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EFFECTS OF KETAMINE AND DIAZEPAM ON THE MORPHOLOGY OF THE KIDNEY OF RABBIT : AN ELECTRON MICROSCOPIC STUDY (With 13 Figures)

By

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دراسة تأثير عقارى الديازيبام والكيتامين على التركيب الدقيق لكلى الأرانب البيضاء

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استخدم فى هذا البحث سبع وعشرون من أرانب نيوزيلاندا البيض البالغة. وقد قسمت الى ثلاث مجموعات. المجموعة الأولى ضابطة ، المجموعة الثانية حقنت فى الوريد بجرعة واحدة من عقار الديازيبام بينما حقنت المجموعة الثالثة بجرعة واحدة من عقار الكيتامين بالوريد. وأخذت عينات الكلى بعد أسبوع واحد من الحقن من جميع المجموعات. وقد أظهرت عينات المجموعة الثانية تضخم فى الغشاء القاعدى الخاص بشعيرات الجمع وكذلك الغشاء القاعدى للأنيبوبة الملتفة الدانية ، كما ظهر أيضا التحام بين أقدام زوائد الخلايا القديمة وزيادة فى الأجسام المحطلة الموجودة فى سيتوبلازم الأنيبوبة الملتفة الدانية. أما عينات المجموعة الثالثة فقد أظهرت التحامات بين أقدام زوائد الخلايا القديمة بدون تضخم فى الغشاء القاعدى ، كما أظهرت زيادة فى الفجوات الموجودة فى سيتوبلازم الأنيبوبة الملتفة القاصية. ويستنتج من هذا البحث أن العقارين المستخدمين فى هذا البحث قد أحدثا تأثيرا واضحا وبالأخص عقار الديازيبام ، على التركيب الدقيق للكلى مما قد يؤدى الى خلل فى كفاءة الكلى وعمل الحاجز الرشحى الذى يمنع مرور جزيئات البروتين.

SUMMARY

Three groups of adult Newzeeland white rabbits were used in this study. The first group served as control. The second and third groups were injected intravenously with a single dose of diazepam and ketamine respectively. The animals were sacrificed one week after injection. The specimens taken from diazepam treated animals showed a marked thickening of the glomerular and proximal convoluted tubules basement membrane, thickening of the measangial matrix, fusion of the podocyte foot processes and presence of numerous lysosomes in the cytoplasm of the proximal convoluted tubules. In case of ketamine treatment, the specimens showed fusion of podocyte foot processes and numerous vacuoles in the distal convoluted tubules.

Keywords: Effect, ketamine, diazepam, morphology, kidney, rabbit, electron microscopic, study

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INTRODUCTION

Ketamine is the first drug of the phencyclidin group to be used for intravenous (I.V.) anaesthesia. It has an important and sometimes unrivaled place in the practice of anaesthesiology (ZSIGMOD & DOMINE, 1990). However, the unique pharmacological features of ketamine as well as its propensity to produce unwanted psychological reactions (WHITE *et al.* 1982), have placed ketamine outside the realm of routine clinical use taken up by benzodiazepines (BZ). The latter are commonly used in sedation. According to BURCHARDI & KACZMARCZYK (1994) anaesthesia and surgical stress can affect renal function and body fluid regulation indirectly as well as directly. The indirect effects through influences on haemodynamics, sympathetic activity and humoral regulation are more pronounced than the direct ones. The direct effects are dose and agent dependent and include effects on autoregulation of renal blood flow alteration in the effect of ADH and effects on tubular transport of sodium and organic acids.

Diazepam has been found to decrease renal blood flow. Whereas ketamine increased it in conscious dogs (LAWRANCE, 1982). However, little is known about the effects of these drugs on the morphology of the kidney. Therefore the objective of this study was to examine any changes that would occur in the renal morphology following I.V. administration of diazepam and ketamine.

MATERIAL and METHODS

Twenty seven adult Newzeeland white rabbits weighing 2-3 kg. of both sexes, were used in this study. They were divided into three groups. The first group served as control while the second group received an I.V. injection of 1 mg/kg body weight in the form of 5% solution. The injections were given I.V. through the ear vein. Animals were sacrificed one week following the injection. Small specimens were taken from the kidney and fixed in 2% glutaraldehyde, post fixed in osmium tetroxide and processed for electron microscopy. Ultrathin sections were examined on Philips 300 electron microscope.

