The Effect of Alpha-2 Agonists and Antagonists on the Upper Urinary Tract of the Rat

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Abstract

We examined the effect of the selective alpha-2 agonist dexmedetomidine and antagonist atipamizole on the upper urinary tract, renal pelvic pressure and ureteral peristalsis. Experiments were performed on twelve Sprague-Dawley female rats weighing 275-323 grams, with administration of urethane (1.2 μg/kg). Ventilatory support was provided through a tracheotomy. A continuous normal saline infusion was maintained through the left iliac vein at a rate of 2.5 ml/hr. Arterial pressure was measured at the left iliac artery, which was cannulated with a PE-100 tube connected to a pressure transducer. A mid-line incision was then made from the xyphoid to the symphysis to expose the left kidney, both ureters, and the bladder. The bladder was intubated and drained to avoid bladder pressure increase. Measurements of urine output rate were made from the right ureter and renal pelvic or ureteral pressure was measured using a nephrostomy placed into the left pelvis. A ureterostomy was produced by introducing another catheter, into the upper segment of the left ureter for ureteral pressure measurements. The rats were divided into two groups as follows: 1) dexmedetomidine group (n=6); injected intravenously with 2 μg/kg of dexmedetomidine dissolved in 0.5 ml saline. 2) atipamizole group (n=6); injected intravenously with 2 μg/kg of atipamizole dissolved in 0.5 ml saline. Ureteral peristaltic frequency, baseline pressure, and contraction amplitude were compared before, after, and between the bolus injections of 2 μg/kg dexmedetomidine (n=6) or 2 μg/kg atipamizole (n=6) in 0.5 ml saline.

The results showed that dexmedetomidine at 2 μg/kg produced a significant decrease in arterial pressure and an increase in urine output from 1.2±0.8 to 3.6±1.2 ml/min. There was no effect on the baseline pelvic pressure of 6.8±1.2 cmH₂O or amplitude of the renal pelvic contractions: 3.5±0.6 cmH₂O. The frequency of pelvic contractions was reduced from 0.37±0.03 to 0.27±0.02 Hz. Atipamizole at 2 μg/kg produced a significant reduction in urine flow rate of 1.1±0.8 to 0.6±0.2 ml/min. Atipamizole also showed no significant effects on baseline pelvic pressure or frequency, but increased the amplitude of pelvic contractions from control values of 3.0±0.9 to 3.4±0.9 cmH₂O. Dexmedetomidine reduced both the baseline ureteral pressure of 8.5±2.4 and peristaltic contraction pressure of 11.5±2.3 cmH₂O in 4/6 rats. Atipamizole reduced base-line ureteral pressure and increased peristaltic rate. This study has shown that dexmedetomidine has an inhibitory effect on renal pelvic contraction which is followed by weak excitatory effects of short duration. This effect is expressed by a decrease in the frequency of contractions and a decrease in the baseline pressure which was not significant statistically in view of the increased urine output.
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In contrast, atipamizole causes an excitatory effect on upper urinary tract contractility.

Key words: Renal pelvic pressure, ureteral peristalsis, alpha-2 adrenoceptor, dexmedetomidine, atipamizole

Introduction

The pharmacologic manipulation of adrenergic receptors in the smooth muscle of the urinary tract has many potentially important clinical implications. In the lower urinary tract, blockade of the alpha-1 receptors in the prostate gland and prostatic capsule has been used for the treatment of the symptoms associated with benign prostatic hyperplasia (BPH) (Caine, 1990; Lepor, 1990). There is also evidence that alpha-2 agonists have an effect on bladder function and pathologic changes in the spinal cord after spinal cord injury (Weiss, 1990). The increasing use of alpha-2 agents for urinary tract dysfunction prompted this investigation of the effect of these agents on the upper urinary tract. In particular, the effects of alpha-2 agonists and antagonists on the mechanisms controlling ureteral peristalsis were evaluated. As previously demonstrated, ureteral peristalsis is initiated and controlled by a pacemaker system (Constantinou, 1974; Seki et al., 1990). Since alpha-2 agents also have a profound diuretic effect, their action will influence the flow dependent mechanisms of urine transport in addition to direct pharmacologic effect on the renal pelvis, the ureter, and the bladder.

It has been demonstrated that the alpha adrenoceptor and muscarinic receptor exist in the ureter (Latifpour et al., 1989), and alpha-adrenergic agonists stimulate ureteral activity while alpha-adrenergic agonists inhibit ureteral activity (Weiss et al., 1978). However, there is little information regarding the effect of alpha-2 adrenergic agonists on renal pelvic pressure.

