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Diclofenac and NS-398, a selective cyclooxygenase-2 inhibitor, decrease agonist-induced contractions of the pig isolated ureter

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Abstract Non-steroidal anti-inflammatory drugs (NSAIDs) are currently considered a first-line treatment of renal colic. Their action has been ascribed to the inhibition of renal prostaglandin synthesis, which decreases renal blood flow and diuresis, and consequently lowers the pressure in the renal pelvis and ureter. However, the effects of NSAIDs on induced contractions of ureteral smooth muscle have received little attention. Also, there is a lack of clinically relevant spasmolytic drugs for the ureter. Therefore, we studied the influence of the non-selective cyclooxygenase (COX) inhibitor diclofenac, a NSAID drug customarily used in the treatment of renal colic, and of NS-398, a selective COX-2 inhibitor, on induced contractions of the pig ureter. Serotonin (0.1–30 μM), norepinephrine (0.1–30 μM) and neurokinin A (0.03–10 μM) induced reproducible concentration-dependent contractions, which were inhibited by diclofenac and NS-398 (10–300 μM) in a concentration-dependent manner. The sensitivity of neurokinin A-induced contractions to diclofenac was 3–4 times greater than that of the amines. Depending on the concentration, inhibition ranged between 25 and 96% of the initially induced contractile activity. In the presence of inhibitors, supramaximal concentrations of agonists were unable to trigger recuperation of the initially induced contractions. Prostaglandin $F_{2\alpha}$ did not reverse the effect of diclofenac on agonist-induced contractions. Removal of diclofenac or NS-398 from the organ baths showed that the inhibition was totally reversible. Thus, the non-selective COX inhibitor diclofenac and the selective COX-2 inhibitor NS-398 are almost equipotent in reducing agonist-induced contractions in the isolated porcine ureter. Although the clinical relevance of this spasmolytic effect remains to be demonstrated, the data suggest that patients suffering from renal colic may benefit not only from the anti-diuretic and analgesic effects of diclofenac, but also from its potential spasmolytic properties. Moreover, selective COX-2 inhibitors may have clinical potential, as they may cause fewer side effects.

Key words Pig ureter · Diclofenac · NS-398 · NSAIDs · Prostanoids · Serotonin · Norepinephrine · Neurokinin A

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Introduction

Renal colic is a frequent and painful clinical condition, most often caused by ureteral obstruction by a stone [30]. Pain is due to increased pelviureteral distension above the obstacle, associated with elevated intraluminal pressure. This increase in pressure activates prostanoid synthesis in the renal medulla [34]. One of these prostanoids, prostaglandin (PG) E_2 (PGE_2), causes preglomerular arterial vasodilatation, which increases diuresis, pelviureteral distension and clinical symptoms [11, 21]. Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat renal colic [12, 17, 24], since they decrease prostanoid synthesis through inhibition of cyclooxygenase (COX). Indeed, several studies have suggested that inhibition of prostanoid synthesis during unilateral ureteral obstruction can reduce renal blood flow by decreasing the PGE_2-induced vasodilation, which consecutively reduces glomerular filtration and pelvic pressure [2, 5, 13].

Recently, two isoforms of COX have been identified: COX-1 is expressed constitutively in most tissues and accounts for the majority of physiological PGs synthesis, whereas COX-2 is expressed only at low levels in most

cells (see [49] for a review). Expression of COX-2 can be up-regulated locally by an inflammatory stimulus, and numerous studies have suggested that the therapeutic effects of NSAIDs (owing to COX-2 inhibition) could be separated from their gastrointestinal or renal toxic effects (owing to COX-1 inhibition). The currently available NSAIDs are predominantly COX-1 inhibitors (ketoprofen, for instance) or non-selective COX inhibitors (such as indomethacin or diclofenac); however, selective COX-2 inhibitors have been recently developed and evaluated for their anti-inflammatory effects, with fewer unwanted adverse effects [10, 14]. However, numerous studies have shown that delineation of the roles of COX-1 and COX-2 does not appear to be as clear as suggested [51].

