Nociceptin modulates renal sympathetic nerve activity through a central action in conscious rats

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Shirasaka, Tetsuro, Takato Kunitake, Kazuo Kato, Mayumi Takasaki, and Hiroshi Kannan. Nociceptin modulates renal sympathetic nerve activity through a central action in conscious rats. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R1025–R1032, 1999.—Nociceptin, an endogenous agonist of the opioid receptor-like1 (ORL1) receptor, is expressed in the hypothalamus, where it is implicated in autonomic nervous system control. However, the central actions of nociceptin on sympathetic nerve activity have not been studied. We investigated the effect of intracerebroventricularly administered nociceptin (2–10 nmol) on blood pressure, heart rate (HR), and renal sympathetic nerve activity (RSNA) in conscious rats and sinoaortic-denervated (SAD) rats. Intracerebroventricularly administered nociceptin resulted in a dose-dependent decrease in mean arterial pressure (MAP) and HR in intact rats. RSNA decreased 31.5 ± 2.1 and 19.9 ± 5.0% at a dose of 2 and 5 nmol, respectively. In SAD rats, MAP, HR, and RSNA decreased in a dose-dependent manner, and the maximum responses were larger than those in intact rats. The decrease in HR induced by nociceptin was blocked by propranolol but not by atropine, which indicates that nociceptin is acting by inhibiting cardiac sympathetic outflow. These nociceptin-induced depressor and bradycardic responses were not antagonized by pretreatment with naloxone and nocistatin. These findings suggest that central nociceptin may have a functional role in regulating cardiovascular and sympathetic nervous systems.

sinoaortic-denervated rats; atropine; propranolol; naloxone; nocistatin

NOCICEPTIN, also known as orphanin FQ, is a newly discovered 17–amino acid peptide that is the putative endogenous ligand for the orphan opioid receptor-like1 (ORL1) receptor (20, 26). The ORL1 receptor is the nonopioid, G protein-coupled receptor whose primary structure is related most closely to those of opioid receptors, in particular that of the κ-opioid receptor (20). Nociceptin is similar in composition to the naturally occurring opioid heptadecapeptide dynorphin A (20, 26), an endogenous agonist of the κ-opioid receptor. Nociceptin not only displays amino acid sequence homology with the opioid peptide family but, at the cellular level, it functionally resembles opioid peptides with respect to the inhibition of adenylyl cyclase (20, 26), the activation of inwardly rectifying potassium channels (4, 31), and the inhibition of calcium currents (1, 5).

Despite these similarities, ORL1 has a pharmacology that differs from that of typical opioid receptors, which would include central hyperalgesia (26) and naloxone-insensitive action (7, 8, 31). Nociceptin appears to exert inhibitory responses on different biological systems both in vivo (9, 28) and in vitro (1, 8, 23, 31), but the functional importance of this new peptide is not clear.

Opioids and opioid receptors are located in specific brain nuclei known to regulate cardiovascular activity (17, 24) and to be involved in modulating sympathetic nervous system activity (10, 19) and baroreceptor reflex sensitivity (30). Intracerebroventricular administration of μ-selective and δ-selective agonists has been reported to increase arterial pressure and renal sympathetic nerve activity (RSNA) in conscious rabbits (19). The highest levels of ORL1 receptor mRNA are found in the paraventricular and ventromedial nuclei of the hypothalamus (6, 12). The paraventricular nucleus has been suggested to be involved in the regulation of the autonomic nervous and endocrine systems, the cardiovascular functions in particular (29). Thus it is possible that central nociceptin plays some role in the central control of cardiovascular functions. Intravenous administration of nociceptin has been reported to induce hypotension associated with decreased heart rate (HR) in anesthetized rats (9). In conscious rats (14), intravenous and intracerebroventricular administration of nociceptin produced a decrease in mean arterial pressure (MAP) and HR, which suggests that nociceptin may inhibit sympathetic nerve activity. However, anesthesia is known to affect the cardiovascular and autonomic nervous systems profoundly (13, 32).