RESULTS

I- Ultra structure of the kidney of control animals:

Glomerular capillaries are lined by thin endothelial cells of the fenestrated type (Fig. 1). Visceral epithelium of Bowman's capsule extends cytoplasmic processes that rest on capillary basement membrane. These processes interdigitate with those of adjacent cells. So, the epithelium appears as series of regularly spaced small feet profiles separated by spaces or slits. These slits are spanned by the slit membrane (Fig.2). The mesangial cells of the capillary tuft contain small densely stained nuclei, fine filaments and dense cytoplasmic plaques. They are embedded in an amorphous matrix that appears to be continuous with the lamina rara interna. Long processes extend from the mesangial cells and

appear to project through the endothelium into the capillary lumen (Fig.1). The parietal layer of Bowman's capsule is composed of a simple squamous epithelium with nuclei that protrude slightly into the capsular space.

The proximal convoluted tubules are lined by simple cuboidal epithelium. The apical surface displays numerous closely packed microvilli projecting into the lumen (Fig.3). The basal part of the plasma membrane shows deep infoldings that limit narrow columns of cytoplasm within which elongated mitochondria are enclosed (Fig.4). The cytoplasm also contains dense heterogenous lysosomes (Fig.3). The lining cells are bound together by tight junctions and deeper intermediate junctions. The endothelial lining of the nearby capillaries is characterized by the presence of closed pores or fenestrae (Fig.4).

The distal convoluted tubules are lined by cuboidal cells with irregularly spaced nuclei that tend to be displaced apically (Fig.5). They possess fewer basal infoldings than the proximal convoluted tubules. The apical surface shows few short microvilli and few vacuoles (Figs. 5&6).

II- Ultra structure of the kidney of animals treated with diazepam:

Some areas of the renal corpuscles showed a marked thickening of the matrix of mesangial cells (Fig.7), whereas other areas showed irregular thickening of the basal lamina of the visceral epithelium (Fig.8). The podocyte foot processes terminating on the capillary endothelium were fused with the disappearance of the regularly

spaced small foot processes and appearance of much larger irregular cell process and segments of podocyte cytoplasm resting on the basal lamina (Fig.9). The proximal convoluted tubules showed a marked thickening of the basement membrane and attenuation of the endothelium lining the capillaries (Fig.10). The lining cells of the tubules contained numerous dense bodies (lysosomes). The distal convoluted tubules appeared normal in structure.

III- Ultra structure of the kidney of animals treated with ketamine:

The structure of the proximal convoluted tubules appeared relatively normal. The distal convoluted tubules showed a great number of vacuoles distributed throughout the cytoplasm (Figs.11&12). Other structures appeared approximately normal. The podocyte foot processes terminating on the endothelium lining the capillaries showed a marked fusion (Fig.13). The basal lamina of the capillary endothelium and the matrix of the mesangial cells were of normal thickness (Fig.13).

