

Metabolic Rate and Blood Hormone and Metabolite Levels of Individuals Susceptible to Malignant Hyperpyrexia at Rest and in Response to Food and Mild Exercise

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Resting metabolic rate and the energy cost of performing a specific (light) work load on a bicycle ergometer were measured in nine subjects susceptible to malignant hyperpyrexia (MHS) and nine control subjects, both fasting and following a 600-kcal meal. Blood glucose, lactate, pyruvate and serum triglycerides, thyroxine, cortisol, creatine kinase, growth hormone, and calcium and potassium levels at rest and immediately following exercise, after fasting and eating, were measured. There was no evidence of increased heat production in the MHS subjects compared with controls. The MHS subjects, however, showed a complete absence of dietary-induced thermogenesis with exercise. Compared with the controls, MHS subjects had higher insulin levels for essentially the same blood glucose values. Triglycerides in the MHS group rose steadily over the course of the experiment, whereas in the controls they did not vary from the initial value. Lactate did not rise as much with exercise in the MHS group but did not fall with rest, and pyruvate did not change from resting fasting values, whereas in the controls it rose steadily. Differences were also found in thyroxine and cortisol levels between the MHS and control groups. The shunting of blood away from thermogenic tissue is suggested as a mechanism for the absence of diet-induced thermogenesis with exercise in the MHS group and the possibility of an underlying abnormality of cardiovascular (sympathetic) control mechanisms in these subjects is discussed. The biochemical abnormalities are discussed in relation to previous biochemical data from MHS humans and pigs and in relation to the abolition of dietary-induced thermogenesis. (Key words: Complications: malignant hyperthermia. Hormones: adrenal; insulin; thyroid. Hyperthermia: malignant. Metabolism: fasting; glucose; insulin; lactate; metabolites; oxygen consumption; pyruvate.)

MALIGNANT HYPERTHERMIA (MH) is a rare syndrome seen during general anesthesia when susceptible (MHS) individuals are given one or more of the various triggering agents, most commonly a depolarizing muscle relaxant or an inhalational anesthetic agent, usually halothane. There is a dramatic rise in meta-

bolic rate and generally a rise in body temperature which, if not treated promptly and effectively, usually results in the patients' death. Muscle rigidity, cyanosis, hyperkalemia, myoglobinuria, and severe metabolic and respiratory acidosis may be associated with the increase in metabolism. If the patient survives the acute episode, later complications include renal failure, consumption coagulopathy, and hypokalemia.^{1,2} Susceptibility to MH is determined by muscle biopsy and the response of the muscle fiber to halothane and caffeine exposure *in vitro*.^{3,4}

Certain breeds of pig are known to suffer from a similar condition. MH episodes in these animals are triggered not only by anesthetic agents, but also by various forms of stress. Williams and co-workers have described MH developing in swine during exercise, transportation, breeding, and on merely being coaxed into a calorimeter. They have also found that MHS pigs have resting metabolic rates "several times higher than normal."^{5,6} There are no data, however, on metabolic rate of human MHS individuals either at rest or exercising, or under stress of any sort. Although it has been said that trauma, stress, or exercise can trigger MH episodes in humans,² the evidence is anecdotal,^{7,8} and no systematic study has been made of heat production of MHS individuals during exercise.

In the present study, the metabolic rates of human MHS subjects were measured at rest and during mild exercise, both fasting and following a standard meal. The investigation was undertaken to determine whether MHS individuals have raised metabolic rates at rest, whether it costs them more in terms of energy expenditure to perform a standard work load on a bicycle ergometer, and whether these subjects show a normal thermogenic response to food.

In addition, measurements were made of various hormones and metabolites generally associated with metabolism and/or stress responses (insulin, glucose, triglycerides, lactate, pyruvate, cortisol, thyroxine, and growth hormone) or those associated with malignant hyperpyrexia, either the susceptibility (creatin kinase) or the acute episode (potassium, calcium).

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Materials and Methods

SUBJECTS

The subjects were patients referred for diagnostic muscle biopsy to determine their susceptibility to malignant hyperpyrexia.³ They were either patients who had survived a suspected MH episode or relatives of known MHS individuals.