To explore the central action of nociceptin, we investigated the effects of intracerebroventricular administration of nociceptin on blood pressure (BP), HR, and RSNA in conscious unrestrained rats. The renal sympathetic nerves play important roles in the homeostasis of body fluid and the circulatory system; diuresis and natriuresis are elicited through the inhibition of RSNA in the case of volume overload (2). The baroreceptor reflex system is involved in stabilizing BP and controlling the output of the autonomic nervous system (16). RSNA is influenced by several reflex mechanisms such as the arterial baroreceptor reflex elicited by changes in hemodynamics. To elucidate the direct effect of central nociceptin on RSNA, we then investigated central nociceptin-induced cardiovascular and RSNA responses using conscious sinoaortic-denervated (SAD) rats. The efferent pathway responsible for nociceptin-induced changes in HR was examined in rats pretreated with atropine or propranolol. Finally, receptors associated with nociceptin-induced responses were examined in...
conscious rats pretreated with the classical opioid receptor antagonist naloxone and a putative antagonist nocistatin (22).

METHODS AND MATERIALS

Animals and surgical preparations. Male Wistar rats weighing 350–450 g were housed individually in an environmental room at 24°C with controlled light-dark cycles (lights on 7 AM to 7 PM). Food and water were available ad libitum. Animals were prepared surgically for experimentation as follows. Under anesthesia by intraperitoneal injection of pentobarbital sodium (50 mg/kg), they were implanted with a lateral cerebroventricular cannula. A 24-gauge stainless steel guide cannula (length 19 mm) was positioned 2.5 mm from the cortex surface and 1 mm above the left lateral cerebral ventricle through a burr hole located stereotaxically 0.8 mm posteriorly and 1.5 mm laterally to the bregma. The guide cannula was fixed to the skull with four screws and dental cement. Both an acute elevation (over 20 mmHg) in MAP and a persistent (at least 10 min) water-drinking response to intracerebroventricular administration of 10 pmol ANG II were considered indicators of cannula patency and proper placement in the ventricular system. Approximately 10 days later, the cannulated rats were given pentobarbital anesthesia (50 mg/kg ip), and SP-31 tubing heat-coupled to SP-50 and PE-50 catheters were inserted into the abdominal aorta and inferior vena cava for measurement of BP and intravenous administration of drugs, respectively. The arterial catheter, filled with heparinized (10 U/ml) saline solution, was connected to a Statham pressure transducer (Gould, Saddle Brook, NJ) to monitor BP, and the venous catheter was sealed. HR was monitored with a cardiometer (model 1321; San-Ei, Tokyo, Japan) triggered by an electrocardiogram signal recorded via subcutaneous electrodes implanted into the chest. For the measurement of RSNA, a left renal nerve bundle was dissected carefully via a retroperitoneal approach and freed from the surrounding tissue under stereoscopic microscopy. The nerve was placed on a bipolar electrode made of Teflon-coated wire (Cooner Wire; Chatsworth, CA) and covered with silicone rubber (Semilac 902A and B cement; Wacker Chemicals East Asia, Tokyo, Japan). Spike potentials, which were amplified (Biophysicsoamplifier AVB-9; Nihon Kohden, Tokyo, Japan) and filtered (50–1,000 Hz), were monitored on a storage oscilloscope (model VC-9A; Nihon Kohden) and continuously recorded on a magnetic tape recorder (Sony, Tokyo, Japan). Through the window discriminator, the impulses were then fed into a pulse counter (MET-1100; Nihon Kohden), and the output was digitized, printed as a histogram, and recorded simultaneously with BP and HR on a thermal rectigraph (San-Ei). Tapes were later played back, and the RSNA waveforms were integrated after full-wave rectification using an amplitude analyzer (series 5500; Concurrent, Fort Lauderdale, FL) with the sample-hold function reset to baseline by an internal timer set at 5 s. Absolute values for integrated RSNA were corrected before data analysis by subtracting the residual electrical output (background noise level) recorded from the integrator after intravenous injection of hexamethonium (20 mg/kg iv). All burst-like activity in the RSNA was completely eliminated after hexamethonium, indicating that the neural activity recorded results from efferent but not afferent fibers.

