A Simple Method for Measurement of Ureteric Peristaltic Function In Vivo and the Effects of Drugs Acting on Ion Channels Applied from the Ureter Lumen in Anesthetized Rats

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ABSTRACT—In supine anesthetized rats, two cannulae were inserted into a unilateral ureter near the kidney and urinary bladder, respectively. Fluid from a reservoir placed approximately 27 cm above the rat was infused into the ureter lumen through the cannula near the kidney, and the resulting peristaltic pressure signals were measured from the cannula near the bladder. When drugs acting on ion channels were applied from the ureter lumen and their effects on the peristaltic pressure signals were studied, the K^+ channel opener BRL 38227 (1×10^{-4} M and 1×10^{-3} M) was found to decrease the frequency dose-dependently. However, the K^+ channel blockers glibenclamide and 4-aminopyridine at 1×10^{-3} M did not affect peristaltic movement. Nifedipine (1×10^{-5} M and 1×10^{-4} M) decreased the frequency of peristalsis, but the effect was weaker than that of BRL 38227. Lidocaine at very high concentration (1.5×10^{-2} and 1.5×10^{-1} M) decreased the amplitude and increased the frequency of the peristaltic signals. These results indicate that the K^+ channel opener has the most inhibitory effect on ureteral peristaltic function.

Keywords: Ureteral peristaltic function (rat), BRL 38227, Glibenclamide, Nifedipine, Lidocaine

The function of the ureter is to pump urine from the kidney to the urinary bladder by peristaltic contractions of its smooth muscle. Ureteral peristalsis is controlled by a pacemaker in the renal pelvis (1–3). However, ureteral smooth muscle is autonomous, and ureteral function is controlled entirely within the organ. Accordingly, this function is retained after nephrectomy or resection of the ureteral efferent and afferent innervation (4, 5). The physiological properties of the ureteral peristaltic wave and the effects of drugs on longitudinal muscle contraction have been investigated in isolated ureteral segments (6–10), although few studies have examined the effects of drugs on the urine transport function of the ureter. In the present experiment, using anesthetized rats, we devised a simple experimental method for recording the ureteral peristaltic pressure signals induced by transport of urine to the urinary bladder. As the drugs acting on K^-, Ca^{2+} and Na^+ channels are known to affect the contractility of smooth muscles and the excitability of nerves, using this system, we studied the effects of the drugs on ureteral peristaltic function to clarify the properties of ureteral smooth muscles which generate ureteral peristaltic function and the participation of nerves in this function.

Therefore, the drugs were applied from the ureter lumen in order to investigate the direct effects on the ureteral smooth muscle and nerves.

MATERIALS AND METHODS

Male Sprague-Dawley rats (weighing 450–650 g) were anesthetized with urethane (0.75–1.0 g/kg, i.p.) and alpha-chloralose (19–25 mg/kg, i.p.) and placed in a supine position. The experimental setup used for recording ureteral pressure signals is shown in Fig. 1. In the abdomen, a midline incision extending from the urinary bladder to the kidney was made, and the left ureter was exposed. Two pieces of silicone tube (outer diameter of 1.0 mm, inner diameter of 0.5 mm, about 20-cm-long), each with a needle (1/3) at its end, were prepared. In the region near the kidney, adipose tissue was removed carefully, and the ureter was exposed for a length of about 1 cm. The needle attached to the silicone tube was inserted into the ureter in the direction of the bladder, and this was termed the kidney-side cannula. The needle of the other silicone tube was inserted into the ureter near the bladder in the direction of the kidney and termed the bladder-side
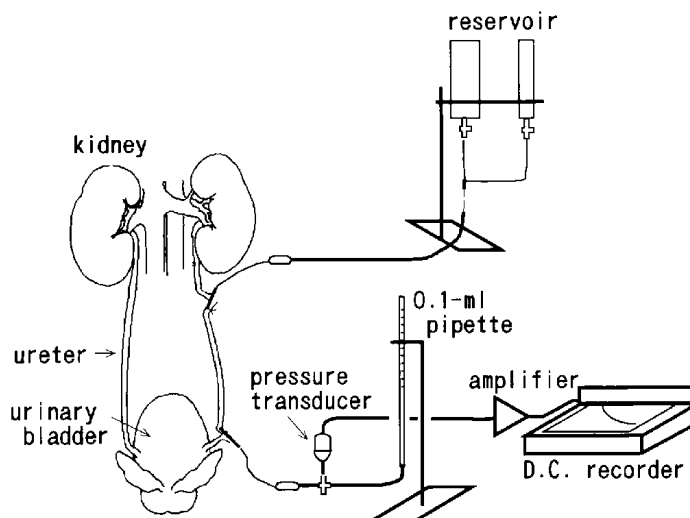
Fig. 1. Schematic representation of the ureter lumen infusion technique and the setup used for measuring ureteral peristaltic pressure in anesthetized rats. The fluid surface in the reservoir was adjusted to a height of about 27 cm, and fluid was infused through the ureter lumen into the 0.1-ml pipette.

