Role of Adenosine in Local Control of Intestinal Circulation in the Dog

HARRIS J. GRANGER AND CARRIE P. NORRIS

SUMMARY Adenosine, a purine nucleoside and powerful vasodilator, may be the chemical messenger elaborated by the intestinal cells to signal local adjustments of vascular tone. Close intra-arterial infusion of adenosine into the superior mesenteric artery elicited a 2.5-fold increase in intestinal blood flow at a calculated plasma concentration of $10^{-4} \text{ M}$, and the half-maximal response occurred at $10^{-7} \text{ M}$. These values are similar to those reported for effects of adenosine on coronary blood flow. In the fasted dog, inhibition of the interaction between adenosine and the vasculature with theophylline did not alter prevailing blood flow, flow autoregulation, or postprandial hyperemia. Moreover, inhibition of parenchymal reuptake of adenosine by $10^{-5} \text{ M}$ dipyridimole did not cause a decrease in vascular resistance of the empty intestine. Thus, in the inactive intestine, adenosine does not appear to be present in sufficient concentration to contribute to the prevailing vascular tone. Furthermore, under these conditions, the nucleoside does not appear to participate in local microvascular responses to mild stresses such as reduction of perfusion pressure or moderate increases in O$_2$ demand. By contrast, theophylline did shorten the duration of reactive hyperemia in the intestine of fasted dogs by 50%, suggesting that adenosine accumulates to vasoactive levels in the fasted state if the stress is severe. In the fed state, theophylline reduced the high degree of flow autoregulation usually observed in the hyperfunctional state. In addition, dipyridimole caused a 20% increase in intestinal blood flow of fed animals. Thus, the contribution of adenosine to local vasoregulation in intestine appears to increase as O$_2$ demand rises.


THE metabolic theory of local intestinal vasoregulation envisages an intimate linkage between parenchymal cell metabolism and microvascular smooth muscle tone (Shepherd and Granger, 1975). In essence, this linkage modulates intestinal blood flow in accordance with the nutritional needs of the small bowel. Adenosine, a purine nucleoside and powerful vasodilator, may be the chemical messenger elaborated by the tissue to signal appropriate adjustments of vascular tone (Berne, 1975; Granger et al., 1978). The aim of the present study was to examine the role of adenosine in local regulation of the intestinal circulation.

Methods

Animal Preparation

Fasted mongrel dogs, weighing 15-22 kg, were anesthetized with sodium pentobarbital (30 mg/kg) iv. The animals were artificially ventilated with a Harvard ventilator set to a stroke volume of 20 ml/kg and a frequency of 15 per minute. During the entire surgical and experimental procedures, systemic arterial pressure was monitored via a brachial artery catheter connected to a Statham P23Db strain gauge transducer. Another polyethylene catheter was placed in the femoral artery and advanced into the aorta to a point near the superior mesenteric branch. The pressure obtained from this catheter is hereinafter referred to as the superior mesenteric perfusion pressure. T-cannulas were inserted into the carotid arteries, and the sidearm of each cannula was connected to a pressurized reservoir via a y- fitting. Through an incision at the 9th intercostal space, an adjustable screw clamp was placed on the thoracic aorta immediately above the celiac branch.

To ensure that the blood flow and arteriovenous O$_2$ difference (A-VAO$_2$) measurements reflected the behavior of a well-defined segment of the small intestine, a collateral-free jejuno-ileum preparation was used (Granger and Norris, in press). Short lengths of Tygon tubing were inserted into the anterior jejunum and posterior ileum, thus providing inflow and outflow ports, respectively, for instillation of predigested food into the lumen of the small bowel. A flow probe was placed on the proximal portion of the superior mesenteric artery, and blood flow was monitored with a square-wave flowmeter. A hooked-needle catheter was inserted into the superior mesenteric artery downstream from the flow probe. This catheter was used for close intra-arterial infusion of chemicals (e.g., adenosine, theophylline, dipyridimole) into the superior mesenteric vasculature. After heparinization with 800 U/kg (Organan), a catheter was inserted into a jejunal mesenteric vein and threaded into the superior mesenteric vein. The venous blood was
pumped continuously through the venous cuvette of an arteriovenous O$_2$ difference analyzer (Shepherd and Burger, 1977). Blood from the right femoral artery was pumped into the arterial cuvette. The extracorporeal venous and arterial flows were returned to the dog via a catheter placed in the right femoral vein.