Medetomidine (4-(1-(2, 3-dimethylphenyl)ethyl)-1H-imidazole) is a newly developed compound which has shown potent and selective activity on alpha-2 adrenoceptors in a number of models (Savola et al., 1986; Virtanen et al., 1988). Dexmedetomidine, an alpha-d stereoisomer of medetomidine, is twice as effective as medetomidine (d, 1 lacemic mixture) while the 1-isomer is inactive (Virtanen, 1989), on alpha-2 adrenoceptors. Dexmedetomidine has been shown to be a very potent, efficacious, and selective agonist of alpha-2 adrenoceptors in the central and peripheral nervous system (Ruffolo et al., 1988). Alpha-2 adrenal agonists inhibit noradrenaline release from nerve terminals and mediate a variety of physiological functions in the central nervous system and in peripheral tissue.

In contrast, atipamizole (4-(2-ethyl-2, 3-dihydro-1H-inden-2-yl)-1H-imidazole) is a novel specific antagonist of alpha-2 adrenoceptors (Langer, 1974). As dexmedetomidine and atipamizole are potentially useful agents for the pharmacologic manipulation of the lower urinary tract functions, it may be important to characterize their action on the upper urinary tract. In this paper we evaluate the pharmacologic modulation of these agents on renal pelvic pressure and ureteral peristalsis. The rat experimental model (Harada, 1992) used in this study is designed to provide an optimum, undisturbed path for urine transport to take place. There has been no report of the effects of dexmedetomidine or atipamizole on the urinary tract function. In this paper, therefore, we have examined the effects of these two agents on upper urinary
tracts of anesthetized rats.

Materials and Methods

Experiments were performed on twelve Sprague-Dawley female rats weighing 275–323 grams. The rats were anesthetized by subcutaneous administration of urethane (1.2 g/kg). For the duration of the study, the animals were placed on thermostatically controlled operating boards and their body temperatures were monitored by a rectal thermometer. Each animal was then placed beneath a Wild binocular microscope to visualize the anatomical structures and aid in surgery.

Surgical Preparation

Details of the experimental procedure used for this study have been previously reported (Harada, 1992). The surgical preparation is briefly described below.

Ventilatory support was provided through a tracheotomy cannulated with a polyethylene tube to room air. A continuous saline infusion was maintained through the left iliac vein at a rate of 2.5 ml/hr, using a Harvard Pump 2681. Arterial pressure was measured at the left iliac artery, which was cannulated with a PE-100 tube. The cannula was connected to a Statham P23b pressure transducer. The output of transducer was amplified by a Gould bridge amplifier and displayed on a Tektronix 465 oscilloscope.

A midline incision was then made from the xyphoid to the symphysis to expose the left kidney, both ureters, and the bladder. The bladder was intubated by a 22 gauge Baxter Quik-Cath for drainage of urine to avoid bladder pressure increase.

Measurement of Urine output rate

The right mid ureter was identified and intubated proximally with a polyethylene catheter PE-10 inserted toward the proximal aspect of the ureter. This catheter was drained into a test tube to collect urine over time.

Measurement of Renal Pelvic or Ureteral Pressure

A nephrostomy was made by introducing a 24-gauge Baxter Quik-Cath catheter into the left pelvis through the parenchyma. The catheter tip was visualized and adjusted to be at the level of the renal papillae to measure renal pelvic pressure. A ureterostomy was produced by introducing a 24-gauge Baxter Quik-Cath catheter, into the upper segment of the ureter though the renal parenchyma and the renal pelvis for ureteral pressure measurements. The nephrostomy or ureterostomy catheter was connected to a Statham P23b pressure transducer and Gould amplifier in a manner similar to the arterial pressure measurements.

Experimental Procedure

Renal Pelvic Pressure: a block diagram of the set up used for the experiment is shown in Figure 1. At least 30 minutes elapsed from the time the surgery was completed to the initiation of recording.

The rats were divided into two groups as follows: 1) dexmedetomidine group (n=6);
intravenously injected with 2 μg/kg of dexmedetomidine dissolved in 0.5 ml saline, and, 2) atipamizole group (n=6); similarly, intravenously injected with 2 μg/kg of atipamizole dissolved in 0.5 ml saline.

