Influence of Glucose on the Transmembrane Action Potential of Guinea-Pig Papillary Muscle

METABOLIC INHIBITORS, OUABAIN, AND CALCIUM CHLORIDE, AND THEIR INTERACTION WITH GLUCOSE, SYMPATHOMIMETIC AMINES, AND AMINOPHYLLINE

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ABSTRACT

In a previous report, we have proposed that anaerobic glycolysis alone can maintain an action potential of normal duration in guinea-pig papillary muscle. This proposal followed from the observation that 50 mM glucose, several sympathomimetic amines, and aminophylline all caused the duration of the action potential of muscles, which had been reduced by incubation in a medium containing 5 mM glucose, to return toward control values. This occurred in the presence or absence of oxygen. It was further proposed that the ATP resulting from anaerobic glycolysis was in some way preferentially utilized in the membrane by a process controlling repolarization and therefore the duration of the action potential. The present experiments were undertaken to determine what metabolic pathways were necessary for the glucose effect mentioned above, by the use of the metabolic inhibitors sodium cyanide, iodoacetic acid, and 2,4-dinitrophenol. Secondly, the effects of ouabain and calcium, which are known to modulate the utilization of ATP, on the glucose effect were studied. It was concluded that an intact glycolytic pathway is necessary for the effect of glucose on the electrical activity of papillary muscle and that the effect can be increased or decreased by low or high doses of ouabain, respectively. The actions of ouabain are thought to be due to a stimulation and depression of a membrane ATP-ase.

ADDITIONAL KEY WORDS duration of action potential glycolysis ATP anoxia contractile force repolarization

In earlier work (1, 2) we were able to show that the duration of the action potential of cat and guinea-pig papillary muscle was influenced by the concentration of glucose in the incubating medium. When the medium contained 50 mM glucose, the duration of the action potential was found to remain near control value for many hours in the complete absence of oxygen. When the medium contained 5 mM glucose and 45 mM sucrose, however, it was found that the duration decreased with time both in the absence and presence of oxygen. If the concentration of glucose in the medium was increased after the duration of the action potential had been reduced by incubation in a medium containing 5 mM glucose, the duration of the action potential was found to return to control levels. This effect of glucose on the reduced duration was concentration-dependent and inhibited by phlorizin. Although insulin was not found to significantly increase the activity of glucose itself, it did reverse or prevent phlorizin-
induced decreases in glucose activity. That the effect of glucose was not due to its transport per se was shown by a large series of experiments with nonmetabolizable sugars in which no sugar was found to duplicate the effect of glucose.

In the same studies, it was shown that an increase in the reduced duration of the action potential of papillary muscle could be produced by the sympathomimetic amines, adrenaline, noradrenaline, and isopropyl noradrenaline, and the xanthine, amiphylline. The activity of isopropyl noradrenaline was found to be blocked by the beta-receptor blocking agent, propranolol, and markedly reduced by acetylcholine and iodoacetic acid. Finally it was shown that muscle incubated in the complete absence of glucose and oxygen until the duration of the action potential was reduced to between 60% and 75% of control did not show an increase in duration of the action potential in response to isopropyl noradrenaline, although an increase in force of contraction occurred.

As a result of these observations, it was proposed that the effect of glucose on transmembrane electrical activity was due to a stimulation of glycolysis. It was further suggested that the ATP produced by glycolysis was preferentially utilized in some membrane process involved in the regulation of repolarization and hence the duration of the action potential.

The present series of experiments was carried out to investigate the effects of several metabolic inhibitors on the electrical activity of papillary muscle and on the action of glucose on the electrical activity. The inhibitors studied were iodoacetic acid, sodium cyanide (NaCN), and 2,4-dinitrophenol. Iodoacetic acid has been shown to block glycolysis (3, 4). NaCN and 2,4-dinitrophenol are known to interfere with aerobic metabolism (5-7). On the basis of the proposal presented earlier, any effect of interference with aerobic metabolism should be reversed by stimulation of glycolysis. Any effect of the blocking of glycolysis should not be affected by glucose but should respond to stimulation of aerobic metabolism.

As it will be seen, the results of experiments with metabolic inhibitors clearly established that the duration of the action potential of papillary muscle could be maintained by glycolysis alone under suitable conditions.

