Electrophysiologic Effects of Dipyridamole on Atrioventricular Nodal Conduction and Supraventricular Tachycardia

Role of Endogenous Adenosine

Bruce B. Lerman, MD, Robert C. Wesley, MD, and Luiz Belardinelli, MD

Exogenous adenosine has been shown to have potent electrophysiologic effects and antiarrhythmic properties within the atroioventricular (AV) node. Endogenous adenosine, a nucleoside with an increased release signaled by ischemia and hypoxia, is not believed to exert significant effects during homeostatic conditions. Recent experimental evidence suggests, however, that under normoxic conditions, the amount of adenosine released may be sufficient to mediate some of its physiologic effects. This study was designed to test the hypothesis that in humans the electrophysiologic effects of endogenously released adenosine on AV nodal conduction can be demonstrated under normoxic conditions by inhibiting uptake and degradation of the nucleoside. In the first protocol, the effects of intravenous dipyridamole (0.56 mg/kg bolus i.v., 5 microgrammes per kg per minute infusion), a nucleoside-transport blocker that elevates endogenous plasma levels of adenosine, on AV nodal conduction were evaluated in seven patients. At a constant atrial paced cycle length, dipyridamole increased the AH interval from 110±19 to 164±26 msec, p=0.002 (SEM). Aminophylline (5.6 mg/kg i.v.), a competitive antagonist of adenosine, completely reversed the effects of dipyridamole on AV nodal conduction. Similarly, dipyridamole increased the cycle length at which pacing-induced AV nodal Wenckebach occurred, from 348±31 (control) to 388±33 msec (dipyridamole) (p=0.002). In a second protocol, the effects of intravenous dipyridamole were evaluated in another group of six patients who had supraventricular tachycardia (SVT) in which the AV node was part of the reentrant circuit. Dipyridamole increased the cycle length of SVT from 344±29 to 379±30 msec (p<0.05), effects that were confined primarily to the AV node (AH interval). Dipyridamole alone terminated SVT (and prevented reinduction) in one of six patients. In the remaining five patients, dipyridamole reduced fourfold the minimum-effective dose of exogenous adenosine required to terminate SVT, that is, from 68±15 to 17±6 microgrammes per kg (p=0.005). These results show that the electrophysiologic and antiarrhythmic properties of endogenous adenosine on the AV node may be demonstrated in the absence of ischemia by attenuating nucleoside transport and degradation. Although the effects of dipyridamole during SVT were modest, the results of this study suggest that the development of more potent and specific nucleoside-transport blockers that elevate endogenous adenosine levels may provide an effective therapeutic modality in patients with SVT. (Circulation 1989;80:1536–1543)

Adenosine is a unique endogenous nucleoside with potent, site-specific electrophysiologic effects and antiarrhythmic properties within the atrioventricular (AV) node.1,2 Similar to its action in atrial myocytes, adenosine is believed to mediate its negative dromotropic effects on the AV node through a receptor-effector complex that links the adenosine A1 receptor to K+ channels by a guanine-nucleotide–regulatory binding protein, Gq3,4 (although an effect on calcium channels has not been entirely ruled out). Activation of K+ channels by adenosine, which hyperpolarizes supraventricular tissue toward EK and shortens action potential duration,5,6 occurs primarily in the N region of the AV node.2

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Adenosine production is increased in response to ischemia and hypoxia and functions to restore a physiologic $O_2$ supply-demand ratio.\textsuperscript{7,8} For instance, increased adenosine release during myocardial hypoxia improves $O_2$ supply by coronary vasodilation\textsuperscript{8} and decreases $O_2$ demand by precipitating sinus bradycardia,\textsuperscript{9} AV block,\textsuperscript{10} and antagonizing the effects of sympathomimetic amines.\textsuperscript{11-13}

