The Control of Sugar Uptake by Metabolic Demand in Isolated Adult Rat Heart Cells

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SUMMARY. To investigate the control of sugar uptake by metabolic demand, we used isolated quiescent adult rat heart cells in suspension, under conditions similar to those found during anoxia. Metabolic demand was varied by exposing cells to rotenone plus various levels of p-trifluoromethoxyphenylhydrazone. Without glucose, the time taken for half of the cells to undergo contracture was inversely proportional to the metabolic demand as measured by the rate of lactate production. For any metabolic demand, the onset of contracture was preceded by a sudden drop in adenosine triphosphate. The permeability of contracted cells to glucose was investigated using 3-O-methylglucose. The rate of 3-O-methylglucose uptake by such cells was strongly dependent on the time taken for half the cells to undergo contracture, with low rates at low times to half contracture, and insulin-like rates at high times to half contracture. This suggests that the full induction of glucose transport by metabolic demand can be prematurely curtailed by the loss of adenosine triphosphate. This phenomenon appeared to limit glucose utilization in cells with a high metabolic demand when glucose was present: such cells underwent contracture unless insulin was also present, the rate of glucose uptake as measured with 2-deoxyglucose was inhibited, and the rate of lactate production was inhibited. Isoproterenol depressed glucose transport by two mechanisms. First, by stimulating the basal metabolic demand of the cell it reduced the time taken for half the cells to undergo contracture and, hence, the level of induced sugar transport. Second, it significantly delayed the onset of sugar permeability with respect to the contracture event. Consequently, cells treated with isoproterenol were more prone to contracture than cells without isoproterenol. (Circ Res 58: 157–165, 1986)
lating metabolic demand and concomitantly reducing glucose transport.

Methods

Preparation of Heart Cells

Cell suspensions were prepared as previously described (Haworth et al., 1980), except that trypsin was omitted and basal Eagle’s medium amino acids (Flow labs) were included at the stage of recirculating perfusion of the hearts, and subsequently until suspension in the experimental medium. Trypsin was not used because it was found to stimulate the basal rate of sugar influx in the absence of insulin, as has also been found with adipocytes (Pilch et al., 1981). We have previously shown that read- dition of Ca** after heart perfusion is the key to obtaining myocytes with a low ion permeability that can resist physiological Ca** levels, and the trypsin addition served to increase the yield of such cells (Haworth et al., 1982a).

The amino acids were used in place of trypsin to increase the yield of Ca**-resistant myocytes (Kao et al., 1980). Yields and percent rod-shaped cells were similar to those previously described (Haworth et al., 1980). The rod-shaped cells were quiescent in the experimental medium (which contained 1 mM CaCl2).

Incubation Conditions

Cells were suspended in the experimental medium containing: 118 mM NaCl, 4.8 mM KCl, 25 mM 4-morpholino C-propane sulfonate (MOPS), 1.2 mM KH2PO4, 1.2 mM MgSO4, 1 mM CaCl2, and 2 mM sucrose, adjusted to pH 7.0 with NaOH. They were incubated at 37°C in a Dub-noff metabolic shaking indicator set at 90 cycles/min, and allowed to equilibrate with air. The protein concentration was measured at this time by the biuret procedure and was adjusted to 2.4 mg/ml for all experiments unless otherwise specified. Experiments were initiated typically after 30 minutes of incubation.

Estimation of Percent Rod-Shaped Cells

Three drops of cell suspension (2.4 mg/ml) were removed at the times shown in the figures, and mixed with one drop of 2% glutaraldehyde in the MOPS buffer in order to fix the cellular configuration. For suspensions of 5 mg/ml, one drop of suspension was mixed with two drops 2% glutaraldehyde. One drop of the mixture was transferred to a glass slide, covered with a coverslip, and examined with a Zeiss binocular microscope at a magnification of 320x. The percent rod-shaped cells (i.e., cells with sarcomere lengths in the region of 1.8 μm) was counted as described previously (Haworth et al., 1981).

