

Hepatectomy and Arterial Blood Ketone-Body Ratio

I. Changes in Arterial Blood Ketone-Body Ratio Following Massive Hepatectomy in Relation to Blood Concentration of Energy Fuels

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Abstract

The changes in energy charge of the remnant liver and ketone-body ratio (acetoacetate/3-hydroxybutyrate) of arterial blood were examined in hepatectomized rabbits in relation to the blood energy fuels and the standard liver function tests. It is suggested that (a) the decrease in energy charge is the basis of the decreased hepatic functional reserve, (b) the change in energy charge is accurately reflected by the change in blood ketone-body ratio and (c) the decreased blood ketone-body ratio is the basis of the sequential changes in the blood concentrations of fuels after hepatectomy.

Introduction

Major hepatic resection represents an aspect of surgery that demands a detailed understanding of the metabolic changes occurring in the remnant liver^{1,2,7,17,18,30,34,35,42}. In this regard, we have reported that after major hepatic resection liver mitochondria play an important role in restoring hepatic energy charge level $(ATP + 1/2 ADP)/(ATP + ADP + AMP)$ which decreases postoperatively¹². Recent studies in our laboratory further show that there is a close relationship between hepatic energy charge level and arterial blood ketone-body ratio (acetoacetate/3-hydroxybutyrate) in jaundiced rabbits³⁶ and shock-induced rats⁴¹. The ketone-body ratio of arterial blood is closely related with the oxido-reduction state of free NAD^+ - $NADH$ couples in liver mitochondria, which regulates the activity of tricarboxylic acid cycle and eventually influences the turnover rate of electron transport system.

In the present study, the changes in ketone-body ratio of arterial blood and energy charge level of the remnant liver were examined in 25, 70 and 93% hepatectomized rabbits, and the

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Key words: Hepatectomy, Hepatic energy charge, Blood ketone-body ratio, Blood energy substrate, Liver function tests.

索引語: 肝切除, 肝エネルギーチャージ, 血中ケトン体比, 血中エネルギー基質, 肝機能検査.

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changes in the blood concentrations of glucose, free fatty acids, ketone bodies, amino acids and the standard liver function tests were examined in 70% hepatectomized rabbits. Evidence will be presented indicating that arterial blood ketone-body ratio serves as a reliable parameter for the severity of the changes in hepatic energy charge levels after hepatic resection, and mitochondrial oxido-reduction state reflected by the blood ketone-body ratio plays an important role in controlling blood glucose, plasma free fatty acids and plasma amino acids following massive hepatic resection.

Materials and methods

Healthy young male rabbits, weighing 1.8–2.3 kg, were maintained on a commercial diet (CR-2, Nippon Clea Co., Ltd., Tokyo, Japan) and water *ad libitum* for 2 weeks before experimental use. Room temperature was kept at 21–25°C and a 12-hr light-dark cycle was employed. All rabbits were fasted for 15 hr before operation and sampling. Operation was carried out between 8–10 a.m. under an intravenous anesthesia of thiamylal sodium (15 mg/kg of body weight). After a preliminary examination to determine the weight of each lobe, the right anterior lobe was resected for 25% hepatectomy; the right anterior, right posterior and left anterior lobes for 70% hepatectomy; and all lobes except for the central lobe for 93% hepatectomy. In sham-operated rabbits, laparotomy and mobilization of liver were carried out.

Blood and liver samples were taken at 12, 24, 48 and 96 hr after operation under the intravenous anesthesia of thiamylal sodium (10 mg/kg). As 93% hepatectomized rabbits scarcely survived for 12 hr, samplings for this group were performed at 4 and 8 hr after operation. When any sample was taken, it was ascertained that the animal maintained ample respiration and an arterial blood pressure of above 80 mmHg.

