Antiarrhythmic drug carvedilol inhibits HERG potassium channels

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Abstract

Objective: The aryloxypropanolamine carvedilol is a multiple action cardiovascular drug with blocking effects on $\alpha$-receptors, $\beta$-receptors, Ca$^{2+}$-channels, Na$^{+}$-channels and various native cardiac K$^{+}$-channels, thereby prolonging the cardiac action potential. In a number of clinical trials with patients suffering from congestive heart failure, carvedilol appeared to be superior to other $\beta$-blocking agents in reducing total mortality. Given the multiple pharmacological actions of carvedilol, this may be due to specific channel blockade rather than $\beta$-antagonistic activity. Since human ether-a-go-go related gene (HERG) K$^{+}$ channels play a critical role in the pathogenesis of cardiac arrhythmias and sudden cardiac death, the effects of carvedilol on HERG K$^{+}$ channels were investigated.

Methods: Double-electrode voltage-clamp experiments were performed on HERG potassium channels which were expressed heterologously in Xenopus oocytes.

Results: Carvedilol at a concentration of 10 $\mu$M blocked HERG potassium tail currents by 47%. The electrophysiological characteristics of HERG, i.e. activation, steady-state inactivation and recovery from inactivation were not affected by carvedilol. Inhibition of current gradually increased from 0% immediately after the test pulse to about 80% at 600 ms with subsequent marginal changes of current kinetics during the resting 29 s, indicating a very fast open channel block by carvedilol as the major blocking mechanism.

Conclusion: This is the first study demonstrating that carvedilol blocks HERG potassium channels. The biophysical data presented in this study with a potentially antiarrhythmic effect may contribute to the positive outcome of clinical trials with carvedilol. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

In cardiomyocytes, the rapid component of the delayed rectifier K$^{+}$ current, $I_{\text{Kr}}$ [4] is an important repolarizing potassium current. $I_{\text{Kr}}$ is encoded by the human ether-a-go-go-related gene (HERG). This has been demonstrated in macroscopic current measurements [37,47] and single channel measurements [22,53]. Many class III antiarrhythmic drugs prolong the cardiac action potential and thereby the refractory period by blocking $I_{\text{Kr}}$. Likewise, block of HERG channels by various drugs has been investigated previously [40,22,23,45,46,3,51,20].

In patients after myocardial infarction [19,36,10] and dilated cardiomyopathy [26,17,50], arrhythmias are a major cause of death. In theory, the prolongation of the cardiac refractory period makes the heart less susceptible for cardiac arrhythmias [18]. Although, prolonging the refractory period has the possibility of both antiarrhythmic and proarrhythmic potential, particularly where Na$^{+}$ channel blockade increases both the refractory period and the vulnerable period [43,44,9]. For class III antiarrhythmic drugs, outcomes of clinical trials show overall beneficial effects for amiodarone [5,35,13] and significant increases of the postinfarction mortality for the pure class III drug D-sotalol [49].

The aryloxypropanolamine carvedilol (1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenox)ethyl]amino]-2-propenol) is a multiple-action cardiovascular drug: a competitive inhibition of $\beta$-1 [41], $\beta$-2 [14] and $\alpha$-1 receptors [42,38] is part of its neurohumoral properties. It is a calcium-
channel blocker [32] and sodium-channel modulator [27]. It has inhibitory effects on N-methyl-D-aspartate (NMDA) receptors [27] and antioxidant activity has also been described for carvedilol [52].

Potassium currents generated by several native K⁺ channels in cardiomyocytes [11], i.e., Iₖᵣ (the rapid component of the delayed rectifier K⁺ current), Iₖₛ (the slow component of the delayed rectifier K⁺ current) and Iₖo (the transient outward K⁺ current), have also been blocked by carvedilol, resulting in a prolongation of cardiac action potential [6]. However, in ECGs of patients treated with carvedilol, a significant QT prolongation was not observed [39].