SADs were performed according to the method of Krieger (15) 3 days after implanting the lateral cerebroventricular cannula. Under pentobarbital anesthesia (50 mg/kg ip), a midline incision was made in the ventral neck region, and the sternocleidomastoid muscles were reflected laterally to expose the common carotid arteries, the external and internal carotid arteries, the vagi, and the cervical sympathetic trunks. The sympathetic trunk, superior laryngeal nerve, and aortic depressor nerve were bilaterally sectioned under a surgical microscope. The bifurcation and all carotid branches were stripped of fibers and connective tissues and painted with a small amount of 10% phenol. Approximately 7 days after SAD, arterial and venous catheters were inserted and chest and RSNA electrodes were implanted. The effectiveness of SAD was confirmed by the lack of bradycardia and sympathetic inhibitory responses to phenylephrine (16 µg/kg iv).

Experimental protocol. All experiments were performed in conscious, freely moving rats 1–5 days after surgery. After BP, HR, and RSNA stabilized, 20 µl of vehicle (physiological saline solution) or vehicle containing synthetic nociceptin (2–10 nmol; Peptide Institute, Osaka, Japan) was infused intracerebroventricularly into intact and SAD conscious rats through an infusion cannula (30-gauge stainless steel tubing) connected to a 50-µl microsyringe by an automatic injector (Laboratory and Medical Supplies, Tokyo, Japan) at a rate of 1 µl/min for 20 min. This injection was made by inserting the infusion cannula 1 mm beyond the tip of the guide cannula. A preliminary study had revealed that 10 nmol of intracerebroventricularly administered nociceptin once per day did not produce tachyphylaxis in the parameters measured for 5 days. Either vehicle or a randomly selected single dose of nociceptin was administered on separate days in each rat. In pretreatment studies, either vehicle or each pretreatment drug was administered only once per rat at random. Under similar experimental conditions in intact rats, to assess the influence of parasympathetic nerve or sympathetic nerve activity on the nociceptin (10 nmol)-induced responses in HR, atropine methyl nitrate (4.0 mg/kg; Sigma Chemical, St. Louis, MO), pranopanol (β₁- and β₂-antagonist; 4.0 mg/kg; Sigma Chemical), or vehicle (saline) was administered intravenously 10 min before intracerebroventricular nociceptin to block vagal or sympathetic efferent activity. Atropine or vehicle was administered in 100-µl volumes over a period of 120 s. Propranolol was administered as an initial bolus in 100-µl volumes, followed by a maintenance infusion of 4 mg·kg⁻¹·h⁻¹ delivered at a volume flow rate of 100 µl/h. Under similar experimental conditions in other intact rats, the effect of pretreatment with naloxone hydrochloride (Sigma Chemical) or nocistatin (Peptide Institute) on nociceptin-induced changes in MAP, HR, and RSNA was investigated. The intracerebroventricular dose of nociceptin (100 nmol) was the dose that had been reported to block responses to intracerebroventricularly administered dynorphin A in conscious rats (27) and caused no significant hemodynamic responses when injected alone (data not shown). Either naloxone (100 nmol) or nocistatin (20 nmol) dissolved in 5 µl of saline or vehicle (5 µl of saline only) was injected intracerebroventricularly over 10 s as pretreatment. Ten minutes after pretreatment, another 10 nmol nociceptin (20 µl) were intracerebroventricularly administered.

After each experiment, Pontamine sky blue was injected to verify the correct placement of the intracerebroventricular cannula tip. Statistical analysis. All data are expressed as means ± SE, and statistical analyses were performed using ANOVA for repeated measurements. If statistically significant effects were found, the Bonferroni multiple comparisons test was applied to the differences between groups. Maximum changes from control values were analyzed using Student’s t-test. P < 0.05 was considered statistically significant.
RESULTS

Figure 1 shows an original tracing demonstrating the effects of nociceptin (10 nmol icv) on MAP, HR, and RSNA in intact (Fig. 1A) and SAD (Fig. 1B) rats. Nociceptin decreased HR and BP in intact and SAD rats. In SAD rats (Fig. 1B), the decreases in HR, BP, and RSNA persisted and did not return to preinjection values during the recording time (40 min).