Systemic arterial pressure, superior mesenteric perfusion pressure, superior mesenteric blood flow, and jejunoileal arteriovenous O$_2$ difference were recorded continuously on a six-channel Grass physiological recorder.

**Experiment Protocol**

After the preparation had stabilized for 20–30 minutes, one or more experimental perturbations were applied. The effect of adenosine on the intestine was studied using graded infusions of a 2.5 mM solution of the nucleoside into the superior mesenteric artery. The effective plasma concentration of adenosine at each infusion level was calculated. In the theophylline experiments, the adenosine blocker was introduced into the superior mesenteric artery as three slug injections of 5 mg/kg spaced 20–30 minutes apart. Dipyridimole was infused into the intestinal arterial supply at a rate (range, 1–4 μmol/min) sufficient to produce a $10^{-5}$ M plasma concentration of the drug. To quantify intestinal flow autoregulation, superior mesenteric perfusion pressure was lowered in steps of 5–15 mm Hg by graded compression of the thoracic aorta with the adjustable screw clamp. During this maneuver, the reservoir compensator maintained systemic arterial pressure within 5 mm Hg of control, except at the lowest perfusion pressures (i.e., 20–35 mm Hg). To study functional hyperemia, predigested dog food was instilled into the small intestine. Dog food was homogenized in an automatic blender and digested for 6 hours with a pancreatic enzyme preparation (Chou et al., 1976). The treated food was diluted 1:2 in distilled water to yield an osmolarity of 250–350 mOsm, and the final pH of the mixture was adjusted with NaHCO$_3$ to pH 7. The mixture was infused into the jejunum at an initial rate of 15 ml/min; with the appearance of the food at the ileal orifice, the instillation rate was reduced to 3 ml/min. Reactive hyperemia was studied by occluding the superior mesenteric artery for 15, 30, 60, and 120 seconds. In all experiments and during all drug infusions, systemic arterial pressure was maintained at the control level by the pressure compensation system. At the end of all experiments, the empty intestinal segment was weighed. Blood flow and O$_2$ uptake (blood flow × A-VAO$_2$) were expressed as ml/min per 100 g.

**Data Analysis**

In general, linear or polynomial regression analyses were used to quantify the effects of graded perturbations on the monitored variables (Neter and Wasserman, 1974). The regression equations were obtained on an Amdahl 470 V/b computer using the SAS program STEPWISE (Barr et al., 1976). Statistical comparison of two groups of dogs was accomplished with an F-test for analysis of variance (Neter and Wasserman, 1974). In some cases, group comparisons were accomplished with paired or unpaired t-tests (Snedecor, 1956). To quantify the degree of flow autoregulation at specific perfusion pressures, the closed-loop gain (Gc) for the flow control system was calculated from $Gc = (ΔF/F)/(ΔP/P) - 1$, where $(ΔF/F)/(ΔP/P)$ is the normalized slope of the pressure-flow relation.

**Results**

Figure 1 summarizes the effects of close intraarterial infusion of adenosine on intestinal O$_2$ uptake, arteriovenous O$_2$ difference, and blood flow.