The electrophysiologic effects of adenosine have been primarily demonstrated by administering an exogenous preparation of the nucleoside because endogenous adenosine is not believed to be produced in sufficient amounts to have significant effects during normoxic conditions.\textsuperscript{14,15} Recent evidence from studies in guinea pigs, however, suggests the contrary, that is, endogenous adenosine may have some physiologic role under normoxic conditions.\textsuperscript{16} The purpose of this study was to test the hypothesis that the electrophysiologic effects and antiarrhythmic properties of endogenously released adenosine on AV node conduction can be demonstrated under normoxic conditions in humans by perturbing metabolism of the nucleoside with dipyridamole. Dipyridamole, a nucleoside-transport blocker, increases the extracellular concentration of endogenous adenosine.\textsuperscript{17-19}

**Methods**

**Electrophysiologic Study**

All studies were performed in patients in the nonsedated, postabsorptive state after informed consent was obtained for a protocol approved by the Human Investigations Committee of the University of Virginia. All antiarrhythmic drugs were discontinued for at least five half-lives before the study. Four quadripolar electrode catheters were inserted percutaneously and advanced under fluoroscopic guidance to the high right atrium, coronary sinus, right ventricular apex, and AV junction for recording of the His bundle potential. Bipolar intracardiac recordings were filtered at 30–500 Hz and simultaneously displayed with three electrocardiographic leads on a multichannel oscilloscope (VR-16, Electronics for Medicine, White Plains, New York). Real-time recordings were made with an ink-jet recorder (Siemens Elema Mingograph, Iselin, New York), and data were stored on magnetic tape (Honeywell Model 101, Waltham, Massachusetts). Systemic arterial pressure was continuously monitored (Dinamap, Critikon, Tampa, Florida). Stimulation was performed with a programmable stimulator and isolated constant-current source (Bloom Associates, Narberth, Pennsylvania). Stimuli were delivered as rectangular pulses of 2-msec duration at fourfold the diastolic threshold. The stimulation protocol included the introduction of single, double, and triple extrastimuli from multiple atrial and ventricular sites at several paced-cycle lengths and during sinus rhythm.

**Protocols**

**Protocol A.** In this protocol, potentiation of endogenous adenosine’s effects on AV nodal conduction with dipyridamole was evaluated. All seven patients entered in this protocol were chemically denervated with intravenous propranolol, 0.1 mg/kg, and atropine, 0.04 mg/kg. During the control phase of the protocol, patients were paced from the high right atrium to determine the cycle length at which AV nodal Wenckebach periodicity was induced. The right atrium was then paced for 60 seconds at a cycle length greater than that required for induction of AV nodal Wenckebach. The maximal stable AH interval recorded was used for subsequent analysis. Dipyridamole was then infused, 0.56 mg/kg i.v. over 4 minutes, followed by a continuous infusion of 5 $\mu$g/kg/min. Fifteen minutes after the continuous infusion began, AV nodal conduction, that is, pacing-induced Wenckebach-cycle length and the maximal AH interval during atrial pacing (same cycle length as control), was reassessed. In four patients, the effect of dipyridamole on AV nodal refractoriness was also evaluated.

Measurements of AV nodal conduction were also repeated during the continuous infusion of dipyridamole after administration of 5.6 mg/kg i.v. of aminophylline, a competitive adenosine antagonist.\textsuperscript{14} Aminophylline was infused over 20 minutes.

**Protocol B.** The effects of intravenous adenosine and dipyridamole were evaluated in six other patients with supraventricular tachycardia (SVT) involving the AV node. SVT was induced in all patients with atrial or ventricular programmed extrastimuli. The minimum dose of exogenous adenosine required to reproducibly terminate SVT was sequentially determined. Crystalline adenosine (Sigma Chemical, St. Louis, Missouri) was dissolved in normal saline at a concentration of 5 mg/ml. The concentration of adenosine in the stock solution was confirmed by high-performance liquid chromatography. Adenosine, which has a less-than-5-second half-life in blood,\textsuperscript{20} was rapidly injected into a central line and flushed with 10 ml saline. Incremental doses of adenosine (18.75 $\mu$g/kg) were injected until the tachycardia terminated. SVT was then reinduced, and dipyridamole was administered (0.56 mg/kg i.v. bolus, followed by a continuous infusion of 5 $\mu$g/kg/min). The effects of dipyridamole on cycle length, AH, HV, and ventriculoatrial (VA) intervals were evaluated 15 minutes after the bolus dose was given. If tachycardia did not terminate in response to dipyridamole, then the minimum effective dose of exogenous adenosine required to terminate SVT was determined.