The pharmacological profile of carvedilol explains the wide spectrum of therapeutical effects. Carvedilol is advantageous in the treatment of hypertension and chronic stable angina [48]. It reduces infarct size by protecting against lethal reperfusion injury [2]. It has been demonstrated that carvedilol inhibits aortic lipid deposition in hypercholesterolemia [15] and attenuates vascular remodeling by inhibiting vascular smooth muscle cell proliferation [34]. Several clinical studies demonstrated a beneficial effect of carvedilol on the overall survival in congestive heart failure [1,33,12,8]. However, the reason for the particular effectiveness of this agent in congestive heart failure remains unclear, so far. One theoretical explanation would be a decline of fatal arrhythmia, which represent a major complication of congestive heart failure. So, in this study, we demonstrate the blockage of the HERG potassium current by carvedilol contributing to its putative class-III antiarrhythmic properties.

2. Methods

2.1. Solutions and drug administration

Two-microelectrode voltage clamp measurements of Xenopus oocytes were performed in a physiologically low K⁺ solution containing (in mM) 5 KCl, 100 NaCl, 1.5 CaCl₂, 2 MgCl₂, and 10 HEPES (pH 7.3). Current and voltage electrodes were filled with 3 M KCl solution. Carvedilol (Hoffmann-La Roche, USA) was dissolved in ethanol to a stock solution of 100 mM and stored at +4°C. On the day of experiments, aliquots of the stock solution were diluted to the desired concentration with the bath solution. With the highest concentration of 100 μM of the drug, the ethanol concentration was 0.1%; although, 0.1% ethanol alone only minimally reduced inward tail currents (by 2.07±0.89%, n = 3, at −120 mV, after a test pulse to 100 mV; data not shown). All measurements were carried out at room temperature (20°C). The volume of the bath chamber was 150 μl; after solution switch, it took about 4 s for the new solution to reach the bath (tubing length of about 37 cm); at a flow-rate of 1 ml/min, solution in the bath was totally exchanged within 9 s. In general, recording began 30 s after solution switch. All measurements were done under steady-state conditions at least 2 min after total solution exchange.

2.2. Electrophysiology and data analysis

The two-microelectrode voltage-clamp configuration was used to record currents from Xenopus laevis oocytes. Microelectrodes had tip resistances ranging from 1 to 5 MΩ. Data were low-pass filtered at 1–2 kHz (−3 dB, four-pole Bessel filter) before digitalization at 5–10 kHz. Recordings were performed using a commercially available amplifier (Warner OC-725A, Warner Instruments, Hamden, CT, USA) and pCLAMP software (Axon Instruments, Foster City, CA, USA) for data acquisition and analysis. No leak subtraction was done during the experiments. For activating currents, absolute values have been taken for analysis. For description of tails, currents were expressed relative to the baseline at the holding potential (−80 mV). Dose–response curves were fitted with the Hill equation

\[ \frac{I/I_0}{I/I_{C50}} = \frac{1}{1 + \frac{X}{IC_{50}}} \]

where \( I/I_0 \) is the relative current, \( I_0 \) the unblocked current amplitude, \( X \) the carvedilol concentration, \( IC_{50} \) the dose for half maximal block and \( n \) the Hill coefficient.

Steady-state inactivation curves were fitted with a Boltzmann distribution

\[ Y = \frac{1}{1 + \exp \left( \frac{V_{1/2} - V}{k} \right)} \]

where \( V_{1/2} \) represents the half-maximal activation potential, \( Y \) the degree of steady-state inactivation and \( k \) is the slope factor.

Statistical data are expressed as mean±standard error where \( n \) represents the number of experiments performed. Statistical significance was evaluated using the paired Student’s t-test. Differences were considered to be significant when the \( P \) value was <0.05.

2.3. Expression of HERG channels in Xenopus oocytes

The HERG clone was a gift from M.T. Keating (Salt Lake City, UT, USA). HERG complementary RNA was prepared from the HERG cDNA [37] in the pSP64 plasmid with the mMESSAGE mMACHINE in vitro transcription kit (Ambion) by use of SP6 polymerase after linearization with EcoRI (Boehringer Mannheim). Injection of RNA (50–500 ng/μl) into stage V and VI defolliculated oocytes was performed by using a Nanoject automatic injector (Drummond, Broomall, USA). The volume of injected cRNA solution was 50 nl per oocyte, and measurements were made 2–10 days after injection. The investigation conforms with the Guide for the Care and Use of Laboratory animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996).
3. Results

