-3000 Hz band pass filters. All of the recordings were repeated twice to see their reproducibility.

For MEP recording, two needle electrodes were inserted into the right crus muscles. Right parietal epidural screw was used as positive stimulation electrode and recordings were done both from caudal spinal cord and right crus muscles. Ten-20 traces were averaged with 20 ms analysis time.

The latencies of the first positivity (P1) and negativity (N1) and amplitude difference between these peaks (P1N1) were measured in cortical SEPs. For muscular MEPs the initial phase of the muscle response and the maximum amplitude of poliphasic muscle response were measured. The latency of initial phase of epidural spinal cord potentials were measured in both settings.

Both SEP and MEP recordings were repeated after injury with time intervals of postinjury 1 minute, 15 minutes, 1 hour, 2 hours, 3 hours and 4 hours. The data were recorded on diskettes and off line analysis were done. The technical details of the experimental model and electrophysiologic recordings had been published before (34,35).

Trauma: Spinal cord trauma was produced utilizing the Allen's weight-dropping method by leaving a 5 gm of weight 10 cm of height (50 gm-cm) through a fiberglass guide tube onto an alluminium impounder that lies on the exposed dura mater. This doses of trauma causes an incomplete cord damage and they partially recover at the end of two weeks.

Post-traumatic care: Cranial screws were taken out and the skin incisions were closed at the end of the recording session. Five mg/kg/day gentamycin was injected intraperitoneally for 5 days. They had manual bladder massage for the first 3 days and the lower extremity motor scores were measured using inclined table method on 1st, 3rd and 7th postinjury days (22).

Groups: Three groups of animals were used. Ten animals received CPPene, 15 animals received MK-801 and 12 animals received physiologic saline. CPPene was given 15 minutes and 3 hours after injury in two consecutive doses of 4.5 mg/kg with slow intraperitoneal injections. MK-801 was given initially at a doses of 1 mg/kg 30 minutes after injury and 3 consecutive doses of 0.5 mg/kg every 75 minutes. Control group had similar doses of intraperitoneal saline.

Analysis: Electrophysiologic recordings of all animals were analysed by the senior author (MZ), who was unaware of the individual groups. The mean values and the standart deviations of preinjury and postinjury SEPs and MEPs of the groups were compared by means of t-test. An additional analysis to find out whether a potential was present or not was also done by means of Fisher's chi-square test. Motor function scales on 1st, 3rd and 7th days were compared between each groups by means of Kruskal-Wallis analysis of variance.

## RESULTS

There were 12 animals in control group, 15 animals in MK-801 group, and 10 animals in CPPene group. We compared the number of animals with preserved SEP and MEP after injury (Table I, Figure 1,2). Latency and amplitude changes after injury in each group were also compared with preinjury values (Table 2, 3).

Analysis of SEPs: After weight dropping injury, there were significant changes in SEPs of all the three groups (Table I, Figure 3a, 4a, 5a). Although SEP loss remained unchanged in most of the animals till the late hours of the monitoring period, they recovered after the 120th minute in CPPene group (Figure 1).

SEP recordings of one animal from each group are shown in Figures 3a, 4 and 5a. One animal in control group (#C9) had prominent latency delays and amplitude depression in the 1st and 15th minutes

Table I: The Number of Animals with Preserved SEPs and MEPs throughout the Recording Period

| | | 1 min | 15 min | 60 min | 120 min | 180 min | 240 min |
|---|---|---|---|---|---|---|---|
| SEP | Control (n=12) | 3 | 2 | 3 | 3 | 3 | 2 |
| | MK-801(n=15) | 4 | 5 | 6 | 6 | 5 | 5 |
| | CPPene (n=10) | 1 | 1 | 5 | 8 | 7 | 8 |
| MEP | Control (n=12) | 8 | 8 | 10 | 10 | 11 | 9 |
| | MK-801 (n=15) | 13 | 10 | 10 | 12 | 13 | 12 |
| | CPPene (n=10) | 7 | 7 | 6 | 8 | 9 | 9 |