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1** Effect of adenosine (Ad) on O$_2$ uptake, arteriovenous O$_2$ difference, and blood flow in canine intestine. Polynomial regressions: O$_2$ intake = 1.03 – 0.05 Ad, $r^2 = 0.76$; A-VAO$_2$ = 0.96 – 0.02 Ad – 0.02 Ad$^2$, $r^2 = 0.83$; Blood flow = 0.98 + 1.52 Ad – 0.50 Ad$^2$ + 0.05 Ad$^3$, $r^2 = 0.83$. Number of dogs = 6. Control values: O$_2$ uptake = 1.8 ± 0.3 (SD) ml/min per 100 g; A-VAO$_2$ = 4.0 ± 0.7 volumes%; blood flow = 42.5 ± 10.2 ml/min per 100 g. The postinfusion values of O$_2$ uptake, A-VAO$_2$ and blood flow were normalized to their control levels.
Blood flow increased with exogenous adenosine levels of $10^{-8}$ M and reached a plateau at approximately $10^{-6}$ M. In this same concentration range, intestinal O$_2$ uptake changed less than 5%. In the face of a rising blood flow and a stable O$_2$ uptake, arteriovenous O$_2$ difference fell as plasma adenosine rose from $10^{-8}$ to $10^{-6}$ M. Tissue O$_2$ uptake fell by 10% at an average adenosine concentration of 2 µM. In three experiments, tissue O$_2$ uptake declined to less than 50% of control when adenosine levels were increased to $10^{-5}$ M. To characterize the adenosine/vessel interaction, we regressed the blood flow and adenosine concentration data in the Lineweaver-Burk reciprocal form. The slope of the regression line yields the ratio $K_m/F_{max}$, where $K_m$ is the adenosine concentration required to achieve 50% of maximal blood flow, and $F_{max}$ is the maximum flow. Our results indicate that $K_m$ is $0.1 \times 10^{-6}$ M, and $F_{max}$ is 2.5 times the control blood flow.

After preliminary experiments on five dogs, we ascertained that three close intra-arterial injections of theophylline, 5 mg/kg, spaced 30 minutes apart yielded a 75–95% block of the vascular effects of exogenous adenosine. The test doses of adenosine in these experiments were 3 times the amount required to produce a maximum vasodilatory response. After each dose of theophylline, blood flow and A-VAO$_2$ exhibited transient increases and decreases, respectively. The transients lasted 1–3 minutes. Table 1 shows the steady state levels of intestinal flow, A-V O$_2$ difference, and O$_2$ uptake after the third dose of theophylline. The adenosine blocker had no significant effect on any of the variables when compared to the control state. Thus, theophylline blocks the vasodilator effects of adenosine without altering the hemodynamic and metabolic state of the intestine. However, in this group of animals and in the protocols described below, vascular resistance was elevated in 10–30% of theophylline studies. The vasoconstrictor effect seen in these experiments may reflect a potentiating effect of theophylline on adrenergic vasomotor tone (Kalnsner, 1971).

To delineate the role of adenosine in functional hyperemia of the intestine, the superior mesenteric flow responses to placing predigested food in the gut lumen were analyzed (Table 2). The flow responses observed in the theophylline-treated group were not significantly different from those elicited in the control dogs. These results indicate that adenosine does not contribute to the moderate vasodilation associated with absorption.

To determine the contribution of adenosine to local flow autoregulation, intestinal pressure-flow relations were obtained for fasted and fed dogs under normal conditions and after treatment with theophylline. In the fasted state, theophylline had no effect on the pressure-flow relation (Fig. 2). Consequently, the autoregulatory compensation at each perfusion pressure was similar to that observed in the control experiments. Table 2 shows the effect of theophylline on functional hyperemia and oxygen utilization after placement of predigested food into intestinal lumen.

### Table 2 Effect of Theophylline on Functional Hyperemia and Oxygen Utilization after Placement of Predigested Food into Intestinal Lumen

<table>
<thead>
<tr>
<th>% Change in postprandial state</th>
<th>Blood flow</th>
<th>A-VAO$_2$</th>
<th>O$_2$ uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, $n = 7$</td>
<td>16 ± 4</td>
<td>40 ± 7</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>After theophylline treatment, $n = 6$</td>
<td>14 ± 6</td>
<td>42 ± 10</td>
<td>58 ± 12</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± 1 SD. No significant differences at 0.05 level.