Blood pressure and pelvic pressure were measured continuously from 10 minutes before the bolus injection of each drug to 60 minutes after the bolus injection. Urine output rate was measured at 10 minute intervals during the procedure. The recordings of blood and renal pelvic pressure and urine output rate were analyzed. Mean blood pressure, baseline pelvic pressure, amplitude of pelvic contraction, and frequency of pelvic contraction were calculated before the drug was administered and for 0 to 10, 10 to 20, 20 to 40, and 40 to 60 minutes after the drug was administered.

Ureteral Pressure: Ureteral peristaltic frequency, baseline pressure and contraction amplitude were compared before, after, and between the bolus injections of 2 μg/kg dexmedetomidine (n=6) or 2 μg/kg atipamizole (n=6) in 0.5 ml saline.

Data Collection and Statistical Analysis

The analogue signals of the blood, pelvic, and ureteral pressures were digitized in real time by a PRO350 computer at a sampling rate of 1-3 Hz and stored on disc. Subsequently the dates were retrieved and the waveform from pelvis was analyzed using FFT frequency domain spectral analysis techniques. The maximum spectra were used to identify the rate of contraction. Low frequencies (<0.01 Hz) were excluded.

Statistical analysis was done, using the Student’s paired T-test, or nonpaired T-test as applicable. Values were expressed as the mean±standard deviation.
Results

Blood pressure and urine output

Dexmedetomidine produced a sustained reduction in arterial mean blood pressure which was significantly lower than the value before drug administration (p<0.05). The reduction in arterial pressure was evident for 20 minutes after the injection (Figure 2, 4). Before the longer lasting hypotensive effect, a transient hypertensive phase with of a short duration (1-2 minutes) immediately after the injection of dexmedetomidine in three rats.

As shown in Figure 2, atipamizole increased mean blood pressure significantly, to a maximum of about 40 mmHg from the basal blood pressure level.

![Figure 2: Effects of dexmedetomidine and atipamizole on mean arterial blood pressure (MBP).](image)

![Figure 3: Effects of dexmedetomidine and atipamizole on urine output rate (UO).](image)
Urine output rate increased rapidly after the injection of dexmedetomidine (Figure 2). The rate of urine output was increased to a maximum rate, about three times higher than the urine output rate before injection ($p<0.05$) and occurred approximately 10 minutes following injection. Urine output rate was reduced for a period of 40 minutes after the injection of atipamizole, and then recovered to basal level (Figure 3).

**Renal Pelvic Pressure**

A typical recording of pelvic pressure following dexmedetomidine injection is shown in Figure 4 indicating that the decrease in baseline pressure is followed by the transient increase. Contraction amplitude also increased after the injection of dexmedetomidine in three out of six rats. Dexmedetomidine reduced the frequency of pelvic contraction significantly (Figure 4, 5, 6)

Atipamizole increased contraction amplitude ($p<0.05$) (Figure 5). Atipamizole exhibited no significant effects either on pelvic baseline pressure or on the frequency of pelvic contractions (Figure 5).

Numerical data showing the effects of dexmedetomidine and atipamizole on baseline pressures, amplitude and frequency of pelvic activity are presented in Table 1.

**Ureteral Pressure**

Dexmedetomidine reduced both the baseline and contraction pressure of the ureter after a transient increase immediately following the injection in four out of six rats. In the remaining two rats, a slight increase in baseline pressure was observed. Peristaltic intervals between ureteral contractions shortened immediately after the injection of dexmedetomidine, then lengthened significantly in one rat (Figure 8). On the other hand, atipamizole reduced baseline ureteral pressure and shortened the peristaltic interval after a transient prolonging action of the peristaltic interval in two out of six rats (Figure 8). Numerical data, and the effects of drug
Fig. 5. Effects of dexmedetomidine, and atipamizole on pelvic contraction. PP: baseline pelvic pressure, AP: amplitude of pelvic contraction, FP: frequencies of contraction *: p<0.05, **: p<0.01, ***: p<0.005.