Besides their major anti-diuretic effect, NSAIDs relieve renal colic pain by an analgesic mechanism. Interestingly, a further therapeutic effect may include inhibition of smooth muscle activity, since several investigators have reported that NSAIDs decrease spontaneous or electrically induced ureteral contractions [4, 8, 22, 26, 46–48]. However, the effects of NSAIDs on agonist-induced ureteral contractions have not been tested yet. Therefore, the aim of the present study was to assess the effect of prostanoid synthesis inhibition on ureteral contractions induced by established neural messengers of the upper urinary tract, i.e. norepinephrine (NE) and neurokinin A (NKA) [3, 52]. Additionally, serotonin (5-hydroxytryptamine; 5-HT) was also used, as it has been proven to be a good model of agonist-induced ureteral contractions in the pig [19]. It is known that the effect of several neurotransmitters and hormones [40], including NE [45], 5-HT [25] and neurokinins [42], can sometimes result from both a direct action on specific receptors and an indirect action through the activation of prostanoid synthesis. Thus, the possibility that in the pig ureter NSAIDs could affect agonist-induced contractions by decreasing agonist-induced prostanoid synthesis was investigated. Diclofenac was chosen as it is one of the most frequent NSAIDs used in the treatment of renal colic. Furthermore, the effects of this non-selective COX inhibitor were compared to those of a preferential COX-2 inhibitor, *N*-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulphonamide (NS-398), a widely accepted anti-inflammatory but non-ulcerogenic pharmacological agent [16, 28].

Materials and methods

Tissue processing

Ureters obtained from freshly killed young pigs (3–6 months old) at a local slaughterhouse were immediately put into ice-cold and aerated (95% O_2–5% CO_2) Krebs solution, transported to the laboratory within 30 min and transferred into aerated and fresh ice-cold Krebs solution. Under a microscope one ureter per animal was carefully cleaned of adjacent connective and fatty tissues, and a segment, approximately 1 cm in length, was taken from the lower third (at least 2 cm proximal to the bladder). Transverse strips of approximately 6 × 1 mm were prepared and silk threads were attached at both extremities. Preparations were then suspended in 120-µl thermostated (37 °C) chambers and connected to an isometric force transducer (Grass FT03; Quincy, Mass., USA). The preparations were continuously superfused at a flow rate of 1 ml/min with Krebs solution (95% O_2–5% CO_2; 37 °C; pH 7.4). Mechanical tension was amplified and recorded on a 6-channel paper recorder (W + W, DCR 520, Syntrel Electronic, Basel, Switzerland), and on a personal computer through an analog-to-digital converter and a data acquisition system (MacPacq MP100; Biopac Systems, Goletta, Calif., USA).

Pharmacological tests

A resting tension of 1 g was selected according to previous experiments. After an equilibration period of 60 min, during which time the resting tension was readjusted, the tissues were exposed to 5-HT (10^{-6} M) to test tissue viability. Concentration-response curves to 5-HT, NE and NKA were constructed in a non-cumulative manner in order to avoid tachyphylaxis. Each agonist was infused for 4 min through the organ chambers; between each agonist application preparations were washed for 30 min. The responses to the agonists were then tested in the presence of diclofenac (Voltaren, 10–300 µM) or NS-398 (10–300 µM). NE concentration-response curves were also generated in the presence of prazosin (1×10^{-6} M) or sotalol (3×10^{-5} M) to block α_1- and β-adrenoceptors, respectively, in order to determine which adrenoceptor is present in the pig ureter. Sotalol was chosen because, unlike propranolol, it appears devoid of a membrane-stabilizing activity [20], which could interfere with the effect of diclofenac. Each inhibitor was infused at least 30 min before agonist-induced contractions. In some experiments $PGF_{2\alpha}$ was administered after blockade of agonist-induced activity by diclofenac in order to determine whether agonist-induced contractile activity could be restored. In other experiments $PGF_{2\alpha}$ was added before diclofenac application.