Informed consent was obtained. The study was performed on the day before the biopsy so it was not known at the time whether or not the subject was susceptible. Following the results of the biopsy, each subject was assigned to the control or the MHS group. The control group consisted of nine individuals (six men and three women) and the MHS group of nine individuals (five men and four women). Mean age of the MHS group was 34 years, mean height 179 cm, and mean weight 79.7 kg. Mean age of the control subjects was 33 years, mean height 172 cm, and mean weight 71.5 kg. There was no significant difference in age, height, or weight between the two groups.

TEST PROCEDURE

Subjects were admitted to the hospital the day prior to the study. Chest x-ray, ECG, complete blood count, and a routine physical examination were carried out. No subject suffered from any detectable systemic illness. Food and drink, except for water, were withheld after 10 P.M. the day of admission. The patients were taken to the laboratory at about 7:45 A.M. the following day.

On arrival, a cannula was inserted into an ante cubital vein under local anesthesia. They then rested supine for 30 min, after which metabolic rate was measured for four periods of 5 min with 5-min intervals between each measurement. They then rode a mechanically braked bicycle ergometer for 20 min at a work rate of 67 watts, equivalent in effort to walking on the level at a rate of 5 km/hr. Metabolic rate was

measured from the sixth to the tenth, and from the sixteenth to the twentieth min of the exercise period. Subjects then rested and consumed a standard 600-kcal meal of 135 g of Complax® (Farley Health Products Ltd.), in 350 ml of water over a 10-min period. Measurements of resting metabolic rate were resumed 10 min after the finish of the meal, at the same frequency and the same duration as the fasting measurements. After four resting measurements (50 min after the meal), the exercise on the bicycle was repeated and metabolic rate again measured from the sixth to the tenth, and from the sixteenth to the twentieth min.

Resting metabolic rate was taken as the mean of the last three of the four resting measurements, both fasting and fed, and the exercising metabolic rate as the mean of the two measurements made during each exercise period.

Blood was taken through the indwelling venous cannula at the end of the resting periods and at the end of each exercise period. The fed resting sample was taken 55 min after the start of the meal, and the fed exercising sample 80 min after the start of the meal.

MEASUREMENT OF METABOLIC RATE

Metabolic rate was measured by indirect calorimetry. Expired air was collected in a Douglas® bag and its volume measured using a Tissot® spirometer. Oxygen percentage in the expired air was measured with a paramagnetic oxygen analyzer (Taylor Servomex®, Model OA 272) calibrated with oxygen free nitrogen and with room air. Metabolic rate was calculated using the Weir formula.⁹

BIOCHEMICAL ANALYSIS

With the exception of glucose, lactate, and pyruvate where whole blood was used, all biochemical measurements were made on serum. The following analytical techniques were employed. Glucose was determined

TABLE 1. Metabolic Rate and Thermic Effect of Food on MHS and Control Subjects at Rest and Exercising*

	Resting			Exercising		
	Fasting	Fed	Thermic Effects	Fasting	Fed	Thermic Effects
MHS subjects (n = 9) (kcal/min) (kcal·m ⁻² ·h ⁻¹)	1.23 ± 0.05 38.39 ± 0.91	1.38 ± 0.05 43.00 ± 1.14	0.15 ± 0.03 4.57 ± 1.10	4.94 ± 0.16 —	4.92 ± 0.19 —	-0.02 ± 0.04† —
Control subjects (n = 9) (kcal/min) (kcal·m ⁻² ·h ⁻¹)	1.14 ± 0.05 37.29 ± 1.09	1.28 ± 0.05 41.79 ± 1.18	0.12 ± 0.03 4.50 ± 0.74	4.82 ± 0.13 —	5.17 ± 0.14 —	0.35 ± 0.08 —

* Values are means ± SE.

† Significantly different from controls; P < 0.05.