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![Figure 2. Pressure-flow relationship and closed-loop gain of the flow control system before (solid lines) and after (broken lines) administration of theophylline into the superior mesenteric artery of nine fasted dogs. Pre-theophylline case: $F/F_0 = -0.33 + 2.33 (P/P_0) - 1.00 (P/P_0)^2$, 61 data points, $r^2 = 0.98$. Post-theophylline case: $F/F_0 = -0.031 + 2.19 (P/P_0) - 0.88 (P/P_0)^2$, 66 data points, $r^2 = 0.98$. An F-test comparison of the two data pools indicates that the adenosine blocker had no significant ($P > 0.05$) effect on intestinal flow autoregulation. Blood flow and perfusion pressure during aortic compression are normalized to their control values.](http://circres.ahajournals.org/lookup/doi/10.1161/01.RES.46.6.766)
prior to infusion of theophylline. By contrast, theophylline significantly reduced the degree of flow autoregulation in fed dogs (Fig. 3). Near the control perfusion pressure, blood flow actually rose slightly as superior mesenteric pressure was reduced prior to theophylline administration. This superregulation of intestinal flow (Norris et al., 1979) in the fed state reflects an overcompensation in terms of a flow control system (i.e., the closed-loop gain is more negative than \(-1\)). After injection of theophylline, superregulation was abolished, and the autoregulatory responses resembled those seen in the fasted state.

The participation of adenosine in reactive hyperemia also was tested in fasted dogs. Figure 4 shows typical responses of the intestinal vasculature to sudden release of a 2-minute arterial occlusion before and after theophylline infusion. Although peak hyperemic flow was similar in the two experiments, the repayment of the flow debt was smaller after administration of adenosine blocker. Figure 5 summarizes the effects of theophylline on the vascular responses to 15-, 30-, 60-, and 120-second occlusions. The vascular reactions are expressed as peak hyperemic flow (normalized to preocclusion flow) and the half-time of decay of hyperemic flow. Theophylline reduced the duration of the hyperemia by 50%. In absolute terms, the magnitude of the reduction of half-time rose with increasing duration of the occlusion. By contrast, aminophylline had no effect on duration of the hyperemic response in the cat; peak hyperemic flow was diminished to a small extent (Granger et al., 1978).

Adenosine degradation and reuptake in intestine are partially blocked by dipyridimole (Kolassa et al., 1978). Thus, dipyridimole can cause vasodilation when the prevailing endogenous adenosine levels are near or above the vasodilatory threshold. Table 3 shows that dipyridimole \((10^{-5} \text{ M})\) had no effect on the intestinal vasculature of fasted dogs. In the postprandial state, however, dipyridimole elicited a 20% increase in blood flow.

**Discussion**

According to the metabolic theory of local vaso-regulation, intestinal blood flow is modulated in accordance with tissue \(O_2\) requirements via a vasodilator metabolite released continuously from the parenchymal cells (Shepherd and Granger, 1973). Ideally, the concentration of the metabolite varies inversely with the \(O_2\) availability-to-demand ratio. Thus, local perturbations causing elevated tissue \(P_{O_2}\) elicit a compensatory vasoconstriction tending to return cell oxygenation toward normal. On the other hand, the metabolite accumulates in hypoxic states, and the intrinsic vasodilation increases intracellular \(P_{O_2}\) toward normal. In this manner, the chemical linkage between the vasculature and in-
testine serves to control the rate of delivery of oxygen to the parenchyma in accord with tissue O₂ demand. To be considered as an important vasoregulator, the metabolite must elicit appropriate vasodilatory responses when infused directly into the intestinal circulation. Moreover, if the local vasodilator is an important determinant of intrinsic vascular tone, inhibition of vasodilator/microvessel interaction should cause a vasoconstriction. In addition, a vasodilation should be observed when endogenous metabolite destruction is inhibited. Furthermore, the metabolite should exert minimal influences on the metabolic state of the parenchymal cells. Finally, inhibition of the effects of the vasodilator metabolite on vascular smooth muscle should abolish or diminish flow autoregulation, functional hyperemia, and reactive hyperemia. With these considerations in mind, we attempted to define the role of adenosine as a primary chemical mediator of local control phenomena in the intestinal circulation.