cannula. The distance between the two needle tips was at least 4 cm. Tyrode solution lacking glucose was infused into the ureter lumen. Two syringes with injection volumes of 10 and 2 ml were used as reservoirs for the Tyrode solution and drug-containing solution, respectively. For exchange of the infusion solution, the two syringes were connected to each other via three-way cocks and silicone tubing. To maintain the flow speed at a low and constant rate, infusion solution from the reservoir was passed through a thin polyethylene tube (SP-8, Natsume, Tokyo) approximately 8-cm-long, and then allowed to flow into the kidney-side cannula. The bladder-side cannula was connected to a pressure transducer and a vertically-positioned 0.1-ml pipette via a T-tube. The pressure signals were delivered by an amplifier (AP-601G, Nihon Kohden, Tokyo) and recorded by a D.C. recorder. The fluid surface in the reservoirs was adjusted so that it was approximately 27 cm above the animal's back. When fluid was infused through the ureter lumen and rose to a maximum level in the 0.1-ml pipette, the bladder-side cannula was disconnected from the T-tube, and fluid in the ureter lumen and the pipette was drained off. When the effects of drugs were studied, the drug-containing solution was infused through the ureter lumen and drained from the bladder-side cannula for at least 10 min. Then the fluid surface in the reservoir was adjusted to approximately 27 cm in height, and the bladder-side cannula was connected to the T-tube. After the effect of each drug had been studied, the infusion solution was changed to fluid without drug, and the same procedures as those described above were performed.

The following parameters were calculated from the

recorded traces of the pressure signals: 1) S as the flow rate of fluid in the ureter lumen: the time (min) taken for fluid in the 0.1-ml pipette to rise from 10 to 20 cm. 2) A as the average amplitude of the peristaltic pressure signals (cmH_2O). 3) N as the frequency of the peristaltic pressure signal: the number of signals in 2 min. S and A were measured to detect the changes in the diameter of ureter lumen and the contractile force of the smooth muscle induced by drugs, respectively, and N was measured to detect the effect on peristaltic function. A and N were measured when the fluid in the 0.1-ml pipette rose almost to the level of the reservoir or maximally.

The rats were warmed with a lamp, which was controlled with a thermoregulator, and the abdomen was covered with tissue paper to prevent drying during the experiment.

Drugs used were BRL 38227 ((−)6-cyano-3,4-dihydro-2,2-dimethyl-trans-4-(2-oxo-1-pyrrolidyl)-2H-1-benzopyran-3-ol; a gift from Smith-Kline Beecham, Tokyo), glibenclamide (a gift from Yamanouchi Pharmaceutical Co., Ltd., Tokyo), nifedipine (Sigma, St. Louis, MO, USA), lidocaine hydrochloride (4% Xylocaine® solution, Fujisawa-Astra, Ltd., Osaka) and 4-aminopyridine (Wako Pure Chemical Co., Ltd., Osaka). Glibenclamide and nifedipine were dissolved in pure ethanol and BRL 38227 was dissolved in 70% ethanol solution to give a 10^{-2} M stock solution. The stock solution was diluted with Tyrode solution before use. The drug concentrations are expressed in terms of the respective salt. Experimental values are expressed as the mean±S.E. The significance of differences was analyzed by Student's t-test at $P < 0.05$.