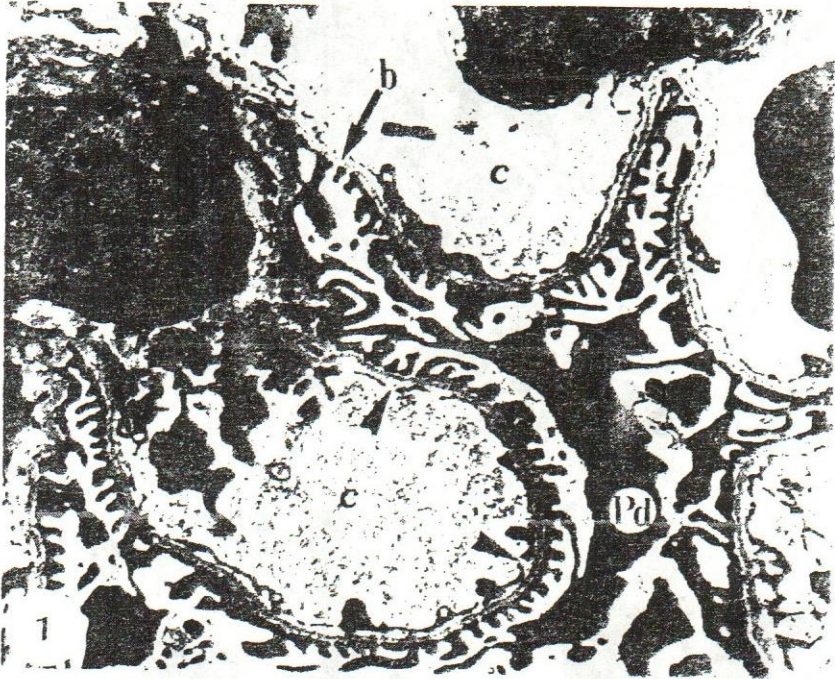
DISCUSSION

The specimens taken from diazepam treated animals showed a marked thickening of the glomerular basement membrane. The thickening was irregular. Thickened glomerular basement membrane is a common finding of many pathologic and experimental conditions (TAYLOR *et al.*, 1980). IN most cases, thickened basement membranes are more permeable to proteins than are normal basement membranes. Increased permeability has been attributed to the