Since there exists a relationship between ATP metabolism and active ion transport (8, 9), it seemed possible that repolarization in cardiac muscle might be influenced by some mechanism utilizing ATP. Although a mechanism whereby utilization of ATP alters potassium efflux during activity is not known, it was considered to be useful to know whether availability or utilization of ATP was important for normal membrane electrical activity. To this end, a series of experiments was carried out in which the effects of ouabain and calcium on the transmembrane electrical activity of papillary muscle were studied. In addition, the interaction of these agents with sympathomimetic amines, amiphylline, and glucose and their effect on the reduced duration of the action potential of muscle incubated in the absence of oxygen, or adequate glucose, or both were studied.

Materials and Methods

All experiments were carried out with papillary muscles obtained from the right ventricle of guinea-pig hearts. Dissection of the muscles was carried out in cool modified Krebs-Ringer solution of the following composition in mEq/liter: Na, 138.5; K, 4.6; Ca, 4.9; Mg, 2.3; HCO₃, 21.91; PO₄, 3.48; SO₄, 2.32; Cl, 125; and glucose, 50 mM, equilibrated with 5% CO₂ in O₂. Guinea-pig papillary muscle tended to be flat, 6 to 8 mm long, 1 to 2 mm wide, and 0.5 to 1 mm thick. The muscles were mounted horizontally at a resting tension of 500 mg in a jacketed, 100-ml, constant-temperature bath at 37°C. Stimulation was at a rate of 60/min through platinum electrodes which were close to but did not touch the muscles. Force of contraction was recorded on a Grass polygraph by means of a Grass force-displacement transducer. Single cell electrical activity was recorded by means of hand-pulled glass microelectrodes filled with 3M KCl using the floating-electrode technique of Woodbury and Brady (10).

Results

In eighteen experiments the effects of 10⁻⁵M...
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5min 10min 20min 25min 30min 40min

CONTROL

FIGURE 1

Effect of $10^{-5}$ M iodoacetic acid on the action potential of a papillary muscle incubated in Krebs solution containing 5 mM glucose and equilibrated with 5% CO$_2$ in O$_2$ (arrow 1). At arrow 2, iodoacetic acid. Times given above records are measured from previous arrow. Voltage calibration 100 mV, time calibration 200 msec.

or $0.25 \times 10^{-3}$ M iodoacetic acid on the electrical activity of papillary muscle incubated in Krebs solution containing 5 mM glucose equilibrated with either 5% CO$_2$ in O$_2$ or 5% CO$_2$ in N$_2$ were investigated. The lower concentration of iodoacetic acid ($10^{-5}$ M) markedly reduced the duration of the action potential within 20 to 30 minutes without a reduction in the resting potential or overshoot as can be seen in Figure 1. Further exposure of the muscle to iodoacetic acid reduced both the overshoot and resting potential (Fig. 1). The effects of $10^{-5}$ M iodoacetic acid were almost completely reversed within 1 hour after washing the preparations with iodoacetic acid-free Krebs solution. At a concentration of $0.25 \times 10^{-3}$ M, the effects of iodoacetic acid occurred much more rapidly and were almost irreversible.

In nine experiments in which a reduction in the duration of the action potential was induced by $10^{-5}$ M iodoacetic acid in the presence of oxygen, glucose (5, 10, or 30 mM) did not cause an increase in the duration whereas sodium pyruvate (5 to 10 mM) restored it essentially to control level (Fig. 2). When the duration of the action potential was reduced by $0.25 \times 10^{-3}$ M iodoacetic acid, neither 50 mM glucose nor 10 mM pyruvate produced an increase in the duration. It is not surprising that the effect of the higher concentration of iodoacetic acid could not be reversed by sodium pyruvate since it has been demonstrated (4) that at higher concentrations iodoacetic acid is a general sulfhydryl inhibitor.

