ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 107 SECTIO D 2004

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Histological examination of the kidney after experimental administration of MK-801 and dexamethasone

MK-801 (*Dizocilpine maleate*) belongs to the group of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists with a high affinity to NMDA-receptor (4, 5, 6). It is the first drug consistently shown to be neuroprotective *in vivo* (8, 9, 10). Mechanism of its action is connected with the inhibition of the Ca^{2+} entry through the NMDA-operated Ca^{2+} channel and subsequently reduction in the increase of the intracellular calcium concentration (5). On the other hand, the side-effects of MK-801 are serious and need to be considered before clinical use. Despite numerous neuropsychological symptoms this drug has important cardiovascular effects, especially hypotension (1, 6, 7).

Considering the necessity to establish the indications and contraindications for the therapy with drugs derived from this group and a lack of data regarding the influence of neuroprotective doses of MK-801 on morphology of the kidney we decided to assess the histological structure of the kidney after experimental administration of MK-801. We performed histological examination of the kidney after concomitant administration of MK-801 and toxic doses of dexamethasone that were used to increase the kidney workload.

MATERIAL AND METHODS

The experiments were carried out on male Albino Swiss mice weighing 24–25 g at the beginning of the experiment. Care and treatment of the animals were in accordance with the guidelines for laboratory animals of the Local Ethical Committee of the Medical University of Lublin. The animals were kept under standard laboratory conditions, with free access to granular standard diet and tap water. The animals were divided into three groups (including 10 animals each). Animals of the control group received distilled water (i.p. 0.2 ml/24 h) for 8 days. Animals in experimental group I received MK-801. Experimental group II animals received dexamethasone. Experimental group III animals received MK-801 and dexamethasone. MK-801 was administered i.p. in a dose 0.3 mg/kg/24 h for 8 days. Dexamethasone (Dexaven-Jelfa SA, Poland) was administered s.c. in a dose 120 mg/kg/24 h for 8 days. Twenty-four hours after the last MK-801 or last dexamethasone injection all animals were decapitated and the left kidneys were taken for histological examinations.

Specimens of the kidney fixed in 4% formalin were dehydrated in graded ethanol solutions and embedded in paraffin. The routine H+E (hematoxylin and eosin) staining and PAS reaction for the detection of neutral mucopolysaccharides were performed on 7 μm thick paraffin slices. The slides were assessed using a light microscope. The pictures were taken with the use of the Carl Zeiss Jena microscope and photo camera.

RESULTS

Control group (Fig. 1A, B). Kidney stained with hematoxylin and eosin and with PAS method evidenced a regular histological structure. H+E staining showed regular stainability of renal corpuscle components and renal tubule components.

Experimental group I – MK-801 (Fig. 2A, B). Histological changes in the shape of a slight narrowing of the urinary spaces in renal corpuscles and narrowing of the lumen of the proximal convoluted tubules located in the juxtamedullary region were observed after MK-801 administration.

Experimental group II – dexamethasone (Fig. 3A, B). Administration of dexamethasone in toxic doses caused morphological changes in the shape of hyperemia of the renal parenchyma (the dilated arteries, capillaries surrounding tubules and glomerular capillaries). We also observed a slight dilatation of the urinary spaces in many renal corpuscles and dilatation of the lumen in the main part of nephron tubules.

Experimental group III – MK-801+ dexamethasone (Fig. 4A, B). We observed morphological changes in the shape of a strong hyperemia of the renal parenchyma and distinct dilatation of the urinary spaces in many renal corpuscles. These changes were more intensive than in the case of dexamethasone itself.

