Method for Simultaneous Recording of the Prostatic Contractile and Urethral Pressure Responses in Anesthetized Rats and the Effects of Tamsulosin

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ABSTRACT—We simultaneously recorded the prostatic contractile and urethral pressure responses to electrical stimulation (ES) of the hypogastric nerves (HGNs) or phenylephrine in anesthetized rats and studied the effects of tamsulosin on these responses. At 0.01 and 0.1 mg/kg, i.v., tamsulosin inhibited the prostatic responses to ES of the HGNs in a dose-dependent manner, while at 1 μg/kg, i.v., it reduced the response to phenylephrine (0.01 mg/kg, i.v.) to about 26% of the nonantagonized level. These inhibitory effects on prostatic responses were maintained for 60 min. Tamsulosin exerted an inhibitory effect on the urethral response to ES of the HGNs at 0.01 mg/kg, i.v. but not at 0.1 mg/kg, i.v. At 1 μg/kg, i.v., tamsulosin also reduced the urethral response to phenylephrine to about 46% of the nonantagonized level; this effect was maintained for 60 min. Furthermore, tamsulosin was found to exert a stronger inhibitory effect on the prostatic response than on the urethral response induced by sympathetic nerve activation. Our findings suggest that rat urethral sympathetic nerve terminals may contain prejunctional α1 adrenoceptors that modulate the release of norepinephrine.

Keywords: Rat prostatic contraction, Urethral sphincter contraction, Hypogastric nerve, Tamsulosin

In patients with benign prostatic hyperplasia (BPH), prostatic enlargement is accompanied by urine outflow obstruction, which is caused by both physical obstruction resulting from growth of the prostate and elevated smooth muscle tone resulting from over-stimulation of α1-adrenoceptors by norepinephrine (NE) released from sympathetic nerve terminals (1). Compared with normal human prostatic tissue, the maximal number of α1-adrenoceptors is significantly increased, and these receptors occur at a greater density, in hypertrophied prostates from patients with BPH (2). Clinical studies have demonstrated the efficacy of several α1-adrenoceptor antagonists in ameliorating bladder outlet obstruction in patients with BPH, and novel prostate-selective drugs that effectively treat the symptoms of BPH without causing undesirable side effects are under development (3–5). Experimental animal studies of the effects of such drugs have mostly investigated their ability to antagonize contraction of the isolated prostate induced by either an α1-adrenoceptor agonist, for example phenylephrine, or electrical field stimulation (6–9). An in vivo experiment that studied the inhibitory effect of an α1-adrenoceptor blocker on the intraurethral pressure response to electrical stimulation (ES) of the hypogastric nerves (HGNs) in decerebrate dogs, and compared the potency in terms of hypotensive effects, has also been reported (4). As the prostate and urethra are innervated by the HGN and the activities of the prostatic smooth muscles and internal urethral sphincter are mediated through α1-adrenoceptors, measurement of the intraurethral pressure reflects changes in the tone of the smooth muscles of the prostate and prostatic urethra. In the present study, we devised a simple method by which the prostatic contractile response and the urethral pressure elevation responses induced by ES of the HGNs or injection of phenylephrine...
MATERIALS AND METHODS

Animals

Male Wistar rats (Japan SLC, Shizuoka), aged 9 – 10 weeks and with a body weight of about 250 – 270 g, were used. The animals were kept in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society. The study was carried out under the control of a committee and in line with the Guidelines to Animal Experiments in the Hokuriku University Faculty of Pharmaceutical Sciences. All experiments were performed in rats anesthetized with urethane (1.0 g/kg, s.c.) and α-chloralose (25 mg/kg, s.c.).