Table 1. Effect of dexmedetomidine and Atipamizole on pelvic contraction.

|                      | before  | 10   | 20   | 40   | 60   |
|----------------------|---------|------|------|------|------|
| **Baseline pressure (cmH₂O)** |         |      |      |      |      |
| Dexmedetomidine (n=6) | 6.8±1.2 | 5.9±1.4 | 5.4±1.6 | 5.2±1.7 | 5.4±1.5 |
| Atipamizole (n=6)    | 5.0±1.4 | 5.0±1.2 | 5.1±1.2 | 5.2±1.4 | 5.5±1.6 |
| **Amplitude (cmH₂O)** |         |      |      |      |      |
| Dexmedetomidine (n=6) | 3.5±0.6 | 3.3±0.6 | 3.5±1.1 | 3.5±1.2 | 3.5±1.2 |
| Atipamizole (n=6)    | 3.0±0.9 | 3.2±1.0 | 3.4±0.9 | 3.4±0.9 | 3.4±0.9 |
| **Frequency (Hz)**   |         |      |      |      |      |
| Dexmedetomidine (n=6) | 0.37±0.03 | 0.35±0.05 | 0.29±0.05 | 0.28±0.03 | 0.27±0.02 |
| Atipamizole (n=6)    | 0.40±0.07 | 0.39±0.08 | 0.40±0.07 | 0.41±0.06 | 0.40±0.06 |

Values are expressed as mean±SD
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Fig. 6. Effects of dexmedetomidine on pelvic pressure (A: before injection, C: after injection) and their frequency spectra (B and D respectively). Note the decrease of pelvic pressure and shift to left of the peak frequency.

Table 2. Effect of dexmedetomidine and Atipamizole on ureteral peristalsis.

|                      | before (min) | after (min) |
|----------------------|--------------|-------------|
| Baseline pressure (cmH₂O) |             |             |
| Dexmedetomidine (n=6) | 8.5±2.4      | 9.5±2.5     | 8.3±2.7     | 8.0±3.2  | 7.6±3.6     |
| Atipamizole (n=6)    | 7.5±2.7      | 7.8±1.7     | 8.2±1.3     | 7.6±2.1  | 7.8±2.4     |
| Amplitude (cmH₂O)    |             |             |
| Dexmedetomidine (n=6) | 11.5±2.3     | 13.3±3.7    | 12.0±3.8    | 11.1±3.7 | 10.8±3.0    |
| Atipamizole (n=6)    | 10.5±3.6     | 9.2±4.6     | 9.5±4.3     | 10.5±4.1 | 10.5±4.1    |
| Frequency (peristalsis/min) |         |             |
| Dexmedetomidine (n=6) | 1.03±0.35    | 1.27±0.38   | 0.92±0.36   | 0.85±0.38 | 0.95±0.43   |
| Atipamizole (n=6)    | 1.10±0.32    | 0.70±0.39   | 1.20±0.43   | 1.25±0.23 | 1.35±0.24   |

Values are expressed as mean±SD

Discussion

It has been reported that alpha-2 activation is known to mediate a variety of physiological functions in the central nervous system and peripheral tissues (Ruffolo et al., 1989; Langer, 1974; Langer, 1981; Sheinin et al., 1989). In the central nervous system, alpha-2 adrenoceptors regulate the neuronal release of noradrenaline and several other transmitter substances, and are intimately involved in the modulation of sympathetic outflow, cardiovascular and endocrine function, vigilance and emotion (Langer, 1974). In peripheral tissue, alpha-adrenoceptors located on smooth muscle cells mediate contraction. The alpha-1 and alpha-2 subtypes are represented in varying proportion in different tissue types (Ruffolo et al., 1988). Presynaptically located alpha-2 adrenoceptors regulate the release of the sympathetic transmitter substance, noradrenaline, from nerve endings (Langer, 1974; Langer, 1981).

Generally it is believed that renal pelvic or ureteral contraction can occur without innerva-
Fig. 7. Effects of dexmedetomidine (A) and atipamezole (B) on ureteral peristalsis (UP). Note biphasic effect on frequency of ureteral peristalsis after injection of dexmedetomidine and atipamezole respectively.

It is, however, also apparent that adrenergic and cholinergic receptors are present in the renal pelvis and ureter and that neurotransmitters are released from neural tissue intrinsic within the wall of the ureter (Weiss et al., 1978) and the renal pelvis (Longrigg, 1974).