**Statistical Analysis**

The effect of perturbing AV nodal conduction with either dipyridamole or aminophylline was analyzed by paired $t$ test. Differences were considered
TABLE 1. Effects of Dipyridamole and Aminophylline on Atrioventricular Nodal Conduction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Cardiac diagnosis</th>
<th>Control PCL (msec)</th>
<th>Control AH (msec)</th>
<th>Control AVNW (msec)</th>
<th>Dipyridamole AH (msec)</th>
<th>Dipyridamole AVNW (msec)</th>
<th>Aminophylline AH (msec)</th>
<th>Aminophylline AVNW (msec)</th>
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<td>ND</td>
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<td>270</td>
<td>190</td>
<td>290</td>
<td>ND*</td>
<td>ND*</td>
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<td>310</td>
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<td>340</td>
<td>90</td>
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<td>100</td>
<td>420</td>
<td>120</td>
<td>480</td>
<td>90</td>
<td>340</td>
</tr>
</tbody>
</table>

*Patient developed atrial flutter during atrial pacing and dipyridamole infusion. AVNW, atrioventricular nodal Wenckebach; ND, not done; NL, normal; PCL, paced-cycle length.

significant for $p$ values less than 0.05. All values are given as mean±SEM.

Results

**Effects of Dipyridamole on AV Nodal Conduction**

The seven patients in this group were 15–76 years old. There were three men and four women; no patient had structural heart disease (Table 1). The AH interval during control was 110±19 msec and increased to 164±26 msec in response to dipyridamole ($p=0.002$). Aminophylline (in the presence of autonomic blockade) reversed the effects of dipyridamole, decreasing the AH interval to 102±7 msec ($p=0.03$). A representative example of the effects of dipyridamole on AV nodal conduction is shown in Figure 1. During control, pacing at a cycle length of 400 msec from the high right atrium resulted in an AH interval of 85 msec. After dipyridamole, the AH interval increased to 160 msec. Aminophylline nearly completely reversed the effects of dipyridamole, shortening the AH interval to 110 msec.

AV nodal conduction was also evaluated by determining the cycle length at which Wenckebach periodicity was induced. During control, AV nodal Wenckebach occurred at a paced-cycle length of 348±31 msec, whereas after dipyridamole, it increased to 388±33 msec ($p=0.002$). Aminophylline decreased the Wenckebach cycle length to 336±25 msec ($p=0.007$) (aminophylline versus dipyridamole). An example from a patient is shown in Figure 2.

Reversal of dipyridamole’s effects on Wenckebach periodicity by aminophylline could not be evaluated in one patient (patient 4). In this patient,
atrial flutter was induced during simultaneous atrial pacing and dipyridamole infusion (Figure 3). Because adenosine has been observed to occasionally precipitate atrial flutter, the effects of dipyridamole on atrial flutter were evaluated in three of the four patients in whom atrial extrastimulus testing was performed because the effective refractory period (ERP) of the AV node was less than or equal to the atrial ERP. In the single patient in whom the AV nodal ERP could be assessed (patient 1), the ERP increased by 10 msec in response to dipyridamole.

**Effects of Dipyridamole on SVT**

Six patients were included in this protocol. There were four men and two women aged 23–52 years. Only one patient had structural heart disease; one patient had a cardiomyopathy probably due to inces-sant SVT. The mechanism of SVT was AV-reciprocating tachycardia in four patients, AV nodal reentry in one, and the permanent form of junctional reciprocating tachycardia (PJRT) in another one (Table 2). SVT was easily and reproducibly initiated with single atrial, or ventricular extrastimuli. Patients were observed in stable tachycardia for at least 30 minutes before testing. The cycle length of SVT during control was 344±29 msec. During dipyridamole infusion, the cycle length increased to 379±30 msec, p<0.05. The increase in cycle length was confined primarily to the AV node because the AH interval increased from 157±19 msec (control) to 196±35 msec (dipyridamole) (p=0.03). There was virtually no effect of dipyridamole on the His-Purkinje system conduction (HV 52±3 msec, control, versus 53±2 msec, dipyridamole; p=NS) or on the retrograde limb (VA interval) of the reentrant circuit (136±38 msec, control, vs. 132±39 msec, dipyridamole; p=NS).