Effects of nociceptin in intact rats. The effects of nociceptin on MAP, HR, and RSNA on intact conscious rats are shown in Fig. 2. When nociceptin (5 and 10 nmol, n = 11 each dose) was injected intracerebroventricularly, MAP and HR decreased, whereas RSNA did not change at a dose of 10 nmol. MAP decreased gradually with a peak decrease at 25 min from time 0. HR decreased immediately after starting the injection, decreasing maximally within 15 min. The decrease in RSNA produced by 5-nmol intracerebroventricular nociceptin was only transient and attained statistical significance only at the 10-min period compared with the vehicle. In contrast, intracerebroventricular administration of 2 nmol nociceptin (n = 11) did not produce a significant decrease in MAP or HR (Fig. 2), but it did produce a significant decrease in RSNA. RSNA began to decrease at 5 min after the start of injection, reaching the maximal decrease within 10 min. Significant differences were observed between 2 and 10 nmol in HR and RSNA. The vehicle (n = 6) did not elicit any effects on MAP, HR, or RSNA (Fig. 2). Leakage of intracerebroventricular nociceptin into the systemic circulation was ruled out because intravenous bolus administration of nociceptin (10 nmol, n = 11), the highest dose of this peptide used in this study, caused a transient but not significant decrease in MAP (control value 95.8 ± 3.6 mmHg, minimum value 92.4 ± 4.6 mmHg, P > 0.9), HR (control value 363.4 ± 6.2 beats/min, minimum value 337.7 ± 7.2 beats/min, P > 0.6), and RSNA (control value 100%, minimum value 90%).
83.7 ± 4.5%, P > 0.2). MAP and HR, but not RSNA, decreased in a dose-dependent manner in response to nociceptin administered intracerebroventricularly in intact rats.

Effects of nociceptin in SAD rats. The possible involvement of the arterial baroreceptor reflex in nociceptin-induced responses was examined using SAD rats. SAD treatment virtually eliminated phenylephrine-induced decreases in ∆HR/∆MAP from −5.4 ± 0.9 to −0.6 ± 0.1 beats·min⁻¹·mmHg⁻¹; P < 0.01 and ∆RSNA/∆MAP (from −1.3 ± 0.3 to −0.3 ± 0.1 %/mmHg; P < 0.01). These results indicate that the denervation of the arterial baroreceptors was complete. When various doses (2, 5, and 10 nmol) of nociceptin were injected intracerebroventricularly into SAD rats (n = 6), the decreases in MAP and HR were augmented compared with those observed in intact rats, and RSNA decreased

83.7 ± 4.5%, P > 0.2). MAP and HR, but not RSNA, decreased in a dose-dependent manner in response to nociceptin administered intracerebroventricularly in intact rats.

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dose dependently (2 nmol 39.3 ± 2.2%, 5 nmol 45.2 ± 3.0%, 10 nmol 65.8 ± 4.2%; n = 6, as shown in Figs. 3 and 4). Significant differences were observed between 2 and 10 nmol in MAP (P < 0.05), HR (P < 0.05), and RSNA (P < 0.01). For each dose, the maximum changes from control values were compared between intact and SAD rats, and the decreases in all of these parameters were greater in SAD rats (Fig. 4). The vehicle (n = 6) did not affect MAP, HR, or RSNA in SAD rats (Fig. 3). Intracerebroventricular nociceptin decreased MAP, HR, and RSNA dose dependently in SAD rats.

Intracerebroventricular nociceptin decreased MAP, HR, and RSNA dose dependently in SAD rats.

Effects of atropine and propranolol on HR. We next examined the possible involvement of vagal or sympathetic efferent activity in the nociceptin (10 nmol)-induced decrease of HR using intact rats. Either vehicle (saline intravenously, n = 7), atropine (4 mg/kg iv, n = 7), or propranolol (4 mg/kg iv, n = 6) was administered as a pretreatment (Fig. 5). Because HR was different for the control period between vehicle (362 ± 9.5 beats/min), atropine (390.8 ± 3.9 beats/min), and propranolol (321 ± 5.6 beats/min) pretreatments, maximum changes from the control values were used for comparison. The maximum decrease in HR (vehicle 89.0 ± 12.4 beats/min, atropine 72.7 ± 11.0 beats/min, propranolol 8.7 ± 1.1 beats/min) by nociceptin was attenuated by propranolol (P < 0.01) but not by atropine (P > 0.3).