Recording of the urethral pressure and prostatic contractile responses

The experimental schema are shown in Fig. 1. The preparation and recording methods for the measurement of urethral pressure signals were as described in our previous paper (10). The bladder and prostate were exposed through a midline incision in the abdomen. The connective tissue covering the ventral lobes of the prostate lying on the bladder neck was cut very carefully to avoid injuring the prostate, and the right and left prostatic lobes were carefully separated from the bladder neck. A polyethylene needle intended for administration of oral solutions to rats (Fuchigami Kikai, Kyoto) was used as a urethral cannula. The bladder was cut through the apex and the cannula was inserted through the opening toward the bladder neck. The point of the needle was pressed against the bladder wall near the bladder outlet, and the bladder neck was ligated onto the tube below the ureterovesical junction, so that urine from the ureter drained into the abdominal cavity through the incision in the bladder. After insertion of the cannula, the bladder was replaced in the abdominal cavity. Tyrode’s solution without glucose was continuously infused into the urethral lumen through the cannula at a constant rate (0.5 ml/10 min) using a syringe pump (Top-5200; Top, Tokyo). The composition of the Tyrode’s solution was as follows: 137 mM NaCl, 2.7 mM KCl, 1.8 mM CaCl₂, 1.1 mM MgCl₂, 0.42 mM NaH₂PO₄, and 11.9 mM NaHCO₃. The solution was adjusted to about pH 7.4 with diluted HCl. The infusion pressure signals from the urethra were measured using a pressure transducer (Gould P23 ID, Statham, GA, USA), which was connected to the urethral cannula via a T-tube, passed through an amplifier (AP 601G; Nihon Kohden, Tokyo) and recorded using a DC recorder (056; Hitachi, Tokyo). These infusion pressure signals were used to represent the urethral pressure.

For the recording of prostatic contractions, small stainless steel clips were attached to the tops of the right and left prostatic lobes after separation from the bladder neck.

Fig. 1. Scheme showing the method for recording the prostatic contractile and urethral pressure responses to electrical stimulation of the hypogastric nerves in anesthetized rats. The lamp used to warm the abdominal part has been omitted. The right and left prostatic lobes were connected by a fine nylon thread, the center of which was mounted on the hook of an isometric transducer, and prostatic contractions were recorded. Fluid was infused into the urethral lumen through a cannula inserted into the bladder outlet at a constant rate (0.5 ml/10 min). The infusion pressure signals were recorded and used as a measure of the urethral pressure. Electrical stimulation (ES) of the hypogastric nerves at 5, 10 and 20 Hz was performed at about 3-min intervals, and a series of ESs at all three frequencies was delivered at about 20-min intervals.
The two clips were connected to each end of a length of fine nylon thread, the center of which was mounted on the hock of an isometric transducer (TB-651T, Nihon Kohden) (Fig. 1). Cotton-wool swabs soaked with Tyrode’s solution were placed around the mounted prostate to keep it moist and were occasionally rewetted with Tyrode’s solution. The abdominal part was kept warm with a lamp, and a thermometer was laid below the swabs to ensure that the temperature was maintained close to 36°C. The contractile force was measured using the transducer, passed through an amplifier (EF-601G, Nihon Kohden) and recorded using a DC recorder, together with the urethral pressure. Before starting the measurements, the prostatic lobes were suspended under an initial resting tension of 1 g and were retensioned (to 1 g) twice or three times at about 30-min intervals. Experimental measurements were started 30 min after this equilibration period.

The HGNs on both the right and left sides were freed from their connective tissue to the level of the bifurcation of the aorta. The proximal ends were ligated with thread and rested on the interior of the abdomen. A pair of silver electrodes was placed in the abdominal cavity, and the HGNs were laid on these only when ES was being performed. The HGNs were stimulated using an electrical stimulator (MES-3R, Nihon Kohden; pulse duration of 1 ms, amplitude of 5 V). Thirty-second trains of ES were delivered at 5, 10 or 20 Hz at about 3-min intervals. When the reproducibility of the response was assessed, a series of six ESs comprising all three frequencies was repeated about once every 20 min. When the effects of drugs on the response to ESs were studied, the ESs were delivered at 5, 10 or 20 Hz, delivered for 30 s, was therefore repeated six times at about 20-min intervals. The prostatic responses to ES were not frequency-dependent, as indicated by the lack of any significant difference in the magnitudes of the prostatic responses to ES at three different frequencies within each series of ES or in the responses at each frequency among the six repetitions. On the other hand, there was a slight tendency towards an increase in the urethral response to ES at all three frequencies when ES was repeated three times; after this, the responses were reduced, except for those at 20 Hz. When the three responses were analyzed within each series of ES, there was a significant difference between the urethral responses at 5 and 20 Hz (except on the first and third occasions) and between the responses at 10 and 20 Hz on the sixth one. However, comparing among the six repetitions, there were no significant differences in the magnitudes of the six urethral responses to ES at the various frequencies used.