TABLE 2. Blood Hormone and Metabolite Levels of Control Subjects* (n = 9)

	Rest Fasting	Exercise Fasting	Rest Fed	Exercise Fed
Glucose (mg/dl)	82 ± 2	81 ± 2	113 ± 6	82 ± 3
Insulin (μU/ml)	6 ± 1.5	15 ± 3	52 ± 8	19 ± 4
Triglycerides (mmol/l)	1.31 ± 0.13	1.28 ± 0.15	1.21 ± 0.14	1.22 ± 0.15
Cortisol (nmol/l)	539 ± 52	504 ± 50	461 ± 42	531 ± 48
T ₄ (nmol/l)	121 ± 9	128 ± 10	123 ± 9	126 ± 10
Growth hormone (mU/l)	3 ± 1	3 ± 2	3 ± 1	4 ± 2
CK (IU/l)	72 ± 14	81 ± 13	83 ± 12	79 ± 12
Lactate (mmol/l)	0.85 ± 0.10	1.62 ± 0.23	1.04 ± 0.12	1.81 ± 0.36
Pyruvate (mmol/l)	0.035 ± 0.011	0.050 ± 0.007	0.079 ± 0.048	0.094 ± 0.038
K ⁺ (mmol/l)	4.2 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.5 ± 0.1
Ca ⁺⁺ (mmol/l)	2.37 ± 0.03	2.41 ± 0.03	2.37 ± 0.04	2.44 ± 0.02

* Values are means ± SE.

by the glucose oxidase method¹⁰ using blood anticoagulated with potassium oxalate and preserved with sodium fluoride; insulin by a radioimmunoassay method using the Phadebas Insulin Test[§]; triglycerides by alkaline hydrolysis followed by enzymatic analysis of the glycerol released[¶]; lactate and pyruvate were enzymatically determined according to Hadjivasiliou and Rieder¹¹ using blood taken into tubes containing 250 mg of Longs mixture;¹² cortisol by fluorimetry as described by Mattingley;¹³ creatine kinase by spectrophotometry;¹⁴ growth hormone by a double antibody radioimmunoassay; thyroxine (T₄) by a radioimmunoassay;¹⁵ potassium by flame photometry; and calcium by colorimetry using orthocresol phthalate complexone.

Statistical comparisons were made on the results of metabolic rate measurements using Student's *t* test for paired and unpaired data, and on the hormone and metabolite results using the Mann Whitney U test and the Wilcoxon signed-rank Test.

Results

METABOLIC RATE (TABLE 1)

There was no difference in resting metabolic rate, between the MHS subjects and the controls when fasting (table 1). Likewise, energy expenditure of both groups when exercising while fasting was the same. The thermic effect of food was calculated as the difference between metabolic rate in the fed and fasting states. At rest, this effect was about 12 per cent in both groups. The increase in resting metabolic rate was significant in both cases ($P < 0.001$) but there was no difference between the two groups. The thermic effect of food during exercise was an increase of 0.35 kcal/min in the energy expenditure of the control group

($P < 0.001$), but the metabolic rate of the MHS group did not change, being the same when fed as it had been fasting.

HORMONE AND METABOLITE LEVELS (TABLES 2 AND 3)

Blood glucose. Blood glucose levels of the MHS subjects tended to be higher than the control subjects throughout the experiment but at no stage was this difference significant. Glucose values did not change significantly with exercise from the fasting resting level, but rose markedly in both groups with the liquid meal, and fell with the ensuing exercise.

Serum insulin. The MHS group had fasting insulin levels significantly higher than the controls ($P < 0.025$). This difference persisted throughout the experiment although it was statistically significant again only with the fed exercising measurements. Glucose/insulin ratios (table 4) were significantly lower in the MHS group than in the controls at rest and exercising fasting, and at rest, fed ($P < 0.05$).

Serum triglyceride. Serum levels of both groups were comparable when fasting, at rest. Triglyceride values of the control group did not change significantly during the experiment but in the MHS group rose persistently such that by the end of the experiment, they were significantly higher than the initial fasting levels, at rest ($P < 0.01$).

Serum cortisol. MHS subjects tended to have lower cortisol levels than the controls although this was significant only with the combination of food and exercise ($P < 0.05$).

Serum thyroxine. Fasting thyroxine values of the two groups at rest were very similar. Thyroxine levels of the control group rose significantly with exercise ($P < 0.05$), fell significantly resting fed ($P < 0.05$), and rose again significantly with the second exercise period. Thyroxine concentrations of the MHS group did not alter over the period of the experiment. Thyroxine levels of the MHS group tended to be lower

§ Pharmacia Diagnostics, Upsala, Sweden.

¶ Boehringer Test Combination, 126012.