Table II: SEP Latencies and Amplitudes (Mean±SD) throughout the Recording Period

| | | | Preinjury | 1 min | 15 min | 60 min | 120 min | 180 min | 240 min |
|---|---|---|---|---|---|---|---|---|---|
| SEP | Latency (ms) | Control | 10,5±2,9 | 16,6±4,2 | 16,5±3,5 | 14,3±4,9 | 12,8±4,3 | 13,7±4,8 | 14,2±2,9 |
| | | MK-801 | 11,6±2,6 | 16,9±2,7 | 15,5±3,5 | 16,3±4,9 | 16,7±5,6 | 14,1±3,8 | 14,7±2,9 |
| | | CPPene | 11,3±1,6 | 20 | 21,1 | 16,6±3,2 | 14,4±2,9 | 16,6±4,4 | 16,8±6,6 |
| | Amplitude (μV) | Control | 3,2±1,4 | 1,6±1,1 | 3,1±2,2 | 3,7±1,7 | 2,1±2,2 | 2,7±1,8 | 2,8±1,4 |
| | | MK-801 | 3,3±1.5 | 4,4±3,4 | 4,7±5,9 | 4,5±5,1 | 4,4±2,6 | 4,9±3,3 | 4,3±2,8 |
| | | CPPene | 2,9±2,9 | 1,9 | 2,5 | 2,3±1,3 | 2,5±2,6 | 4,1±2,4 | 5,8±5,4 |

Table III: MEP Latencies and Amplitudes (Mean±SD) throughout the Recording Period

| | | | Preinjury | 1 min | 15 min | 60 min | 120 min | 180 min | 240 min |
|---|---|---|---|---|---|---|---|---|---|
| MEP | Latency (ms) | Control | 5,8±1,5 | 5,5±0,9 | 5,3±1,1 | 4,5±0,8 | 6,1±2,2 | 5,03±1,3 | 4,6±0,4 |
| | | MK-801 | 6,0±1,8 | 5,5±0,7 | 5,4±0,8 | 6±2,1 | 5,9±1,8 | 5,8±1,5 | 5,2±1,7 |
| | | CPPene | 5,2±0,9 | 5,7±1,2 | 5,6±0,7 | 4,8±0,7 | 4,9±0,4 | 4,9±0,4 | 4,9±0,4 |
| | Amplitude (μV) | Control | 3,6±1,3 | 4,4±2,5 | 5,5±2,9 | 7,5±6,1 | 7,4±5,6 | 4,3±3,37 | 5,6±3,7 |
| | | MK-801 | 6,2±4,4 | 13,3±17,3 | 10,9±10,9 | 10,3±9,4 | 9,4±8,7 | 16,1±16,8 | 10,7±11,3 |
| | | CPPene | 2,6±1,5 | 10,2±9,6 | 6,4±6,8 | 4,2±4,5 | 9,5±8,3 | 14,9±11,9 | 8,7±6,4 |

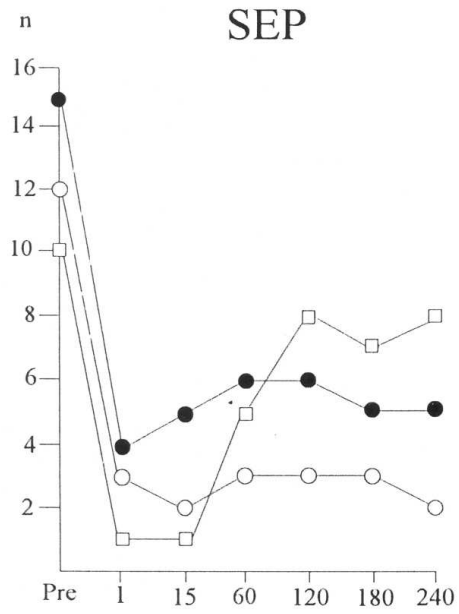



Figure 1. The number of animals with preserved SEPs throughout the recording period.

