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Autonomic Receptor Functions in the Normal and Dilated Renal Pelvis: An in Vitro Study in Man and Rabbit

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Summary. Autonomic receptor functions in muscle strips of normal and dilated renal pelves from man and rabbit have been studied. Strips from dilated pelves of both species were more reactive to alpha-adrenergic and tryptaminergic agonists than strips from normal kidneys. Cholinergic receptor functions were missing in all specimens.

Key words: Renal pelvis, Hydronephrosis, Autonomic receptor functions.

The part played by the autonomic nervous system in the muscular activity of the renal pelvis in man is not yet known. The resting tension and the frequency of contractions of the isolated renal calix of the pig is increased by local application of catecholamines (9). This has been confirmed in other species e.g. in rats (4) and in rabbits (5). In renal pelves of patients with malignant kidney tumours adrenoceptors were demonstrated in studies on muscle strips (7). The method of transmural field stimulation was applied by Del Tacca (1) to renal pelvis specimens from man and rabbit to produce contractions. He suggested that this response was initiated by noradrenaline from sympathetic nerve terminals.

Receptor studies of hydronephrotic renal pelves have, to our knowledge, not been published previously. In hydronephrosis there is often a functional obstruction at the ureteropelivic junction though no anatomical stenosis can be seen. This functional stenosis could hypothetically be caused by dysfunction in the autonomic nervous system. To explore this hypothesis we studied muscle strips from normal and dilated pelves for their autonomic receptor functions.

MATERIAL AND METHODS

Specimens from Humans

The material consisted of kidneys from 21 patients; 13 kidneys had dilated pelves and 8 kidneys had normal renal pelves according to intravenous urography. Nine of the patients with dilated pelves had an Anderson-Hynes pyeloplasty performed because of functional stenosis at the ureteropelvic junction according to radiologic examination. The other four patients in this group had nephrectomy because of advanced kidney stone disease with obstruction and severely reduced renal function. Five of the patients without pelvic dilatation underwent nephrectomy because of malignant tumours, two were operated upon because of calculi and one had a urinary diversion performed because of a vesico-vaginal fistula. Urinary cultures were negative in all patients but one. As there were three children among the hydronephrotic patients the mean age in this group was lower (37.3 years) than in the group with normal pelves (56.6 years). The sex ratio was six men to seven women in the hydronephrotic group and six men to two women in the control group.

As premedication all patients received morphine-scopolamine (0.8-1.5 mg i.m.). The time lapse from administration of premedication to excision of the renal pelvic specimen was 2.5-3.5 hours. At operation there was no difference in anaesthetic methods between the groups. All patients were initially anaesthetised with barbiturate intravenously. The narcosis was then supplemented by halothane-nitrous oxide and oxygen or by neuroleptic analgesics.

Specimens of the renal pelvis and, if possible, of the cranial part of the ureter were taken. The

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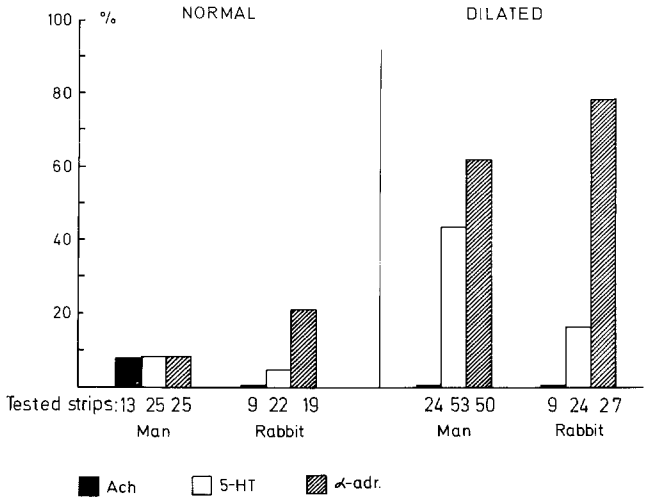

Fig. 1 Number of muscle strips (in per cent) from normal and dilated renal pelves giving dose dependent contractions to acetylcholine (ACh), serotonin (5-HT), and α-adrenergic agonists (see text).