For the assay of adenine nucleotides in hepatic tissue, the left posterior lobe or the central lobe was clamped and frozen *in situ* with stainless steel tongs precooled in liquid nitrogen. The entire procedure was completed within 10 sec. Frozen tissue was then pulverized to a fine powder with a mortar and pestle in a liquid nitrogen bath. One gram of powdered tissue was homogenized in 3 ml of ice-cold 6% (wt/vol) perchloric acid. The homogenate was then centrifuged at $10,000 \times g$ for 15 min at 0–4°C. The supernatant was adjusted to pH 6.0 with 69% (wt/vol) K_2CO_3 and recentrifuged at $10,000 \times g$ for 5 min at 0–4°C. The final supernatant was immediately used to determine the amounts of adenine nucleotides. ATP, ADP and AMP contents were measured enzymatically^{11,15)}. Adenylate energy charge was calculated from the equation $(ATP + 1/2 ADP)/(ATP + ADP + AMP)^{4,5)}$.

For the assay of ketone bodies in arterial blood, 2 ml of blood was taken via the femoral artery. It was added to 4 ml of ice-cold 6% perchloric acid and mixed well immediately. The suspension was centrifuged at $10,000 \times g$ for 15 min at 0–4°C. The supernatant was adjusted to pH 6.0 and recentrifuged at $10,000 \times g$ for 5 min at 0–4°C. The final supernatant was immediately used to determine the concentrations of blood ketone bodies. Acetoacetate was measured by a modification of the method of MELLANBY and WILLIAMSON¹⁹⁾, and 3-hydroxybutyrate by a modification of the method of WILLIAMSON and MELLANBY²⁰⁾.

Standard liver function tests using arterial blood were carried out by the following methods: prothrombin time according to QUICK *et al.*³¹⁾, serum total protein by biuret reaction⁶⁾, serum albumin by dye binding method⁶⁾, cholinesterase according to MICHEL²⁰⁾, GOT (glutamic oxaloacetic transaminase) according to LADUE *et al.*¹⁴⁾, LDH (lactate dehydrogenase) according to WROBLEWSKI *et al.*³⁹⁾, and OCT (ornithine carbamoyl transferase) according to REICHARD³²⁾ and modified by OHSHITA *et al.*²²⁾. Plasma amino acids were analyzed with liquid-chromatographic method using LC-4A (Shimazu Co., Ltd., Kyoto, Japan). Blood glucose level was determined by the *o*-toluidine method⁹⁾ and serum free fatty acids by the method of LAURELL *et al.*¹⁶⁾.

All results were expressed as mean values $\pm$ SEM. Significant differences between the means were determined using Student's *t* test, and the level of significance being regarded as $p < 0.05$. A linear regression was calculated by the method of least squares and its significance tested by determining the correlation coefficient (γ).

Results

Table 1 shows the changes in the adenine nucleotide contents and the resultant energy charge of the remnant liver in 70% hepatectomized rabbits. Energy charge level fell markedly to 0.767 within 24 hr after hepatectomy with a concomitant decrease in ATP to about 60% of normal rabbits and a slight increase in ADP. In addition, total adenine nucleotide contents were lower than that of normal rabbits. Afterwards, ATP contents increased gradually with a concomitant decrease in ADP, resulting in the restoration of decreased energy charge level.

Table 2 shows the changes in glucose, free fatty acids, total ketone bodies and ketone-body ratio in the arterial blood of 70% hepatectomized rabbits. Blood glucose level decreased to below 100 mg/dl at 12 and 24 hr. Free fatty acids increased rapidly to about twice that of normal

Table 1. Adenine Nucleotide Contents and Energy Charge Levels of Remnant Liver in 70% Hepatectomized Rabbits