3.1. Inhibition of HERG $K^+$ currents by carvedilol

To investigate the effect of carvedilol on cloned HERG $K^+$ currents, two-microelectrode voltage clamp experiments were performed on *Xenopus* oocytes heterologously expressing the HERG channel. First the control measurements were obtained (Fig. 1A), then the carvedilol (10 μM) was washed into the bath for 10 min, and the measurements with carvedilol (Fig. 1B) were made. Currents were measured with an $I-V$ protocol. From a holding potential of −80 mV test pulses from −80 to +80 mV in 10-mV increments (400 ms) were applied at a frequency of 0.2 Hz to measure activating currents. Each pulse was followed by a constant return pulse to −60 mV (400 ms) to evoke outward tail currents. HERG currents had an activation threshold of −40 mV, reached a current maximum at 10 mV before a considerable current reduction at higher test pulse amplitudes could be measured, as a result of inward rectification. Fig. 1C shows the current–voltage relationship ($I-V$ curve) at the end of the test pulse. After application of 10 μM carvedilol (Fig. 1B), the peak current amplitude (at 10 mV) was reduced by 46.1±3.6% ($n=4$; 

Fig. 1. Inhibition of HERG $K^+$ currents by carvedilol. Upper graph: Original recordings obtained before (A) and after (B) exposure to 10 μM carvedilol for a typical measurement in a *Xenopus* oocyte expressing HERG potassium channels. The maximum outward current (after a test pulse to 0 mV) was reduced by 44.1% (C). The peak tail current was reduced by 50.7% after the test pulse to 30 mV (D). Activating currents normalized to their peak are shown in (E) tail currents normalized to their maximum are shown in (F). Pulse protocol: Holding potential −80 mV, test pulses from −80 to +80 mV (400 ms) in 10-mV increments, followed by a return pulse to −60 mV.
Fig. 1C). Under carvedilol, the increase of activating current graph with subsequent saturation developed faster than in the control, which has to be interpreted as a sign of open channel block.

The amplitude of the outward tail currents in the return pulse partially exceeded the amplitude of the activating current due to slow activation, fast inactivation, rapid recovery from inactivation and slow deactivation. (This has been described elsewhere [22,24,37,40]). Tail currents saturated after a test pulse amplitude of +40 mV or above (Fig. 1D). Carvedilol in a concentration of 10 μM reduced the peak tail current amplitude (after a test pulse to 40 mV) by 46.5±3.7% (n = 4) (Fig. 1D). Normalized activating and normalized tail currents for control and 10 μM carvedilol were scaled in Fig. 1E and F.

3.2. Onset of block and washout of the carvedilol effect

Subsequently, a series of 50 constant pulses to 30 mV (400 ms) at a frequency of 0.07 Hz served to investigate the onset of carvedilol-induced inhibition of HERG K⁺ outward tail currents (Fig. 2A). After nine recordings,
demonstrating steady-state conditions, carvedilol was washed into the bath at a concentration of 10 μM. Steady-state block was already achieved at step 16, i.e. within 90 s. Thereby, the current was reduced by 36.2%. Finally, at step 50, i.e. after 750 s from the beginning of the experiment, a total reduction by 47.7% could be measured (Fig. 2E). A similar result was found in n = 6 experiments; thereby, 50% of maximal block was achieved within 28.33±1.08 s, 75% in 45.67±0.88 s and 90% in 60.67±1.78 s.

The washout of carvedilol was investigated with the same electrophysiological protocol (Fig. 2B). After nine recordings during steady-state block by 10 μM carvedilol, the substance was washed out. The washout was almost complete within 3 min, reaching 80.0±1.0% (n = 3) of the current amplitude at the beginning of the experiment (Fig. 2F). Currents in Fig. 2A and B were normalized to the peak activating current in Fig. 2C and D. During the first 400 ms of activation, a time-dependent decrease of current with 10 μM carvedilol could be registered (Fig. 2C), a sign for fast open channel block. After washout, this current decrease was reversible (Fig. 2D).