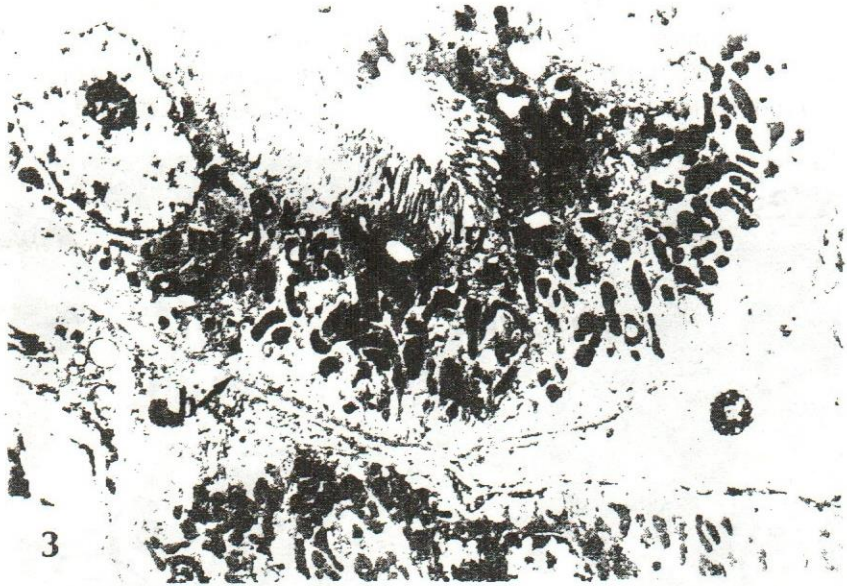
LEGEND

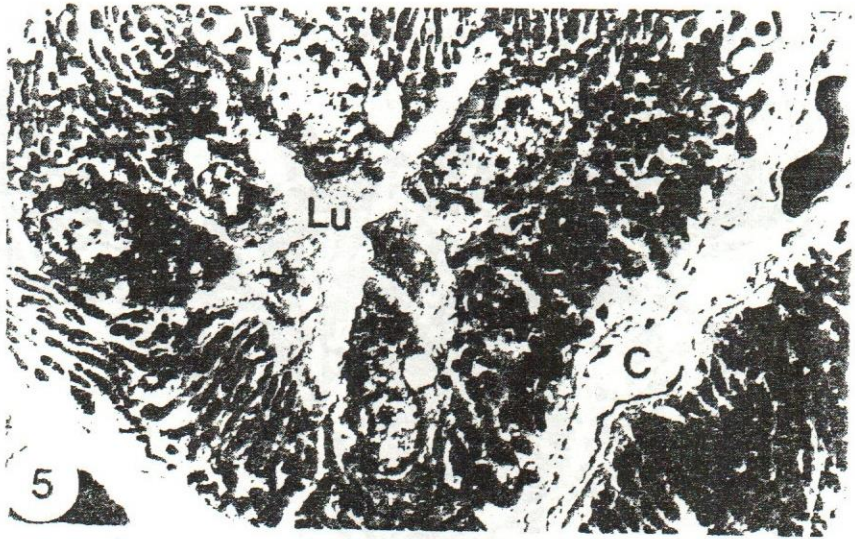
- Fig. 1** : Electron micrograph of a portion of a renal corpuscle showing a capillary lumen (C) with fenestrated endothelium (arrow head), basal lamina (b), podocyte (Pd) with its end feet. Mesangial cell (m) with its matrix (*) can also be seen. (Normal x 12.000).
- Fig. 2** : Electron micrograph of the filtration barrier. Note the capillary lumen (C) containing plasma, endothelium with pores (arrow heads), basal lamina (b), pedicles (end feet) (F), slit pores closed by slit membrane (small arrow). (Normal x 24.000)
- Fig. 3**: Electron micrograph of transverse section in proximal convoluted tubule. Note the apical microvilli (V), numerous mitochondria (mt) and few lysosomes (ly). Basal lamina (b). Basal infolding of plasma membrane can also be noted. (Normal x 2000)
- Fig. 4**: Higher magnification of the previous figure showing the base of the tubule. Note the deep infolding of the plasma membrane and the elongated mitochondria in the cytoplasmic compartments. Note the peritubular capillary (C) with fenestrated endothelium (arrow head) and basal lamina of the tubule (b). (Normal x 19.500)
- Fig. 5**: Low power electron micrograph of a distal convoluted tubule. The apical surface possesses few microvilli. The nuclei are apically displaced. Lu (Lumen) C (capillary). (Normal x 3.450)
- Fig. 6**: Higher magnification of the previous section showing a few apical microvilli (mv) and vacuoles (V). Basal infolding of the plasma membrane can also be noted. C (capillary), b (basal lamina). (Normal x 7.500)
- Fig. 7**: Electron micrograph of a portion of a renal corpuscle showing capillaries (C), podocytes (Pd) and their processes. Note the marked thickening of the matrix of mesangial cells (asterisks). (D x 6.000)
- Fig. 8**: Electron micrograph of the renal corpuscle showing capillary lumen (C) containing erythrocytes. Note the irregular thickening of the basal lamina (asterisk). Fusion of the foot process of podocytes can also be noted (arrows). (DZ x 6.000)
- Fig. 9** : Electron micrograph of a portion of a renal corpuscle showing capillaries (C). Note the fusion of podocyte foot process terminating on capillary endothelium (arrows). (DZ x 12.000)
- Fig. 10** : Electron micrograph of a proximal convoluted tubule showing thickening of its basal lamina (b) and numerous dense bodies (lysosomes) (Ly). (DZ x 2.400)
- Fig. 11** : Electron micrograph of a distal convoluted tubule showing numerous vacuoles particularly toward the apex as well as numerous mitochondria. (Ketamine x 3.450)

- Fig. 12 : High magnification electron micrograph of a part of a distal convoluted tubule. The cytoplasm is replet with numerous vacuoles. (Ketamine x 11,2500)
- Fig. 13 : Electron micrograph of a part of renal corpuscle showing a capillary (C) with its basal lamina (b). Note the fusion between the podocyte foot processes (f). PD (podocyte).

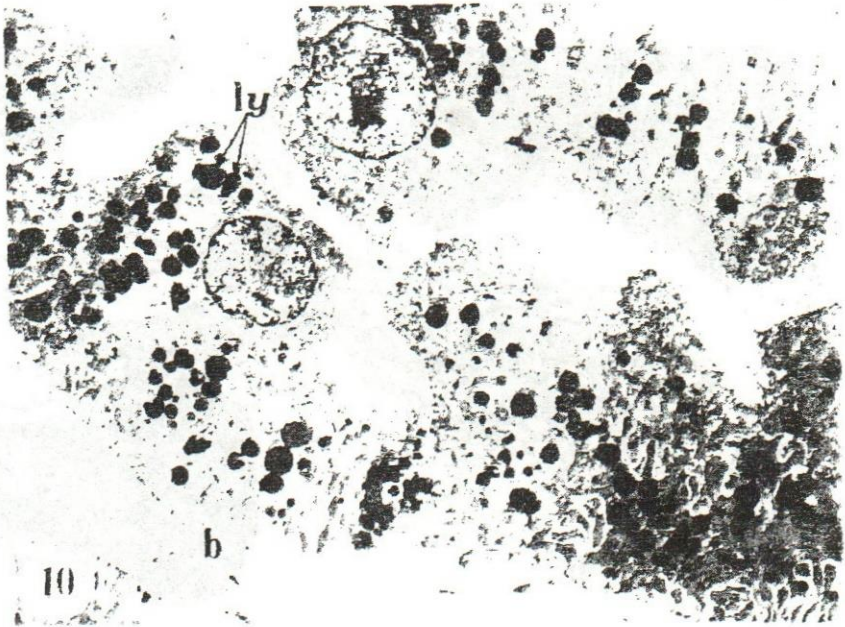


KETAMINE, DIAZEPAM AND KIDNEY RABBIT & ELECTRON MICROSCOPIC STUDY





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