TABLE 3. Blood Hormone and Metabolite Levels of MHS Subjects* (n = 9)

	Rest Fasting	Exercise Fasting	Rest Fed	Exercise Fed
Glucose (mg/dl)	86 ± 5	88 ± 4	109 ± 16	87 ± 7
Insulin (μIU/ml)	14 ± 2†	22 ± 2	63 ± 10	36 ± 6†
Triglycerides (mmol/l)	1.20 ± 0.20	1.45 ± 0.23	1.39 ± 0.26	1.61 ± 0.32
Cortisol (nmol/l)	504 ± 31	514 ± 43	414 ± 48	430 ± 31†
T ₄ (nmol/l)	120 ± 9	121 ± 9	120 ± 9	121 ± 8
Growth hormone (mU/l)	3 ± 2	3 ± 2	3 ± 2	3 ± 2
CK (IU/l)	224 ± 94	228 ± 95	212 ± 77	228 ± 96
Lactate (mmol/l)	1.18 ± 0.22	1.32 ± 0.30	1.47 ± 0.15	1.52 ± 0.17
Pyruvate (mmol/l)	0.028 ± 0.005	0.050 ± 0.019	0.045 ± 0.023	0.031 ± 0.020
K ⁺ (mmol/l)	4.2 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.6 ± 0.1
Ca ⁺⁺ (mmol/l)	2.35 ± 0.04	2.36 ± 0.05	2.40 ± 0.03	2.41 ± 0.03

* Values are means ± SE.

† Denotes significant difference from control subjects (P < 0.05).

than the control group, but this difference was not significant.

Growth hormone. Growth hormone levels were the same in both groups of subjects and did not alter over the course of the experiment.

Serum creatine kinase (CK). Mean CK levels of the MHS group were markedly higher than the controls, but this difference was not statistically significant. CK levels of six of the MHS subjects actually fell within the normal range, but CK levels of the other three MHS individuals were so elevated as to create a marked difference in the two means.

Blood lactate. Lactate values rose significantly in the control subjects (P < 0.025) with each exercise period and fell significantly at rest. Lactate concentrations in the MHS subjects rose less acutely than the controls with exercise, but did not fall with rest. Lactate values in the resting fed and exercising fed MHS group were significantly higher than the resting fasting measurement at the start of the experiment (P < 0.05).

Blood pyruvate. Pyruvate levels of the control group rose throughout the experiment and with the exercise period, fed, were significantly higher than when fasting resting (P < 0.025). In the MHS group, pyruvate rose slightly with the first exercise period then fell. At no time did it differ significantly from the resting fasting value.

Serum potassium and serum calcium. There was no difference in potassium or calcium concentrations between the two groups. Potassium levels of both groups tended to rise very slightly with exercise and fall at rest, but calcium values did not alter throughout.

Discussion

There was no evidence in the present study for increased metabolism in the MHS subjects either at rest or during exercise. Both the MHS and the control groups expended the same amount of energy in the performance of the same work load on the ergometer. Although Williams *et al.*⁶ have stated that MHS pigs

have basal metabolic rates several times higher than normal, closer inspection of their data does not entirely bear this out. In one publication,⁵ oxygen consumption results are presented only for two pigs who developed MH under the stress of being placed in a calorimeter and none for the three who adjusted quickly to their new environment and went to sleep. In a later publication,⁶ the calorimeter data shows oxygen consumption, carbon dioxide production, and heat production continually rising. It is difficult to see how this could be considered a basal measurement. Gronert and Theye,¹⁶ and Gronert *et al.*¹⁷ give values for oxygen consumption under light thiopental nitrous oxide-oxygen anesthesia which show no difference between the two groups.

