Effects of Various Catecholamines on High-Energy phosphates of Rat Liver and Brain during Hemorrhagic Shock Measured by ^{31}p-NMR Spectroscopy

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The effects of dopamine, epinephrine and norepinephrine on energy metabolism as well as intracellular pH in rat liver and brain during hemorrhagic shock were examined by in vivo ^{31}P-NMR spectroscopy. The hemorrhagic shock was induced by arterial bleeding to a mean arterial pressure (MAP) of 30–40 mmHg. Upon the induction of hemorrhagic shock, there was a dramatic fall in adenosine triphosphate (ATP) and a rise in inorganic phosphate (Pi) in the liver. The intracellular pH indicated severe acidosis. However, no change in these parameters was observed in the brain during hemorrhagic shock. After infusion of the above catechollamines following 10 min of hemorrhagic shock, MAP increased to 90–100% of its control value. Only dopamine improved hepatic energy metabolism, whereas brain evergy metabolism was not affected by any of them. This suggests that dopamine protects liver function during hemorrhagic shock without affecting brain energy metabolism. (Key words: ^{31}P-NMR, hemorrhagic shock, catecholamine, liver, brain)

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Hemorrhagic shock is usually treated with blood transfusion or intravenous fluid administration. However, upon drastic induction of this condition, the use of catecholamines may become important if a vessel with a diameter large enough to accommodate a rapid infusion is difficult to obtain during emergency treatment. Many studies have examined the effects of catecholamines on the splanchnic circulation[1–4], most of them concerning the non-shocked state. There are also many reports about the effect of these catecholamines on cerebral blood flow (CBF) under normal conditions[5–9]. However, to our knowledge, there are no data about the effects of catechol-amines on hepatic and cerebral energy metabolism during hemorrhagic shock, and therefore the present study was carried out to investigate these aspects of catecholamine action. ^{31}P-NMR spectroscopy was used for these studies because in vivo ^{31}P-NMR spectroscopy has proven to be a valuable non-invasive techinique for the assessment of phosphorus-containing metabolites and intra-cellular pH (pHi)[10,11]. Thus the dynamic changes in hepatic and cerebral adenosine triphosphate (ATP), inorganic phosphate (Pi) and phosphocreatine (PCr), as well as pHi during

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Table 1. Summary of data from rat liver and brain during hemorrhagic shock

		A	B	C	D	E
[Liver]						
MAP	mmHg	115 ± 6	38 ± 2**	36 ± 3**	38 ± 2**	105 ± 6
pHi		7.18 ± 0.02	7.04 ± 0.04*	6.89 ± 0.02**	6.77 ± 0.04**	7.15 ± 0.02
MP	%	100	133.5 ± 15.3	164.0 ± 14.0*	183.8 ± 16.0**	102.0 ± 2.7
Pi	%	100	176.0 ± 18.5*	230.5 ± 30.4*	263.5 ± 26.1**	114.5 ± 5.7
ATP	%	100	57.8 ± 5.2**	34.3 ± 2.1**	21.8 ± 3.0**	96.3 ± 2.7
Pi/ATP		0.61 ± 0.02	1.79 ± 0.35*	4.22 ± 0.55**	7.66 ± 0.73**	0.76 ± 0.07
[Brain]						
MAP	mmHg	124 ± 4	39 ± 5**	40 ± 6**	38 ± 4**	126 ± 6
pHi		7.22 ± 0.03	7.21 ± 0.02	7.17 ± 0.03	7.11 ± 0.03	7.22 ± 0.02
MP	%	100	101.8 ± 7.4	100.4 ± 11.3	120.2 ± 10.1	109.4 ± 5.2
Pi	%	100	111.8 ± 4.6	128.4 ± 9.3	133.0 ± 8.6	123.0 ± 8.6
PCr	%	100	93.4 ± 2.2	93.2 ± 3.9	89.4 ± 3.2	97.2 ± 3.8
ATP	%	100	99.2 ± 3.6	105.6 ± 2.8	105.6 ± 3.8	105.4 ± 2.5
PCr/Pi		5.23 ± 0.25	4.70 ± 0.37	4.52 ± 0.56	4.28 ± 0.50	4.55 ± 0.50

The concentrations of each metabolite are expressed as a percentage of their control values. The experimental conditions were the same as described in the legend to figure 1.

Values are means ± SEM. Significant difference from control (*$P < 0.05$, **$P < 0.01$).

hemorrhagic shock and catecholamine infusion, were evaluated by ^{31}P-NMR.