	Levels of adenine nucleotides (μ moles/g of wet tissue)				Energy Charge
	ATP	ADP	AMP	Total	
Normal rabbits (5) (15 hr fasted)	2.40 $\pm$ 0.04	0.68 $\pm$ 0.04	0.17 $\pm$ 0.01	3.25 $\pm$ 0.06	0.843 $\pm$ 0.007
12 hr after					
sham operation (4)	2.02 $\pm$ 0.04 ^a	0.59 $\pm$ 0.06	0.15 $\pm$ 0.09	2.76 $\pm$ 0.01 ^a	0.840 $\pm$ 0.014
hepatectomy (4)	1.67 $\pm$ 0.07 ^a	0.74 $\pm$ 0.09	0.19 $\pm$ 0.03	2.60 $\pm$ 0.16 ^b	0.782 $\pm$ 0.015 ^a
24 hr after					
sham operation (7)	2.02 $\pm$ 0.04 ^a	0.48 $\pm$ 0.04 ^b	0.14 $\pm$ 0.06	2.67 $\pm$ 0.09 ^a	0.860 $\pm$ 0.007
hepatectomy (7)	1.48 $\pm$ 0.05 ^a	0.74 $\pm$ 0.04	0.19 $\pm$ 0.01	2.41 $\pm$ 0.05 ^a	0.767 $\pm$ 0.008 ^a
48 hr after					
hepatectomy (4)	1.61 $\pm$ 0.06 ^a	0.60 $\pm$ 0.05	0.20 $\pm$ 0.01	2.41 $\pm$ 0.11 ^a	0.793 $\pm$ 0.001 ^a
96 hr after					
hepatectomy (4)	1.63 $\pm$ 0.07 ^a	0.53 $\pm$ 0.06 ^c	0.14 $\pm$ 0.02	2.30 $\pm$ 0.14 ^a	0.828 $\pm$ 0.011

Results shown are mean values $\pm$ SEM with *n* values in parentheses. Statistical significance (^a $p < 0.001$, ^b $p < 0.01$ and ^c $p < 0.05$), compared with the values in normal rabbits (15 hr fasted). Energy charge = $(\text{ATP} + 1/2\text{ADP})/(\text{ATP} + \text{ADP} + \text{AMP})$.

Table 2. Glucose, Free Fatty Acids, Total Ketone Bodies (Acetoacetate Plus 3-Hydroxybutyrate) and Ketone-body Ratio (Acetoacetate/3-Hydroxybutyrate) of the Arterial Blood in 70% Hepatectomized Rabbits

	Glucose (mg/dl)	Free fatty acids (mEq/l)	Total Ketone bodies (m moles/l)	Ketone-body ratio
Normal rabbits (10) (15 hr fasted)	125± 7	0.51±0.05	0.082±0.012	0.932±0.136
12 hr after sham operation (4)	112± 8	0.46±0.05	0.138±0.030 ^c	0.726±0.078
hepatectomy (12)	97± 4 ^a	0.98±0.11 ^a	0.210±0.024 ^a	0.415±0.141 ^a
24 hr after sham operation (4)	118±11	0.45±0.07	0.133±0.016 ^c	0.820±0.151
hepatectomy (10)	95± 4 ^a	0.92±0.09 ^a	0.237±0.025 ^a	0.615±0.051 ^a
48 hr after hepatectomy (10)	109± 3 ^b	0.59±0.12	0.250±0.032 ^a	0.707±0.050 ^c
96 hr after hepatectomy (10)	115± 4	0.52±0.09	0.133±0.012 ^b	0.856±0.087

Results shown are mean values±SEM with n values in parentheses. Statistical significance (^a p<0.001, ^b p<0.01 and ^c p<0.05), compared with the values in normal rabbits (15 hr fasted).

rabbits within 12 hr, and decreased to normal levels at 48 hr. With the increase in free fatty acids, blood ketone bodies increased rapidly to more than twice that of normal rabbits within 12 hr, after which they remained at a steady state until 48 hr after hepatectomy. Blood ketone-body ratio declined rapidly from 0.932 to 0.415 within 12 hr, and then increased gradually to the subnormal levels of 0.615 at 24 hr and 0.707 at 48 hr. The ratio was restored to normal at 96 hr after hepatectomy.