Measurement of Sugar Analog Uptake

Additions of 14C-labeled sugar analogs and 3H2O were made as described in legends to the figures. We removed 0.5-ml aliquots of cell suspension at the times shown, using plastic pipet tips with the ends cut off so that the opening was about 2 mm across. Aliquots were centrifuged through 0.5 ml of bromododecane into 0.1 ml of 16% perchloric acid, with a Beckman Microfuge B bench centrifuge. A spin time of 45 seconds was used, although the pellet was formed within seconds. The supernatants were collected with a Pasteur pipet and pooled, and the surface of the bromododecane layer was aspirated free of traces of remaining supernatant. The perchloric acid layer (pellet) was removed with a Pasteur pipet, put into 10 ml Aquasol scintillator, and counted. Supernatant (50 μl) plus an unlabeled cell pellet and 50 μl perchloric acid were also counted for 10 minutes. After correction for background and overlap of 3H and 14C counts, results were expressed either as percent permeation of cell pellet water (for methylglucose), or uptake in nmol/mg (for deoxyglucose).

In the case of methylglucose uptake, the supernatant 14C:3H ratio defines the 100% value. Thus, when pellet 14C:3H values are 100%, this means that the [14C]methylglucose has permeated as much space as the 3H2O, which rapidly equilibrates across the cell membrane and determines the total aqueous space available.

Biochemical Assays

ATP was measured in neutralized perchloric acid extracts by the enzymatic assay of Lowry and Passonneau (1972).

Lactate was measured in neutralized perchloric acid extracts of aliquots of cell suspension as previously described (Haworth et al., 1983).

Presentation of Data

Data shown usually are from single representative experiments, since the within-experiment error was much less than the between-experiment variability. All experiments were done at least three times. When data are shown with error bars or numerically, they are given as the mean ± SD from at least three experiments. The significance of differences between treatments was evaluated by paired t-test (Wallenstein et al., 1980).

Results

Contracture and Metabolic Demand

First, the effect of glucose, insulin, and isoproterenol on the rate of onset of contracture was investigated. Contracture was induced by adding rotenone (3 μM), which completely inhibits mitochondrial NAD-linked respiration, plus various levels of FCCP to alter the rate of ATP utilization. The change in medium pH was very small (<0.05 pH unit) over the course of experiments. With rotenone plus 6 pmol FCCP/mg, half of the cells without glucose underwent contracture after time t1/2 = 16.5 ± 1.6 minutes without isoproterenol and t1/2 = 13.4 ± 2.0 minutes with isoproterenol, and the presence of glucose alone was not effective in protecting the cells against contracture (Fig. 1A). In the presence of insulin, cells without glucose underwent contracture with the same time course as cells without insulin (Fig. 1B). With insulin plus glucose, however, the cells were well protected against contracture (Fig. 1B). When only 3 pmol FCCP/mg were present in addition to rotenone, the onset of contracture without insulin or glucose was delayed: t1/2 = 27.9 ± 0.6 minutes without isoproterenol, t1/2 = 22.5 ± 0.5 minutes with isoproterenol. Glucose plus insulin again protected against contracture, but this time glucose alone also gave some protection (data not shown). When only rotenone (no FCCP) was added, the onset of contracture without insulin or glucose
Figure 1. Effect of glucose, insulin, and isoproterenol on contracture induced by rotenone plus FCCP. Cells in experimental medium were treated with glucose (11 mM) ± insulin (1 \( \mu \mathrm{M} \)) 18 minutes before time zero, ± 1-isoproterenol (1 \( \mu \mathrm{M} \)) 2 minutes before time zero, as shown. Rotenone (3 \( \mu \mathrm{M} \)) was added 2 minutes after time zero, along with FCCP (6 pmol/mg). Cell samples were removed at the times shown, fixed, and the morphology determined, as described in Methods. Panel A: no insulin; panel B: plus insulin. O, no glucose; \( \Delta \), plus glucose; filled symbols, also plus isoproterenol.

was delayed further: \( t_{1/2} = 56.5 \pm 0.4 \) minutes without isoproterenol, \( t_{1/2} = 39.6 \pm 1.7 \) minutes with isoproterenol. Again, glucose plus insulin protected against contracture, but this time the presence of glucose alone was just as effective as when insulin was also present (data not shown). This suggests that, with rotenone alone, the ability of glucose to protect against contracture was not limited by the transport of glucose across the sarcolemma, but as the metabolic demand is increased by the addition of FCCP, the rate of transfer of glucose across the sarcolemma increasingly limits the ability of glucose to protect the cells.