Drugs and solutions

The following drugs were used: serotonin hydrochloride (5-HT), prazosin hydrochloride, dimethyl sulfoxide (DMSO), prostaglandins E_2 and $F_{2\alpha}$ (Sigma); norepinephrine hydrochloride (Hoechst, Frankfurt, Germany); sotalol hydrochloride (Bristol-Myers Squibb, Baar, Switzerland); neurokinin A (NKA; Bachem, Basel, Switzerland); sodium diclofenac (Voltaren; Geigy), *N*-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulphonamide (NS-398; Alexis, Switzerland). Stock solutions were prepared in ethanol (diclofenac, 40 mg/ml ethanol and then diluted in NaCl (0.9%) to reach 10^{-2} M), DMSO (NS-398, 3.14 mg/ml, idem) or distilled water (5-HT, prazosin and NKA). At their final concentrations, the solvents were without effect on the ureteral contractile activity. The Krebs solution used had the following composition (mM): 119 NaCl, 4.6 KCl, 1.5 $CaCl_2$, 1.2 NaH_2PO_4, 1.2 $MgCl_2$, 15 $NaHCO_3$, 11.1 glucose, pH 7.4. Krebs solutions with higher Ca^{2+} concentrations (2.5 and 7.5 mM) were also used.

Data analysis

As agonist-induced ureteral contractions frequently showed an irregular pattern, where tonic and phasic activities could be rhythmically interrupted by transient complete relaxations, mean induced contractile activity was measured as the mean tension during a fixed time (4 min) using computer assistance (data acquisition system MP100WS and waveform analysis program Acq-Knowledge, Biopac Systems, Goletta, Calif., USA). The results are expressed either in grams or in percent of the maximal response obtained in the absence of diclofenac or NS-398. This method is commonly used with other isolated organs displaying a mixture of tonic and phasic contractile activities, such as the rodent portal vein [29].

The maximal contractile response (E_{max}) and the concentration of agonist inducing half-maximal response (EC_{50}) were calculated from each individual concentration-response curve adjusted with the polynomial curve-fitting program CA-Cricket Graph. Results obtained from strips showing low maximal response to agonists (below 50% of the mean maximal response obtained in the absence of COX inhibitor) were discarded. Results are given as mean values ± standard error of the mean (SEM), and n denotes the number of animals. Probability values were determined by a two-tailed paired Student's t-test considered significant if lower than 0.05.

Results

Agonist-induced contractions

Strips exposed to 5-HT, NE and NKA responded by phasic contractions at low concentrations and by tonic contractions on which phasic contractions were superimposed at higher concentrations (Figs. 1a, 2a). In numerous preparations (more than 50%), the phasic and tonic components of the response were rhythmically interrupted by transient complete relaxations, whose duration was inversely related to the agonist's concentration (Fig. 1b). The response induced by a single submaximal concentration of agonist was reproducible for as many as eight exposures. Furthermore, two consecutive concentration-response curves to the agonists could be constructed without a significant variation in the response.

The contractile response to NE was completely abolished by 1 μM of the α_1-antagonist prazosin (result not shown). In the presence of 30 μM of the β-antagonist sotalol, the sensitivity (EC_{50}) for NE was increased from 7.5 to 2.0 μM, whereas E_{max} remained unchanged (Table 1). These results show that α_1- and β-adrenoceptors coexist in the pig ureter, which respectively activate and decrease motility. Consequently, the following tests with NE were all done in the presence of sotalol in order to eliminate the inhibitory part of the response to NE. The pig ureter showed a greater sensitivity for NKA ($EC_{50} = 0.7$ μM) than for the amines ($EC_{50} = 1.6$ μM for 5-HT and 2.0 μM for NE in the presence of sotalol), but NE was able to induce a greater maximal response than 5-HT and NKA ($E_{max} = 2.15$, 1.69 and 1.14, respectively; Table 1).