Dipyridamole terminated SVT in one of six patients. In this patient (patient 4), SVT was due to AV-reciprocating tachycardia using a left-sided accessory pathway (Figure 4). SVT terminated in this patient 10 minutes after receiving the dipyridamole bolus. The cycle length of SVT before dipyridamole was 360 msec with an AH interval of 190 msec. After dipyridamole was administered, the AH interval progressively increased to 270 msec, and the cycle length slowed to 430 msec before SVT terminated in the AV node (anterograde limb). At this time, tachycardia could not be reinitiated in this patient.

In the five patients in whom dipyridamole did not terminate SVT, potentiation of the effects of exog-enously administered adenosine could be demonstrated (Figure 5). During control (i.e., absence of dipyridamole), the minimum effective dose of aden-
TABLE 2. Effects of Dipyridamole and Adenosine on Supraventricular Tachycardia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Diagnosis</th>
<th>SVT (msec)</th>
<th>CL (msec)</th>
<th>AH (msec)</th>
<th>HV (msec)</th>
<th>VA (msec)</th>
<th>Lowest effective dose of ADO (µg/kg)</th>
<th>Control</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27/F</td>
<td>NL</td>
<td>AVRT</td>
<td>300</td>
<td>130</td>
<td>50</td>
<td>120</td>
<td>75 (msec)</td>
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<td>145</td>
</tr>
<tr>
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<td>25/M</td>
<td>NL</td>
<td>AVRT</td>
<td>290</td>
<td>125</td>
<td>60</td>
<td>105</td>
<td>75 (msec)</td>
<td>305</td>
<td>155</td>
</tr>
<tr>
<td>3</td>
<td>52/M</td>
<td>NL</td>
<td>AVNR</td>
<td>325</td>
<td>225</td>
<td>55</td>
<td>55</td>
<td>56.25 (msec)</td>
<td>425</td>
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<tr>
<td>4</td>
<td>25/M</td>
<td>NL</td>
<td>AVRT</td>
<td>360</td>
<td>190</td>
<td>40</td>
<td>120</td>
<td>37.5 (msec)</td>
<td>430</td>
<td>270</td>
</tr>
<tr>
<td>5</td>
<td>33/M</td>
<td>CM</td>
<td>PJRT</td>
<td>480</td>
<td>100</td>
<td>45</td>
<td>95</td>
<td>18.75 (msec)</td>
<td>320</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>23/F</td>
<td>NL</td>
<td>AVRT</td>
<td>310</td>
<td>170</td>
<td>45</td>
<td>95</td>
<td>18.75 (msec)</td>
<td>320</td>
<td>180</td>
</tr>
</tbody>
</table>

* Tachycardia terminated during dipyridamole infusion.

SVT, supraventricular tachycardia; CL, cycle length; ADO, adenosine; NL, normal; AVRT, atrioventricular reciprocating tachycardia; AVNR, atrioventricular nodal reentry; CM, cardiomyopathy; PJRT, permanent form of junctional reciprocating tachycardia.

Adenosine required to terminate SVT was 68±15 µg/kg; however, in the presence of dipyridamole, the minimum effective adenosine dose was reduced four-fold, that is, to 17±6 µg/kg (p=0.005). All tachycardia terminated within the AV node, including in the patient with PJRT. The accessory pathway in these particular patients has also been reported to be sensitive to adenosine.22