In the present study the MHS subjects had normal "basal" (resting, fasting) metabolic rates. Both groups exhibited a normal thermic response (or specific dynamic action) to food with a 12 per cent rise in resting metabolic rate. This postprandial rise in metabolism is a phenomenon normally seen with ingestion of food, and is thought to be due to the energy expended in absorption and assimilation via the splanchnic circulation and the liver. Following the test meal the energy cost of riding the bicycle rose by 0.35 kcal/min (7 per cent) in the control group but was the same after the meal in the MHS subjects as it had been fasting. The abolition of dietary thermogenesis with exercise has been observed previously on exposure to high altitude¹⁸⁻²⁰ and was ascribed to the shunting of blood

TABLE 4. Glucose/Insulin Ratios of MHS and Control Subjects at Rest and Exercising, Fasting and at Rest and Exercising Fed*

	Rest Fasting	Exercise Fasting	Rest Fed	Exercise Fed
Controls	21.8 ± 7.9	6.4 ± 0.7	2.6 ± 0.3	6.36 ± 2.2
MHS	6.8 ± 1.3†	4.6 ± 0.8†	1.6 ± 0.2‡	2.9 ± 0.5

* Values are means ± SE.

† Denotes significant difference from control P < 0.05.

‡ P < 0.01.

away from thermogenic tissue, *e.g.*, liver, to the exercising muscle. It was suggested that this was mediated by and occurred secondary to changes in sympathetic vascular control mechanisms brought about by the hypoxia of altitude.^{21,22} If the same mechanism is responsible for the abolition of dietary thermogenesis in the MHS subject, it is possible that differences may exist between the two groups in vasomotor control mechanisms which by implication may involve the sympathetic nervous system. An alternative explanation for the abolition of dietary thermogenesis would be a failure in the MHS subject to absorb the test meal, but as the rise in resting metabolism and the rise in blood glucose after ingestion of the meal were similar in both groups, this is unlikely.

The sympathetic nervous system certainly plays a part in MH, but its precise role is uncertain. High circulating levels of epinephrine and norepinephrine have been found in many studies of the acute MH episode in animals.^{17,23-25} The condition has been prevented by adrenergic blockade²⁵ (phentolamine) and by epidural analgesia,²⁶ although it has also been induced in totally sympathectomized animals.¹⁷ The severity of the episode in this instance, as judged by arterial pH, was equal to that in pigs with their sympatho-adrenal system intact, but there was no change (rise) in catecholamine levels. Signs of sympathetic over activity—tachycardia, peripheral vasoconstriction—are features of the episode in humans, and Mogensen *et al.*²⁷ suggested that extreme nervousness preoperatively with consequent sympathetic overactivity predisposes to the development of the condition intraoperatively. Williams^{6,28-30} postulated that MHS individuals have an excess of norepinephrine possibly caused by a defect in its degrading enzymes and suggested that MH is “an acute norepinephrine toxicity reaction.”²⁸ Gronert³¹ considered that the rise in catecholamines which occurs during an MH episode is secondary to the stress of the reaction, and while contributing to its severity, is not in itself the primary cause. This view has been put forward previously by Moulds.³² The absence of dietary thermogenesis in exercising MHS subjects is indirect evidence that there may possibly be a difference in the sympathetic control of vasomotor activity in MHS individuals compared with normal subjects.

The biochemical changes during an acute episode of MH are well documented, especially in pigs, but little work has been reported on susceptible pigs or humans under any other circumstances. Van den Hende *et al.*³³ showed that a period of exercise prior to halothane challenge raised both the incidence and severity of an MH episode in a population of Belgian Landrace pigs. Eikelenboom and Weiss³⁴ demonstrated elevated thyroxine levels in Pietrain pigs, a breed known to be

particularly susceptible to MH. A similar observation has been made by Eighmy *et al.*³⁵ although they were unable to show any difference between triiodothyronine or thyroxine levels of suspected human MHS and normal subjects. Lister³⁶ noted a fall in free thyroxine index during acute MH and was able to abort an MH episode by giving incremental doses of triiodothyronine during the onset of the syndrome. Judge *et al.*³⁷ observed higher protein bound iodine levels and lower ¹³¹I uptakes in stress susceptible pigs compared with resistant animals. Ludvigsen³⁸ has been able to reproduce, in normal pigs, the characteristic postmortem changes seen in stress susceptible animals, by feeding them thyrostatic drugs. He found that feeding iodinated caseine to susceptible animals abolished the syndrome.

