MK-801 Prevents the Post-Ischemic Cerebral Hypoperfusion, but Not the Dysfunction of the Vagal Baroreflex in Dogs

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ABSTRACT—Pretreatment with MK-801, a non-competitive N-methyl-D-aspartate (NMDA) antagonist, failed to protect the vagal component of reflex bradycardia from 5-min global cerebral ischemia in dogs under pentobarbital anesthesia. On the other hand, MK-801 completely prevented the development of the post-ischemic cerebral hypoperfusion without affecting the cerebral blood flow in sham-operated animals. The results suggest that NMDA receptors may participate in the development of the secondary disturbance of the cerebral circulation, but are not involved in the post-ischemic dysfunction of the baroreflex system.

Keywords: Cerebral ischemia, Baroreflex, MK-801

The non-competitive N-methyl-D-aspartate (NMDA) antagonist MK-801 has been used to investigate the pathological role of excitatory amino acid in ischemic neuronal injury (1). In the present study, we examined the effect of MK-801 on the post-ischemic dysfunction of the vagal baroreflex and the secondary cerebral hypoperfusion in a canine model of transient global cerebral ischemia (2, 3).

Mongrel dogs of either sex, weighing about 7 to 15 kg, were anesthetized with sodium pentobarbital (32 mg/kg, i.v. followed by an infusion of 3.2 mg/kg/hr, i.v.). The animals were artificially ventilated (a tidal volume of 20 ml/kg at a rate of 20 breaths/min) and immobilized with suxamethonium chloride (2 mg/kg, i.v., followed by an infusion of 1 mg/kg/hr, i.v.). Arterial Po2 and Pco2 were maintained at about 100 and 35 mmHg, respectively, providing an appropriate volume of O2 and CO2 gasses via a respirator. The rectal temperature was maintained at about 38°C using a heating pad and lamp.

Arterial blood pressure was measured from the left femoral artery by means of a pressure transducer (Nihon Kohden, TP-200T), and heart rate was measured by a heart rate counter (Nihon Kohden, AT-600G) triggered by the lead II ECG. The cortical EEG was continuously monitored from the parietal skull using a frequency analyzer (Nihon Kohden, OEE-7102). The reflex increase in pulse interval by l-phenylephrine hydrochloride (0.3 to 10 µg/kg injected into the left cephalic vein) was correlated with the increase in mean blood pressure by a method of least squares. The slope of the regression line (msec/mmHg) was used as a measure of baroreflex sensitivity (BRS).

Incomplete global cerebral ischemia was produced by a 5-min occlusion with clamps of the brachiocephalic artery and the left subclavian artery following ligations of about 14 intercostal arteries. Regional cerebral blood flow (rCBF) in the dorsal medulla oblongata was continuously measured by a tissue flow monitor (Unique Medical, UMW-101) using a plate-type thermocouple electrode, and the mean residual blood flow during ischemia was calculated as an index of the severity of ischemia (2). Furthermore, the absolute value of rCBF in the dorsal medulla oblongata was obtained by a hydrogen clearance method (4).

MK-801 (Research Biochemical, Inc.) was dissolved in saline and infused according to the dosage regimen by Michenfelder et al. (5), which produces the steady plasma concentration of 20 to 30 ng/ml. The infusion was started 10 min prior to ischemia at a rate of 30 µg/kg/min, i.v. Five minutes later, the infusion rate was reduced to 1.25 µg/kg/min, i.v., and the infusion was continued until the end of ischemia. In addition, trimethaphan camsylate (4.65 to 17.0 µg/kg/min, i.v., from 15 min before MK-801 administration to 3 min after the onset of ischemia) was infused into the right saphenous vein to reduce the mean blood pressure by about 30 mmHg, because the preliminary experiment
showed that MK-801 potentiated the rise in blood pressure during ischemia, which prevented the appropriate decrease in rCBF. Control animals were also treated with trimethaphan and given saline instead of MK-801.