Table 1. Values of parameters when infusion of fluid into the ureter lumen was repeated eight times at about 40–50-min intervals

	First time			Second time			3rd time			4th time		
	S	A	N	S	A	N	S	A	N	S	A	N
Mean	3.3	2.8	13.7	2.6	2.8	11.7	2.4	2.7	11.3	2.3	2.7	12.6
S.E.	0.8	0.3	0.9	0.4	0.2	0.3	0.3	0.2	1.2	0.2	0.2	2.6

	5th time			6th time			7th time			8th time		
	S	A	N	S	A	N	S	A	N	S	A	N
Mean	2.3	2.7	11.0	2.5	2.6	11.3	2.1	2.6	10.9	2.4	2.5	10.1
S.E.	0.2	0.2	2.1	0.3	0.2	2.2	0.3	0.2	2.8	0.2	0.2	2.3

The parameters (S, A and N) were calculated from the recorded traces of the pressure signals. S: the time (min) taken for fluid in the vertically-stood, 0.1-ml pipette to rise from 10 to 20 cm. A: amplitude (cmH_2O) of the ureteral peristaltic pressure. N: numbers of pressure peaks of ureteral peristaltic movement in 2 min. n = 6.

RESULTS

General

When fluid was infused, the pressure that corresponded to the elevation of fluid in the 0.1-ml pipette and peristaltic pressure signals were recorded. The pressure that corresponded to the fluid level in the 0.1-ml pipette rose almost linearly up to about 20 cm. The amplitude of the peristaltic pressure signals increased gradually as the fluid level in the 0.1-ml pipette rose, and became almost constant when the fluid level approached that in the reservoir, although in some rats the maximal amplitude of the peristaltic pressure signals appeared before the fluid reached the maximal level. Peristaltic pressure signals appeared at almost constant intervals. In some rats, alternation between a few pressure signals and a period of quiescence was observed. Table 1 shows the values of parameters recorded from the traces when infusion of Tyrode solution for about 20 min was repeated eight times at 40–50-min intervals. There was no significant difference between the parameters represented by the trace and those before it.

Effects of drugs on ureteral peristaltic function

Effects of drugs are shown in Figs. 2–6 and summarized in Table 2. Ethanol at 10%, which was the maximum concentration used for the vehicle, decreased the flow rate, and the effect was reversible. The frequency of peristaltic pressure signals during the second infusion of ethanol solution decreased in two out of five rats, but the value of N obtained from the trace of the infusion of the ethanol solution did not differ significantly from the value obtained from the foregoing trace (Table 1). Infusion of glibenclamide (1×10^{-3} M)-containing solution decreased the flow rate, but the decrease was not different from that induced by foregoing infusion of 10% ethanol solution (Fig. 2), and the patterns of traces recorded during the in-
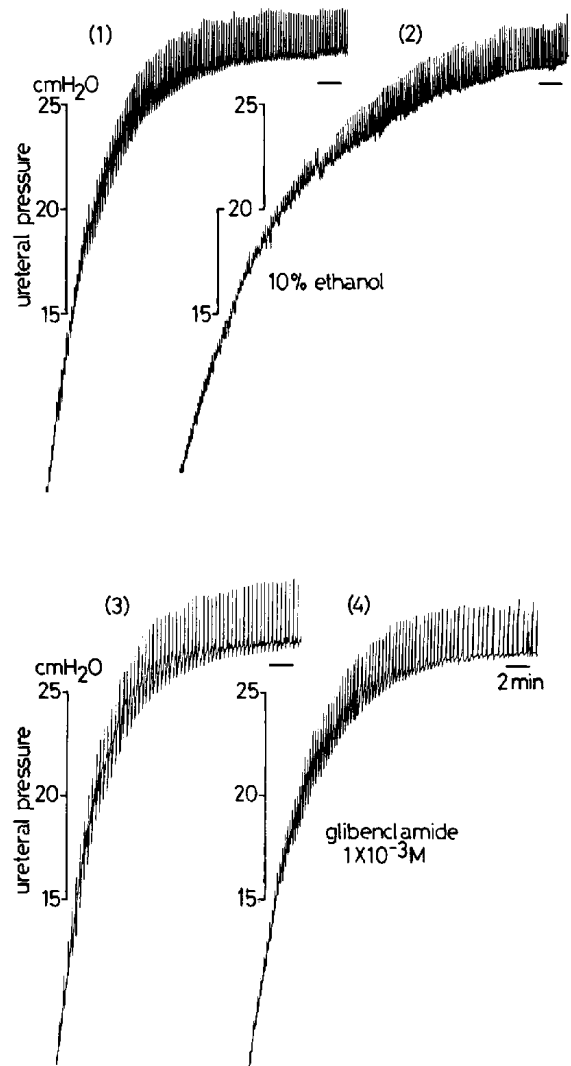