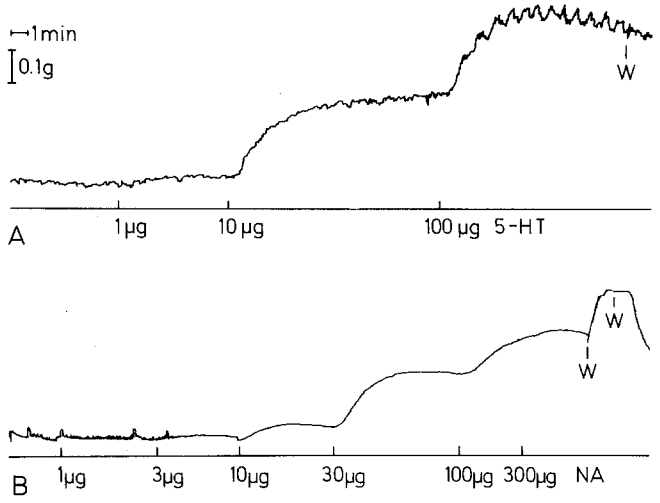

Fig. 2. Dose-effect curves of A) serotonin (5-HT) and B) noradrenaline in strips from hydronephrotic patients (w = wash out of drugs)

specimens were immediately immersed in Tyrode solution and transported to the laboratory. Several strips were prepared from each pelvic wall specimen. Some were taken just above the ureteropelvic junction, some closer to the calices. Most of the strips were cut perpendicularly to the cranial extension of the longitudinal axis of the ureter. Each strip was 15 mm long and 3 mm wide and weighed 0.10-0.16 g. Mean weight of the strips in the dilated pelvis group was 0.12 g and in the normal pelvis group 0.11 g.

Specimens from Animals

Specimens were taken from both renal pelves of ten healty adult male rabbits. In a first operation the bladders and ureters were exposed through an abdominal incision under pentobarbital anaesthesia (0.6-0.8 mg/kg i.v.). The right ureter was ligated 3 cm above the bladder. In order to achieve only a partial stenosis two pieces of 2-0 chromic catgut were placed as a splint along the ureter before a ligature was tied around them and the ureter. When this was completed the two pieces of suture parallel to the ureter were removed. To be sure that a limited passage of urine was possible methylene blue was injected into the right renal pelves of two operated animals. The dye passed to the bladder.

A second operation was done 2-7 weeks later using the same technique and anaesthesia as before. The pelves with the ligated ureters were considerably dilated. The intrapelvic pressure was measured in both kidneys and the mean value was 9 mm Hg in the normal pelves but 38 mm Hg in the hydronephrotic ones. Urine was collected from the dilated pelves as well as from the bladder for bacterial cultivation, but no bacteriuria was found. Bilateral nephrectomy was done and the animals were sacrificed. From the dilated and the normal renal pelves strips were prepared in the same way as in the human material.

Measurement of Pharmacological Effects

Each specimen was mounted in a 20 ml water-jacketed overflow type organ bath with Tyrode solution at 37°C. A gas mixture of 93.5 vol % oxygen and 6.5 vol % carbon dioxide was slowly bubbled through the bath to keep a constant pH at 7.4. A load of 1 g was applied to the strips to produce a basal tension which, after one hour of accomodation, was remarkably stable throughout the experiment. Variations in isometric tension of the strips in response to drugs were registered with a strain gauge transducer and recorded on a polygraph. Four strips were run in parallel in separate baths.

The presence and functional significance of cholinergic, tryptaminergic and adrenergic receptors were tested by cumulative addition of increasing doses of selective agonists and antagonists in volumens of 0.1-1 ml directly to the bath. Dose-response curves for the agonists were established. The degree of blockade induced by an antagonist was determined by comparison of dose-effect curves of the agonist before and after the antagonist had been present in the bath for 30 minutes. The reversibility of blockade was followed by repeating the dose-response curve of

an agonist at regular intervals after washout of the antagonist.

The following drugs were used: acetylcholine iodide (ACh, mol wt 273.10), adrenaline bitartrate (mol wt 183.20), noradrenaline bitartrate (NA, mol wt 169.18), neosynephrine hydrochloride (Neo, mol wt 203.67), 5-hydroxytryptamine sulphate (5-HT, mol wt 387.4), propranolol hydrochloride (mol wt 259.34) and phentolamine methansulphonate (mol wet 281.35). All concentrations were given as salts.

RESULTS

The results are summarized in Figure 1.

Cholinergic receptor functions were determined with cumulative addition of ACh to the organ bath, in doses from 1 - 1000 µg.

Only one out of thirteen strips from normal pelves from three patients reacted with dose dependent contractions. No cholinergic receptor functions were found in nine segments from five rabbits.