Contracture, Lactate Production, and Metabolic Demand

The relationship between the onset of contracture and lactate production was investigated for cells without glucose or insulin. Since no glucose was present, glycolytic ATP came from glycogen metabolism, so 1 mol of lactate is equivalent to 1.5 mol of ATP produced. Without rotenone, the rate of lactate production was very low: 0.36 ± 0.05 nmol/min per mg without isoproterenol, and 2.00 ± 0.48 nmol/min per mg with isoproterenol. With rotenone, the rate of lactate production was stimulated, and more so as more FCCP was added (Fig. 2, A and B, inset). However, the rate of lactate production was always approximately linear for a period, and a similar end point was observed at which lactate production ceased, regardless of FCCP level (Fig. 2A). The initial linear rate of lactate production was linearly related to the level of FCCP added, and the effect of isoproterenol was to increase the rate of ATP production by a constant amount, independent of the FCCP effect (Fig. 2B, inset). The isoproterenol effect, which amounts to 4.70 ± 0.36 nmol ATP/min per mg, appears to be a measure of the metabolic cost of \( \beta \)-stimulation independent of inotropic effects. When the inverse of the rate of lactate production was plotted against the time taken for half the cells to undergo contracture (\( t_{1/2} \) from the experiments in Fig. 1), a linear relationship was observed (Fig. 2B), whether isoproterenol was present or not. This suggests that contracture occurs after a finite amount of endogenous substrate has been used up, and that the acceleration of contracture by isoproterenol is caused by its effect of increasing the rate of consumption of endogenous substrate.

ATP and Contracture

When ATP levels were measured in the same suspensions in which contracture was followed, it was found that ATP levels were maintained at their initial level until a short time before contracture occurred, and then declined in parallel with the onset of contracture (Fig. 3, shown for cells with rotenone plus 6 pmol FCCP/mg, without isoproterenol). A similar pattern was observed at all levels of FCCP, with or without isoproterenol, although the time lag between half-loss of ATP and half-loss of rod-shaped cells tended to increase with \( t_{1/2} \), i.e., as the metabolic demand was lowered (Fig. 3, inset). In each instance, the cellular ATP level was maintained constant at its original level for a period,
FIGURE 2. Relationship of metabolic demand, as measured by rate of lactate production, to the rate of onset of contracture without glucose. Cells in experimental medium (no glucose) were exposed to l-isoproterenol (1 μM), as shown, 4 minutes before time zero. Rotenone and FCCP (as shown) was added at time zero. Samples of cell suspension (0.2 ml) were removed at the times shown and added to 0.2 ml of cold 16% perchloric acid. Lactate content was then measured as described in Methods. Panel A: lactate accumulation vs. time; panel B: correlation between inverse of rate of lactate production and $t_{1/2}$, Time to Half Contracture (min).

FIGURE 3. Relationship between contracture and ATP. Cells were suspended in experimental medium (no glucose) at 5 mg/ml to facilitate ATP measurement. Rotenone (6 μM plus FCCP (6 pmol/mg)) was added at time zero. Samples (0.5 ml) were removed at the times shown and added to 0.5 ml cold 16% perchloric acid for ATP analysis, or a few drops were removed and fixed for morphological analysis.

Inset: difference between time of onset of contracture and ATP loss [$t_{1/2}$ (contracture) - $t_{1/2}$ (ATP)], as a function of metabolic demand [$t_{1/2}$ (contracture)]. N.B. symbols of inset as in figure 2.

before the drop began, and the original level was the same at all levels of FCCP, with or without isoproterenol. This justifies our use of the rate of lactate production in the presence of rotenone as a measure of the metabolic demand, because the rates are measured at a time when ATP levels are maintained constant at their original value: since almost all the ATP produced is coming from glycolysis, the rate of glycolysis is a measure of the rate at which ATP is being utilized. This suggests that the cells maintain their ATP levels until the endogenous substrate is used up, and then use up most of their ATP at a rate proportional to the metabolic demand, before undergoing contracture. We have previously given evidence that a similar contracture observed under conditions simulating ischemia is caused by a sudden and near total loss of cellular ATP (Haworth et al., 1981). A difference here is that we do not observe an initial phase of ATP loss seen under conditions simulating ischemia (Haworth et al., 1981).