Fig. 2. Effects of 10% ethanol solution and glibenclamide dissolved in the solution on flow rate in the ureter lumen and ureteral peristaltic pressure in an anesthetized rat. Vertical bar: ureteral pressure. Horizontal bar: time scale for 2 min. Number in parenthesis above each trace indicates the order of the experiment.
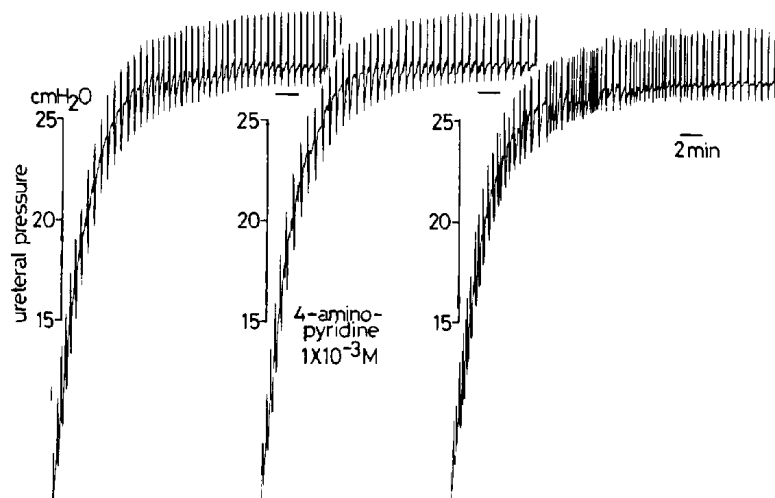
Fig. 3. Effects 4-aminopyridine on the flow rate in the ureter lumen and ureteral peristaltic pressure in an anesthetized rat. For details, see Fig. 2.

fusions of 10% ethanol solution and glibenclamide containing solution were similar to those during the infusions of 10% ethanol solution twice. 4-Aminopyridine $(1 \times 10^{-3}\,M)$ did not change the values of the parameters (Fig. 3). BRL 38227 $(1 \times 10^{-4}\,M)$ decreased the frequency of pressure signals but did not change the amplitude. BRL 38227 $(1 \times 10^{-3}\,M)$ completely abolished peristaltic movement, and the solution in the 0.1-ml pipette did not rise to the level in the reservoir within 20 min (Fig. 4). The ratio of the fluid level in the 0.1-ml pipette to that in the reservoir before and after infusion of solution containing BRL 38227 $(1 \times 10^{-3}\,M)$ was 1.1 ± 0.0 and 0.8 ± 0.1 $(n = 6)$, respectively. When the infusion solution was changed to fluid without drug, the peristaltic signals resumed, but their frequency was very low. Nifedipine $(1 \times 10^{-5}\,M)$ decreased the frequency of the pressure signals, and the frequency further decreased when the infusion solution was changed to fluid without drug. Afterwards, nifedipine $(1 \times 10^{-4}\,M)$ did not cause a further decrease in frequency (Fig. 5). Lidocaine at $1.5 \times 10^{-3}\,M$ did not affect peristaltic function, but at $1.5 \times 10^{-2}\,M$, if caused an increase in frequency and a decrease in amplitude. When lidocaine at $1.5 \times 10^{-1}\,M$ was applied, the pressure signals became small and irregular in shape, and therefore their frequency increased (Fig. 6). The effects of lidocaine were not reversed by infusion of fluid without drug.