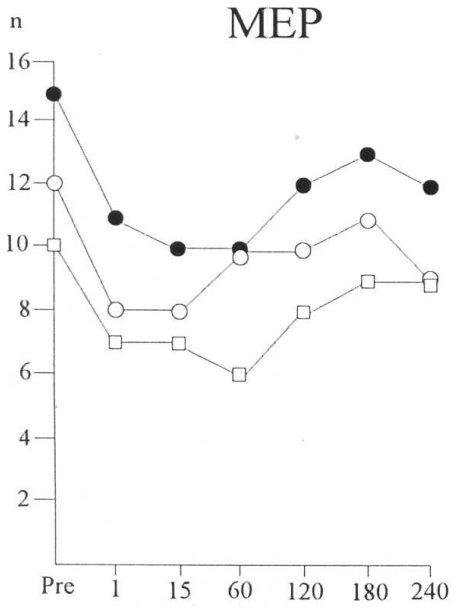
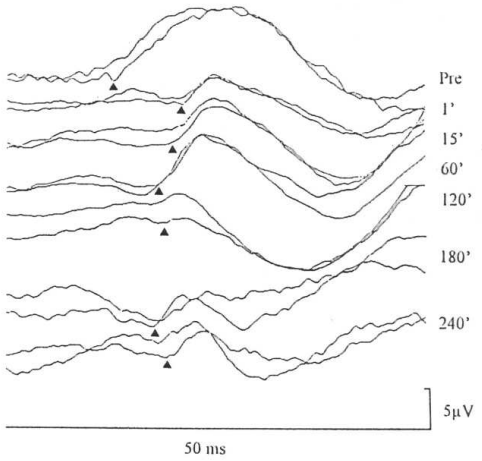



Figure 2. The number of animals with preserved MEPs throughout the recording period.

after injury. Amplitudes recovered after the 60th minute and latencies remained unchanged (Figure 3a). In one animal from MK-801 group (#M11) a prominent amplitude depression and latency delay could be seen just after injury and remained so till the end of the monitoring (Figure 4). If we examine one animal from CPPene group (#CP3) we can see a total loss of waves during 1st and 15th minutes but



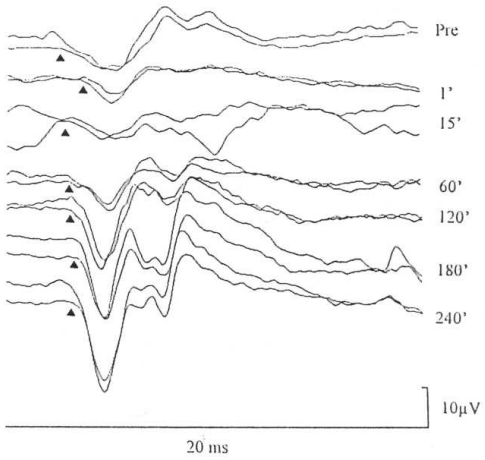




Figure 3. The SEP recordings of one animal in control group (#C9) had prominent latency delays and amplitude depression in 1st and 15th minutes after injury. Amplitudes have recovered after 60th minutes and latencies remained unchanged (Figure 3a). MEP latencies increased at first, but fully recovered afterwards (Figure 3b).

slight recovery after the 60th minute returning to the preinjury levels in the next hours. When we examine with examples in the other two groups, in spite of a total wave loss just after the injury, the SEP waves in CPPene group recovered afterwards and returned to the preinjury levels.

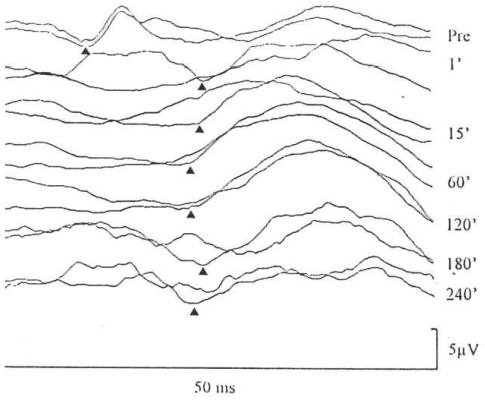


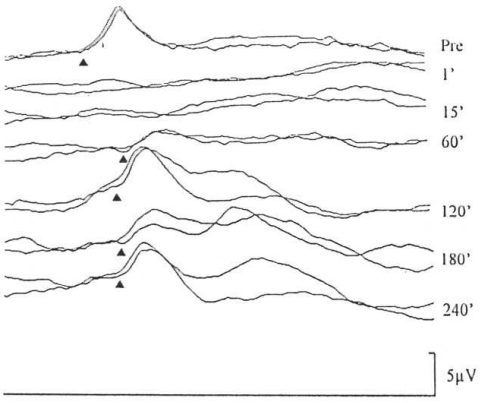

Figure 4. The SEP recordings of another animal from MK-801 group (#M11) has a prominent amplitude depression and latency delay just after injury. It remained so till the end of the monitoring period.