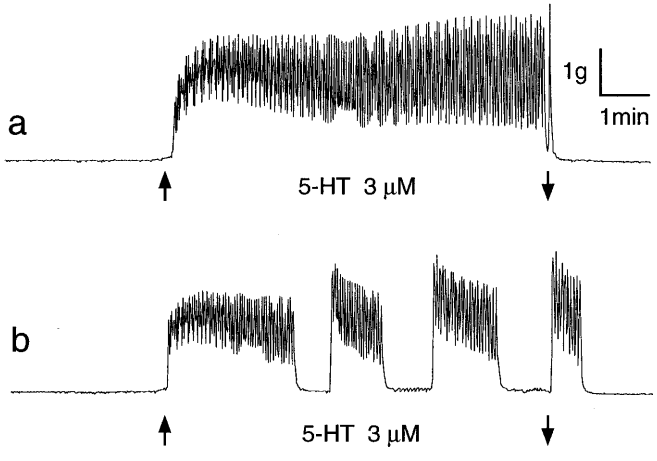

Fig. 1a, b Original tracings showing the effect of 3 μM 5-HT on pig isolated ureters. At this concentration, phasic contractions were superimposed on a tonic contraction (**a**). In numerous preparations (more than 50%), the phasic and tonic components of the response were rhythmically interrupted by transient complete relaxation (**b**)

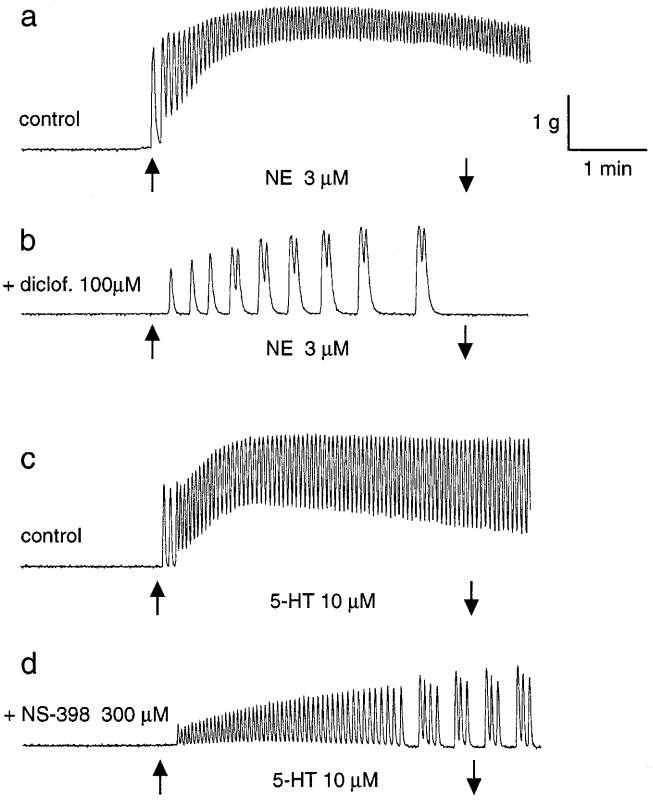

Fig. 2a–d Original tracings showing the effect of diclofenac (100 μM) on NE (3 μM) on the pig isolated ureter: control in the presence of sotalol 30 μM (**a**) and after application of diclofenac (**b**). Consecutive recordings from one preparation. **c, d** Original tracings showing the effect of NS-398 (300 μM) on 5-HT (10 μM) on the pig isolated ureter: control (**c**) and after application of NS-398 (**d**). Consecutive recordings from one preparation