In sham-operated animals, MK-801 produced a significant decrease in BRS during the period corresponding to reperfusion for 60 to 210 min (Fig. 1). Since it has been shown that glutamate receptors may be involved in the central pathways of baroreflexes (6, 7), the decrease in BRS in sham-operated animals may result from the central effect of MK-801 and imply that the brain concentration of MK-801 was within the range that effectively blocks the NMDA receptor system for more than 3 hr. Such a long duration of the central effect of MK-801 was consistent with the observation by Michenfelder et al. (5), who reported that the sedative effect of MK-801 persisted even 16 hr after the cessation of the infusion at the rate used in the present study. Bilateral section of the cervical vagosympathetic trunk (vagotomy) decreased BRS by 49.2 ± 2.3% (n = 6) in MK-801-treated, sham-operated animals; the extent of decrease in BRS was similar to that in saline-treated, sham-operated animals (45.0 ± 3.3%, n = 6). These results suggest that MK-801 at the dose used in the present study attenuates the vagal and sympathetic component of BRS to similar extents.

In animals that received ischemic insult, a marked decrease in BRS was observed during the reperfusion period (Fig. 1). Although the severity of ischemia was similar (the mean residual blood flow during ischemia was 36.4 ± 5.9% in 6 saline-treated animals and 40.4 ± 5.3% in 6 MK-801-treated animals), the extent of decrease in BRS in MK-801-treated animals was greater than that in saline-treated animals. In these animals, vagotomy failed to affect BRS, which indicates that the vagal component of BRS was completely damaged in MK-801-treated animals as well as saline-treated animals. The greater decrease in BRS in MK-801-treated animals may result from the direct inhibitory effect of MK-801 as observed in sham-operated animals. These results suggest that NMDA receptors are involved in the physiological function of the central pathway of the baroreflex, but not in the pathogenesis of the ischemic dysfunction of the vagal baroreflex.

Although MK-801 has been shown to be cerebroprotective in animal models of focal cerebral ischemia, conflicting results exist in the model of global cerebral ischemia (8). In this context, the present result is not an unexpected one, because the model used was that of global cerebral ischemia. Such a difference in the involvement of NMDA receptors between focal and global cerebral ischemia has been explained by the difference in the extent of acidosis-mediated blockade of NMDA receptor function (9). Thus, there still exists a possibility that excitatory amino acids might deteriorate the vagal baroreflex via non-NMDA glutamate receptors. Furthermore, since our previous study demonstrated that ifenprodil, an alpha-adrenoceptor blocking agent with an additional NMDA antagonistic property, prevented the ischemic dysfunction of the baroreflex (3), adrenergic neurotransmitters might play a pathological role.

During the reperfusion period, a secondary decrease in rCBF was developed in the saline-treated animals (Fig. 2). MK-801 completely prevented this post-ischemic hypoperfusion, while it failed to affect rCBF in the sham-operated animals. The result is consistent with that by Stevens and Yaksh (10), who found in a feline model of 15-min complete global cerebral ischemia that pretreatment with MK-801 prevented the development of post-ischemic cerebral hypoperfusion without affecting resting rCBF. In addition, Tortella et al. (11) reported that dextromethorphan, the non-competitive NMDA antagonist, attenuated the post-ischemic hypoperfusion in a rat model of 15-min incomplete...
global cerebral ischemia. These results suggest that NMDA receptors may participate in the development of the cerebral hypoperfusion following transient global cerebral ischemia. Although the mechanism of prevention of the secondary hypoperfusion by NMDA antagonists has not been fully clarified, Stevens and Yaksh (10) demonstrated that prevention of the increase in thromboxane A₂/prostaglandin I₂ ratio in cerebrospinal fluid may be relevant to the beneficial effect of MK-801.

In conclusion, the present study suggests that the mechanisms underlying the post-ischemic disorders in the cerebral function and circulation are not necessarily identical. Although the NMDA receptors may play a pathological role in the development of the post-ischemic cerebral hypoperfusion, they play no major role in the pathogenesis of the dysfunction of the vagal baroreflex. A possible involvement of non-NMDA glutamate receptors or neurotransmitters other than excitatory amino acids remains to be elucidated.

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