To understand the effect of alpha-2 adrenoceptors in the renal pelvis it is important to specifically analyze the general pharmacologic effects of drugs and their action on the pacemaker tissues. In particular, it is important to consider how these agents effect the pacemaker action of the renal pelvis, and the mechanism of pelvic conduction to the ureter. Pacemaker pharmacologic response has been evaluated by separating the pelvis into regions and exploring the regional differences in frequency of pelvic contractions which are reflected in terms of their pharmacologic sensitivity. It is known that acetylcholine dose not affect the contraction frequency of the most proximal region of the renal pelvis but increases the contraction frequency of the middle and distal regions. These distal regions, having an inherently lower contraction frequency are stimulated to increase their frequency to the levels of the proximal regions. Pretreatment with reserpine causes a decrease in the frequency of spontaneous contraction in the proximal but not in the middle or distal regions of the pelvis. The regional pharmacologic response to catecholamines, stimulating all regions (del Tacca et al., 1981),
appears to be almost exclusively mediated through alpha receptors. The increased contraction frequency in the proximal regions, exceeding its maximal physiological level, supports the view that the pelvic regions possess an inversely proportional sensitivity to acetylcholine and adrenaline. In a sense norepinephrine might have an important role in the modulation of the spontaneous activity in the main pacemaker region while acetylcholine appears to be important at the ureterovesical junction regions.

This study has shown that dexmedetomidine has an inhibitory effect on renal pelvic contraction following a weak excitatory effect of short duration in anesthetized rats. This effect is expressed by a decrease in the frequency of contractions and decrease in the baseline pressure which was not significant statistically in view of the increased urine output. In contrast, atipamizole causes an excitatory effect on the upper urinary tract contractility.

Savola (1989) reported that medetomidine behaves as a “clonidine-like anti-hypertensive drug” on the cardiovascular system: it has a direct stimulatory effect on peripheral alpha-adrenoceptors and hypotensive and bradycardiac central effects. It is suggested that dexmedetomidine may have a similar effect on the renal pelvis as in the cardiovascular system. In these studies dexmedetomidine produced a biphasic effect on pelvic contraction, with reduction of frequency (originating from the central nervous system) after an initial increase (direct effect of the alpha-adrenoceptors on the smooth muscle of the pelvis). The central alpha-2 adrenoceptor mediated decrease of pelvic pressure is counteracted partly by the concomitant stimulation of the peripheral postsynaptic alpha 2-adrenoceptors and possibly by the strong diuretic effect of dexmedetomidine. We reported that the increased urine flow rate caused an increase in pelvic pressure and broadened the frequency spectrum in rats (Harada et al. 1992).
The mechanism of the bradycardiac effect of alpha-2 adrenergic agonist is an enigma. De Jonge et al. (1982) reported that the bradycardia produced by clonidine and other related products was centrally driven via an increase in the vagal tone. On the other hand, Savola (1989) reported that the bradycardiac response due to medetomidine was not modified by atropine. In this study, dexmedetomidine decreased pelvic contraction frequency, and ureteral peristaltic frequency in two of three rats. The mechanism of this phenomenon could not be clarified under the conditions of the present study, but it is speculated that dexmedetomidine involves little increase in parasympathetic tone, because dexmedetomidine did not cause contraction of the bladder which is considered to be sensitive to parasympathetic action (Harada, 1981).

In this study, dexmedetomidine induced a diuresis which the antagonist atipamezole reversed, decreasing urine output rate. The mechanism of the diuretic or anti-diuretic action of alpha-2 adrenergic agents may vary depending on the species. Clonidine was shown to inhibit diuresis by the reduction of anti-diuretic hormone (ADH) (Kimura et al., 1981), to block renal tubular action of ADH (Gellai et al., 1980), to increase the glomerular filtration rate (Standhoy et al., 1985), or to inhibit renin release (Smyth et al., 1987).

Solez et al. (1980) reported that clonidine prevented ischemic microvascular injury in the kidney and decreased formation of obstructive hialine casts in collecting ducts. Furthermore, the efficacy of clonidine therapy on kidney function in renal transplant hypertension (Green et al., 1984) or cyclosporine-induced nephrotoxicity (Luke et al., 1990) have been reported.

Medetomidine has already been launched as a veterinary sedative and anesthetic use in dogs and cats in the Scandinavian countries (Jaranka, 1989). Further studies are required to establish the pharmacodynamic profile of dexmedetomidine in humans, however, dexmedetomidine may also have therapeutic applications in human urological diseases. Due to its inhibitory effect on upper urinary tract contractility, diuretic action, inhibition of renin release, protective effect of kidney function, and sedation, dexmedetomidine will have potential therapeutic applications for humans in treatment of renal colic from urinary tract stones or obstructive disease, Steinstrasse after extracorporeal shockwave lithotripsy, and renal hypertension.

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