The mean values of SEP latency and amplitudes are shown on Table II. Latencies of all the three groups delayed and did not show a significant recovery till the end of the recording period. However, no significant difference between the preinjury and postinjury amplitudes could be seen in all three groups (Table II).

In general, there were major losses of SEPs after injury till the end of the 60th minute.

Analysis of MEPs: The number of animals with preserved MEPs after injury can be observed in Table 1. If they are preserved, their latencies and amplitudes remain unchanged (Table III). Otherwise, if MEPs are influenced by injury, they will be lost; if not, they remain unchanged both in latency and amplitudes. Figure 2 shows the number of animals with preserved MEPs in different monitoring periods. There is little change among the three groups.

Figures 3b and 5b show examples taken from one animal in two groups. There are not many differences in latencies of all groups. The animal in CPPene group, however, had a loss in waves at 15th minutes and recovered on the 2nd hour (Figure 5b).



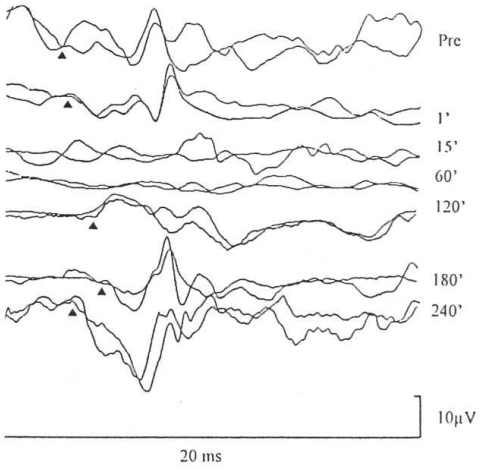




Figure 5a. This animal from CPPene group (#CP3) had a total loss of waves during 1st and 15th minutes. But slight recovery after 60th minutes occurred and they recovered to the preinjury levels in the next hours. When we examine with examples in the other two groups, in spite of a total wave loss just after the injury, the SEP waves in CPPene group recovered afterwards and returned to the preinjury levels; Figure 5b. MEPs of this animal have a loss in waves at 15th minutes, but they recovered on 2nd hours.

If we examine the mean values of amplitudes and latencies, there is no difference between preinjury and postinjury values ($p>0.05$). However, the amplitudes increased in some monitoring periods (Table III).

Analysis of Motor Function: Motor function scales according to the inclined table method were measured on the 1st, 3rd and 7th days after injury. The angle that an animal could stand for at least 10-15 seconds is regarded as the motor score of that animal (Table IV).

Table IV: Motor Function Scales According to Inclined Table Method on First, 3rd and 7th Days Postinjury (Mean±SD of Angles)

| | 1st day | 3rd day | 7th day |
|---|---|---|---|
| Control | 28.3± 6.8 | 31.2±6 | 31.2±6 |
| MK-801 | 30±5 | 30.6±6.5 | 34.3±6.5 |
| CPPene | 30±6.6 | 32±4.8 | 31.5±3.3 |

The differences among the motor scores in one group on the 1st, 3rd and 7th days and among each group were compared statistically. There was no difference in postinjury days, nor was it among each group.

Groups: CPPene was given on the 15th minute of postinjury period. SEP waves slowly recovered after the 120th minute and this difference was found to be statistically significant, yet the latency values did not reach the preinjury levels. There was, however, no difference in mean values of amplitudes. Neither latency nor amplitudes of MK-801 and control groups recovered afterwards.

## DISCUSSION

Excitotoxin induced cell death mediated through NMDA receptors were found to be responsible for the brain injury after ischemia, or trauma (12,15,29).

Following experimental spinal cord injury in rats the non-competitive NMDA antagonist MK-801 was found to improve neurological outcome and histological and neurological status of the spinal cord (10,11). Another non-competitive NMDA antagonist dextrorphan and the competitive NMDA antagonist CPP when administered intrathecally 15 minutes after trauma was found to be beneficial on the behavioral recovery (13).

This study has failed to demonstrate a beneficial effect of two NMDA antagonists on behavioral outcomes of rats after impact spinal cord injury. The axonal conduction has somewhat recovered in CPPene group compared to saline and MK-801 treated groups. These results are somewhat different from the others which report beneficial effects even with MK-801 (1,8,10,11,13-15,27,28). However, most of these studies, except Faden et al (10), have used MK-801 before injury.