3.3. Concentration-dependence of block

The concentration-dependence of carvedilol-induced inhibition was measured on HERG K⁺ tail current amplitudes. From a holding potential of −80 mV, test pulses to +30 mV (400 ms) and return pulses to −60 mV (400 ms) were applied (Fig. 3A). The effect of carvedilol on the tail current at −60 mV was concentration dependent, i.e. carvedilol in a concentration of 0.1, 1, 10, 100 μM blocked the tail current to 96.0±1.8, 91.6±2.2, 53.1±4.5, 14.4±7.6% (n = 4) of the control, respectively. The normalized dose response curve was fitted with a concentration response curve and gave an IC₅₀ of 10.4 μM (Fig. 3B).

3.4. Carvedilol does not affect the steady-state inactivation of HERG K⁺ current

To measure inactivation, a special protocol was used that inactivates the channel at a holding potential of +20 mV, recovers the channel from inactivation at various potentials from −120 to 30 mV (15 ms) in 10-mV steps, and measures the resulting peak outward current at constant +20 mV as a measure of steady-state inactivation (Fig. 4C). Having obtained the control measurement shown in Fig. 4A, we washed in carvedilol at a concentration of 10 μM for 15 min and held the oocyte during this period of time at −80 mV. In this set of experiments, a holding potential of −80 mV was necessary to prevent destruction of the oocyte that usually occurs when holding the oocyte 15 min at +20 mV. Finally, the measurements with carvedilol were made, as shown in Fig. 4B. In Fig. 4D, the inactivating outward current amplitude (measured at constant 20 mV) was normalized and plotted against the test pulse potential, giving the steady-state inactivation curve. This curve could be fitted with a Boltzmann distribution and did not show any significant shift after the application of carvedilol in four experiments [ΔV₁/₂ = −0.91±2.85 mV, P > 0.05, (n = 4 experiments)].

3.5. Carvedilol does not affect activation of HERG K⁺ currents

The effect of carvedilol on activation kinetics of HERG K⁺ currents was investigated by measuring activation curves. Activation curves were obtained with a protocol, where we applied variable test pulses ranging from −120 to +100 mV (200 ms) in 10-mV increments, and measured
Fig. 4. Carvedilol does not affect steady-state inactivation of HERG K⁺ current. To measure inactivation, a special protocol was used that inactivates the channel at a holding potential of +20 mV, recovers the channel from inactivation at various potentials from −120 to 30 mV (15 ms) in 10-mV steps, and measures the resulting peak outward current at constant +20 mV as a measure of steady-state inactivation. Resulting outward currents 2 ms after the final step to +20 mV were displayed for control (A) and 10 μM carvedilol (B) as a function of the test pulse potential in (C). Current amplitudes were normalized resulting in the inactivation curves in (D). Carvedilol did not produce any shift in the normalized steady-state inactivation curves from n=4 experiments.

Fig. 5. Carvedilol does not affect activation of HERG K⁺ currents. Activation curves of HERG K⁺ currents were measured in a protocol with inward tail currents in a representative experiment. The control measurement is shown in (A). The measurement with carvedilol is shown in (B). In (C) the tail current amplitude is displayed against the test pulse voltage in the previous step. In (D) the inverted tail current amplitude was displayed as a function of the previous test pulse potential resulting in an activation curve. There was no significant shift in the normalized activation curve from n=4 experiments (D). Voltage protocol: Holding potential −80 mV, test pulses from −80 to +80 mV in 10-mV increments (200 ms) return pulses constant −120 mV to measure tail currents.

3.6. No frequency and no use-dependence of carvedilol block

After carvedilol block reached steady-state conditions (after 2 min) the frequency dependence of block was investigated. HERG K⁺ channels were activated by depolarizing pulses to 100 mV (400 ms) at intervals of 15 s (Fig. 6A) and 1 s (Fig. 6B) under control conditions and in the presence of carvedilol. The outward tail currents at −60 mV were subsequently used for analysis. The level of
blocked by carvedilol, we measured outward currents with a special experimental design: Firstly we did the control measurements without carvedilol, then we washed in carvedilol in a concentration of 100 μM for 2 min while holding the cell at −80 mV to keep all channels in the closed state and then made a measurement with a long test pulse of 30 s at 0 mV. Experiments with the same pulse protocol, but washin-periods of 5 and 10 min were added.