In six experiments NaCN (0.5 to 4 mM) was found to markedly increase the rate of reduction of the duration of the action potential of papillary muscle incubated in Krebs solution containing 5 mM glucose and equilibrated with either 5% CO$_2$ in N$_2$ or 5% CO$_2$ in O$_2$. Sodium pyruvate was found to

20min 15min 15min

CONTROL

FIGURE 2

Effect of 10 mM sodium pyruvate on the duration of the action potential of papillary muscle reduced by iodoacetic acid. At arrow 1, Krebs solution containing 5 mM glucose and $10^{-5}$ M iodoacetic acid and equilibrated with 5% CO$_2$ in O$_2$. Arrow 2, 20 mM glucose; arrow 3, sodium pyruvate. Times and calibration as in Figure 1.
have no effect on the duration of the action potential of the NaCN-poisoned muscle, whereas glucose was able to completely restore the duration to normal (Fig. 3, A). In the presence of both iodoacetic acid and NaCN neither glucose nor sodium pyruvate was able to restore it to normal (Fig. 3, B).

Since 2,4-dinitrophenol is believed to uncouple aerobic oxidation and the generation of energy-rich phosphate bonds (7), normal energy sources are quickly reduced but anaerobic and aerobic metabolic pathways are essentially intact. For these reasons, the effect of 2,4-dinitrophenol on the electrical activity of papillary muscle was investigated. This was found to reduce the duration of the action potential to an extent greater than that occurring as a result of incubation of the muscle in Krebs solution containing 5 mM glucose. The rate of development and the extent of the effect increased with concentration. The earliest effect of 10^-5M 2,4-dinitrophenol was a decrease in the duration with no associated decrease in height of the action potential. At twice this concentration, 2,4-dinitrophenol caused a marked decrease in duration of the action potential, overshoot, and resting potential. All of the observed changes in electrical activity could be completely reversed by washing the muscle with 2,4-dinitrophenol-free Krebs solution. In six experiments it was shown that an elevation in
Effect of 2,4-dinitrophenol on the duration of the action potential and force of contraction of papillary muscle and the influence of glucose on the effect. At arrow 1, Krebs solution containing 5 mM glucose equilibrated with 5% CO₂ in O₂; arrow 2, 10⁻³ M 2,4-dinitrophenol; arrow 3, 45 mM glucose. Force calibration 1 g. Times and electrical calibration as in Figure 1.

The glucose concentration in the medium was able to restore the duration of the action potential, which had been reduced by 2,4-dinitrophenol, to normal (Fig. 4).

The results of experiments with iodoacetic acid, NaCN, and 2,4-dinitrophenol established the importance of anaerobic glycolysis in glucose-induced increases in the duration of the action potential of papillary muscle and suggested the following experiments with agents which are thought to alter ATP utilization in cell membrane.

When papillary muscle is incubated in Krebs solution containing 5 mM rather than 50 mM glucose and equilibrated with 5% CO₂ in O₂ or 5% CO₂ in N₂ until the duration of the action potential has been reduced to between 35% and 45% of control and then exposed to various concentrations of ouabain, changes in the duration of the action potential occur as shown in Figure 5. In this series, six experiments were carried out at each of 10⁻⁴, 10⁻³, and 10⁻²M ouabain. It may be seen that ouabain at both 10⁻⁴ and 10⁻²M, maintained the duration or actually increased it in comparison to control incubation. Although there was no effect of 10⁻³M ouabain on contractile force, a definite increase occurred with 10⁻²M. It may also be noted that the effect of 10⁻³M ouabain on the duration of the action potential was the same whether the gassing mixture was 5% CO₂ in O₂ or 5% CO₂ in N₂. With both 10⁻³M and 10⁻²M ouabain there was a clear decrease in the duration in comparison to the control. At the same time, however, there was a marked increase in contractile force as shown for 10⁻²M ouabain in Figure 6. At this concentration of ouabain a decrease in both resting potential and overshoot occurred.

Effect of ouabain on the reduced duration of the action potential (APD) of papillary muscle incubated in Krebs solution containing 5 mM glucose and equilibrated with 5% CO₂ in O₂. Zero time refers to that point in the incubation when ouabain was added to the bath and when the duration of the action potential was reduced to between 35% and 45% of control. Percent change in the duration of the action potential relates to the duration at zero time. Note that both 10⁻⁴ and 10⁻³M ouabain maintain the duration above control level and that 10⁻²M actually causes an increase in it. Curve labeled 10⁻³M (N₂:CO₂) shows a similar effect of ouabain when the experiment was carried out in the absence of oxygen.
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Effect of 10^{-6}M ouabain on the reduced duration of the action potential and force of contraction of papillary muscle. At arrow 1, incubation in Krebs solution containing 5 mM glucose equilibrated with 5% CO_{2} in O_{2} began; 20 minutes later, at arrow 2, ouabain was added. Note marked increase in force of contraction associated with marked decrease in action potential duration and height. Calibration as in Figure 4.