Effect of diclofenac on agonist-induced contractions

In the presence of low and medium concentrations of diclofenac, the responses were rhythmically interrupted by transient complete relaxations, whose duration was directly related to the concentration of the inhibitor, whereas the amplitude of the remaining phasic contractions was scarcely affected; at the highest concentrations (300 μM) the responses were almost totally abolished (Figs. 2a, b, 3). This inhibition was non-competitive, since supramaximal agonist concentrations were unable to trigger recuperation of the initially induced contractions (Fig. 3). Figure 4a shows that the responses to NKA were more sensitive to the presence of diclofenac than those to 5-HT and NE. The drug

Table 1 Comparative effects of 5-HT, NE and NKA on the pig isolated ureter in the absence or in the presence of diclofenac (*S* in the presence of 30 μM sotalol, E_{max} maximal response in grams of tension, *Inhib* inhibition induced by diclofenac on the maximal response (in the presence of sotalol for NE), EC_{50} effective concentration giving 50% of maximal response, *n* number of strips, *In.* almost inactive). Results are mean ± SEM. In each group (5-HT, NE + S and NKA) statistical evaluations were made between values obtained in the same tissues; however, values obtained in the absence of diclofenac are pooled together to simplify the presentation

Agonist	Diclofenac (μM)	E_{max} (g)	Inhib (%)	EC_{50} (μM)	*n*
5-HT	0	1.69 ± 0.09	–	1.6 ± 0.3	35
	30	0.91 ± 0.10***	38.3 ± 5.5	1.8 ± 0.3	16
	100	0.53 ± 0.06***	66.5 ± 4.2	4.5 ± 0.5***	13
	300	0.08 ± 0.03***	94.0 ± 2.6	In.	6
NE	0	2.05 ± 0.31	–	7.5 ± 0.3	13
NE + S	0	2.15 ± 0.20	–	2.0 ± 0.3†††	17
NE + S	30	1.55 ± 0.29**	33.2 ± 7.3	4.2 ± 1.0†	8
NE + S	100	0.65 ± 0.11**	66.3 ± 6.8	5.1 ± 1.0††	5
	300	0.07 ± 0.07**	95.5 ± 4.4	In.	4
NKA	0	1.14 ± 0.15	–	0.7 ± 0.1	28
	10	0.87 ± 0.21*	25.1 ± 7.7	1.0 ± 0.2	11
	30	0.28 ± 0.14**	80.6 ± 5.8	0.9 ± 0.2	6
	100	0.08 ± 0.04***	93.6 ± 1.5	In.	11

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs 5-HT, NE + S or NKA controls, respectively. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ vs NE + S, $^{\dagger\dagger\dagger}P < 0.001$ vs NE alone

concentrations that produced a 50% inhibition of the 5-HT and NE responses (IC_{50}) were comparable (51 and 56 μM), whereas the IC_{50} value for NKA was lower (16 μM). The values of the inhibition on the agonist-induced responses are given in Table 1. Removal of the inhibitor from the superfusion Krebs solution showed that the inhibition was totally reversible after a washing period of 30–45 min.

To test whether the inhibitory effect of diclofenac was due to a decrease in PG synthesis, PGE_2 (10^{-7} to 3×10^{-4} M) or $PGF_{2\alpha}$ (10^{-6} to 10^{-4} M) was applied, alone or after diclofenac application. These PGs exerted no effect on ureteral motility ($n = 10$ and 12, respectively); furthermore, the application of $PGF_{2\alpha}$ 10^{-5} M for 30 min before NE did not reverse the inhibition induced by diclofenac 3×10^{-5} M ($n = 12$; results not shown).

Diclofenac has been shown to decrease intracellular Ca^{2+} influx in gastrointestinal, vascular and uterine smooth muscle [35, 39]. However, in this study the inhibitory effect of diclofenac was not reversed by the presence of higher concentrations of Ca^{2+} (up to 7.5 mM) in the Krebs solution ($n = 8$; results not shown).