Materials and Methods

Animal preparations: Male Wistar rats (weighing around 300 g) were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). After a tracheotomy, the animals were connected to a constant-volume respirator (AIKA EVM 50A) and mechanically ventilated wit a 60% nitrogen and 40% oxygen gas mixture via the intubated cannula. The right femoral artery and vein were cannulated for blood pressur monitoring and drug injection, respectively. When all these procedures had been completed, the animals were divided into two groups for ^{31}P-NMR spectral analysis of the liver and the brain. Both groups were subdivided into four groups: 1, hemorrhagic shock with no treatment (liver, n=4; brain, n=5); 2, hemorrhagic shock with dopamine infusion (liver, n=4; brain, n=5); 3, hemorrhagic shock with epinephrine infusion (liver, n=4; brain, n=5); 4, hemorrhagic shock with morepinephrine infusion (liver, n=5; brain, n=5). For ^{31}P-NMR spectral analysis of the liver, the peritoneal cavity was opened via a midline incision and a surface radiofrequency coil (two turns, 10 mm in diameter) was attached to the left medial hepatic lobe. For ^{31}P-NMR spectral analysis of the brain, the coil was placed on the skull, after the removal of hair from the head.

NMR spectra: ^{31}P-NMR spectra were recorded at 80.65 MHz on a spectrometer (phospho-Energetics, Inc.) equipped with a wide-bore BEM-140/200 magnet (4.7 Tesla). The spectra were obtained with a pulse-repetition time of 2 s; the sum of 75 scans was recorded using15-μs (for the lover) and 22.5-μs (for the brain) radiofrequency pulses at 2.5 min intervals. For data analyses, a line broadening of 10 Hz was applied. The intensity of the signals was evaluated as the area under the peaks, and the intracellular pH (pHi) of the liver was calculated from the chemical shift of the Pi signal using α-ATP as an internal standard and the following equation[12]:

$$\text{pHi (liver)} = 6.75 + \log \frac{\alpha - 10.85}{13.25 - \alpha}$$

The pHi of the brain was calculated from the chemical shift of the Pi signal using phosphocreatine (PCr) as an internal standard and the following equation[13,14]

$$\text{pHi (brain)} = 6.75 + \log \frac{\alpha - 3.15}{5.65 - \alpha}$$

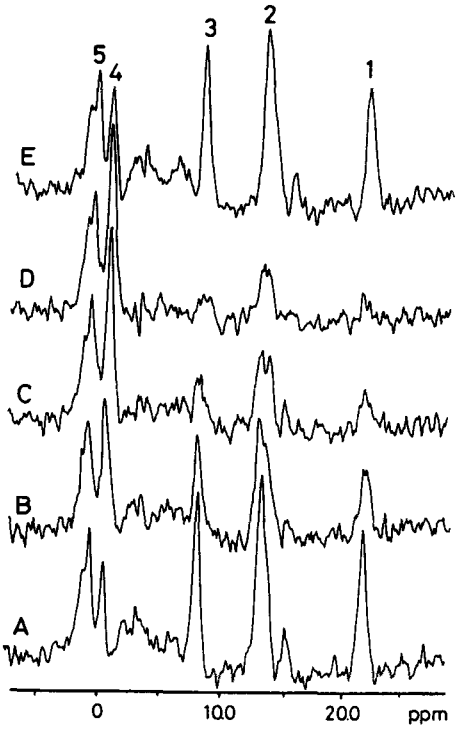

Fig. 1. ^{31}P-NMR spectra obtained from in vivo rat liver during hemorrhagic shock.

A, control spectrum; B, C and D, 2.5–5, 7.5–10 and 17.5–20 min after the induction of hemorrhagic shock, respectively; E, 7.5–10 min after the reinfusion of blood. 1, ATP-β-phosphate; 2, ATP-α-phosphate and ADP-α-phosphate; 3, ATP-γ-phosphate and ADP-β-phosphate; 4, Pi; 5, phosphomonoesters, including AMP and glucose-6-phosphate.

where α represents the chemical shift of Pi.

After the recording of control spectra, hemorrhagic shock was induced by withdrawing a total of about 6 ml of blood in several protions and the mean arterial blood pressure (MAP) was maintained at 30–40 mmHg. In the non-treatment group, this state was maintained for 20 min and the blood was reinfused over approximately 2.5 min. Spectra were analyzed at 2.5–5, 7.5–10 and 17.5–20 min of hemorrhagic shock and at 7.5–10 min of recovery. In the catecholamine infusion group, following 10 min of hemorrhagic shock, each catecholamine was infused for 10 min. The infusion was then stopped and the blood was reinfused over approximately 2.5 min. The spectra were analyzed at 7.5–10 min of hemorrhagic shock, after 2.5–5.0 and 7.5–10 min of catecholamine infusion and at 7.5–10 min of recovery. The infusion rates of the catecholamines were initially a 10-μg bolus followed by 15 μg/kg/min for dopamine, and a 0.5-μg bolus followed by 0.2 μg/kg/min for both epinephrine and norepinephrine.

Results are given as mean±SEM. Statistical comparisons were performed using Student's paired t-test, with a P value of < 0.05 considered statistically significant.