Punctual inhibition immediately after the test pulse would be a measure of closed state block. The amount of block that would occur gradually during the long test pulse would be a measure of open state block [20].

Control currents and currents after application of carvedilol were normalized to their peak currents and in additional graphs, the degree of inhibition was shown with logarithmic and linear time scale.

Normalized macroscopic currents over 30 s scaled for washin periods of 2 and 5 min (Fig. 7A and B). Although, analysis of the first 600 ms revealed a steady increase of inhibition from almost 0% immediately after the test pulse to about 80% at 600 ms (Fig. 7C). This can be interpreted as a very fast open channel block within the first 400 ms of the measurements. Other experimental findings support this result as well: The faster development of stable current under carvedilol where control activating current still increased (Fig. 1) and a slight decrease of activating current under 10 μM carvedilol during the first 400 ms of Fig. 2C. In Fig. 7, the peak current was reached after about

Fig. 6. Carvedilol block is not use-dependent. Repetitive test pulses at 0.07 Hz (A) and 1 Hz (B), i.e. every 15 s and 1 s, were performed under control conditions and after an equilibrium time for carvedilol-induced block (3 min perfusing 10 μM carvedilol into the bath). There was no difference in the amount of steady-state block between 0.07 Hz (A) and 1 Hz pulsing (B), demonstrating non frequency, and non use-dependent block. Protocol: holding potential −80 mV; test pulse to 100 mV (during 400 ms); return pulse always −60 mV to measure tail current amplitudes. Shown are representative experiments for consecutive pulses at different frequencies.

steady-state block after 70 s of repetitive step pulses might be taken as a measure for the frequency dependence of block. We found, that at both frequencies the current amplitudes did not change. Therefore the block of HERG currents by carvedilol is not frequency and not use-dependent within this protocol that has a test pulse duration of 400 ms according to the QT-interval in the ECG. The lack of use-dependence despite an open channel block by carvedilol is mainly caused by the fast velocity of block, which allows complete inhibition within one single step. So the subsequent pulses cannot intensify the block.

3.7. HERG K⁺ channels are blocked by carvedilol mainly in the open state

To address the question of which state of the channel is blocked by carvedilol, we measured outward currents with a special experimental design: Firstly we did the control measurements without carvedilol, then we washed in carvedilol in a concentration of 100 μM for 2 min while holding the cell at −80 mV to keep all channels in the closed state and then made a measurement with a long test pulse of 30 s at 0 mV. Experiments with the same pulse protocol, but washin-periods of 5 and 10 min were added.

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4. Discussion

This study demonstrates that the HERG potassium channel is blocked by carvedilol. The HERG potassium channel produces the I_{Kr} potassium current in cardiac myocytes. Recently it has been shown that carvedilol blocks I_{Kr} in isolated rabbit cardiomyocytes. This indicates that the block of this channel occurs also in native cardiac cells [6]. The effects of carvedilol on HERG in our study and I_{Kr} currents in the study by Cheng et al. [6] occurs in a concentration range similar to concentrations achieved by carvedilol in a clinical setting. In hypertensive patients which are treated with carvedilol, plasma concentrations in a range of 32–252 μg/l have been found [29,31], which corresponds to concentrations of 0.1–0.6 μM. In com-
Fig. 7. HERG K⁺ channels are blocked by carvedilol in the open state. Channels were held at $-80$ mV, i.e., in their closed state, before a test pulse to $0$ mV (for 30 s) was applied. Shown are mean absolute ($n=4$) (A) and scaled overlay experiments (B) for control and $100 \mu M$ carvedilol. Per oocyte, only one control pulse and one consecutive pulse after 2 or 5 min wash-in of $100 \mu M$ carvedilol (at $-80$ mV) was applied. After 2 min, mean recordings ($n=4$) show a carvedilol-induced peak current reduction by 69.9%. Normalized graphs scale for 2 and 5 min of washin. Additional graphs show the degree of inhibition (carvedilol-sensitive current at time x/control current at time x) in percent, beginning 20 ms after the test pulse, with extrapolation for the first 20 ms (C and D). Inhibition of current steadily increased from 0% immediately after the test pulse to about 80% at 600 ms with subsequent marginal changes of current kinetics during the resting 29 s, indicating that mainly open channels were blocked, with weak open channel unblock.

comparison to the block of $I_{Kr}$ in cardiomyocytes ($IC_{50}=0.4 \mu M$; [6]) a higher concentration of carvedilol was necessary in our study to inhibit HERG channels expressed in *Xenopus* oocytes ($IC_{50}=10.4 \mu M$). This difference is attributed to the viteline membrane and yolk of the oocytes, which requires up to 10- to 30-fold higher concentrations for the drug effects [28,20]. Taking this into consideration, this study and the study of Cheng et al. [6] indicate that the block of HERG channels by carvedilol is of therapeutical relevance for treated patients.