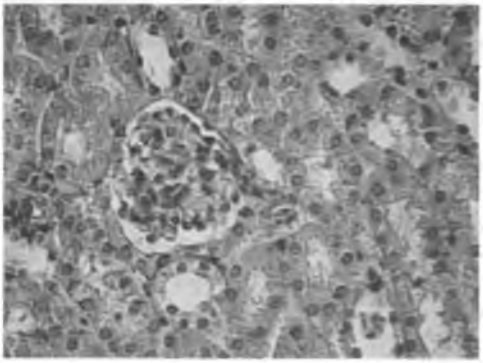

Fig. 1A

Fig. 1B

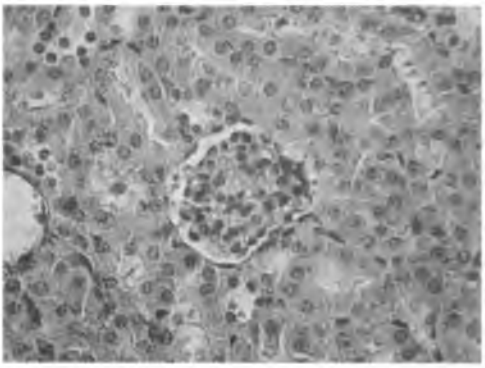

Fig. 2A

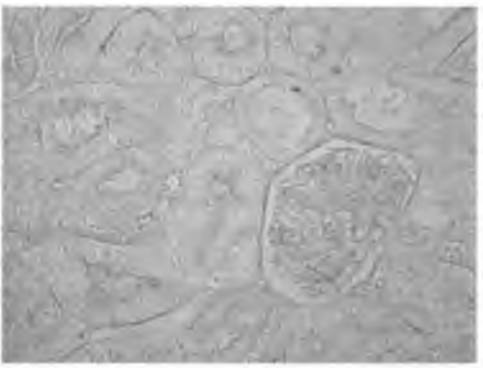

Fig. 2B

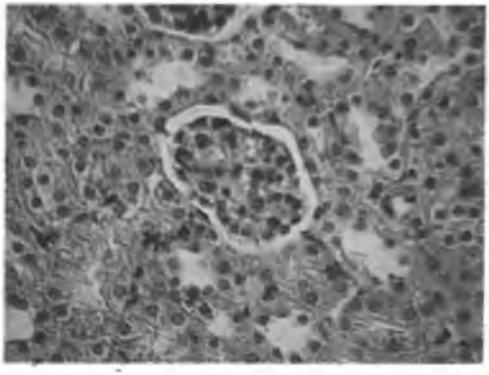

Fig. 3A

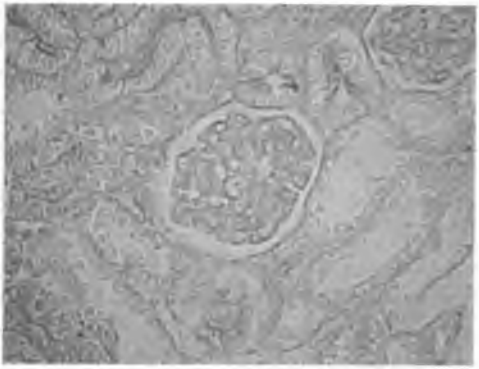

Fig. 3B

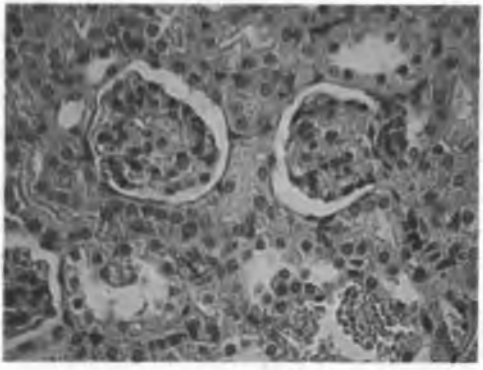

Fig. 4A

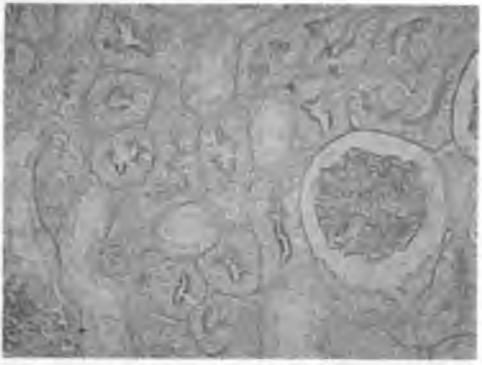

Fig. 4B

Fig. 1. The kidney from the control animal (control), MK-801 treated animal (MK-801), dexamethasone treated animal (dexamethasone) and MK-801+dexamethasone treated animal (MK-801+dexamethasone). The left photomicrographs (1A, 2A, 3A, 4A) show kidney slices stained with hematoxylin and eosin in respective groups – magn. 400x. The right photomicrographs (1B, 2B, 3B, 4B) show slices of the kidney stained with PAS method in respective groups – magn. 400x. MK-801 was injected i.p. in a dose 0.3 mg/kg/24 h for 8 days. Dexamethasone was injected s.c. in a dose 120 mg/kg/24 h for 8 days

DISCUSSION

Regarding a lack of data about the influence of NMDA-antagonists on the kidneys, the investigation of MK-801 influence on this organ is very purposeful. However, the kidneys play a significantly smaller role in MK-801 metabolism in comparison with the liver. Our research showed that MK-801 does not exert nephrotoxic influence. However, it exerts the action inhibiting diuresis. Narrowing of the utrinary spaces and narrowing of the lumen of the proximal convoluted tubules indicate decreased filtration after administration of MK-801 (3).

In our experiment in all animals receiving the toxic doses of dexamethasone (experimental group II) we observed hyperemia of the renal parenchyma in the form of the dilatation of arteries, capillaries surrounding tubules and glomerular capillary loops. We noticed a slight dilatation of the urinary spaces in renal corpuscles and dilatation of the lumen in the main part of nephron tubules which indicate stimulation of diuresis (3). R i c h et al. presented an experimental model in which steroids cause a

lesion comparable to glomerular hyalinosis in rabbits (11). Chan et al. reported renal lesions in the dexamethasone-treated mice after 23 days of glucocorticosteroid therapy which were characterized by mild mesangial expansion, segmental or global hyalinosis/sclerosis in deep cortical glomeruli, and focal tubular changes. No glomerular inflammatory cell infiltration or proliferative lesion was noted in any of the mice (2). We did not observe changes typical of hyalinosis after administration of toxic doses of dexamethasone in our experiment.