Results

Liver: The mean arterial pressure (MAP) was maintained at 30–40 mmHg during hemorrhagic shock (table 1). The ^{31}P-NMR spectra recorded from rat liver showed the characteristic resonances of phosphomonoesters (MP), inorganic phosphate (Pi), and α, β, and γ nuclei of ATP (figs. 1 and 2). Characteristic changes in ^{31}P-NMR spectra during hemorrhagic shock are shown in figure 1. When the hemorrhagic shock was induced, the intensity of the β-ATP signal rapidly decreased along with a marked increase in that of Pi. After the reinfusion of blood, the changes in each resonance peak returned to control levels.. The data obtained from ^{31}P-NMR spectra in the non-treatment group are summarized in table 1. The concentrations of ATP decreased repidly with a concomitant increase in Pi and MP. The intracellular pH (pHi) dropped within 5 min from 7.18 to 7.04. The liver energy metabolism worsened progressively during 20 min of hemorrhagic shock. After 10 min of blood reinfusion, all these changes returned almost to the control values. In the catecholamine infusion groups, MAP was maintained at 120% of its control value during the infusion of catecholamines in each group. After reinfusion of the blood that had previously been withdrawn following the cessation of catecholamine infusion, MAP was 90–110% of its control value. Typical ^{31}P-NMR spectra obtained from rat liver before and after the infusion of catecholamines are shown in figure 2. In all the groups, a reduction in the

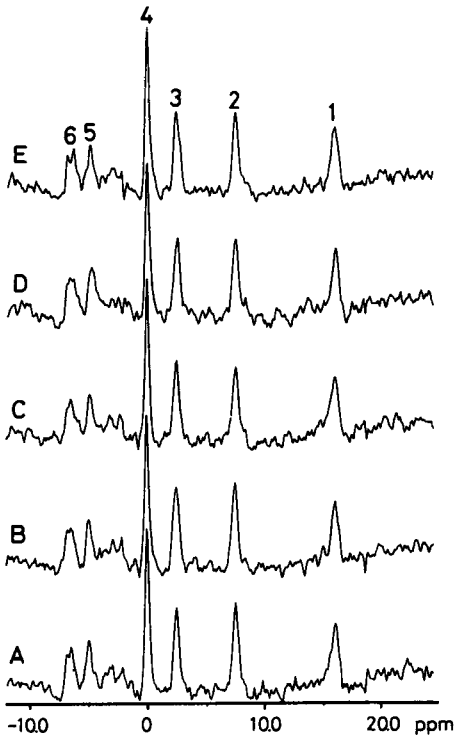

Fig. 2. ^{31}P-NMR spectra obtained from in vivo rat brain during hemorrhagic shock.

The experimental conditions were the same as described in the legend to figure 1.

1, ATP-β-phosphate; 2, ATP-α-phosphate and ADP-α-phosphate; 3, ATP-γ-phosphate and ADP-β-phosphate; 4, PCr; 5, Pi; 6, phosphomonoesters, including AMP and glucose-6-phosphate.

intensity of the β-ATP signal and an increase in that of Pi were recongized after the induction of hemorrhagic shock(fig. 2-B). After the infusion of dopamine, the β-ATP and Pi signals almost returned to those in the control spectra (fig. 2-a). When epinephrine was infused, slight restorations were seen in the intensities of the β-ATP and Pi signals. There was no obvious restoration of individual peaks after the infusion of norepinephrine. The changes in MP, Pi and ATP obtained from the areas under the peaks, pHi and Pi/ATP ratio are summarized in table 2. The Pi value in all the groups increased to 230–240% of the control value 10 mim after the induction of hemorrhagic shock, and the levels of ATP decreased to 20% those of the controls. Ten minutes after the infusion of dopamine, the levels of Pi, ATP and Pi/ATP ratio returned to those of the control and the severe intracellular acidosis induced by the hemorrhagic shock was markedly improved. When epinephrine was infused, there was a slight improvement in hepatic energy metabolism and intracellular acidosis, but this was not statistically significant. When norepinophrine was infused, there was no improvement in hepatic energy metabolism. All these returned to control values after a volume of blood equal to that which had previously been withdrawn was reinfused.

Brain: The characteristic resonance peaks of phosphomonoesters (MP), inorganic phosphate (Pi), phosphocreatine (PCr) and the α, β, and γ nuclei of ATP were recognized in each spectrum obtained from rat brain (figs. 3 and 4). There were no obvious changes in individual peaks during hemorrhagic shock and catecholamine infusion (figs. 3 and 4). Changes in MAP, pHi, MP, Pi, Pcr, ATP and PCr/Pi are summarized in tables 1 and 3. Neither hemorrhagic shock nor catecholamine infusions caused any major fluctuations in MP, Pi, Pcr and ATP relative to controls nor any significant changes in pHi.