Effects of naloxone and nocistatin on nociceptin-induced responses. The intracerebroventricular administration of naloxone (100 nmol, n = 7) or nocistatin (20 nmol, n = 7) alone did not provoke significant changes in MAP, HR, or RSNA (data not shown). In other intact rats, the effects of pretreatment with naloxone (100 nmol, n = 7) or nocistatin (20 nmol, n = 7) on MAP, HR, and RSNA in response to nociceptin (10 nmol) were investigated (Fig. 6). Decreases in MAP and HR in naloxone-treated rats were equal to decreases in vehicle pretreatment rats. RSNA, on the other hand, decreased significantly, which was not observed in vehicle pretreatment rats. Nocistatin (20 nmol) did not significantly affect nociceptin-induced responses compared with those by vehicle (Fig. 6).
The present study shows that intracerebroventricular–administered nociceptin causes a dose-dependent decrease in MAP, HR, and RSNA in conscious, unrestrained SAD rats. Although nociceptin provoked a similar dose-dependent decrease in MAP and HR in intact rats, RSNA was inhibited significantly only at doses of 2 and 5 nmol. The renal sympathoinhibitory effect of 5 nmol nociceptin was only transient, although a prominent decrease in HR and MAP was attained. Ten nanomolar nociceptin, which provoked prominent decreases in MAP and HR, did not decrease RSNA. This demonstrates that central nociceptin induces different responses according to the doses administered. The reduction in MAP produced by intracerebroventricular nociceptin appears to have activated the baroreceptor reflex, thereby preventing a direct renal sympathoinhibitory response to the drug from being observed. The hypotensive and bradycardic responses observed in this study are in agreement with previous reports (14). A profound inhibition of cardiomotor neurons in the rostral ventrolateral medulla by nociceptin was reported (3). These data suggest that intracerebroventricularly administered nociceptin directly inhibits sympathetic outflow through a central action, since intravenously bolus administered nociceptin (10 nmol) caused no significant changes in MAP, HR, or RSNA. In contrast, the transient depressor and bradycardic responses induced by intravenous-administered nociceptin (10–100 nmol/kg) have been observed in anesthetized rats (9). This difference may be due to anesthesia effects and/or injected doses. In conscious rats, hypotension in response to intravenous and intracerebroventricular nociceptin has been reported (14), showing that the dose of nociceptin that elicits cardiovascular responses was lower for intracerebroventricular injection than for intravenous injection. Accordingly, the results of the present study confirm those of the previous study (14).

Moderate levels of ORL₁ receptor mRNA have been localized to sites involved in central cardiovascular control, such as the paraventricular nucleus (6, 12), which is a major site for the integration of sympathetic outflow (29), and the nucleus tractus solitarius (6), where baroreceptor and chemoreceptor afferents terminate (11). In SAD rats, MAP, HR, and RSNA decreased dose dependently, and the maximal responses were larger and longer-lasting than those in intact rats. Accordingly, these data indicate that the later recovery of these parameters in intact rats is attributable to a sensitized arterial baroreceptor reflex.