Abnormalities of corticosteroid metabolism in stress susceptible pigs have been recognized for some time as have structural abnormalities in the adrenal cortex.³⁸⁻⁴¹ Lower cortisol levels have been found in response to environmental stresses than seen in stress resistant pigs. Early studies suggested a defect in cortisol production, but more recent work has demonstrated that stress susceptible pigs have a rate of cortisol production and utilization several times higher than stress resistant animals.⁴²

Ludvigsen³⁸ showed that in stress susceptible pigs, lactate levels in the blood did not rise with exercise as much as in controls because the lactate appeared to remain within the body of the muscle. Blood cortisol values in these animals were abnormally low and he demonstrated that with injected hydrocortisone, blood flow through the muscle appeared to be improved and lactate levels in the circulation rose toward those of control animals.

In the present study several differences in hormone and metabolite levels were demonstrated. The significantly lower glucose/insulin ratios in the MHS group and the significant rise in triglycerides would support the hypothesis made earlier of differences in sympathetic activity between the two groups. The rise in triglycerides could be explained by increased lipolysis and re-esterification of the free fatty acids released following sympathetic stimulation.⁴³ The decreased glucose/insulin ratios could be interpreted as representing insulin resistance which again could be due to sympathetic nervous activity. Higher insulin levels have been observed previously by Denborough *et al.*⁴⁴ although they were ascribed to a possible abnormality of calcium metabolism within the cells of the islets of Langerhans. The blood glucose values were not reported.

There was no statistically significant difference in lactate or pyruvate levels between the two groups in this investigation at any stage. However, in the MHS

subjects, lactate did not rise as much with exercise as it did in the controls, and did not fall with rest, but actually continued to rise. A decrease in splanchnic blood flow which was suggested earlier could account for the impaired ability of the MHS subjects to metabolize lactate while resting, although this could also be explained by lactate accumulating in the muscle during exercise and leaching out over the ensuing rest period. This mechanism would be compatible with the corticosteroid abnormalities discussed above.³⁸ Hall *et al.*⁴⁵ found evidence for reduced hepatic blood flow during the acute MH episode in Pietrain pigs but also found that lactate uptake by the liver at this time was in fact increased.

Cortisol levels of the MHS subjects were lower than the controls following the combined "stress" of food and exercise. There appears to be no data available on adrenocortical function in human MHS subjects although steroids have been used successfully in the treatment of acute MH episodes in humans.^{46,47} As mentioned earlier, low cortisol levels and a faster turnover rate of cortisol have been found in stress susceptible pigs when compared with controls. Hall *et al.*⁴⁸ found relatively low cortisol levels in pigs undergoing an acute hyperthermic episode. They thought that the very high catecholamine levels they found in these animals may have decreased the plasma cortisol concentrations by an action on the hypothalamus. The MHS subjects showed an abnormality similar to the pigs with low serum cortisol levels described by Ludvigsen, in that lactate failed to rise significantly with exercise.

The effect of exercise on thyroxine levels is ill defined. Both rises and falls in thyroid related substances have been described. The precise picture may depend upon such variables as severity and duration of exercise, and physical fitness,^{49,50} but the MHS subjects in the present study failed to show the rise in thyroxine levels with mild exercise that occurred in the control subjects.

The significance of the elevated CK levels in MH and the prediction of MH susceptibility has been the subject of some controversy. An elevated CK is generally thought to raise the index of suspicion of MH susceptibility but is non specific. The fact that the mean CK of the MHS subjects was markedly higher than the controls (fasting resting levels 154 IU/l higher) while the difference failed to reach statistical significance reflects the very wide variation of CK values to be found in susceptible subjects. The fact that the CK concentration of six of the susceptible subjects fell within the normal range also throws serious doubt on the value of this measurement as a screening test for MH.

In summary, a number of abnormalities have been demonstrated in MHS subjects during exercise and on

the ingestion of food. There was no evidence of increased metabolism, but the abolition of dietary-induced thermogenesis suggested that there could be an abnormality of cardiovascular control mechanisms which by implication must involve the sympathetic nervous system. The decreased glucose/insulin ratios (implying insulin resistance) and the steady rise in triglyceride concentrations would support this contention. The low cortisol concentration found with the combination of food and exercise is consistent with previous findings in stress susceptible pigs, and could provide an explanation for the failure of lactate to rise significantly with mild exercise. These findings could be explained by a primary abnormality in the central control of the sympatho-adrenal axis or they could equally be a reaction secondary to some process occurring elsewhere in the body. The most obvious site for this would be within the exercising muscle.

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