Discussion

Recently ^{31}P-NMR spectroscopy has been adopted in research concerning phosphate compounds in organs, tissues and cells. The conventional method used for the determination of phosphate compounds requires the excision of tissue, freezing and extraction. Therefore degradation, which occurs during these procedures, makes it difficult to obtain the real in vivo value. The use of in vivo NMR techniques allows us to follow non-invasively the dynamic changes in high-energy phosphates as well as pHi. The present experiments demonstrated that ^{31}P-NMR spectroscopy is a practical method for in vivo evaluation of drugs influencing hepatic and cerebral metabolism during various conditions.

Energy metabolism during hemorrhagic shock

Table 2. Summary of data from rat liver during hemorrhagic shock and catecholamine infusion

	A	B	C	D	E
[dopamine]					
MAP mmHg	121 ± 8	39 ± 2**	156 ± 8**	143 ± 4**	117 ± 6
pHi	7.21 ± 0.02	6.84 ± 0.04**	7.04 ± 0.04*	7.15 ± 0.02	7.16 ± 0.02
MP %	100	179.8 ± 6.7**	120.5 ± 8.4	102.5 ± 4.5	102.5 ± 5.1
Pi %	100	230.8 ± 26.2*	134.0 ± 13.9	106.5 ± 7.6	100.8 ± 3.5
ATP %	100	23.8 ± 9.5*	71.0 ± 6.3*	90.5 ± 5.8	95.0 ± 2.2
Pi/ATP	0.69 ± 0.03	10.01 ± 2.38*	1.38 ± 0.34	0.80 ± 0.03	0.73 ± 0.03
[epinephrine]					
MAP mmHg	114 ± 11	40 ± 2**	149 ± 7*	148 ± 6*	119 ± 7
pHi	7.19 ± 0.01	6.79 ± 0.04**	6.82 ± 0.05**	6.95 ± 0.05*	7.16 ± 0.02
MP %	100	178.3 ± 19.1*	187.0 ± 15.1*	172.8 ± 22.8*	105.8 ± 1.7
Pi %	100	236.5 ± 27.0*	239.3 ± 30.2*	201.5 ± 24.9*	106.5 ± 6.8
ATP %	100	24.8 ± 4.0**	17.8 ± 5.0**	31.5 ± 11.2*	94.3 ± 2.7
Pi/ATP	0.70 ± 0.01	7.07 ± 1.30*	10.55 ± 2.95*	10.81 ± 3.17	0.80 ± 0.08
[norepinephrine]					
MAP mmHg	113 ± 9	38 ± 4**	150 ± 9**	151 ± 8**	110 ± 15
pHi	7.21 ± 0.03	6.81 ± 0.03**	6.84 ± 0.02**	6.86 ± 0.04**	7.18 ± 0.03
MP %	100	194.4 ± 6.8**	195.6 ± 7.3**	177.6 ± 14.5**	99.8 ± 7.7
Pi %	100	229.8 ± 22.3**	235.4 ± 29.5**	212.2 ± 31.7**	113.6 ± 9.0
ATP %	100	18.2 ± 2.5**	21.6 ± 5.0**	36.8 ± 4.8**	94.4 ± 6.6
Pi/ATP	0.71 ± 0.04	10.10 ± 2.28*	8.71 ± 1.38**	6.21 ± 1.1*	0.08 ± 0.10

The concentrations of each metabolite are expressed as a percentage of their control values. The experimental conditions were the same as described in the legend to figure 3.

Values are means ± SEM. Significant difference from control (*$P < 0.05$, **$P < 0.01$).

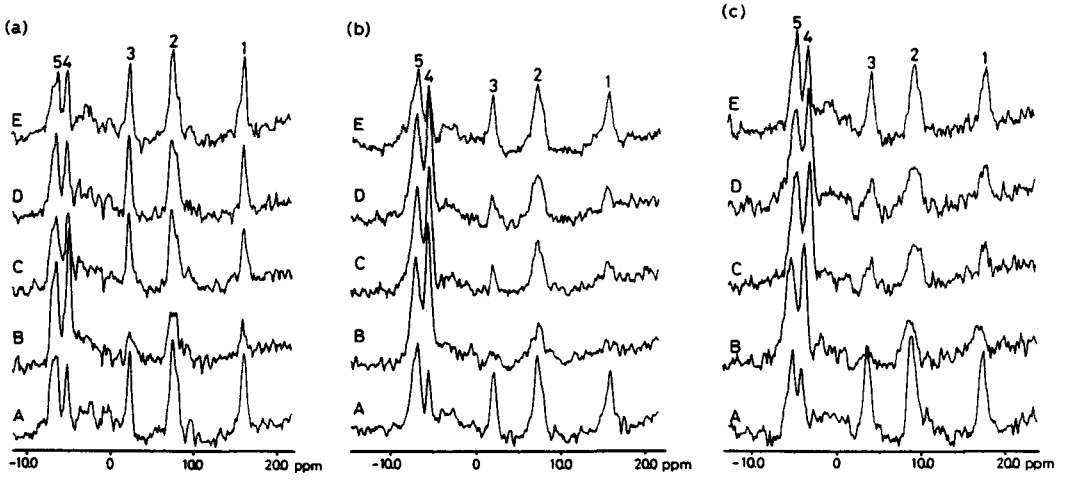

Fig. 3. ^{31}P-NMR spectara obtained from in vivo rat liver during hemorrhagic shock and catecholamine infusion.