At 0.01 and 0.1 mg/kg, i.v., tamsulosin inhibited the prostatic contraction induced by ES of the HGNs in a dose-dependent manner, and this inhibitory effect was maintained for over 60 min. On the other hand, although tamsulosin at 0.01 mg/kg, i.v. inhibited the urethral pressure elevation induced by ES of the HGNs, repeat ES applied 60 min later produced urethral pressure elevation responses almost the same as those obtained before the tamsulosin injection. Furthermore, tamsulosin at 0.1 mg/kg, i.v. that was administered 60 min after injection of the 0.01 mg/kg dose produced no inhibitory effect on the urethral responses to ES (Fig. 3). When tamsulosin at 0.01 mg/kg, i.v. was injected three times at intervals of

**Drugs**

Tamsulosin hydrochloride was kindly donated by Yamanouchi Seiyaku Inc. (Tokyo). 1-Phenylephrine was purchased from Tokyo Kasei Kogyo Co. Ltd., Tokyo; clonidine hydrochloride, from Sigma Chemical Co., St. Louis, MO, USA; and yohimbine hydrochloride, from Wako Pure Chem., Osaka. All drugs were dissolved in saline and all concentrations are expressed as those of their respective salts. The drugs were administered through the femoral vein. When the effects of a drug on the prostate and urethral responses to ES of the HGNs or phenylephrine were studied, the drug was injected 3 min before the responses were elicited.

**Statistical methods**

All experimental values are expressed as the mean ± S.E.M. Differences between responses obtained before and after injection of tamsulosin were analyzed using the Student’s paired t-test. One-way analysis of variance (ANOVA) was used to compare the prostatic and urethral responses to ES of the HGNs or phenylephrine at each time point during the experiment. If statistical significance was indicated, comparisons were performed using Dunnett’s multiple range test. ANOVA was also used to analyze the extent of blockade of clonidine-induced responses by yohimbine. If statistical significance was indicated, comparisons were performed using Tukey’s multiple range test. A P value of less than 0.05 was considered significant.

**RESULTS**

*Simultaneous recording of the prostatic contractile and urethral pressure responses to ES of the HGNs and phenylephrine and the effects of tamsulosin on these responses*

Although ES of the HGNs at 5 Hz caused prostatic contraction and an increase in urethral pressure (Fig. 2), ES at 1 Hz induced no detectable response in either organ. A series of ESs comprising three different frequencies (5, 10 and 20 Hz), delivered for 30 s, was therefore repeated six times at about 20-min intervals. The prostatic responses to ES were not frequency-dependent, as indicated by the lack of any significant difference in the magnitudes of the prostatic responses to ES at three different frequencies within each series of ES or in the responses at each frequency among the six repetitions. On the other hand, there was a slight tendency towards an increase in the urethral response to ES at all three frequencies when ES was repeated three times; after this, the responses were reduced, except for those at 20 Hz. When the three responses were analyzed within each series of ES, there was a significant difference between the urethral responses at 5 and 20 Hz (except on the first and third occasions) and between the responses at 10 and 20 Hz on the sixth one. However, comparing among the six repetitions, there were no significant differences in the magnitudes of the six urethral responses to ES at the various frequencies used.

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about 60 min, only the first injection exerted an inhibitory effect on the urethral pressure responses to ES (Fig. 4). When repeated doses of tamsulosin at 0.1 mg/kg, i.v. were injected at about 60-min intervals, neither the first nor the second doses exerted an inhibitory effect; however, when tamsulosin at 1 mg/kg, i.v. was administered after these injections, the urethral response to ES at 5 Hz was reduced (Fig. 4).

Phenylephrine (0.01 mg/kg, i.v.) caused prostatic contraction and urethral pressure elevation, and there were no significant differences in the responses when phenylephrine was injected four times at intervals of about 60 min.