It may be concluded that MK-801 administered for 8 days in neuroprotective doses causes only functional changes manifestating as lower diuresis and dexamethasone administered in toxic doses for 8 days stimulates diuresis.

The concomitant administration of MK-801 and toxic doses of dexamethasone caused a stronger hyperemia of the renal parenchyma than in the case of dexamethasone itself. A dilatation of the spaces between two layers of the Bowman's capsule in the renal corpuscles was also more significant than in the case of dexamethasone itself. Morphological changes observed in the kidneys may be a result of the liver damage induced by both medicines and connected with it increased kidney workload.

CONCLUSIONS

1. MK-801 administered in the dose corresponding to the neuroprotective dose used in human causes morphological changes of the kidney in the shape of a slight narrowing of the urinary spaces in renal corpuscles and narrowing of the lumen of the proximal convoluted tubules located in the juxtamedullary region.

2. Dexamethasone administered in toxic doses caused kidney's hyperemia with a slight dilatation of the urinary spaces in renal corpuscles and dilatation of the lumen in the main part of nephron tubules which indicate stimulation of diuresis

3. Concomitant administration of MK-801 and toxic doses of dexamethasone intensifies morphological changes caused by dexamethasone itself.

REFERENCES

1. Auer R. N. et al.: The nature and time course of neuronal vacuolation induced by the N-methyl-D-aspartate antagonist MK-801. Acta Neuropathol., 87, 1, 1994.
2. Chen A. et al.: Administration of dexamethasone induces proteinuria of glomerular origin in mice. Am. J. Kidney Diseases, 31, 443, 1998.
3. Heptinstall R. H.: Pathology of the Kidney. Little, Brown and Company, Boston/Toronto 1983.
4. Kostowski W., Pużyński S.: Psychofarmakologia doświadczalna i kliniczna. PZWL, Warszawa 1996.
5. Krieglstein J. et al.: Neuroprotection by memantine is increased by hypothermia and nimodipine. Eur. J. Pharmac. Sci., 5, 71, 1997.
6. Muir K. W.: Clinical experience with excitatory amino acids antagonist drugs. Stroke, 26, 503, 1995.
7. Olney J. W. et al.: Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science, 244, 1360, 1989.
8. Ozyurt E. et al.: Protective effect of the glutamate antagonist, MK-801 in focal cerebral ischemia in the cat. J. Cereb. Blood Flow Metab., 8, 138, 1988.

9. Park C. K. et al.: Focal cerebral ischemia in the cat: treatment with the glutamate antagonist MK-801 after induction of ischemia. J. Cereb. Blood Flow Metab., 8, 757, 1988.
10. Park C. K. et al.: The glutamate antagonist MK-801 reduces focal ischemic brain damage in the rat. Ann. Neurol., 24, 543, 1988.
11. Rich A. R.: The effect of ACTH and cortisone upon experimental glomerulonephritis. Trans. Assoc. Am. Physicians, 64, 257, 1951.

SUMMARY

The aim of the research was histological assessment of the influence of MK-801 (NMDA receptor antagonist) and dexamethasone on the kidney. The experiment was carried out on adult Albino-Swiss mouse males. MK-801 was administered in the dose of 0.3 mg/kg/24 h for 8 days, dexamethasone – in the toxic dose of 120 mg/kg/24 h. Kidney slices stained with hematoxylin and eosin and with PAS method were examined with light microscope. The performed experiments revealed that MK-801 causes morphological changes in the shape of slight narrowing of the urinary spaces in renal corpuscles and narrowing of the lumen of the proximal convoluted tubules and dexamethasone administered in toxic doses causes dilatation of these spaces with kidney's hyperemia. MK-801 intensifies morphological changes of the kidney induced by toxic doses of dexamethasone.

Ocena histologiczna nerki po doświadczalnym podaniu MK-801 i deksametazonu

Celem pracy była ocena histologiczna wpływu MK-801 (antagonisty receptora NMDA) oraz deksametazonu na nerki zwierząt doświadczalnych. Badania wykonano na dorosłych samcach myszy Albino-Swiss. MK-801 podawano w dawce 0,3 mg/kg/24h przez 8 dni, deksametazon w dawce toksycznej 120 mg/kg/24h przez 8 dni. Przy pomocy mikroskopu świetlnego oceniano preparaty nerki barwione hematoksyliną i eozyną oraz metodą PAS. Przeprowadzone badania wykazały, że MK-801 powoduje zmiany morfologiczne w postaci nieznacznego zwężenia przestrzeni moczowych ciałek nerkowych oraz zwężenie światła kanalików krętych pierwszego rzędu, natomiast deksametazon w dawkach toksycznych powoduje poszerzenie tych przestrzeni z przekrwieniem miąższu nerki. MK-801 nasila zmiany morfologiczne nerki, wywołane toksycznymi dawkami deksametazonu.