(a) dopamine, (b) epinephrine, (c) norepinephrine. A, control spectra; B, 7.5–10 min after the induction of hemorrhagic shock; C and D, 2.5–5 and 7.5–10 min after the infusion of catecholamines, respectively; E, 7.5–10 min after the reinfusion of blood.

1, ATP-β-phosphate; 2, ATP-α-phosphate and ADP-α-phosphate; 3, ATP-γ-phosphate and ADP-β-phosphate: 4, Pi; 5, phosphomonoesters, including AMP and glucose-6-phosphate.

Table 3. Summary of data from rat brain during hemorrhagic shock and catecholamine infusion

		A	B	C	D	E
[dopamine]						
MAP	mmHg	127 ± 8	39 ± 3**	147 ± 6**	142 ± 10**	131 ± 8
pHi		7.21 ± 0.01	7.23 ± 0.01	7.19 ± 0.03	7.18 ± 0.01	7.17 ± 0.02
MP	%	100	107.4 ± 4.1	105.8 ± 5.5	105.8 ± 5.9	111.8 ± 4.9
Pi	%	100	105.0 ± 5.5	102.8 ± 4.8	107.6 ± 7.1	108.4 ± 6.4
PCr	%	100	98.2 ± 2.1	98.2 ± 3.9	97.8 ± 3.2	98.2 ± 2.5
ATP	%	100	98.0 ± 4.1	100.8 ± 2.8	97.0 ± 1.5	95.4 ± 1.0
PCr/Pi		4.75 ± 0.74	4.42 ± 0.21	4.52 ± 0.60	4.34 ± 0.50	4.30 ± 0.50
[epinephrine]						
MAP	mmHg	121 ± 10	37 ± 3**	141 ± 8*	142 ± 7*	116 ± 6
pHi		7.23 ± 0.01	7.22 ± 0.01	7.22 ± 0.01	7.22 ± 0.02	7.22 ± 0.01
MP	%	100	111.2 ± 3.8	107.6 ± 4.2	109.2 ± 4.4	104.6 ± 4.5
Pi	%	100	107.8 ± 4.7	110.6 ± 3.8	110.8 ± 8.0	110.4 ± 3.1
PCr	%	100	99.4 ± 0.6	100.8 ± 1.3	99.8 ± 1.7	100.8 ± 1.9
ATP	%	100	100.0 ± 1.6	100.6 ± 2.1	99.0 ± 4.1	101.4 ± 2.6
PCr/Pi		4.89 ± 0.20	4.56 ± 0.52	4.50 ± 0.19	4.52 ± 0.78	4.49 ± 0.53
[norepinephrine]						
MAP	mmHg	126 ± 6	35 ± 5**	146 ± 7**	144 ± 8*	121 ± 8
pHi		7.23 ± 0.01	7.17 ± 0.02	7.16 ± 0.02	7.15 ± 0.03	7.22 ± 0.02
MP	%	100	110.2 ± 7.5	109.6 ± 5.8	108.0 ± 9.05	110.8 ± 7.5
Pi	%	100	115.2 ± 6.2	117.2 ± 11.7	114.2 ± 6.0	112.2 ± 5.2
PCr	%	100	94.4 ± 1.4	92.0 ± 2.2	91.2 ± 2.6	95.8 ± 3.1
ATP	%	100	101.8 ± 2.7	100.4 ± 2.6	100.0 ± 3.4	104.4 ± 4.7
PCr/Pi		5.05 ± 0.76	4.83 ± 1.04	4.24 ± 1.19	4.27 ± 0.90	4.33 ± 0.66

The concentrations of each metabolite are expressed as a percentage of their control values. The experimental conditions were the same as described in the legend to figure 3.

Values are means ± SEM. Significant difference from control (*$P < 0.05$, **$P < 0.01$).