The prostatic contraction response induced by phenylephrine was reduced to $25.8 \pm 0.14\%$ of the nonantagonized level by tamsulosin at 1 $\mu$g/kg, i.v. and was completely abolished by tamsulosin at 3 $\mu$g/kg, i.v. (Fig. 5). At doses of 1 and 3 $\mu$g/kg, i.v., tamsulosin reduced the urethral pressure elevation responses induced by phenylephrine to $46.0 \pm 0.09\%$ and $10.8 \pm 0.11\%$ of the nonantagonized levels, respectively (Fig. 5). The inhibitory effects of tamsulosin on the prostatic and urethral responses to phenylephrine were maintained for over 60 min.
The effect of clonidine on the prostatic contraction and urethral pressure response

Clonidine at 0.03 mg/kg, i.v. caused sustained prostatic contraction and urethral pressure elevation. The prostatic contractions induced by two consecutive injections of clonidine were not different, and the subsequent clonidine-induced prostatic contraction after injection of yohimbine at 0.1 mg/kg, i.v. was significantly smaller than those before injection of yohimbine (Fig. 6). As yohimbine at 1 mg/kg, i.v. itself caused a transient urethral pressure elevation, clonidine at 0.03 mg/kg, i.v. was injected when the pressure elevated by yohimbine returned to the baseline. The urethral pressure elevation induced by clonidine was not inhibited by this larger yohimbine dose (Fig. 6). Yohimbine at 0.1 mg/kg and 1 mg/kg, i.v. produced no changes in the prostatic response and urethral responses to ES of the HGNs (data not shown). Furthermore, when the HGN was stimulated at 10 Hz either as the urethral pressure was nearing its peak after the injection of clonidine or at 60 min after the injection of clonidine and those magnitudes of the responses were compared with that of the response before injection of clonidine, there were no significant differences in the three responses as determined by ANOVA. Tamsulosin at 0.01 mg/kg, i.v. inhibited the
Fig. 4. Effects of repeated injections of the same dose of tamsulosin on the urethral pressure response to electrical stimulation of the hypogastric nerves in anesthetized rats. For details of the recording method and hypogastric nerve stimulation, see the legend to Fig. 1. Each column and vertical bar represents the mean and S.E.M. Responses to the same frequency were compared before and after injection of tamsulosin (tam) using Student’s paired t-test. *P<0.05 and **P<0.01.

Fig. 5. Effects of tamsulosin on the prostatic contractile and urethral pressure responses to phenylephrine in anesthetized rats. For details of the recording method see the legend to Fig. 1. Phenylephrine (0.01 mg/kg, i.v.) was injected at 60-min intervals and tamsulosin was injected 3 min before the phenylephrine. Each column and vertical bar represents the mean and S.E.M. The responses obtained before and after injection of tamsulosin (tam) were compared using Student’s paired t-test. **P<0.01.
Fig. 6. Prostatic contraction and urethral pressure elevation responses induced by clonidine and the effects of yohimbine on these responses in anesthetized rats. For details of the recording method, see the legend to Fig. 1. Clonidine (0.03 mg/kg, i.v.) was injected at 60-min intervals (columns with horizontal hatching). The columns with meshed hatching indicate the urethral pressure elevations induced by yohimbine. Each column and vertical bar represents the mean and S.E.M. Statistical analysis of the responses to clonidine before and after the injection of yohimbine (yoh) was performed using ANOVA followed by Tukey’s test. *P<0.05 and **P<0.01.

Fig. 7. Urethral pressure responses to electrical stimulation of the hypogastric nerve in anesthetized rats after injection of clonidine and tamsulosin. For details of the recording method, see the legend to Fig. 1. A: Typical recording of the urethral pressure response (UP) to clonidine and the response to electrical stimulation of the hypogastric nerves before and after injection of clonidine. The symbols (triangles) represent hypogastric nerve stimulation at 10 Hz. At the point indicated by the arrow, tamsulosin (tam) was injected. B: Responses (bar graphs calculated from data; the data for the first three graphs are not shown in A). Each column and vertical bar represents the mean and S.E.M. Statistical analysis of the responses to ES at 10 Hz before and after the first injection of clonidine was performed by ANOVA followed by Dunnett’s test. The responses to ES at 10 Hz before and after the first injection of tamsulosin (tam), and the responses to ES at 10 Hz before and after the second injection of clonidine, were compared using Student’s paired t-test. **P<0.01.
urethral responses to both ES and clonidine (0.03 mg/kg, i.v.); however, even at this tamsulosin dose, ES after the injection of clonidine caused an increase in urethral pressure almost the same as that obtained before the tamsulosin injection (Fig. 7).