Figure 1 shows that blood ketone-body ratio was positively correlated with hepatic energy charge level in 70% hepatectomized rabbits ($\gamma=0.696$, $p<0.01$), although blood ketone-body ratio decreased maximally at 12 hr and hepatic energy charge decreased maximally to 24 hr

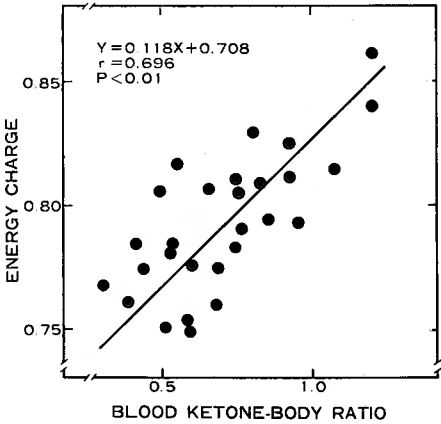


Fig. 1. Relationship between the ketone-body ratio (acetoacetate/3-hydroxybutyrate) of arterial blood and the energy charge (ATP+1/2 ADP)/(ATP+ADP+AMP) of the remnant liver in 70% hepatectomized rabbits. Correlation coefficient: $\gamma=0.696$, $p<0.01$; regression equation: $Y=0.118X+0.708$.

Table 3. Prothrombin Time, Serum Protein, Serum Albumin and Serum Enzyme Activities in 70% Hepatectomized Rabbits

	Normal (6) (15 hr fasted)	After 70% hepatectomy			
		12 hr (6)	24 hr (9)	48 hr (6)	96 hr (4)
Prothrombin time (sec)	6.7±0.1	7.4±0.2 ^b	8.1±0.3 ^b	7.3±0.4	6.6±0.2
Total protein (g/dl)	5.4±0.2	4.6±0.1 ^b	4.5±0.1 ^a	5.0±0.1	5.2±0.3
Albumin (g/dl)	3.9±0.2	3.3±0.1 ^b	3.2±0.1 ^a	3.4±0.2 ^c	3.6±0.2
Cholinesterase (Δ pH/hr)	0.76±0.05	0.48±0.04 ^b	0.49±0.03 ^b	0.55±0.05 ^c	0.64±0.10
GOT (mU/ml)	20±5	648±111 ^a	565±66 ^a	82±23 ^b	32±12
LDH (mU/ml)	296±94	1292±306 ^b	753±76 ^b	367±100	166±26
OCT (mU/ml)	12±3	1052±171 ^a	824±104 ^a	234±23 ^a	56±12 ^a

Results shown are mean values±SEM with n values in parentheses. Statistical significance (^a $p<0.001$, ^b $p<0.01$ and ^c $p<0.05$), compared with the values in normal rabbits (15 hr fasted).

postoperatively.

Table 3 shows the changes in several liver function tests in 70% hepatectomized rabbits. Prothrombin time was prolonged maximally at 24 hr and restored to the preoperative level at 96 hr. Serum protein, particularly serum albumin, decreased rapidly at 24 hr and increased to near normal levels within 96 hr. Cholinesterase activity decreased at 12 hr and remained at reduced levels during the 96 hr period. Serum levels of GOT, LDH and OCT were extremely high at 12 hr and returned to normal levels at 96 hr.

Figure 2 shows the changes in total serum amino acid concentration compared with those in the energy charge levels and the blood ketone-body ratio following 70% hepatectomy. The total serum amino acid concentrations increased until 24 hr after hepatectomy in inverse pro-

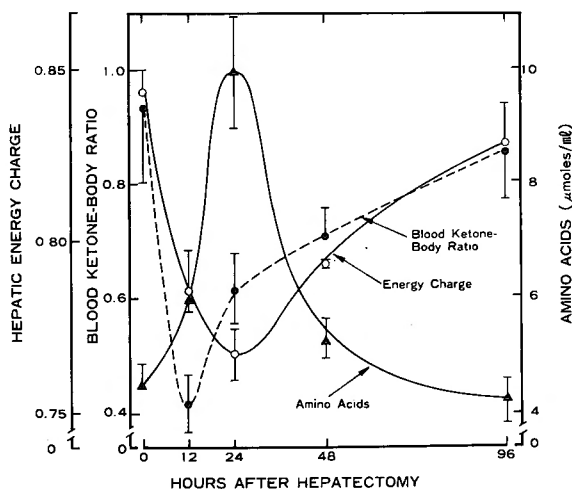


Fig. 2. Changes in total plasma amino acid concentration, energy charge of the remnant liver and blood ketone-body ratio after 70% hepatectomy. Amounts of total amino acids are the sum of each amino acid listed in Table 4 and the others such as hydroxyproline and methylhistidines.

portion to hepatic energy charge and blood ketone-body ratio. Afterwards, these parameters decreased to normal levels concomitant with a rise in hepatic energy charge and blood ketone-body ratio.