3-O-Methylglucose Transport and Metabolic Demand

To investigate the relationship of induced glucose transport to metabolic demand, we measured the rate of 3-O-methylglucose uptake by contracted cells which had undergone contracture after exposure to rotenone plus various levels of FCCP, without glucose. 3-O-Methylglucose is a glucose analog which is carried into the cell by the glucose transporter, but which is not phosphorylated. Transport is a
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Passive process. Consequently, 3-O-methylglucose equilibrates with the cell water at a rate governed by the glucose permeability of the cell membrane (Whitesell and Gliemann, 1979; Haworth et al., 1984). Low concentrations of 3-O-methylglucose (<K_m>) were used in order to gain a measure of uptake rate uncomplicated by variable rates of back exchange (Whitesell and Gliemann, 1979). At equilibrium, the concentration of 3-O-methylglucose inside the cell is equal to that outside the cell. In the uptake assay (Fig. 4A), this is measured as 100% permeation of the cell pellet, when the ratio of pellet ^14C counts from 3-O-methylglucose to pellet ^3H counts from ^2H_2O is equal to the ratio of counts in the supernatant. (Uptake beyond 100% could suggest a small degree of 3-O-methylglucose binding inside the cell.) The cell pellet contains some extracellular medium, and this is allowed for by measuring the [^14C]sucrose-permeable space (Fig. 4A), since sucrose is not carried into the cell by the glucose transporter. 3-O-methylglucose permeation beyond the sucrose permeable space thus corresponds to intracellular penetration. Figure 4A shows the rate of 3-O-methylglucose uptake by cells contracted after the addition of rotenone plus 6 pmol FCCP/mg. Such cells had undergone contracture completely after 30 minutes. The rate of 3-O-methylglucose uptake after 35 minutes was slower in cells exposed to isoproterenol than in cells that had not been exposed (Fig. 4A). If the rate of sugar uptake was measured 15 minutes later, uptake rates were not significantly changed (Fig. 4A). This suggests that the post-contracture rate of uptake is fixed. Sucrose was not found to enter contracted cells (Fig. 4A), consistent with the cells’ continued ability to exclude trypan blue (Haworth et al., 1981). When the rate of 3-O-methylglucose uptake was measured after contracture induced by rotenone plus different levels of FCCP, it was found that the rate of entry was strongly dependent on what the metabolic demand had been (Fig. 4B). Cells treated with rotenone alone were able to induce a rate of 3-O-methylglucose uptake comparable to that in normal cells by insulin. With higher metabolic demands, however, the rate of induced 3-O-methylglucose uptake was increasingly curtailed. At each metabolic demand, the rate of induced 3-O-methylglucose uptake was found to be independent of the time after contracture (data not shown), like that shown in Figure 4A.

The effect of increasing levels of FCCP cannot be explained as direct inhibition of 3-O-methylglucose transport by FCCP: this level of FCCP had no observable effect on the rate of sugar uptake, either in normal cells or in contracted cells to which FCCP was added after contracture (data not shown).

The slower rates of 3-O-methylglucose uptake observed with isoproterenol (Fig. 4A) could be explained by the increased metabolic rate of such cells, inasmuch as cells with isoproterenol showed a dependence of sugar uptake rate on t_1/2 similar to that of cells without isoproterenol (Fig. 4B).