There is one study that reports a negative effect of MK-801 in the forebrain ischemia model of rats (6). Holz and Gerdin have also reported no improvement of spinal cord blood flow and neurologic function with MK-801 (18). The relative failure of the NMDA antagonists to afford neuronal protection in vivo, as compared with in vitro, can be contrasted with the remarkable cytoprotective effects of non-NMDA glutamate antagonists (5,24,27).

Recent progress in spinal cord injury research has led to a dramatic turnaround because of the results of a clinical trial (3,20). The National Acute Spinal Cord Injury Study (NASCIS) showed that very high doses of methylprednisolone given within 8 hours after injury improves neurologic recovery (3). The mechanism of that is believed to be the inhibition of lipid peroxidation. Many other drugs have been claimed to be beneficial in animal studies, including other lipid peroxidation inhibitors, free radical scavengers, opiate receptor blockers, NMDA receptor blockers, calcium channel blockers, inhibitors of arachidonic acid metabolism, and protease inhibitors.

SEP losses are observed in each group. In the control group this difference last for whole monitoring period. The recovery rate was higher in CPPene group. In another study CPPene was found to be useful depending on the dosage (13). There are also some other studies that report a positive effect of MK-801 on central nervous system injuries (10,11,14,15,17) but it is in contrast to this study. The reason for that can be the application form and dosage. Other studies have used MK-801 in intravenous route (10,11,14,15).

The minimum effective plasma concentration of MK-801 in the rat was found to be 8.0 ng ml-1 and the greatest protection was seen with a plasma level of 18.9 ng ml-1 (15). We used MK-801 intraperitoneally to obtain optimal plasma concentrations according to the other studies carried out with gerbils that optimal plasma concentrations

were obtained with 0.3 mg/kg i.p. injections (15,21).

According to Young et al the time course of K+ changes explains the loss of SEP conduction across the impact site (30). The timing of SEP recovery seems to be a better indicator of tissue damage than the amplitude of initial SEP loss. The authors have estimated that 5% disruption of cells in the tissue will result in a loss of SEPs for about 50 minutes. Likewise, 10%, 25%, and 50% disruptions should block SEP conduction for about 80, 180 and 250 minutes (31). We observed that the SEP loss lasted about 60-120 minutes in this 50 gm-cm impact injury. It means that 10-20% cell disruption is probably the case in this model.

If amplitudes and latencies of SEPs and MEPs are examined in different recording times, the latencies are found to have a significant delay in all recording periods. But they recover partially during the later monitoring times. This improvement is not statistically significant. SEP amplitudes did not show significant difference compared to preinjury values. For that reason, we can say that latency measurement is more sensitive to traumatic cord injury than amplitudes.

In this study it seems that SEPs are more sensitive to spinal cord injury than MEPs. This is in contrast to some other workers (2,19). There can be three explanations for the insensitivity of MEPs to the rat spinal cord injury: The descending volley in response to motor cortex stimulation in rats could follow some different ways other than the pyramidal tract. Zappulla et al have reported that cortex stimulation of rats could easily provoke a stimulation through brain stem and extrapyramidal pathways. For that reason, a volley resulting from cortex stimulation of rats could show the function of more than one spinal cord pathway (32). Another pitfall is that the muscle response recorded from distal muscles could be a volume conduction response. We discussed this issue on another paper, and found that it was not a volume conduction response in the light of some other recordings made with neuromuscular blocking agents (34). It is likely that a posteriorly applied weight dropping injury can spare the pyramidal tract located anterior and central to the posterior columns that should primarily be responsible for the conduction of MEPs. For some of these reasons MEPs in this model of spinal cord injury seems to be less sensitive than SEPs. Haghighi et al. have also reported similar results to the ones in this study. Although SEPs were lost in all tetraplegic cats after moderate injury, MEPs were present in 60% of tetraplegic animals (16).

As a result, in this trauma model either MK-801 or CPPene did not have a positive effect on the lower extremity motor functions during the first week after spinal cord injury. CPPene, however, has a positive effect on the recovery of SEPs that were in fact lost after injury. These findings suggest that CPPene given 15 minutes after the injury could have a positive effect on some long tract function after weight dropping spinal cord injury in rats.

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