In the strips from dilated pelves from five humans (24 strips) and five rabbits (9 strips) no reactions at all were registered when ACh was added. All preparations tested for cholinergic receptor functions were responding to other drugs used in these experiments.

Tryptaminergic Receptor Functions. The dose range of 5-HT used was 1 - 1000 µg.

Twenty-five strips from eight patients were used to study receptor functions of normal pelves. Two segments from two different patients reacted to 5-HT. Only one of twenty-two strips from ten normal pelves of rabbits contracted after cumulative addition of 5-HT to the bath. The threshold dose was 10 µg/ml.

Fifty-three strips from all dilated human pelves were examined for tryptaminergic response. Twenty-three of these segments responded with contractions (threshold dose was usually 3 µg/ml) (Figs. 1 and 2). Four out of twenty-four strips from ten rabbits responded with contraction to a threshold concentration of 10 µg/ml (Fig. 1). The reactive strips come from three kidneys.

Alpha-Adrenergic Receptor Functions. Neosynephrine (Neo), noradrenaline (NA) and adrenaline were used in the same dose range as ACh and 5-HT (1 - 1000 µg/ml). When the alpha-adrenergic receptor functions were examined with adrenaline-noradrenaline as agonists, the beta-adrenergic antagonist propranolol (5 µg/ml) was present in the bath to prevent masking of alpha-adrenergic effects by beta activity in the tissue.

Twenty-five strips from normal pelves of eight patients were investigated. Two of the segments from two different patients gave dose-related responses to NA and Neo. These contractions were blocked by phentolamine (0.15 µg/ml). The inhibition was reversible. Four out of nineteen strips tested from the normal kidneys of ten rabbits reacted with increasing contractions to cumulative addition of NA and Neo (Fig. 1).

From the thirteen patients with dilated pelves fifty strips were examined as to alpha-adrenergic receptor functions. Thirty-three reacted with dose-dependent contractions (Fig. 2). The segments showing alpha-adrenergic activity originated from eleven patients. The threshold dose given to the bath was 10-30 µg/ml of NA and Neo. Blockade of alpha receptors and the reversibility of inhibition was tested in the same way as described above. In the twenty seven strips from hydronephrotic rabbit kidneys twenty one responded to the alpha-adrenergic agonists.

DISCUSSION

In idiopathic hydronephrosis the renal pelvis and calices are dilated but the ureter is of normal calibre. Sometimes the condition results in progressive renal failure. The aetiology of hydronephrosis has been much discussed in recent years. Earlier opinions regarding aberrant vessels, post-infectious adhesions or congenital malformation with pelvi-ureteric junctions located abnormally high are now doubted to be primary causes of dilatation (11).

An aetiological analogy with Hirschsprung's disease of the bowel, where the dilatation of colon is associated with a lack of ganglion cells in the sigmoid colon and upper part of rectum, has been discussed. However, in the functionally obstructed first part of the ureter in hydronephrosis a normal innervation has been observed in electron microscopic studies (10). With EMG and pressure examinations in the dog the normal peristalsis of the ureter at a constant diuresis was found to be regular and strictly correlated to the electrical activity in the renal pelvis (2, 6).

In manometric studies of perfused pelviureteric segments from hydronephrotic patients Murnaghan (8) showed that the contractions often faded out and were not transmitted to the ureter. His results have been confirmed and it has also been shown by methods using EMG of the smooth muscle of the hydronephrotic pelvis that there can sometimes be a total dissociation between the peristaltic activity in the renal pelvis and the ureter (3). The extent of the electrophysiological disturbances seems to increase with rising intrapelvic pressure and seriousness of the disease.

The most important result of the present study is that there exists a clear difference in adrenergic and tryptaminergic receptor functions between the normal and dilated pelvis. This difference means that the musculature of the hydronephrotic renal pelvis reacts to catecholamines and serotonin (5-HT) with contractions, which are more consistent and pronounced than in the same kind of tissue from control kidneys. With histochemical methods we intend to examine the possibility of the difference in contractility being accompanied by changes in autonomic innervation.

The pathophysiological importance of the increased contractility is difficult to evaluate. The phenomenon of dissociated electrophysiological activity in the hydronephrotic pelvis (3) could be an indication of the hypersensitivity of the musculature to catecholamines and serotonin. This hypersensitivity is, according to the present results, a consequence of dilatation under increased pressure. Increased sensitivity may disorganize the peristalsis and function of the dilated renal pelvis.

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