**Discussion**

The results of this study indicate that endogenously released adenosine, under normal homeostatic conditions, can exert significant electrophysiologic effects in humans. That the antiarrhythmic properties of endogenous adenosine on AV nodal conduction can be demonstrated in the absence of ischemia by attenuating nucleoside transport and metabolism suggests an alternative therapeutic approach to SVT. This conclusion is based on the finding that dipyridamole potentiates the effects of endogenous adenosine by increasing levels of the nucleoside. The evidence to support this mechanism of action can be summarized as follows: 1) dipyridamole reduces adenosine uptake in a dose-dependent manner, resulting in an increased extracellular concentration of adenosine17; 2) a linear relation exists by guest on July 26, 2017 http://circ.ahajournals.org/ Downloaded from

**FIGURE 4.** Recording of termination of supraventricular tachycardia with dipyridamole. Panel A: AV reciprocating tachycardia in patient with left-sided accessory pathway (patient 4, Table 2). Panel B: Ten minutes after bolus dose and continuous infusion of dipyridamole, cycle length of tachycardia increased from 360 to 430 msec, an increment confined to AV node. Tachycardia terminated in AV node and could not be reinitiated. HRA, high right atrium; HBE, His bundle electrogram; CS, coronary sinus; RV, right ventricle.
between adenosine-uptake inhibition by dipyridamole and prolongation of AV nodal conduction (AH interval)\textsuperscript{17}; 3) dipyridamole increases the effluent and interstitial levels of adenosine in guinea pig hearts\textsuperscript{15,23}; 4) intravenous and oral dipyridamole increase plasma adenosine levels in humans\textsuperscript{18,19,24}; and 5) adenosine deaminase and adenosine antagonists, that is, methylxanthines, reverse the electrophysiologic effects of dipyridamole.\textsuperscript{15} (For example, dose-dependent increases in AV block due to dipyridamole, associated with parallel increases in coronary venous adenosine release, are inhibited by adenosine deaminase and methylxanthines.\textsuperscript{15,25})

Due to its negative dromotropic action, exogenous adenosine has been shown to be highly effective in terminating reentrant SVT, which includes the AV node as part of the circuit.\textsuperscript{1} Its mechanism of action is similar to that of acetylcholine (ACh),\textsuperscript{5} but its effect is mediated by activation of different membrane receptors. Unlike ACh, adenosine is believed to have a minimal effect on the AV node during normal physiologic conditions. Evidence supporting this assumption includes the lack of effect of adenosine deaminase and methylxanthines (competitive adenosine A\textsubscript{1} antagonists) on AV nodal conduction during normoxia.\textsuperscript{14} Recent evidence suggests, however, a potential role for adenosine under basal conditions. Chronic exposure of guinea pig hearts to methylxanthines up-regulates the number of adenosine receptors, resulting in supersensitivity.\textsuperscript{16} These data imply that, under basal conditions, endogenous adenosine levels are sufficient to partially occupy and downregulate the adenosine A\textsubscript{1} receptor. Similar findings for adenosine receptors have also been reported in the rat brain.\textsuperscript{26}

Adenosine levels can be elevated by either increased production or inhibition of cellular uptake and metabolism. Although plasma concentrations were not measured in this study, previous clinical studies in which administered doses of dipyridamole were similar to those used in the present study demonstrate an approximate doubling of venous plasma concentrations of adenosine, from 0.15 (control) to 0.29 \textmu M after intravenous dipyridamole.\textsuperscript{19} Similarly, oral dipyridamole has been shown to increase plasma adenosine levels.\textsuperscript{24}

Dipyridamole is not known to have direct electrophysiologic effects on supraventricular tissues; its effects on AV nodal conduction can be entirely explained through potentiation of endogenous adenosine.\textsuperscript{15,17} Additional evidence from this study that dipyridamole’s effects are mediated through enhanced adenosine levels is that aminophylline, a competitive antagonist of adenosine, reversed dipyridamole’s negative dromotropic effects on AV nodal conduction. Consistent with this mechanism of action, aminophylline is known to reverse dipyridamole-induced coronary vasodilation (mediated by adenosine)\textsuperscript{27} and to antagonize the dromotropic effects of adenosine in humans.\textsuperscript{28} It is unlikely that aminophylline mediated its effects through mechanisms other than adenosine antagonism. Although methylxanthines also cause phosphodiesterase inhibition and induce norepinephrine release from nerve terminals and the adrenal medulla, these effects occur at levels at least 20-fold greater than that required to antagonize the A\textsubscript{1} receptor.\textsuperscript{29} Furthermore, in this study, all patients received \beta-adrenergic antagonists.