Table 4 shows the changes in individual amino acids following 70% hepatectomy. The plasma concentrations of all amino acids except for tryptophane and arginine were increased until 24 hr after hepatectomy and then decreased to normal levels at 96 hr. The molar ratio (valine+isoleucine+leucine)/(tyrosine+phenylalanine) decreased until 48 hr after hepatectomy and returned to normal levels at 96 hr.

Figure 3 shows the time course of changes in energy charge level of the remnant liver of 25, 70 and 93% hepatectomized rabbits. Energy charge level remained virtually unchanged in 25% hepatectomy, all rabbits tolerating the operation well. In 70% hepatectomy, however, energy charge level fell remarkably within 24 hr, and rose gradually to near normal levels after 96 hr. The mortality rate was 30% at 12-24 hr, after which few rabbits died. After 93% hepatectomy, energy charge level declined drastically within 8 hr and most of the rabbits died

Table 4. Changes in Serum Amino Acids in 70% Hepatectomized Rabbits

Amino acids (n mol/ml)	Normal (4) (15 hr fasted)	After sham operation 24 hr (4)	After 70% hepatectomy			
			12 hr (4)	24 hr (4)	48 hr (5)	96 hr (4)
Aspartic acid	13±2	8±3	9±5	25±5 ^c	17±6	14±5
Threonine	103±24	121±5	155±6 ^c	335±64 ^b	191±39 ^c	176±15 ^c
Serine	262±41	157±15	351±33	389±28 ^c	413±56 ^c	291±57
Asparagine	78±11	87±4	172±31 ^b	312±17 ^a	140±33 ^c	121±18 ^c
Glutamic acid	50±9	98±9	114±36 ^c	165±27 ^b	59±10	54±8
Proline	188±14	117±19	348±47 ^b	562±34 ^a	238±45	173±40
Glycine	1669±399	1020±524	1487±355	2022±107	1493±261	1073±374
Alanine	416±60	249±38	925±156 ^b	1039±66 ^a	447±45	365±41
Valine	192±32	184±18	200±12	268±53	258±24	219±37
Methionine	28±6	28±5	72±6 ^b	128±18 ^a	61±16 ^c	41±10
Isoleucine	76±15	80±7	83±7	111±20	96±9	88±17
Leucine	119±24	130±11	152±12	207±38 ^c	176±30	140±25
Tyrosine	58±4	57±18	104±17 ^c	101±12 ^b	75±11	71±5
Phenylalanine	51±7	50±21	91±10 ^b	109±16 ^b	82±8 ^b	81±8 ^b
Ornithine	78±8	54±27	207±31 ^b	326±66 ^a	213±22 ^a	126±20 ^c
Lysine	200±25	144±78	273±43	794±197 ^b	374±55 ^b	339±41 ^b
Histidine	104±14	83±18	201±9 ^a	347±47 ^a	154±18 ^c	120±12
Tryptophane	22±3	24±4	14±3	17±7	16±3	12±5
Arginine	133±19	74±11	12±4 ^a	11±6 ^a	38±12 ^b	72±20 ^c
Total	4468±385	3969±628	6115±271 ^b	9913±1290 ^b	5306±420	4225±470
Molar ratio*	3.52±0.42	3.50±0.37	2.28±0.37 ^c	2.76±0.24 ^c	2.76±0.24 ^c	3.59±0.19

Results shown are mean values±SEM with n values in parentheses. Statistical significance (^a p<0.001, ^b p<0.01 and ^c p<0.05), compared with normal rabbits (15 hr fasted). Molar ratio* was calculated from the equation (valine+isoleucine+leucine)/(tyrosine+phenylalanine). Total amino acids are the sum of each amino acid listed and the others such as hydroxyproline, methylhistidines.