Metabolism of Purine Nucleoside in Intestine

The cascade of intermediary reactions involved in ATP degradation and adenosine formation in myocardium is well-established (Berne, 1975; Rubio and Berne, 1969). Table 4 compares the concentrations of purine nucleotides and nucleosides in intestine (Bronk and Leese, 1973; Mortillaro, personal communication) and myocardium (Foley et al., 1978; Parker et al., 1977). The myocardium/intestine ATP ratio probably reflects the 10-fold difference in O₂ utilization in the two tissues (i.e., 15 vs. 1.5 ml/min per 100 g). During ATP hydrolysis to ADP, myokinase catalyzes the salvage of one ATP from two ADP molecules. AMP is the second product of the myokinase reaction and is further degraded to either adenosine or IMP. In rat jejunal mucosa, IMP accumulation was not detectable after AMP loading, suggesting that the AMP-deaminase pathway is relatively inactive in intestine (Wilson and Wilson, 1962). Thus, the primary pathway of AMP degradation in mucosal cells appears to be the 5'-nucleotidase reaction involving dephosphorylation of AMP to adenosine. However, after AMP loading of jejunal mucosa, adenosine appears only in small amounts and only during the initial 5–15 minutes (Wilson and Wilson, 1962). During this period, inosine levels rise dramatically, suggesting that adenosine is maintained at low concentrations due to its rapid deamination to inosine. Indeed, several studies indicate that adenosine deaminase activity is very high in intestine (Brady, 1942; Conway and Cooke, 1939). Perhaps the high inosine:adenosine ratio in cat intestine (Mortillaro and Mustafa, 1978) reflects this rapid deamination of adenosine. In addition, adenosine levels may be low due to rapid reuptake of interstitial nucleoside into the parenchymal cells of the intestine (Kolassa et al., 1977; Moritoki et al., 1978). In any event, the adenosine

**Table 3** Effect of Dipyridimole on Intestinal Circulation and O₂ Uptake in Fasted and Fed States

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fasted Control</th>
<th>Dipyridimole</th>
<th>Fed Control</th>
<th>Dipyridimole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (ml/min per 100 g)</td>
<td>42.1 ± 10.3</td>
<td>42.4</td>
<td>49.6</td>
<td>59.5*</td>
</tr>
<tr>
<td>A-VΔO₂ (volumes %)</td>
<td>3.9 ± 0.9</td>
<td>3.8</td>
<td>5.3</td>
<td>4.4*</td>
</tr>
<tr>
<td>O₂ uptake (ml/min per 100 g)</td>
<td>1.6 ± 0.3</td>
<td>1.6</td>
<td>2.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

n = 8. Values are expressed as mean ± 1 sd. * Significantly different from control value at 0.05 level.
concentration in intestinal tissue in only 1/20 of the myocardial level (Mortillaro, personal communication). Since most of the metabolite data are derived from rat and cat intestine, the application of these findings to the dog intestine must be approached with caution. However, the above considerations indicate that pathways of adenosine production and degradation are well developed in intestine. Consequently, it may be reasonable to assume that the nucleoside possibly could play a role in intestinal vasoregulation.

**Physiological Effects of Adenosine on the Intestine**

In the dog, exogenous adenosine can elicit a 2- to 3-fold increase in the conductance of the intestinal vasculature. This response is well within the maximal vasodilation observed during reactive hyperemia, flow autoregulation, hypoxic vasodilation, or functional hyperemia in the canine small bowel (Granger and Shepherd, 1979). The sensitivity of canine intestinal microvessels to adenosine is similar to that of coronary microvasculature (Schrader et al., 1977). By contrast, the vasculature of cat intestine (Granger et al., 1978) requires 40 times higher adenosine concentration to elicit maximal vasodilation (i.e., 40 μM in cats vs. 1 μM in present study).

We observed a 10% decrease in intestinal O₂ uptake in the presence of 1 μM adenosine. In the same concentration range, a quantitatively similar result was obtained for canine myocardium (Gross et al., 1976). During flow autoregulation in intestine, intestinal O₂ uptake remains nearly constant, indicating that the local metabolite does not greatly alter tissue metabolism (Granger and Shepherd, 1979). Thus, the weak effect of adenosine on intestinal metabolism in the vasodilatory range is compatible with one of the major criteria to be met by a potential metabolite vasoregulator. However, supramaximal doses (5–10 μM) of adenosine reduced canine intestinal O₂ utilization to 50% of normal. In the cat, adenosine at a concentration of 40 μM depresses O₂ uptake by 32% (Granger et al., 1978). Several studies have shown that adenosine inhibits the response of intestinal smooth muscle to intramural electrical stimulation (Hayashi et al., 1978; Okwuasaba et al., 1977), possibly by inhibiting acetylcholine release from nerve terminals. In addition, the in vitro O₂ uptake of feline mucosal cells is reduced in the presence of 1μM adenosine (Granger et al., 1978). In any event, our data suggest that, at least in the dog, the actions of adenosine on intestinal function are minimal in the vasoregulatory range.