DISCUSSION

Using the present method, it was possible to detect the ureteral pressure signals when fluid in the ureter lumen was pumped to the bladder. The pressure signals are
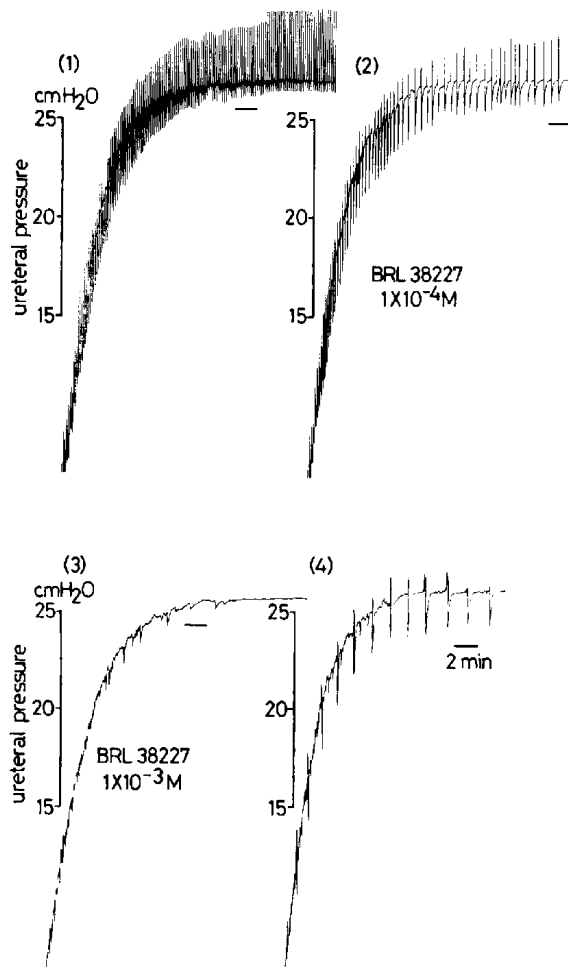