Clinical trials with carvedilol have proven that this drug is effective in the therapy of ischemic and idiopathic heart failure. Beneficial effects on mortality and hospitalisation rate have been demonstrated in the trial of the US Carvedilol Heart Failure Study Group. Carvedilol reduced the mortality by 65% in patients with either form of cardiomyopathy [33]. In the trial of the Australia–New Zealand Heart Failure Research Collaborative Group, carvedilol increased the left ventricular ejection fraction of patients with heart failure due to ischemic heart disease by 5.3% and the rate of death or hospital admission was lower in the carvedilol group [12]. The MOCHA multicenter trial for patients with mild to moderate heart failure demonstrated a decrease of mortality risk by 73% in carvedilol-treated patients [1]. In the PRECISE trial, a significant decrease in the combined risk of morbidity and mortality could be shown for moderate to severe heart failure [33]. Sudden cardiac death due to malignant arrhythmias and pump failure are the most common causes of death in patients with severe heart failure. Although some clinical trials describe a reduction of ventricular arrhythmias under carvedilol treatment [39,7], the reduction of sudden death mortality under carvedilol in the clinical trials have not yet been explained. It may be possible that the reduction of malignant arrhythmias and consequently the reduction of sudden cardiac death may be at least, in part, the result of an antiarrhythmic effect of carvedilol by blocking HERG potassium channels. This potentially antiarrhythmic effect together with its β-blocking properties may be responsible for the positive outcome of the clinical trials.

We found, that blockade of HERG potassium channels by carvedilol appears to occur rather quickly and almost exclusively on open states (Fig. 7C). The lack of use-dependence is a sign of very fast development of complete block already during one short test pulse. The onset of block by carvedilol is fast and occurred within 2–3 min. This is much faster than block of HERG channels by dofetilide [22] or block of HERG channels by amiodarone.
[25]. We speculate, that carvedilol blocks HERG channels with low affinity from the extracellular site of the membrane, because the onset of block is faster than intracellular block by dofetilide.

In the literature, inactivated HERG channels, though, might be inhibited by the gastrointestinal prokinetic agent cisapride [30] and by haloperidol [46]. Activated open (or reactivated closed) HERG channels are blocked by the class III antiarrhythmic drug dofetilide from the intracellular site by binding to the HS segment [16,21].

After the negative outcome the SWORD trial [49] with the pure Class III drug d-sotalol, recent discussions have led to the widespread opinion that block of HERG channels is a negative feature of drugs with the induction of proarrhythmia. We do not support this opinion in general since the action of a drug on the HERG channel and the resulting cardiac electrophysiological changes depend strongly on the pharmacological profile of the drug. For example, the class III drug amiodarone blocks HERG channels in the closed and open state [25] and clinical data strongly suggest, that amiodarone is a very safe and efficacious antiarrhythmic drug [5,35,13]. It may be possible, that an additional therapy with β-blocking agents, or intrinsic β-blocking activity of the drugs is necessary to prevent proarrhythmias in a so far unknown mechanism. In the same line the additional HERG blocking activity of amiodarone or carvedilol may lead to superior clinical results compared to conventional therapy with pure β-blocking agents.

This pharmacological study provides new and detailed information about the block by carvedilol of the cloned HERG potassium channel. Such detailed pharmacological studies are not possible to obtain in isolated cardiomyocytes from guinea pig or rabbit or human, because the $I_{Kr}$ current is usually very small. Even more so because in isolated cardiomyocytes it is necessary to block other currents with compounds that possibly also act on the $I_{Kr}$ current and the voltage protocols in such studies with cardiomyocytes are very restricted.

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