In all instances similar results were obtained when experiments were carried out in the absence of glucose, or oxygen, or both. It was found in earlier work (2) that the complete absence of glucose and oxygen produces a maximum rate of reduction of the duration of the action potential under all circumstances. When muscles were exposed to concentrations of ouabain of 10^{-7}M or greater, the rate of decrease in the duration was also always greater in the absence of glucose.

Nine experiments were carried out in which the effect of 25 mM glucose on the reduced duration of the action potential of papillary muscle was determined before and after exposure of the muscle to 10^{-6}M ouabain for 20 minutes. It can be seen in Figure 7 that the effect of glucose on the reduced duration of the action potential was depressed by ouabain but that the addition of glucose caused a marked increase in the force of contraction. Similar results were obtained in six experiments in which the effects of isoproterenol or aminophylline (Fig. 8) on the reduced duration of the action potential were determined before and after ouabain. In this instance, however, changes in force of contraction induced by isoproterenol or aminophylline were not influenced by ouabain.

When muscles were exposed to 10^{-9}M ouabain, it was found that the subsequent response to isoproterenol was potentiated (Fig. 9). It will be recalled that this con-
Effect of 1 mg/ml aminophylline on the reduced duration of the action potential and force of contraction of papillary muscle before (A) and during (B) exposure of the muscle to $10^{-6}$M ouabain. At arrow 1, incubation in Krebs solution containing 5 mM glucose equilibrated with 5% CO$_2$ in N$_2$ began with $10^{-6}$M ouabain in muscle bath B. At arrow 2, aminophylline. Calibration as in Figure 4.

centration of ouabain, although not causing an increase in the reduced duration, prevented further decrease when muscles were incubated in Krebs solution containing 5 mM glucose equilibrated with 5% CO$_2$ in N$_2$ (Fig. 5).

It has been reported (11, 12) that the effect of calcium on ATP utilization in vitro is similar to that of ouabain. At concentrations of 4 and 7 mM in the present study, CaCl$_2$ was found to further decrease the duration of the action potential of muscle incubated in Krebs solution containing 5 mM glucose and equilibrated with 60% N$_2$:35% O$_2$:5% CO$_2$ while causing a slight increase in force of contraction (Fig. 10).

When the effects of glucose and adrenaline on the reduced duration of the action potential were determined before and after 7 mM CaCl$_2$, they were found in both instances to be less.

Discussion

Iodoacetate which inhibits the formation of pyruvate from glycogen or glucose by inhibiting triosephosphate (3, 4) reduced the duration of the action potential of guinea-pig
FIGURE 10

Effect of 4 and 7 mM CaCl₂ on the reduced duration of the action potential and force of contraction of papillary muscle incubated in Krebs solution containing 5 mM glucose equilibrated with 60% N₂:35% O₂:5% CO₂. Incubation began at arrow 1 and at arrow 2, 4 mM CaCl₂ (I) and 7 mM CaCl₂ (II). Calibration as in Figure 4.

papillary muscle incubated in Krebs solution containing 5 mM glucose and equilibrated with either 5% CO₂ in O₂ or 5% CO₂ in N₂. These findings are in agreement with those in the frog ventricle (13, 14), in rabbit auricle (15, 16), in turtle ventricular strips (17), in rat auricle and dog and cat ventricular muscle (18). The iodoacetate-induced reduction in duration of the action potential in the presence of 5% CO₂ in O₂ was slow, indicating that certain aerobic pathways for oxidation of metabolites such as lactate and pyruvate are unaffected by iodoacetate. A similar observation was made by Marshall (17). Glucose in concentrations of 15 to 30 mM was ineffective in reversing the effect of 10⁻⁵M iodoacetic acid on the duration of the action potential, whereas 5 to 10 mM sodium pyruvate in the presence of oxygen was partially effective. At a concentration of 0.25 x 10⁻⁵M iodoacetate, neither glucose nor pyruvate was effective in reversing the effect of iodoacetate on the duration of the action potential. The irreversibility of the effects of high concentrations of iodoacetate is likely due to its general sulfhydryl inhibiting effect (3, 4). Iodoacetate is not a specific inhibitor of glycolysis in mammalian cardiac muscle and even in low concentrations it is likely that other enzyme systems are affected (19). Not only is the synthesis of ATP diminished, but it is likely that iodoacetate interferes with the utilization of ATP (20).