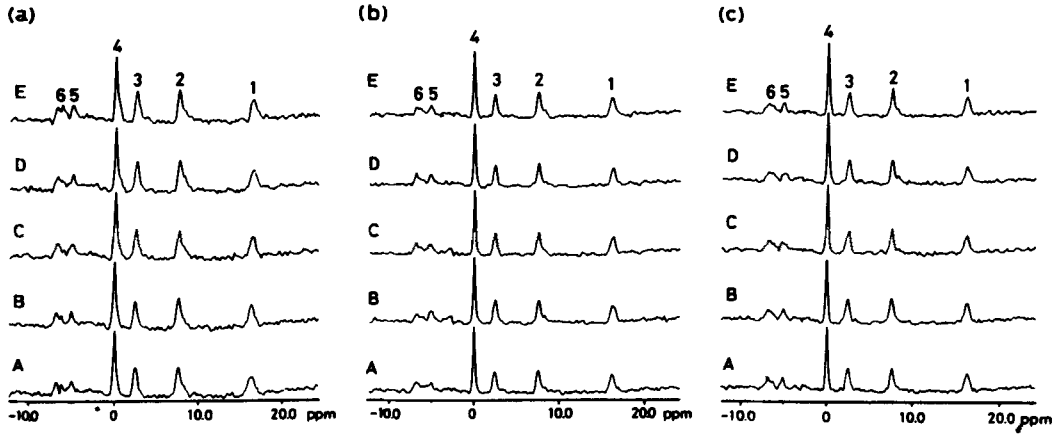

Fig. 4. ^{31}P-NMR spectra obtained from in vivo rat brain during hemorrhagic shock and catecholamine infusion. (a) dopamine, (b) epinephrine, (c) norepinephrine. The experimental conditions were the same as described in the legend to figure 3.

1, ATP-β-phosphate; 2, ATP-α-phosphate and ADP-α-phosphate; 3, ATP-γ-phosphate and ADP-β-phosphate; 4, PCr; 5, Pi; 6, phosphomonoesters, including AMP and glucose-6-phosphate.

It is generally accepted that there is decreased total hepatic blood flow as well as a reduction in portal venous and mesenteric blood flow after hemorrhage[15–18]. Hanson and Johnson [19]reported that autoregulation of the hepatic artery was most evident at pressures above 80 mmHg. Krarup[15] demonstrated that hemorrhagic shock resulted in hepatic glycogenolysis and peripheral glycolysis, but that splanchnic elimination of ethanol, consumption of oxygen and hepatic dye elimination did not decrease, and the hepatic redox level remained unaltered in the cat. In the present study, however, hemorrhagic shock caused a dramatic fall in ATP and a rise in Pi accompanied by a fall in pHi. This difference might have been due to the severity of the shock. In kararup's study, MAP was maintained at around 88 mmHg during hemorrhagic shock, but MAP in the present study was around 30 mmHg. Kamiike[20] showed a rapid decrease of ATP in ischemic rat liver, whick was produced by clumping of the pedicles. A severe decrease or interruption of liver blood flow therefore leads to rapid deterioration of the liver energy state.

As far as we know, there are no reports about brain energy metabolism during hemorrhagic shock studied by ^{31}P-NMR spectroscopy. Kassik et al.[21] reported the effect of hypotension on the concentration of phosphorus metabolites in brain tissue using the freeze-clumping method, and also its effect on the intracellular pH calculated from CO_2 tension and bicarbonate concentration. They reported that a mean arterial pressure of 25–35 mmHg caused moderate decreases in phosphocreatine and ATP concentrations and a fall in pHi. Brierley et al. [22] demonstrated that the beginning of circulatory and metabolic changes, and the occurrrence of irreversible structural tissue damage, both occurred below a perfusion pressure of 25 mmHg. In the present study, 30–40 mmHg of hypotension did not lead to any changes in phosphate compounds or pHi. Our results are thus in agreement with these previous studies[21,22]

Effect of catecholamines on the liver

Many investigators have reported an increase in hepatic blood flow after epinephrine administration. Shoemaker et al.[1] showed that increased hepatic blood flow produced by epinephrine occurred with and closely paralleled the increase in pressure gradient across the liver. On the other hand, intravenous administration of norepinephrine decreased the pressure gradient across the liver and reduced the hepatic blood flow[2]. Robie et al.[23] demonstrated that dopamine infusion increased renal and mesenteric blood flow and decreased vascular resistance. These findings suggest that epinephrine and dopamine improve liver energy metabolism, whereas norepinephrine worsens it. However it is not clear whether these catecholamines act in the same manner in severe hemorrhagic shock. In the present study epinephrine showed a slight non-significant improvement in the energy metabolism and pHi. Norepinephrine showed no improvements, but did not worsen the condition further. On the other hand, energy metabolism modified by hemorrhagic shock was restored markedly by infusion of dopamine. The presence of vasoactive receptor sites in the liver vascular bed has been reported by many investigators[24,25]. Although alpha-receptors have been reported to be present in the hepatic arterial and portal venous vessels and beta receptors appear to be present in the hepatic arterial bed, beta-receptors have not been shown to have much, if any, significance in the portal vessels[26,27]. It is difficult to explain why the epinephrine infusion group showed slight improvement in hepatic energy metabolism compared with the norepinephrine infusion group. It can be hypothesized that the difference may be due to the beta-agonist property of epinephrine. The alpha-adrenergic property of epinephrine and norepinephrine may lead to vasoconstriction of the hepatic and the mesenteric arteries, but total hepatic blood flow was maintained due to an increase in, or redistribution of cardiac output, by vasoconstriction of peripheral vascular beds. This effect may be more prohounced due to the beta-adrenergic property of epinephrine.