Glucose Uptake and Metabolic Demand

The above experiments suggest that the inability of glucose to protect cells against contracture as metabolic demand increases (Fig. 1) is caused by the decreased ability of such cells to transport the glu-
cose into the cell where it is needed. However, the experiments showing a dependence of induced uptake rate on metabolic demand (Fig. 4B) were necessarily done in the absence of glucose. It is possible that glucose would itself ameliorate this effect, since any glucose which enters will promote ATP production and, possibly, potentiate the further induction of glucose uptake capability. Unfortunately, 3-O-methylglucose cannot easily be used in the presence of glucose to measure glucose transport activity, because the unequal concentrations of glucose at either side of the membrane causes distortion of 3-O-methylglucose kinetics. We therefore investigated the effect of metabolic demand on glucose uptake by cells in the presence of glucose by using trace levels of 2-deoxyglucose (Sokoloff et al., 1977). 2-Deoxyglucose is another glucose analog that is carried by the glucose transporter. Unlike 3-O-methylglucose, it is phosphorylated inside the cell, but unlike glucose, it is metabolized no further (Wick et al., 1957). Since the rate of dephosphorylation is slow, it tends to accumulate at a linear rate inside the cell (Haworth et al., 1982b). The disadvantage of 2-deoxyglucose is that it does not simply measure the transport step. The rate of 2-deoxyglucose accumulation does, however, faithfully report the rate of glucose phosphorylation in rat heart (Takala and Hassinen, 1981), and so the ordinate in Figure 5A is labeled "glucose" uptake. Figure 5A shows that the basal uptake rate for glucose was very low (0.21 ± 0.02 nmol/min per mg), and was stimulated by rotenone plus various levels of FCCP, after a lag period comparable to the lag period before the onset of contracture without glucose (Fig. 1). However, the rate of glucose uptake was first stimulated and then inhibited as the metabolic demand was increased (Fig. 5A, inset). This uptake rate could reflect the rate of glucose phosphorylation by hexokinase (England and Randle, 1967), as well as the rate of glucose entry, but hexokinase will tend to become more active, not less, as the metabolic demand increases. The inhibition of "glucose" uptake seen at high metabolic demands (Fig. 5A, inset) is thus consistent with the effect of high metabolic demands on the rate of 3-O-methylglucose uptake in the absence of glucose (Fig. 4B). The increasing glucose uptake rate with demand seen at lower demands (Fig. 5A, inset) presumably reflects activation of the phosphorylation step, similar to that seen in insulin-treated hearts (Morgan et al., 1961). The effect of isoproterenol on glucose uptake at first appears equivocal, giving stimulation without FCCP and inhibition with FCCP. This is not inconsistent, however, since it can be understood in terms of the stimulation of metabolic rate by isoproterenol: this stimulation is approximately equivalent to the addition of a further 2 pmol FCCP/mg (dashed lines, Fig. 5A, inset; c.v. Fig. 2B, inset).

We then sought evidence that the inhibited rate of glucose uptake under these conditions limited the
glycolytic rate. When the lactate production of cells treated with rotenone plus 6 pmol FCCP/mg in the presence of glucose was measured, it was found that the rate of lactate production became inhibited after 10 minutes, like that of cells without glucose, although the inhibition was not quite so complete (Fig. 5B). If insulin was also present, the rate of lactate production was not inhibited (Fig. 5B). This shows that the inhibition of sugar transport under these conditions (Figs. 4B and 5A) limited the rate of glycolysis.

Chronology of Contracture and Induction of Glucose Transport

Since the above data suggested a possible correlation between the time at which cells without glucose would undergo contracture and the time at which glucose transport capability is induced, we investigated this relationship more closely by measuring 3-O-methylglucose uptake and the onset of contracture in the same suspension of cells. Cells as isolated have an extremely low basal rate of 3-O-methylglucose uptake. This basal rate is biphasic, reflecting a small population of cells with finite uptake rates and most cells with rates that are essentially zero (Haworth et al., 1984). This property allowed us to monitor 3-O-methylglucose uptake continually on the same time scale and in the same experiment as we monitored the onset of contracture. Figure 6 shows the time course of 3-O-methylglucose uptake by cells to which the 3-O-methylglucose was added 30 minutes before time zero. The subsequent addition of rotenone plus 6 pmol FCCP/mg clearly induced the further uptake of 3-O-methylglucose after a lag period. Unexpectedly, 3-O-methylglucose uptake was induced in cells without isoproterenol significantly before it was induced in cells with isoproterenol (Fig. 6; Table 1). The onset of contracture (Fig. 6; Table 1). The onset of contracture, on the other hand, occurred significantly later for cells without isoproterenol than for cells with isoproterenol (Table 1), in agreement with the data in Figure 1. Some idea of the relative timing of events was gained by comparing the time at which the inhibitor-stimulated 3-O-methylglucose uptake was half complete (t1/2 3-O-methylglucose) to the time at which half of the cells had undergone contracture (t1/2 contracture). For cells without isoproterenol, there was no significant difference between these t1/2 values. For cells with isoproterenol, 3-O-methylglucose influx appeared to occur significantly later than the onset of contracture, by about nine minutes under these conditions (Table 1). It thus appears that isoproterenol can reduce the impact of glucose influx, not only by reducing its extent, but also by delaying its onset with respect to the contracture event.