In contrast to the effect of iodoacetate, the decrease in the duration of the action potential caused by either NaCN or 2,4-dinitrophenol could be reversed by glucose. These agents interfere with oxidative metabolism; NaCN by inhibiting cytochrome oxidase (21), and 2,4-dinitrophenol by uncoupling the production of ATP from aerobic oxidation (7). The results demonstrate that when oxidative phosphorylation is interfered with, glycolytic activity can maintain the duration of the action potential at control level if its rate is sufficiently increased. Increased extracellular glucose seems to cause this increase to a greater extent than the possibly physiological mechanism of anoxia. Since the catecholamines also are capable of causing an increase in the reduced duration of the action potential, lack of substrate does not appear to be the factor limiting anoxia-induced stimulation of glycolysis.

The present investigation, coupled with previous studies (1, 2), demonstrates the sensitivity of single cell transmembrane electrical activity of guinea-pig papillary muscle...
to changes in metabolic activity within the cell. This is especially so in preparations which have been incubated in vitro for several hours and which have been repeatedly exposed to periods of anoxia or incubation medium containing a glucose concentration of 5 mM or lower. The finding (2) that an apparent increased rate of glycolysis, induced either by high extracellular glucose concentrations or increased phosphorylase activity, can maintain or restore the duration of the action potential at a control value during inhibition of aerobic metabolic activity suggests the possibility of a close association between glycolytically produced ATP and membrane activities. Changes in force of contraction were not shown to be sensitive to alterations in glucose concentration in the absence of aerobic metabolism. The latter finding supports the contention that, although ATP produced aerobically is available for contractile activity and membrane function, that originating from glycolysis appears to be restricted to membrane function. An additional piece of supporting evidence is the finding (2) that the duration of the action potential of papillary muscle incubated in the presence of oxygen but in a medium containing 5 mM glucose will decrease to a relatively greater degree than force of contraction. Under these circumstances, an elevation of the glucose concentration rapidly restores the duration of the action potential to control. Although it is undoubtedly true that a much greater proportion of cellular ATP is required to maintain contractile activity than total membrane activity, our data do not seem consistent with the concept of a single pool of ATP.

With the currently available information, it is difficult to establish a link between energy production and the membrane phenomenon of repolarization. Although a relationship between ATP metabolism in the membrane and active ion transport has been established (22, 23), the role, if any, of ATP in the movement of ions down their electrochemical gradient is unknown. It has been suggested by MacFarlane (24) that an active ion transport mechanism may be involved. If one accepts that the reduction in the duration of the action potential in the present study is due to the rise in potassium conductance occurring earlier and to a greater degree in response to depolarization, then certain possibilities may be considered. Of primary importance is the observation that the duration of the action potential and therefore probably potassium conductance during repolarization can be maintained at control level in the complete absence of oxygen in a high glucose environment (1, 2). This effect can be qualitatively duplicated by adrenaline, noradrenaline, isoproterenol, aminophylline (2), and, as shown in the present study, 10^{-8}M ouabain. The effect of restoring the duration of the action potential toward control level, which is the usual experimental protocol in these studies, is prevented by 2-deoxyglucose and iodoacetic acid (2) but not by compounds which are thought to interfere with aerobic metabolism as shown in the present study. Concentrations of ouabain of 10^{-7}M and larger have been shown to prevent the restoration of the reduced duration of the action potential toward control by those agents studied and also to cause a reduction in the duration of the action potential.