Goldberg[28], Yeh[29], and Higgins[3] have suggested a specific vasodilator action of dopamine on splanchnic and hepatic dopaminergic receptors. However, Maestracci et al. [30] reported that dopamine increased the hepatic blood circulation by increasing cardiac output, and that there was no evidence for the presence of splanchnic and hepatic dopaminergic receptors. In the present study, dopamine, like epinephrine and norepinephrine, produced an increase in arterial blood pressure. In contrast to these two catecholamines, dopamine significantly improved liver energy metabolism. Therefore, it is strongly suspected that dopaminergic receptors are present in mesenteric or hepatic vascular beds. The author postulates that the primary mechanism responsible for restoration of hepatic energy metabolism by dopamine infusion is the dilation of mesenteric artery by dopaminergic receptor stimulation, because the hepatic arterial bed was already maximally dilated during hemorrhage due to the autoregulation mechanism. The dilation of mesenteric artery may produce greater portal venous blood flow through the mesenteric artery covined with increasing cardiac output.

Effects of catecholamines on the brain

In helical strips of dog cerebral artery, norepinephrine constricts the cerebral arteries in a dose dependent manner but its effect was only 20% of that of the peripheral arteries and the effect of epinephrine on the cerebral arteries has been demonstrated to be even weaker[31–33]. Dopamine in low concentration produced a relaxation in helical strips of monkey cerebral artery[34]. After administration of epinephrine and norepinephrine CBF has been noted to increase[35,36], decrease[5], or remain constant[37]. Dopamine has been domenstrated to increase the CBF in medium doses[6]. It si generally beleved that chathecholamines are unable to cross the blood brain barrier (BBB)[38–40]. It is expected that cerebral oxgen consumption would not be affected by these catecholamines. On the other hand, it has been shown that epinephrine increased the cerebral oxygen consumption while norepinephrine did not[35]. Moreover, there is a possibility that the BBB may be disrupted during hemorrhagic shock. Therefore, the complexity of these findings make it difficult to evaluate how these catecholamines affect the cerebral energy metabolism during hemorrhagic shock. In the present study, none of the catecholamines used during hemorrhagic shock caused any worsening of the brain energy state.

It is difficult to state which catecholamine is the drug of choice for the brain during hemorrhagic shock. However, with the effects on the liver in mind, dopamine is considered to be the catecholamine of choice in the emergency treatment of hemorrhagic shock. Furthermore, comparing epinephrine with norepinephrine, the former is recommended because of its beta-agonist properties for the liver. Finally, this study shows that the ^{31}P-NMR technique has proved to be useful in evaluating organ energy metabolism in a critical state, and its management.

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References

1. Shoemaker WC, Turk LN, Moore FD: Hepatic vascular response to epinephrine. Am J Phsiol 210:58–62, 1961
2. Turk LN, Shoewmaker WC:Hepatic vascular response to norepinephrine. Am J Physiol 206:1175–1178, 1962
3. Higgins CB, Millard RW, Braunwald E, Vatner SF: Effects and mechanisms of action of dopamine on regional hemodynamics in the conscious dog. Am J Physiol 225:432–437, 1973
4. Krarup N: The effect of noradrenaline and adrenaline on hepatosplanchnic hemodynamics, functonal capacity of the liver and hepatic metabolism. Acta Physiol Scand 87:307–319, 1973
5. Greenfield Jr JC, Tindall GT:Effect of norepinephrine, epinephrine, and angiotensin on blood flow in the internal carotid artery of man. J Clin Invest 47:1672–1684, 1968
6. Essen C: Effects of dopamine on the cere-