Effect of NS-398 on agonist-induced contractions

Unlike diclofenac, NS-398 did not significantly induce rhythmic interruption of agonist-induced contractions, but above all decreased their amplitude (Fig. 2c, d); at the highest concentration, the responses to the agonists were almost abolished. No difference in sensitivity to NS-398 was noted between the agonists, since the drug concentrations that produced a 50% inhibition of 5-HT, NE or NKA were statistically not different ($IC_{50} = 71$, 92 and 51 μM, respectively; Fig. 4b). As observed with diclofenac, the inhibition was also totally reversible after 30–45 min of washing.

Discussion

The results of the present study demonstrate that in the isolated pig ureter, non-selective COX-inhibitors such as the widely used NSAID diclofenac, as well as the selective COX-2 inhibitor NS-398, decreased in a concentration-dependent manner the contractions induced by 5-HT, NE and NKA, three potentially important regulators of ureteral motility [3, 19, 52]. This adds to the knowledge that NSAIDs inhibit spontaneous or electrically induced contractions of the mammalian ureter [4, 8, 22, 26, 47, 48, 50].

The results herein strongly suggest that diclofenac inhibits amine-induced contractions through non-specific effects since: (1) at concentrations of diclofenac known to block prostanoid synthesis ($IC_{50} = 5$ μM [23]), the responses to 5-HT and NE were barely affected; (2) PGE_2 and $PGF_{2\alpha}$, two PGs active on human and sheep ureters [8, 47], were ineffective on the pig ureter; and (3) $PGF_{2\alpha}$ was unable to reverse the effect of diclofenac. In contrast, it cannot be discounted that COX inhibition may contribute to decrease NKA-induced contractions, since these were more prone to diclofenac inhibition than the responses to 5-HT and NE ($IC_{50} = 16$ vs 51 and 56 μM, respectively). This suggests that these amines act mainly through receptor activation, whereas NKA acts both directly on receptors and indirectly through the activation of prostanoid synthesis (probably different from PGE_2 and $PGF_{2\alpha}$). These observations also suggest that the effects of NKA would be more affected than those of NE and 5-HT by therapeutic doses of diclofenac (plasmatic concentration of 8 μM following i.m. injection of 75 mg of Voltaren [31]). It is interesting to note that NKA-immunoreactive nerves have been located within the ureter, which may promote a dual sensory-effector function in response to ureteral obstruction, such as pain perception, inflammation,

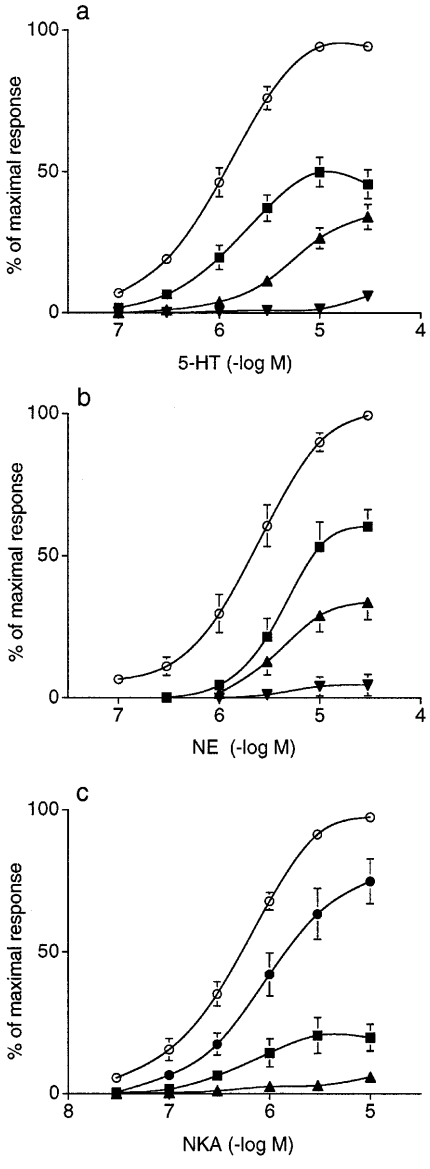

Fig. 3a–c Concentration-response curves for the contractile activity of 5-HT (**a**), NE (**b**) and NKA (**c**) on the isolated pig ureter, in the presence of various concentrations of diclofenac: control 0 μM (○), 10 μM (●), 30 μM (■), 100 μM (▲) and 300 μM (▼). Values are mean ± SEM and are expressed as percent of the maximal response obtained in the absence of diclofenac; $n = 4$–35 (see Table 1)