It is clear from the present results that the effect of ouabain on the configuration of the action potential of papillary muscle incubated in a medium containing 5 mM glucose equilibrated with either N_2:CO_2 or O_2:CO_2 depends on the concentration employed. Under the conditions of the present studies, the duration of the action potential was reduced to less than half prior to addition of ouabain. Three distinct effects of ouabain were observed: (1) at 10^{-6}M the duration of the action potential was prevented from decreasing further as in the control situation; (2) at 10^{-8}M the duration was increased by some 20%; and (3) at 10^{-7} and 10^{-6}M the duration was reduced more rapidly than in the control. An approximate doubling of the Ca^{2+} concentration in the medium produced an effect on the duration similar to 10^{-6} or 10^{-7}M ouabain.

The suggestion that ATP is involved in the
phenomenon of repolarization and the effector of the action of glucose on the duration of the action potential, may be considered in the light of reported effects of ouabain. Repke (12) has reported that cardiac muscle membrane ATPase in vitro is stimulated by low concentrations of glycoside and inhibited by higher concentrations. Similar results have been reported in microsomal fractions of cardiac muscle (25) and kidney (26). If these observations are correct, then it is possible that our findings with ouabain may be explained by a stimulation-depression effect of ouabain on membrane ATPase activity. The interaction of ouabain with glucose and isoproterenol on the duration of the action potential is in agreement with this explanation. The finding that higher concentrations of ouabain reduce or inhibit the action of glucose or sympathomimetic amines on the reduced duration may be interpreted as an inhibition of either utilization or production of ATP. The latter possibility is unlikely in the light of studies (27, 28) in which ouabain has been shown to stimulate several metabolic parameters. At a concentration of ouabain which by itself did very little to the reduced duration of the action potential (10^{-9} M), the action of isoproterenol was potentiated. This finding may be interpreted as an increased utilization of ATP coupled with an increased production.

Although it is not possible to directly relate metabolic activity to potassium membrane conductance, glucose has not been found to significantly change $^{42}\text{K}$ efflux during anoxia or to reverse potassium loss and sodium gain during anoxia (D. P. MacLeod and E. G. Hunter, unpublished observations). Since it does produce a dramatic decrease in the rate of repolarization, which has been increased during anoxia for instance, it seems reasonable to conclude that the potassium conductance during an action potential has been affected in such a way as to increase the outward movement of potassium.

An objection to the proposal that low concentrations of ouabain cause a stimulation of a membrane ATPase and thereby increase the duration of the action potential may be raised by the finding (29) that the ATPase of highly purified calf heart muscle was not stimulated by $10^{-9}$ to $10^{-14}$M ouabain. However, the matter is not resolved to a point sufficient to eliminate the proposal at present.

Although it has been reported (30) that $10^{-4}$M ouabain causes an increase in the duration of the action potential prior to a decrease, the finding does not seem comparable to the present observation. Our observations were made over a similar time course but with various concentrations of ouabain. The low concentrations maintained the duration above control for the observation period, the high concentrations decreased the duration during the same period. Therefore, although the earlier findings (30) may be explained by a developing or biphasic effect of a single dose of ouabain, the present findings cannot.

The finding of a marked reduction in the duration of the action potential concomitant with a marked increase in the force of contraction in guinea-pig papillary muscle with $10^{-4}$M ouabain is in agreement with those in a number of cardiac muscle preparations (30-33). It has been stressed that the inotropic effect of cardiac glycosides cannot be correlated with observed changes of the action potential (30, 31). However, Muller (33) using simultaneous measurements of tension, transmembrane potential, and intracellular potassium content came to the conclusion that there is a temporal parallelism between cellular potassium loss, reduction in duration of the action potential, and positive inotropic effect. A similar correlation has been reported by Reiter et al. (34) in guinea-pig papillary muscle. Under the conditions of the present study, a positive inotropic effect was obtained with $10^{-8}$M ouabain during which time the duration of the action potential was actually increasing. More recent observations (D. P. MacLeod and T. F. McDonald, unpublished observations) have shown clear increases in both the duration of the action potential and contractile force with $10^{-11}$ to $10^{-9}$M ouabain in muscles incubated for long periods of time.
under conditions which depress metabolic activity.

These results differ from those of Muller (33) which showed that a positive inotropic effect of $10^{-6}$ or $5 \times 10^{-6}$M ouabain only occurred when $42K$ loss was coincidentally increased and was not correlated with a particular change in the duration of the action potential. The combined observations would seem to suggest a dissociation of the membrane activity of ouabain from its positive inotropic effect.

References


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