**Adenosine and Local Control of Intestinal Circulation**

Thus far, we have reviewed evidence indicating that: (1) adenosine is produced and degraded in intestinal tissue, (2) the intestinal vasculature is sensitive to adenosine concentrations in the micromolar range, (3) the magnitude of adenosine-induced vasodilation is compatible with its possible participation in local control phenomena, and (4) the metabolic effects of adenosine on intestinal tissue are minimal in the vasoregulatory range, as required by criteria for an ideal vasoactive metabolite. To establish adenosine as an important chemical modulator of microvascular tone in intestine, we must further demonstrate that: (1) endogenous adenosine exerts a tonic influence on vascular smooth muscle under normal conditions and (2) blockade of adenosine/microvessel interaction inhibits intrinsic vasoregulatory reactions to local stresses.

In the fasted state, administration of theophylline or dipyridimole had no effect on intestinal vascular tone. If adenosine contributed to the prevailing vascular tone, theophylline should have induced a vasoconstriction due to blockade of a vasodilator influence. Dipyridimole at a concentration of 10⁻⁵ M reduces mucosal uptake of adenosine by 35% (Kolassa et al., 1978) and probably partially inhibits adenosine deaminase (Deuticke and Gerlach, 1966). Thus, if tissue adenosine levels were close to the threshold concentration, dipyridimole would have elicited a vasodilation. Moreover, in the fasted state, flow autoregulation and functional hyperemia were not blunted by theophylline. By contrast, ischemia of 60 seconds duration is known to produce a 4-fold rise in intestinal adenosine levels.

**Table 4 Content of Adenosine Nucleotides and Derivatives in Small Intestine and Myocardium**

<table>
<thead>
<tr>
<th>Species</th>
<th>Intestine</th>
<th>Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>1.4</td>
<td>(Bronk and Leese, 1973) 11</td>
</tr>
<tr>
<td>ADP</td>
<td>1.0</td>
<td>(Bronk and Leese, 1973) 2.4</td>
</tr>
<tr>
<td>AMP</td>
<td>0.5</td>
<td>(Bronk and Leese, 1973) 0.8</td>
</tr>
<tr>
<td>Adenosine</td>
<td>0.17 X 10⁻³</td>
<td>(Mortillaro, personal communication) 3.6 X 10⁻³</td>
</tr>
<tr>
<td>Inosine</td>
<td>0.74 X 10⁻²</td>
<td>(Mortillaro, personal communication) 3.4 X 10⁻³</td>
</tr>
</tbody>
</table>
(Mortillaro and Mustafa, 1978). Our results indicate that adenosine does rise to threshold concentrations under this stress; theophylline reduced the duration of the reactive hyperemia by 50%.

In the fed state, intestinal O₂ uptake is accelerated (Granger and Shepherd, 1979; Valleur et al., 1979), and adenosine levels are probably elevated. In this hyperfunctional condition, the degree of flow autoregulation is increased. Adenosine may be responsible, in part, for this enhancement of the sensitivity of intestinal microvessels to perfusion pressure alterations. Blockade of the effect of adenosine with theophylline reduced the autoregulatory capacity of the fed animal to that usually observed in the fasted state. Thus, in the hypermetabolic state, adenosine is within or very near the ascending limb of the dose-response curve. This concept is supported by the fact that dipyridimole elicited a vasodilation after feeding.

Thus, the role of adenosine in local control of intestinal blood flow probably is minimal in the fasted state, except when severe stresses such as complete ischemia are imposed on the tissue. In this state, flow autoregulation and functional hyperemia are likely effected by other metabolic or nonmetabolic mechanisms. As the metabolic rate of the small intestine rises, the contribution of adenosine to local vasoregulation increases. Consequently intrinsic vascular responses to subtle perturbations, such as a slight reduction of perfusion pressure, became more closely linked with influences of adenosine on intestinal microvessels.

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