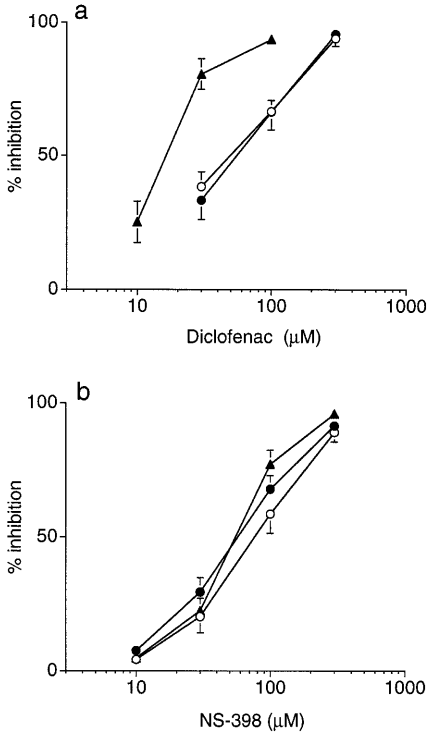

Fig. 4a, b Inhibition of the maximal responses to 5-HT (○), NE (●) and NKA (▲) induced by different concentrations of diclofenac (**a**) or NS-398 (**b**) on the isolated pig ureter. Values are mean ± SEM and correspond to the reduction of the response obtained in the absence of the inhibitor ($n = 4$–35; see Table 1). Note that diclofenac is a more powerful inhibitor of NKA-induced contractions than of amines-induced contractions, whereas NS-398 affects the responses in a similar manner to that of the three agonists

activation of reflexes directed to the kidney or contraction of ureteral smooth muscle [27].

Several mechanisms other than prostanoid synthesis inhibition may account for the decrease of agonist-induced contractions, such as inhibition of transmembrane ion movement [35, 39]. It is well known that agonist-induced contractions depend on an increase in cytosolic free Ca^{2+} concentration, either as a consequence of influx from extracellular space or release from intracellular stores [18]. Interestingly, NSAIDs have been shown to inhibit Ca^{2+} influx from the extracellular space in stomach and aorta of guinea pigs [35] and in rat uterus [39]. In this last preparation, however, whereas increasing concentrations of extracellular Ca^{2+} totally counteract the effects of some NSAIDs (naproxen, tolmetin), those of other NSAIDs, such as diclofenac, were unaffected. A comparable result was obtained in our pig ureteral preparation, in which a high level of extracellular Ca^{2+} did not reverse the inhibitory effect of diclofenac on the agonist-induced contractions, suggesting that this effect can probably not be related to inhibition of calcium influx. NSAIDs are known to exert other effects, such as activation of Na^+/Ca^{2+}-exchange [38], uncoupling the oxidative respiration [32] or uncoupling the receptors from their effector molecules [1, 9]. However, the present study does not enable us to ascribe such mechanisms to the inhibitory effects of NSAIDs on agonist-induced ureteral contractions.

Until now, the effects of NSAIDs on ureteral motility have been studied only with predominantly COX-1 inhibitors or non-selective COX inhibitors [4, 8, 22, 26, 47, 48, 50], whereas the effects of selective COX-2 inhibitors have received little attention. Recently, the selective COX-2 inhibitor NS-398 has been shown to inhibit spontaneous mammalian ureteral contractions in a fashion similar to indomethacin [33]. In the present study, this COX-2 inhibitor was almost as potent as diclofenac in inhibiting agonist-induced contractions. However, as in the case of diclofenac, the concentra-