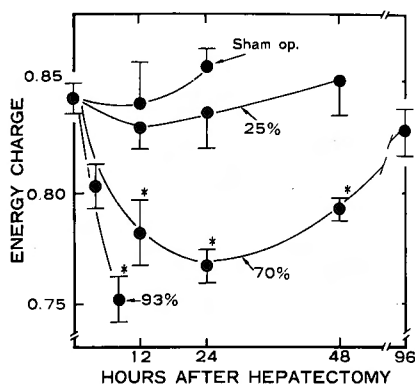


Fig. 3. Changes in adenylate energy charge of the remnant liver after 25, 70 and 93% hepatectomies in rabbits. Each point represents the mean value $\pm$ SEM of 4 or more animals. * $p < 0.001$, compared with normal fasting rabbits.

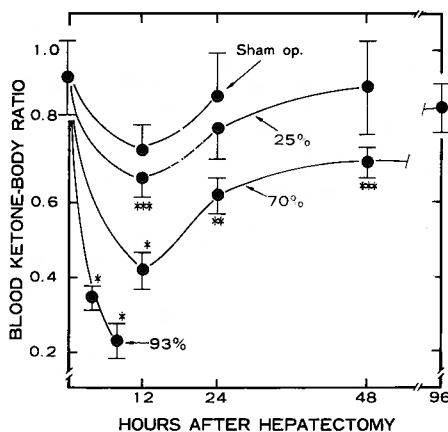


Fig. 4. Changes in blood ketone-body ratio after 25, 70 and 93% hepatectomies in rabbits. Each point represents the mean value $\pm$ SEM of 4 or more animals. * $p < 0.001$, ** $p < 0.01$, and *** $p < 0.05$, compared with normal fasting rabbits.

within 12 hr with profound hypoglycemia of below 60 mg/dl.

Figure 4 shows the time course of changes in blood ketone-body ratio after 25, 70 and 93% hepatectomies in rabbits. In 25% hepatectomized rabbits, blood ketone-body ratio decreased to 0.653 in 12 hr after hepatectomy, a value significant when compared with normal rabbits ($p < 0.05$) but not so when compared with sham-operated rabbits. Blood ketone-body ratio was restored to normal level within 24 hr. In 70% hepatectomy, blood ketone-body ratio decreased rapidly within 12 hr, and then increased gradually. In 93% hepatectomy, a drastic decrease in blood ketone-body ratio was observed within 4 hr.

Discussion

Few studies in the last decade have dealt with the subject of metabolic response to major hepatic resection. Recently, evidence has accumulated indicating that further progress in liver

surgery may be expected from basic studies dealing with the changes in cellular energy status following hepatectomy^{10,24,25,33,40}). Energy charge indicates the metabolically available energy pool that depends upon the differences between energy-yielding and energy-utilizing reactions^{4,5}). Increased energy expenditure results in a markedly decreased energy charge, unless there is a compensatory enhancement of mitochondrial oxidative phosphorylation. In 70% hepatectomy, energy charge decreased markedly at 24 hr despite an enhancement of mitochondrial phosphorylative activity¹²). During that period, prothrombin time was prolonged maximally, and serum protein and albumin decreased markedly. Mortality in this group was high at 12–24 hr, when the energy charge level of the remnant liver had decreased considerably²⁶). This is the period of maximum metabolic load, during which the delicate energy balance in the remnant liver is barely maintained by a compensatory enhancement of mitochondrial phosphorylative activity¹²). However, most rabbits which tolerated the period of 24 hr after hepatectomy survived uneventfully, concomitant with the gradual normalization of the concentrations of blood glucose, ketone bodies, amino acids, blood ketone-body ratios, and the standard liver function tests. In contrast, in 25% hepatectomy, hepatic energy charge and blood ketone-body ratio did not change considerably, all rabbits tolerating the operation well. However, in 93% hepatectomy, hepatic energy charge and blood ketone-body ratio decreased drastically within 8 hr, and most of the rabbits died within 12 hr.