Fig. 4. Effects of BRL 38227 on flow rate in the ureter lumen and ureteral peristaltic pressure in an anesthetized rat. For details, see Fig. 2. Number in parenthesis above each trace indicates the order of the experiment. After application of BRL 38227 $(1 \times 10^{-4}\,M)$, fluid without drug was infused, but the trace for this is not shown.
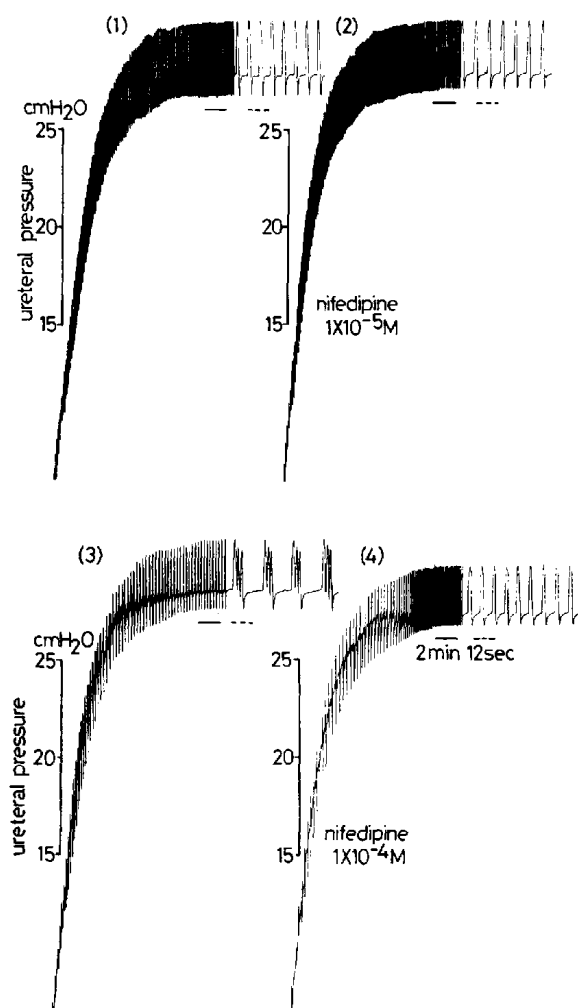
Fig. 5. Effects of nifedipine on flow rate in the ureter lumen and ureteral peristaltic pressure in an anesthetized rat. For details, see Fig. 2. Ureteral peristaltic pressure signals drawn at a chart speed 5 times higher are also added at the end of the trace. Broken horizontal bar: time scale for 12 sec. Number in parenthesis above each trace indicates the order of the experiment.

generated by autonomous contraction of circular smooth muscle when the lumen is distended by fluid. This contraction of circular smooth muscle is synchronous. Occasionally, a very large pressure change due to the motility of the whole ureter occurred. Peristaltic pressure signals appeared independent of the pressure change, but the amplitude of the signals decreased or the record was disturbed by movement of the cannula needle tips.

The ureteral peristaltic motility was very resistant to ethanol and drugs applied from the ureter lumen. Ethanol (0.18 – 1.8 mg/ml) is reported to reduce spontaneous contraction of rat ileum, whereas it induces ileal contraction at high concentration (11). The epithelial cells of the ureter may act as a barrier, and therefore high concentrations of drugs may be necessary to produce an effect. The decrease in flow rate induced by 10% ethanol solution was not due to protein degeneration of the luminal epithelial cells. Although the reason for the reduction in ureter lumen diameter was not clear, swelling of the epithelial cells may occur. Among the drugs used in this experiment, BRL 38227 had a strong inhibitory effect on ureteral peristaltic movement, decreasing the number of peristaltic pressure signals without affecting the amplitude. It has been reported that cromakalim, a racemic compound of BRL 38227, relaxes many types of smooth muscle organs by hyperpolarizing the membrane through activation of K$^-$ channels (12–16), and the inhibitory action of BRL 38227 on the ureteral circular muscles also may be associated with the opening of K$^+$ channels. BRL 38227 decreased the frequency of ureteral peristaltic signals at concentrations lower that those which decreased the contractility of ureteral circular smooth muscle. These results indicate that BRL 38227 at a concentration that does not inhibit the contractility of ureteral smooth muscle inhibits the electrical mechanisms which generate synchronized contractions of the smooth muscles. Because