tions of NS-398 that inhibited these contractions ($IC_{50} = 51–92$ μM) were higher than the concentrations shown to block COX-2 selectively in different cells of various species ($IC_{50} = 0.03–3.8$ μM) [10, 16, 28, 36, 41]. This low sensitivity suggests that the inhibition by NS-398 of the agonist-induced responses could also be ascribed to non-specific effects. However, the fact that diclofenac interrupted the agonist-induced contractions by transient relaxation, whereas NS-398 decreased their amplitude, suggests that each of these agents interferes with a specific mechanism of ureteral contraction. Moreover, the responses induced by the three agonists were equally decreased by the selective COX-2 inhibitor NS-398, whereas the response induced by NKA was more affected than those induced by NE and 5-HT by diclofenac, which inhibits both COX-1 and COX-2. These results are consistent with the view that NKA acts in part through the stimulation of prostanoid synthesis and that this synthesis depends on COX-1 activation.

From a clinical standpoint, it is interesting to note that the plasmatic concentration (8 μM) achieved after an i.m. injection of diclofenac (75 mg) [31] is sufficient to inhibit COX, since the concentration required to produce IC_{50} of COX activity is 5 μM [23]. This suggests that COX inhibition could be involved in the decrease of the ureteral motility observed after diclofenac application, which would agree with previous studies suggesting that prostanoid generation is an important step for the maintenance or the activation of ureteral peristalsis [4, 8, 26, 46–48]. In the pig ureter, however, our results suggest that suppression of contraction may result from a mixed effect on COX and non-specific effects on excitation-contraction coupling. However, one may consider that ureteral motility can be driven by distinct mechanisms. Ureteral smooth muscle belongs to the category of unitary muscles, organized into effector bundles with highly developed intercellular couplings [6]. In such a syncitium, electrotonic coupling contributes predominantly to ureteral peristalsis, the smooth muscle cells being activated by the passage of a propagated action potential; the motility of these cells can be locally modulated by the release of neurotransmitters or autacoids. Both mechanisms, which are linked to intracellular ion regulation, can be affected by non-specific effects of diclofenac. Thus, it is possible that prostanoid synthesis inhibition by clinical dose of NSAIDs may firstly affect generation of ureteral peristalsis, whereas side effects such as Ca^{2+} homeostasis alterations owing to higher doses would in addition affect agonist-induced contractions. This correlates with the view that, in the guinea pig, endogenous prostanoids can modulate the spontaneous activity of the renal pelvis, whereas excitability, contractility or propagation of impulses along the ureter appear almost independent of prostanoids generation [43]. However, our results suggest that prostanoid synthesis inhibition by clinical doses of diclofenac may also affect the contraction induced by NKA locally released by sensory nerves (see above).

Interest in selective COX-2 inhibitors is growing since various reports have suggested that unwanted effects of NSAIDs correlate with their ability to inhibit COX-1, while their therapeutic effects are due to their ability to inhibit COX-2 [49]. It is known that COX-2 expression is most evident at inflammation sites [44]; furthermore, the possibility that the mechanical stretch induced by ureteral obstruction stimulates COX-2 expression in ureteral smooth muscle has not yet been tested, but such an observation has been made in the bladder [37]. Thus, inhibition of COX-2 may be beneficial in the treatment of ureteral obstruction: diclofenac and NS-398, which both inhibit COX-2, could reduce local inflammation induced by stone passage. However, it should be kept in mind that renal PG influence several functions that depend either on COX-1 or COX-2 activity [7, 15] and that NSAIDs can induce unwanted renal effects by interfering with these physiological functions.

In summary, diclofenac and NS-398 appear to be efficient non-competitive inhibitors of ureteral smooth muscle contractions induced by several established neural messengers of the upper urinary tract. NSAIDs seem to suppress ureteral contractions mostly by unspecific effects rather than by an inhibition of prostanoid synthesis. Interestingly, NKA-induced contractions appear to be related to prostanoid synthesis.

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