DISCUSSION

We devised a method by which the prostatic and urethral responses to ES of the HGNs could be measured simultaneously and easily in anesthetized rats. When we studied the effects of tamsulosin on the prostatic and urethral responses to ES of the HGNs using our method, we found that it exerted different inhibitory effects on prostatic contraction and the urethral pressure elevation response. Tamsulosin inhibited prostatic contractions in a dose-dependent manner, and this inhibitory effect was maintained for over 60 min after injection (Fig. 3). On the other hand, although tamsulosin at 0.01 mg/kg, i.v. inhibited the urethral pressure response to ES, its effect had worn off 60 min after injection. This disappearance of the inhibitory effect was not due to metabolism of the drug, since subsequent repeat administrations at the same dose were unable to reproduce the inhibitory effect. (Fig. 4). Furthermore, at 0.1 mg/kg, i.v., tamsulosin had no inhibitory effect on the urethral response to ES, while at 1 mg/kg, i.v., it reduced the urethral response to ES only at 5 Hz. However, tamsulosin at 1 and 3 μg/kg, i.v. exerted an inhibitory effect on the urethral pressure elevation, as well as the prostatic contraction, induced by phenylephrine (0.01 mg /kg, i.v.) in a dose-dependent manner, and these inhibitory effects were maintained for over 60 min after the injection of tamsulosin (Fig. 5). These findings suggest that at a dose capable of blocking the extrajunctional α₁-adrenoceptors, tamsulosin did not block the junctional α₁-adrenoceptors below the sympathetic nerve endings in the urethra. In the prostate, however, the doses of tamsulosin needed to block the extrajunctional and junctional α₁-adrenoceptors were not very different. Based on our finding that tamsulosin exerted an inhibitory effect on the urethral pressure response to ES of the HGNs at 0.01 mg/kg, i.v. but not at 0.1 mg /kg, i.v., we speculate that tamsulosin causes an increase in NE release from the urethral sympathetic nerve endings at 0.1 mg/kg, i.v., and that this increased amount of NE may antagonize tamsulosin-induced inhibition of the urethral response, which is mediated by junctional α₁-adrenoceptors. Prejunctional α₁-adrenoceptors that inhibit NE release from sympathetic nerve terminals have been reported in rat and dog hearts (11, 12) and rat kidney (13 – 15). Furthermore, Selic et al. (15) reported that the effect of 0.2 nM prazosin in reducing periartrial nerve stimulation-induced vasoconstriction was reversed by increasing the concentration to 2.4 μM. At 2.4 μM, prazosin also enhanced fractional tritium-labeled NE overflow in the rat kidney. The effects of prazosin on rat kidney vasoconstriction responses were very similar to those of tamsulosin on the urethral pressure response to ES of the HGNs in our experiments. Thus, there may be prejunctional α₁-adrenoceptors in rat urethral sympathetic nerve terminals, and 0.1 mg/kg, i.v. may be the dose of tamsulosin required to block them. Even at a lower dose (0.01 mg/kg, i.v.), tamsulosin may block these receptors if they remain exposed. However, there was no significant difference in the urethral pressure elevation after injection of tamsulosin, and the urethral responses to ES at 5 and 10 Hz did not differ in magnitude, suggesting that it may be difficult to detect differences even if tamsulosin does increase the amount of NE released from the nerve terminals. At 1 mg/kg, i.v., tamsulosin reduced the submaximal urethral response induced by ES at 5 Hz, indicating that this is the dose required to antagonize the increase in urethral pressure induced by the increased release of NE. In the experiments investigating the effects of tamsulosin on the responses via the junctional α₁-adrenoceptor in isolated rabbit aorta and the prejunctional α₂-adrenoceptor in guinea pig ileum and the affinities of tamsulosin for these α₁- and α₂-adrenoceptors in human hypertrophic adenoma of the prostate, the former and latter reports described that the affinities of tamsulosin for the α₁-adrenoceptor were 5,900 times and 400 times higher than those for the α₂-adrenoceptor, respectively (16, 17). The affinity of tamsulosin even for the α₂-adrenoceptor in human hypertrophic adenoma of the prostate, for which tamsulosin showed relatively high affinity, is lower than that for the α₁-adrenoceptor. These data also suggest that the effects of tamsulosin are due to the blocking action of α₁-adrenoceptors. The difference in the inhibitory potency of tamsulosin against the urethral responses to ES of the HGNs and to phenylephrine suggests that it may be difficult for tamsulosin to penetrate into junctional α₁-adrenoceptors sites.