The factors inducing the decrease in hepatic energy charge following massive hepatectomy have yet to be fully elucidated. The liver is known to play a decisive role in controlling numerous metabolic processes, most of which are coupled with energy metabolism. If the energy charge decreases below 0.80, the ATP-generating sequences are accelerated through the changes in the activities of regulatory enzymes which respond to the relative concentrations of ATP, ADP and AMP. Conversely, the ATP-requiring sequences slow down^{4,5}). ATP-requiring sequences in the liver, such as synthesis of serum albumin and cholinesterase, are inhibited at 12–24 hr after 70% hepatectomy at which time the hepatic energy charge levels are decreased maximally. Also, any decrease in hepatic energy charge levels results in formidable hepatic deterioration in all ATP-dependent cellular functions, such as gluconeogenesis, ureogenesis and protein synthesis, leading eventually to hepatic failure. It has also been found that the restoration of the energy charge in the regenerating processes is the prerequisite for a subsequent increase in nuclear DNA synthesis^{23,25}). Thus, it seems reasonable to assume that the decrease in hepatic energy charge plays an important role in bringing about hepatic insufficiency after major hepatic resection.

The ketonemia following hepatectomy is the result of enhanced ketogenic capacity of the liver and a possibly increased hepatic supply of free fatty acids. Also, the changes in blood ketone-body ratio are found to be positively correlated with those in hepatic energy charge after hepatectomy. With regard to the decrease in blood ketone-body ratio, it has been suggested that it is due to an enhancement of β -oxidation of free fatty acids associated with the production of excess NADH²¹). Commensurate with the greatly enhanced requirement for energy after major hepatic resection, fatty acids are being preferentially oxidized as an efficient energy source.

In this stage, hepatocellular energy could be efficiently supplied by the enhanced electron transport from β -oxidation of free fatty acids associated with excess NADH.

Massive hepatic resection is generally accompanied by a considerable rise in all plasma amino acids, presumably arising from the increased muscle catabolism of actin and myosin, producing large quantities of all amino acids that seem to exceed the remnant liver's capacity to metabolize. In general, protein catabolism is an important process in the overall struggle to maintain glucose homeostasis; in the short term, indeed, amino acids are the major source of gluconeogenic precursors. Alanine, especially, is a major contributor to glucose synthesis⁸⁾. In hepatectomized rabbits, plasma alanine levels were inversely increased with the blood ketone-body ratio, suggesting that the intracellular metabolic derangements, reflected by the fall in the blood ketone-body ratio, work to inhibit hepatic gluconeogenesis. These amino acids gain access to the Krebs cycle and the gluconeogenic pathway. The decreasing blood ketone-body ratios are consistent with a progressive reduction in mitochondrial NAD^+/NADH . The reduced mitochondrial redox potential inhibits the citrate synthase, which decides the turnover rate of the Krebs cycle, and the processes requiring NAD^+ in the mitochondria such as pyruvate dehydrogenase, isocitrate dehydrogenase and α -ketoglutarate dehydrogenase³⁷⁾. These inhibitions thus prevent the entrance of plasma amino acids into the Krebs cycle, resulting in an elevated level of the amino acids. Consequently, it seems likely that gluconeogenesis from plasma amino acids is inhibited at 12–24 hr after 70% hepatectomy, resulting in hypoglycemia. In addition, the enzymes of gluconeogenesis require an abundant supply of mitochondrial ATP during periods of active gluconeogenesis¹³⁾. Therefore, the increase in plasma alanine levels seems to be due to an inhibition of gluconeogenesis by the progressive decrease of hepatic energy charge levels.

On the other hand, the body increased its circulating plasma concentrations of ketone bodies following hepatectomy. This ketonemic adaptation to hepatectomy may reduce the need for energy derived from glucose calories, which in turn spares body protein by decreasing the rate of amino acid usage for glucose synthesis.