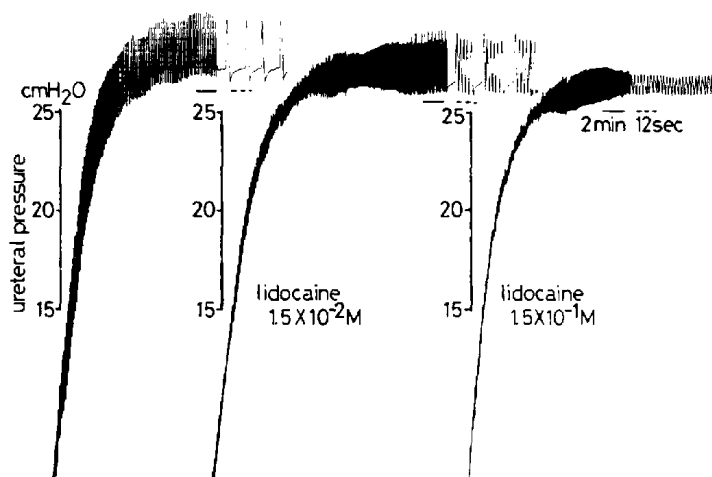Fig. 6. Effects of lidocaine on flow rate in the ureter lumen and ureteral peristaltic pressure in an anesthetized rat. For details, see Fig. 2. Ureteral peristaltic pressure signals drawn at a chart speed 5 times higher are also added at the end of the trace. Broken horizontal bar: time scale for 12 sec. After application of lidocaine (1 × 10^{-2} M), fluid without drug was infused but the trace is not shown.

Table 2. Effects of drug-containing solutions infused into the ureter lumen on ureteral peristaltic pressure signals

10% Ethanol solution (n=5)

	Infusion of fluid without ethanol			Infusion of ethanol solution			Infusion of fluid without ethanol			Infusion of ethanol solution			Infusion of fluid without ethanol		
	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N
Mean	2.7	3.3	11.9	4.6**	3.3	9.3	2.4*	3.6	8.4	4.7*	3.2	5.4	2.4*	3.7	5.0
S.E.	0.2	0.4	2.2	0.5	0.2	0.5	0.5	0.4	0.5	1.0	0.4	1.2	0.2	0.2	0.6

10% Ethanol solution and glibenclamide (1×10^{-3} M) dissolved in the solution (G-solution) (n=5)

	Infusion of fluid without drug			Infusion of 10% ethanol solution			Infusion of fluid without ethanol			Infusion of G-solution			Infusion of fluid without drug		
	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N
Mean	2.2	3.5	14.5	3.8*	3.2	12.8	2.1*	3.2	18.0	3.4*	2.8	10.8	2.2*	3.1	14.8
S.E.	0.2	0.8	3.7	0.5	0.3	3.8	0.3	0.6	8.0	0.4	0.3	2.7	0.2	0.6	5.4

4-Aminopyridine (1×10^{-3} M)-containing solution (4-AP solution) (n=5)

	Infusion of fluid without drug			Infusion of 4-AP solution			Infusion of fluid without drug		
	S	A	N	S	A	N	S	A	N
Mean	2.3	2.4	15.4	2.3	2.5	13.8	2.8	2.5	8.5
S.E.	0.2	0.3	4.1	0.2	0.3	4.4	0.6	0.4	1.7

BRL 38227 (1×10^{-4} M and 1×10^{-3} M)-containing solution (BRL solution) (n=6–7)

	Iinfusion of fluid without drug			Infusion of BRL solution (1×10^{-4} M)			Infusion of fluid without drug			Infusion of BRL solution (1×10^{-3} M)			Infusion of fluid without drug		
	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N
Mean	2.5	4.9	13.6	2.4	4.8	5.5**	2.2*	3.5	9.0	3.2	0	0	2.2	4.4	5.8
S.E.	0.2	0.9	2.6	0.3	1.0	1.4	0.2	0.4	1.6	0.4			0.1	0.8	1.1

BRL 38227 (1×10^{-4} M and 1×10^{-3} M) was dissolved in 0.7% and 7% ethanol solution, respectively.