bral blood flow in the dog. Acta Neurol Scand 50:39–52, 1974
7. MacDonell L, Xanalatos C, Hall S, James IM: Factors affecting the response of cerebral metabolism and blood flow to a noradrenaline infusion in the dog. Europ Neurol 6:208–212, 1971/72
8. Ekstrom-Jodal B, Essen C, Haggendal E: Effects of noradrenaline on the cerebral blood flow in the dog. Acta Neurol Scand 50:11–26, 1974
9. Olesen J: The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. Neurology 22:978–987, 1972
10. Radda GK, Seeley PJ:Recent studies on cellular metabolism by nuclear magnetic resonance. A Rev Physiol 41:749–769, 1979
11. Gadian DG, Radda GK:NMR studies of tissue metabolism. An Rev Biochem 50:69–83, 1981
12. Malloy CR, Cunningham CC, Radda GK: The metabolic state of the liver in vivo measured by ^{31}P-NMR spectroscopy. Biochim Biophys Acta 885:1–11, 1986
13. Roberts JKM, Wade-Jardetzky N, Jardetzky O: Intracellular pH measurements by ^{31}P nuclear magnetic resonance. Influence of factors other than pH on ^{31}P chemical shifts. Biochemistry 20:5389–5394, 1981
14. Seo, Y, Murakami Y, Watari H, Imai Y, Yoshizaki K, Nishikawa H, Morimoto T: Intracellular pH determination by a ^{31}P-NMR technique. The second dissociation constant of phosphoric acid in a biological system. J Biochem 94:729–734, 1983
15. Krarup N: The effect of hemorrhage on hepatosplanchinic hemodynamics, liver function and hepatic metabolism. Acta Physiol Scand 89:269–277, 1973
16. Greenway CV, Lawson AE, Stark RD: The effect of hemorrhage on hepatic artery and portal verin flows in the anaesthetized cat. J Physiol 193:375–379, 1967
17. Muller, W, Smith LL: Hepatic arterial and portal venous circulatory changes following acute hemorrhage in the dog. Surg Gynecol Obstet 117:753–758, 1963
18. Frank ED, Frank HA, Jacob SW, Jacob F: Hepatic blood flow in the expermental hemorrohagic shock. Am J Physiol 202:7–11, 1962
19. Hanson KM, Johnson PC: Local control of hepatic arterial and portal venous flow in the dog. Am J Physiol 211:712–720, 1966
20. Kamiike W, Watanabe F, Hashimoto T, Togawa K, Ikeda Y, Nakao K, Kawashima Y: Changes in cellular levels of ATP and its catabolites in ischemic rat liver. J Biochem 91:1349–1356, 1982
21. Kaasik AE, Nilsson L, Siesjo BK: The effect of arterial hypotension upon the lactate, pyruvate and bicarbonate concentrations of brain tissue and cisternal CSF, and upon the tissue concentrations of phosphocreatine and adenine nucleotides in anesthetized rats. Acta Physiol Scand 78:448–458, 1970
22. Brierley JB, Brown AW, Excell BJ. Meldrum BS: Brain damage in the rhesus monkey resulting from profound arterial hypotension. I. Its nature, distribution and general physiological correlates. Brain Res 13:68–100, 1969
23. Robie NW, Goldberg LI: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. Am Heart J 90:340–345, 1975
24. Hagino Y Nakashima M: Adrenergic receptors in rat liver II. Effects of phynylephrine, isoproterenol and adrenergic blocking agents on gluconeogenesis in perfused liver. Japan J Pharmacol 24:373–381, 1974
25. Ross G, Kurrasch M: Adrenergic responses of the hepatic circulation. Am J Physiol 216:1380–1385, 1969
26. Geumi A, Mahfauz M: The presence of -adrenergic receptors in the hepatic vasculature. Brit J Pharmacol Chemotherap 32:446–472, 1968
27. Hanson KM: Response of intrahepatic vasculature to isoproterenol and epinephrine infusions. Angiologica 10:65–75, 1973
28. Goldberg LI: The dopamine vascular receptor. Biochem Pharmacol 24:651–653, 1975
29. Yeh BK, Mac Nay JL, Goldberg LI: Attenuation of dopamine renal and mesenteric vaso-dilation by haloperidol. Evidence for a specific dopamine receptor. J Pharmacol Exptl Ther 168:303–309, 1969
30. Maestracci P, Grimaud D, Livrelli N, Philip F, Dolisi C: Increase in hepatic blood flow and cardiac output during dopamine infusion in man. Crit Care Med 9:14–16, 1981
31. Toda N: Responses of isolated cerebral and periphiral arteries to vasoconstricting agents. In neurogenic control of brain circulation. Ed. by C. Owman and L. Edvinsson, Pergamon Press, 1977, pp207–217

32. Toda N, Fujita Y: Responsiveness of isolated cerebral and peripheral arteries to serotonin, norepinephrine, and transmural electrical stimulation. Circul Res 33:98–104, 1973
33. Rosenblum WI: Contractile response of pial arterioles to norepinephrine. Arch Neurol 31:197–199, 1974
34. Toda N: Heterogeneity in the response to dopamine of monkey cerebral and peripheral arteries. Am J Physiol 245:H930–H936, 1983
35. King BD, Sokoloff L, Wechsler RL: The effects of l-epinephrine and l-norepinephrine upon cerebral circulation and metabolism in man. J Clin Invest 31:273–279, 1952
36. Michenfelder JD, Theye RA: Effects of cyclopropane on canine cerebral blood flow and metabolism; modification by catecholamine suppression. Anesthesiology 37:32–39, 1972
37. Fazekas JF, Thomas A, Johnson JVV, Young WK: Effect of arterenol (norepinephrine) and epinephrine on cerebral hemodynamics and metabolism. Arch Neurol 2:435–438, 1960
38. Weil-Malherbe H, Axerod J, Tomchick R: Blood brain barier for adrenaline. Science 129:1226–1227, 1959
39. Axelrod J: Noradrenaline. Fate and control of its biosynthesis. Science 1971;173:598
40. Bianchine JR: Drug therapy of parkinsonism. N Engl J Med 295:814–818, 1976