Standard liver function tests are routinely performed on hepatectomized patients. However, the majority of these patients receive supplemental infusions of fresh blood, fresh plasma, fresh frozen plasma, albumin solutions and amino acid solutions which affect prothrombin time, serum protein, serum albumin, serum enzymatic activities and plasma amino acid pattern. This often makes it impossible to use these parameters to evaluate the critical energy status of the remnant liver. By contrast, blood ketone-body ratio is not affected by the intra- and postoperative infusion therapy, because the interconversion between ketone bodies rapidly takes place in liver mitochondria. Therefore, it is possible to evaluate the hepatic energy status by the blood ketone-body ratio during the critical stage after hepatic resection. Actually, the blood ketone-body ratios have been used as criteria for grading hepatic failure or evaluating the liver support for hepatic failure^{3,27,28,29)}.

Summary

The changes in adenylate energy charge of the remnant liver and ketone-body ratio of

arterial blood following 70% hepatectomy were investigated in relation to the changes in blood levels of glucose, free fatty acids, ketone bodies and amino acids and the standard liver function tests. In 70% hepatectomized rabbits, hepatic energy charge decreased from 0.843 to 0.767 within 24 hr and arterial blood ketone-body ratio decreased from 0.932 to 0.415 within 12 hr concomitant with a rise in plasma free fatty acids and amino acids and a fall in blood glucose. Free fatty acids increased to about twice within 12 hr, total amino acid concentration increased until 24 hr, and blood glucose level decreased to below 100 mg/dl at 12 and 24 hr. At that time serum protein, serum albumin and cholinesterase activity decreased maximally and prothrombin time was prolonged. Afterwards, at 96 hr postoperatively, blood ketone-body ratio and hepatic energy charge were restored to near normal levels with the normalization of blood glucose, plasma free fatty acids, plasma amino acids and the standard liver function tests. The mortality rate was 30% at 12–24 hr, after which few rabbits died. In addition, in 25% hepatectomized rabbits, blood ketone-body ratio decreased slightly and hepatic energy charge remained unchanged, all rabbits tolerating the operation well. In contrast, in 93% hepatectomized rabbits, both blood ketone-body ratio and hepatic energy charge fell drastically within 8 hr, and most of the rabbits died within 12 hr. It is suggested by these findings that (a) the decrease in energy charge of the remnant liver is the basis of the decrease in hepatic functional reserve following hepatic resection, (b) the change in energy charge level is accurately reflected by the change in blood ketone-body ratio and (c) the decreased energy charge of the remnant liver concomitant with a fall in blood ketone-body ratio is the basis of the sequential changes in the blood concentration of fuels after massive hepatectomy.

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和文抄録

肝切除と動脈血中ケトン体比

I. 肝切除後の動脈血中ケトン体比の変動

—血中エネルギー基質との関連—

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正常家兎に70%肝切除を行い、残存肝のエネルギーチャージと動脈血中のケトン体比 (アセト酢酸/3-ヒドロキシ酪酸) を経時的に測定したところ、前者は術後24時間で、後者は術後12時間で最低値となり、その後96時間で術前値に戻る事が判明した。一般肝機能検査値は術後12時間から24時間にかけて最も著明な変動を示し、死亡率もこの時期に一致して高値を示した。また、血中のグルコース、遊離脂肪酸、ケトン体、アミノ酸等のエネルギー基質の濃度も血中ケトン体比と密接に関連して変動することが明らかになった。さら

に正常家兎に25%および93%の肝切除を行い、残存肝エネルギーチャージと血中ケトン体比を測定したところ、切除量の増加に従いこれらの指標はより大きく低下することが明らかになった。

以上の実験事実より肝切除後、①残存肝機能の低下は残存肝エネルギーチャージの低下に起因すること、②残存肝エネルギーチャージの変動は血中ケトン体比に鋭敏に反映されること、また③血中ケトン体比の変動は肝切除後の血中エネルギー基質の変化と密接に関連していることが明らかになった。