Discussion

Glucose transport can be induced in whole hearts by uncouplers of oxidative phosphorylation, anoxia

**Table 1**

| Effect of Isoproterenol on the Onset of 3-O-Methylglucose Permeability |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| t<sub>1/2</sub> contracture (min) | 17.2 ± 1.7 | 14.3 ± 2.5 | 2.9 ± 1.1 | <0.025 |
| t<sub>1/2</sub> 3-O-methylglucose (min) | 16.5 ± 3.3 | 23.0 ± 2.2 | −6.5 ± 3.0 | <0.05 |
| Δ | 0.7 ± 5.0 | −8.7 ± 4.0 | |
| P | NS | <0.05 | |

Conditions were as described in the legend to Figure 6. Results are mean ± so from three experiments in which both t<sub>1/2</sub> (contracture) and t<sub>1/2</sub> (3-O-methylglucose) were measured. The significance (P) of differences between t<sub>1/2</sub> values (Δ) was evaluated with the paired t-test.
been found in skeletal muscle (Korbl et al., 1977). However, the beneficial effect of the glucose can itself delay the onset of contracture when metabolic loads are low, thus obscuring the correlation found without glucose (Table 1; Fig. 3).

The induction of glucose transport by insulin is thought to involve the movement (recruiting) of preformed glucose transporters from the Golgi fraction to the plasma membrane (Suzuki and Kono, 1980; Cushman and Wardzala, 1980) by an ATP-requiring process (Siegel and Olefsky, 1980). Since glucose transport cannot be induced by metabolic demand beyond that induced by insulin (Morgan et al., 1959), the induction of transport by metabolic demand could well involve the recruiting of the same pool of glucose transporters. This suggests a possible mechanism for the observed dependence of 3-O-methylglucose transport rate on metabolic demand (Fig. 4B). If the recruiting of transporters by metabolic demand takes a certain amount of time, it could be prematurely terminated in cells with a high metabolic demand by the loss of ATP: the time between the signal to recruit transporters and the loss of ATP could well be inversely related to the rate of ATP utilization, if the signal is itself initiated in some way by near exhaustion of endogenous substrate. Thus, for the sake of illustration, suppose that the signal for recruitment was given when a cell used up its endogenous glycogen, when its only remaining (anaerobic) resources were its ATP plus some creatine phosphate. The time available for the ATP-dependent movement of transporters to the sarcolemma would be short if the cell had a high metabolic demand and used up its residual ATP quickly. This would result in only a partial activation of glucose transport, the process being arrested (see Fig. 4B) by ATP loss (Fig. 3). For cells with a lower metabolic demand, the ATP pool would be available for longer after the initiation of the recruitment signal, allowing the complete movement of transporters to the sarcolemma.

The effect of isoproterenol on the timing of glucose transport induction (Fig. 6; Table 1) appears anomalous in the terms discussed above, since it appears to occur after contracture (Table 1) when the cells have lost their ATP (Fig. 3). This could perhaps be explained by the transporters being recruited at the same time relative to contracture, as in cells not treated with isoproterenol, but being inactivated by phosphorylation. The activation observed (Fig. 6) would then be indicative of the rate of transporter dephosphorylation in cells with very low ATP, rather than of the rate of transporter recruitment.

The metabolic consequences of rotenone addition for the cells here are very similar to those experienced by cells in whole hearts undergoing high flow anoxia. In both cases, the possibility of oxidative substrate metabolism is eliminated, and the cells must resort to glycolysis or glycogenolysis as a source of ATP. In both cases, the pH of the bathing medium remains near normal. In both cases, the permeability of the cell's membrane to glucose is initially low in the absence of insulin; this will be true in the whole heart in the fasted condition. Thus, it is possible that the limitation of glucose transport induction by high metabolic demand shown here in isolated cells is a significant factor determining the survival of heart cells in vivo exposed to high flow anoxia. The effect of isoproterenol on glucose transport in vivo could be greater than that observed here on quiescent cells, since the inotropic effect in vivo will increase the metabolic demand much more.

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