Because intravenous dipyridamole also causes vasodilation and reflex tachycardia, all patients in this study were chemically denervated. As a result, in no patient was there any appreciable change in blood pressure or acceleration of rate in either sinus rhythm (protocol A) or SVT (protocol B) in response to dipyridamole.

Dipyridamole had reproducible although modest effects on AV nodal conduction. This response to dipyridamole (i.e., under normoxic conditions) is consistent with results observed in anesthetized dogs\textsuperscript{10} and guinea pigs.\textsuperscript{15} Proportional increases in the AH interval and pacing-induced AV nodal Wenckebach cycle length were observed for all but one patient (Table 1). During SVT, dipyridamole’s effects on cycle length were confined to the AV node as reflected by prolongation in the AH interval. There was one patient in whom dipyridamole had no effect during SVT (Table 2). It is noteworthy that this patient had a cycle length at least 120 msec greater than the other patients who demonstrated a response. Whether the effects of dipyridamole dur-
ing SVT are cycle length dependent and are enhanced by increased adenosine production due to a relative O₂ supply-demand imbalance remains speculative. However, this possibility has been demonstrated in the guinea pig heart. At slow pacing rates, for example, dipyridamole effects on AV nodal conduction are small, whereas at faster pacing rates, particularly when an imbalance in O₂ supply-demand occurs, more marked prolongation in the AH interval is observed.

Dipyridamole also markedly reduced the lowest effective dose of exogenous adenosine during SVT. These data indicate that dipyridamole potentiates not only endogenous adenosine but also the exogenous form of the nucleoside. An important clinical implication is that patients in SVT, who are taking oral dipyridamole for antiplatelet therapy, should receive approximately one fourth of the usual therapeutic dose of adenosine.

The one patient in whom SVT terminated with dipyridamole alone showed an 80-msec increment in the AH interval before the tachycardia ceased (Figure 4). This observation, along with the effects of dipyridamole on AV nodal conduction observed in remaining patients, suggests that perturbation of endogenous adenosine metabolism may prove to be a clinically valuable tool. It is possible that higher doses of dipyridamole would have proved more effective in the patients who had just AH prolongation because threshold-adenosine levels required for termination may have been approached but not achieved.

It is well recognized that adenosine may induce atrial flutter in some patients, an effect believed to be due to abbreviation of atrial action-potential duration. Therefore, an observation of potential interest was the induction of atrial flutter during atrial pacing and dipyridamole infusion and subsequent termination with aminophylline. This finding was also recorded in another patient not included in this study (unpublished data). Although coincidental spontaneous termination of atrial flutter during aminophylline infusion cannot be dismissed, a causal relation appears more likely because flutter was sustained for 20 minutes before aminophylline was administered.

Implications

The finding that endogenous adenosine has potentially significant electrophysiologic effects on the AV node may have important clinical consequences. Previous clinical studies have shown only that exogenous adenosine has substantive electrophysiologic effects when administered in large bolus doses. In contrast, endogenous adenosine has been believed to be a stress- or ischemic-related metabolite that has little effect during basal conditions. Our data, however, suggest that under normoxic conditions, endogenous adenosine may have a putative role in modulating AV nodal condition if its transport and metabolism are blunted. It also follows that dipyridamole should demonstrate enhanced effects on AV nodal conduction during rapid atrial pacing rates or during rapid SVT when interstitial levels of adenosine are increased. The development of a potent adenosine-transport blocker that is relatively selective for the myocardium may provide a novel and effective therapeutic modality for patients with SVT. The focus of this physiologic approach to therapy would be to potentiate the previously unrecognized antiarrhythmic properties of endogenous adenosine during normoxic conditions.

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References


KEY WORDS • dipyridamole • supraventricular tachycardia • atrioventricular node • adenosine
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