Tamsulosin exerted a stronger inhibitory effect on the prostatic contractile response than on the urethral pressure response to ES of the HGNs. Since a decrease in urethral tone impairs the ability of the bladder to store urine, an α₁-adrenoceptor antagonist that exerts a stronger inhibitory effect on contraction of prostatic smooth muscles than on the urethral muscles may be of benefit to patients with BPH. Therefore it is meaningful to compare the potencies of novel α₁-adrenoceptor antagonists in decreasing the urethral pressure and prostatic contraction, as well as their hypotensive action. Our model using rats is simple and useful for performing this type of study.

Our present findings indicated the possibility that prejunctional α₁-adrenoceptors modulated the release of norepinephrine from sympathetic nerve terminals in rat urethra. It is accepted that prejunctional α₂-adrenoceptors
modulate the release of norepinephrine from sympathetic nerve terminals, and clonidine has been used to study this effect (18). To investigate the presence of prejunctional α2-adrenoceptors, we also examined the effect of clonidine on the urethral pressure response to ES of the HGNs. Clonidine (0.03 mg/kg, i.v.) caused a sustained increase in urethral pressure. Although this response was not inhibited by yohimbine at 1 mg/kg, i.v., it was inhibited by tamsulosin at 0.01 mg/kg, i.v. (Figs. 6 and 7). Clonidine has been reported to cause contraction of isolated rabbit urethral smooth muscle through α1-adrenoceptors or a combination of α1- and α2-adrenoceptors (19, 20). In our rats, clonidine appeared to cause urethral smooth muscle contraction mainly via α1-adrenoceptors. Clonidine (0.03 mg/kg, i.v.) did not alter the urethral response to ES of the HGNs at 10 Hz (Fig. 7). Tamsulosin (0.01 mg/kg, i.v.) inhibited the urethral pressure response to ES of the HGNs before injection of clonidine, whereas it did not inhibit the response to ES of the HGNs after injection of clonidine. The inhibition of the urethral pressure response to ES of the HGNs produced by tamsulosin was reversed by clonidine (Fig. 7). It is unlikely that tamsulosin (0.01 mg/kg, i.v.) could not exert an inhibitory effect on the urethral pressure responses to the second ES of the HGNs, because it inhibited the responses to three continuous ESs at 3-min intervals in rats that had not been administered clonidine (Figs. 3 and 4). These results suggest that clonidine competes with tamsulosin for binding at the junctional α1-adrenoceptors in the urethra. Thus, there may be no prejunctional α2-adrenoceptors that regulate NE release in the rat urethra. Similarly, as yohimbine (0.1 mg/kg, i.v.) and tamsulosin (0.01 mg/kg, i.v.) both inhibited the prostatic contraction induced by clonidine (0.03 mg/kg, i.v.), it is possible that clonidine could induce the prostatic contractile response through α1- and α2-adrenoceptors. However, clonidine did not alter the prostatic contractile response to ES of the HGNs (data not shown), indicating that neither prejunctional α1-adrenoceptors nor α2-adrenoceptors that mediate NE release from the sympathetic nerve terminals exist in the prostate.

In conclusion, we devised a simple method by which the prostatic contractile and urethral pressure responses to ES of the HGNs could be measured simultaneously in anesthetized rats. We then compared the effects of tamsulosin on the prostatic and urethral responses using our method. Tamsulosin exerted a stronger inhibitory effect on the prostatic contractile response than the urethral pressure response to ES of the HGNs. As the inhibitory effect on the urethral pressure response to ES seen with a low dose of tamsulosin was reversed by a higher dose, we speculate that prejunctional α1-adrenoceptors that mediate NE release are present in the sympathetic nerve terminals in the rat urethra.

Acknowledgment

We wish to thank Yamanouchi Seiyaku Inc. for kindly donating the tamsulosin used in this study.

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