Nifedipine (1×10^{-5} M and 1×10^{-4} M)-containing solution (Nif-solution) (n=4)

	Infusion of fluid without drug			Infusion of Nif-solution (1×10^{-5}M)			Infusion of fluid without drug			Infusion of fluid without drug			Infusion of Nif-solution (1×10^{-4}M)			Infusion of fluid without drug			Infusion of fluid without drug		
	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N
Mean	1.6	3.2	17.1	2.1	3.2	14.9*	2.0	3.4	10.2*	2.0	3.6	9.8	2.3	2.6	9.2	2.7	3.1	6.7	1.9	3.1	7.8
S.E.	0.4	0.3	5.9	0.2	0.3	5.6	0.2	0.2	4.4	0.1	0.3	4.5	0.1	0.1	2.6	0.7	0.1	0.7	0.1	0.2	3.3

Lidocaine (1.5×10^{-3} M)-containing solution (Lid-solution) (n=5)

	Infusion of fluid without drug			Infusion of Lid-solution (1.5×10^{-3} M)		
	S	A	N	S	A	N
Mean	2.5	4.1	9.5	2.5	3.7	8.9
S.E.	0.2	0.6	1.5	0.6	0.5	1.2

Lidocaine (1.5×10^{-2} M and 1.5×10^{-1} M)-containing solution (Lid-solution) (n=5–7)

	Infusion of fluid without drug			Infusion of Lid-solution (1.5×10^{-2} M)			Infusion of fluid without drug			Infusion of Lid-solution (1.5×10^{-1} M)			Infusion of fluid without drug		
	S	A	N	S	A	N	S	A	N	S	A	N	S	A	N
Mean	2.3	3.6	13.5	2.3	2.7	35.8*	2.8	3.2	23.9**	3.5	1.7**	52.4*	2.7	2.8	36.0
S.E.	0.3	0.5	4.4	0.2	0.5	9.7	0.6	0.6	7.1	1.3	0.4	6.5	0.4	0.5	6.9

The parameters (S, A and N) were calculated from the recorded traces of the pressure signals. S: time (min) taken for fluid to rise 10 to 20 cm in the vertically-stood, 0.1-ml pipette. A: amplitude (cmH_2O) of the ureteral peristaltic pressure. N: numbers of pressure peaks of ureteral peristaltic movement in 2 min. *P<0.05 and **P<0.01 represent significant differences when the values obtained from the trace and those before it were compared.

several types of K^+ channels are reported (17), two different types of K^+ channel blocker, glibenclamide and 4-aminopyridine, were used in this experiment. In contrast to the K^+ channel opener, they exerted no effect on peristaltic function even at high concentration (Figs. 2 and 3). Tetraethylammonium Br (1×10^{-3} M) also had no effect on the function (data not shown). The currents sensitive to tetraethylammonium Br and 4-aminopyridine have been recorded in guinea pig ureter smooth muscle (18, 19), and glibenclamide has been reported to potentiate or inhibit the spontaneous contractile activity of the portal vein in rats (20, 21), although these drugs may not affect the function of circular smooth muscle or penetrate the ureteral epithelial cells. The K^+ channel of ureteral circular smooth muscle may not be sensitive to these blockers. The Ca^{2+} channel blocker nifedipine reduced the frequency of the peristaltic pressure signals, but its effect was weaker than that of BRL 38227. On the other hand, lidocaine increased the frequency of peristaltic signals at very high concentration. It is confirmed that the ureteral peristaltic movement recorded in our method is myogenetic and is not controlled by nerves. Though we could not explain the mechanism of the lidocaine-induced increase in the frequency of peristaltic movement, we now consider that lidocaine may decompose one synchronized large contraction into several small contractions, since the amplitude of the pressure signals decreased. As another explanation of the increase in the frequency, lidocaine at the high concentration used in this experiment may exert the excitatory effect on the ureter smooth muscles, since it has been proposed that the excitatory effect of procaine at high concentration in the tracheal smooth muscle membranes is attributable to its blocking action on K^+ permeability (22).

The present results indicate that the K^+ channel opener BRL 38227 has a strong inhibitory effect on ureteral peristaltic movement. The drug may interrupt the transport of urine from the kidney to the bladder, and may thus have an adverse effect on the urologic tract. On the other hand, this inhibitory effect may be useful for treatment of pain induced by renal colic, since it is reported that non-steroid anti-inflammatory drugs reduce the contractility of ureteral and renal pelvic smooth muscle and the effects contribute to the pain relief in the patient (6, 9, 23, 24).

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