It is known that the renal sympathetic nerve plays important roles in the homeostasis of body fluids and the circulatory system; diuresis and natriuresis are elicited through inhibition of RSNA in case of volume overload (2). It has been reported that central nociceptin produces a profound dose-dependent increase in urine flow rate and a decrease in urinary sodium excretion. The anti-natriuretic action of central nociceptin is the opposite effect of renal sympathoinhibitory action. The nociceptin-induced anti-natriuresis may be due to a humoral mechanism but not by a neural one. Recently, Doi et al. (7) demonstrated that spontaneous discharge of both oxytocin- and vasopressin-secreting neurons in the supraoptic nucleus was dose dependently and reversibly inhibited by nociceptin in vitro. Therefore, central nociceptin-induced inhibition of RSNA and oxytocin and vasopressin release may participate at least in part in the renal excretory function.
The decrease in HR caused by central nociceptin was blocked by propranolol (4.0 mg/kg) but not by atropine (4.0 mg/kg). Thus it is possible that the bradycardia elicited by central nociceptin was due to inhibition of cardiac sympathetic nerve activity rather than stimulation of parasympathetic outflow. However, we could not exclude the possible effect of the significant decrease in basal level of HR (321 ± 5.6 beats/min compared with 362 ± 9.5 beats/min in vehicles) produced by propanolol pretreatment on the HR response following nociceptin infusion. In contrast to our data, it has been reported that intravenous nociceptin-induced bradycardia is reduced by bilateral cervical vagotomy in anesthetized rats (9). Pretreatment with intravenous atropine (1.2 mg/kg) was shown to reduce nociceptin-induced bradycardia (9). These differences may be due to anesthesia and/or the nociceptin-injection route. Our results show that the decreases in MAP and HR produced by nociceptin were not blocked by naloxone pretreatment (100 nmol), which antagonizes the pressor and tachycardic responses induced by the k-opioid agonist dynorphin A in conscious rats (27). Stanfa et al. (28) reported that a high dose of naloxone (137 nmol) reversed the depressant effect of nociceptin (124 nmol) on C-fiber-evoked responses in rat dorsal neurons in vivo. The present result is in agreement with other studies in which various nociceptin-induced responses have been shown to be insensitive to naloxone (8, 23). Thus this nociceptin effect may not be mediated by activation of the naloxone-sensitive typical opioid receptors. Nociceptin is a putative ligand for the ORL1 receptor, and naloxone is not active at the ORL1 receptor (21). Accordingly, it is likely that the responses induced by intracerebroventricular nociceptin are mediated by the ORL1 receptor and are different from those mediated by the k-receptor in conscious rats. Interestingly, in intact rats pretreated with naloxone, nociceptin (10 nmol) led a decrease in RSNA. Intravenous administered naloxone has been reported to attenuate baroreceptor reflex sensitivity in conscious dogs (30) and rabbits (18) through a central action. The reduction of RSNA in naloxone-treated rats may be due to attenuation of baroreflex sensitivity, thereby canceling a reflex increase in RSNA induced by hypotension and revealing an inherent decrease in RSNA by central nociceptin.

Nocistatin, a biologically active peptide produced from the same precursor as nociceptin, was recently identified and isolated from bovine brain (22). Pretreatment with nocistatin (20 nmol) did not block nociceptin (10 nmol)-induced responses either. Simultaneously administered equal amounts (50 pg) of nocistatin and nociceptin have been reported to inhibit nociceptin-induced allodynia in conscious mice (22). When we injected both peptides simultaneously (nociceptin 10 nmol, nocistatin 10 nmol; n = 6) or 10 nmol nociceptin after pretreatment with 100 nmol nocistatin (n = 5), the responses induced by nociceptin were not abolished either (data not shown). Nocistatin does not bind to the nociceptin receptor (22). It is possible that nociceptin and nocistatin interact in pain transmission but not in the control of the cardiovascular systems. The cardiovascular response produced by intracerebroventricular nociceptin is not mediated via an opioid receptor pathway because naloxone pretreatment did not block the hypotension and bradycardia.

In conclusion, the present study provides the first evidence that central administration of nociceptin in conscious rats produces a dose-dependent decrease in RSNA. These findings suggest that nociceptin may play a role in the regulation of the cardiovascular system and the sympathetic nervous system through a central action.

Perspectives

Nociceptin was initially reported to induce hyperalgesia (26). Despite this, more recent reports attest to its efficacy in neuropathic pain (33). The mechanism of this analgesic action is unknown. Neuropathic pain is relieved by a sympathetic block (25). Although RSNA does not always reflect general sympathetic nerve activity, the present findings support the hypothesis that nociceptin may produce analgesic action through inhibition of sympathetic outflow. It is possible that the sympathoinhibitory effect of nociceptin plays some role in nociceptive modulation. The present result that intracerebroventricular nociceptin at lower doses caused the inhibition of RSNA without significant changes in cardiovascular function suggests that central nociceptin is involved in renal excretory function through RSNA. Therefore, we recognized the possibility that endogenous nociceptin may be a novel peptide involved in the central control of multiple homeostatic functions, such as pain transmission, body fluids, and BP control, through the regulation of sympathetic nerve activity. In the future, selective ORL1 receptor antagonist study will clarify roles of endogenous nociceptin.

This work was supported by Grants-in-Aid for Scientific Research (09670073) from the Ministry of Education, Science, Sports, and Culture, Japan.

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Received 8 March 1999; accepted in final form 28 May 1999.

REFERENCES

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