Three Approaches to Pathophysiology of Shock

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(Key words: organ perfusion, renal blood flow, humoral response, thyrotropin-releasing hormone (TRH), hemorrhagic shock)

Any insult to the body can lead to shock, and when the syndrome is fully developed, the most striking fatal abnormality is hemodynamic in character. Inadequate perfusion of the tissues with oxygenated blood is believed to be common to most forms of shock, even anaphylactic shock reveals this character at its terminal stage. The resultant disturbance in cell function ultimately causes death of the patient soon unless adequate treatment is provided. The patient shows hypotension, tachycardia, pallor, sweating, cyanosis, hyper- then hypoventilation, clouding of consciousness, and oliguria as clinical expression, but pathophysiology of shock reveals rather nonspecific pathological changes. This article summarizes several of our current views based on studies on the pathophysiological disturbances of shock, and serves as an introduction to the recent studies on shock. The pathophysiology of shock is so complicated that multiple approaches must be made to clarify it. We have been trying to investigate it in three now rapidly developing fields.

1. Organ perfusion and pathophysiological responses

Organ failure will be caused primarily by the impairment of organ perfusion and precipitated ischemia in multiple organs. The cause of fatal shock is always ischemia, tissue hypoxia, and resulting cell damage and abolishment of mitochondrial functions. Typical ischemic failure is seen in hemorrhagic shock.

A) Disturbance of tissue perfusion

The most obvious cause of inadequate tissue perfusion is reduced cardiac output due to failure of the heart to function as a pump or to loss of blood from the intravascular compartment which is known as hypovolemia. The proportion of the cardiac output available to individual organs is dependent upon the perfusion pressure and the degree of smooth muscle tone in supplying the vessels. The reduction is cardiac output is usually considerable and is due to the activity of sympathetic vasoconstrictor fibers to the arterioles, which are precapillary resistance vessels, and to the venules, which are postcapillary resistance vessels and veins, and also are capacitance vessels.

One of the most powerful compensatory mechanisms available to the body during acute pump failure or hypovolemia is increased sympathoadrenal discharge. This not only increases myocardial contractility but also leads to constriction of the arterioles and of the capacitance vessels, thereby trying to normalize blood pressure and maintain venous return to the heart. Early in shock, the effect of sympathetic stimulation results in constriction of the resistance vessels on both sides of the capillary bed.

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We examined the animal in shock microscopically[1]. With the progress of hemorrhagic shock, contraction of arteriole and slowing of venular circulation gradually proceed. When hemorrhagic shock progresses, sludging of both arteriole and venule increases, especially the viscositiy in venule increases and velocity of venular flow becomes extremely slow. Arterial sludging is intensified but internal surface of the arteriole is still clear and smooth. In this stage, hemorrhagic shock is still in a reversible state. Precapillary resistance due to arteriolar constriction is increased to a greater extent than postcapillary venular resistance, and mean capillary pressure is decreased. There is a tendency for fluid to move into the circulation from the tissue spaces by osmosis. The hemorrhagic shock further progresses, and arteriovenous anastomosis is opened. Further increased sludging of venular circulation results in the formation of thrombosis, and a change in the direction of blood flow is noticed. Late in shock there is a marked change in vascular reactivity. The response of arteriolar smooth muscle declines more rapidly than does that of venular smooth muscle. Metabolic products such as lactic acid which have a profound vasodilating effect on arteriole than on venule, increase. Increase of capillary permeability will cause a further decrease in circulatory blood. One of the causes of an increase in blood viscosity is hemoconcentration due to continuing postcapillary vasoconstriction and loss of intravascular fluid. Another factor which influences blood viscosity is the fibrinogen level and the hematocrit, both of which are raised in the early stage of shock. With the progress of shock widespread sludging is seen. Not only red cells but also platelet aggregation is induced by the presence of thrombin, norepinephrine, endotoxin and fibers of collagen released from injured vessels. Infarction of the tissue supplied by the obstructed vessel occurs. In this stage, failure of capillary circulation will cause cell damage, and cessation of capillary circulation and tissue ischemia will result in irreversible shock. The injured tissue area, which we call desert formation due to failed capillary circulation, soon will become irreversibly destroyed ischemic tissue. The red cells are at an almost complete standstill of flow, and very often adhere to the wall. The electron micrograph of human skin chamber taken by Brånemark[2] shows a red blood cell which has a fairly large foot-shaped portion outside the endothelium. Meanwhile, destruction of the endothelium of the vessels occurs. When hemorrhagic shock comes to the terminal stage, stasis and dilatation of venules are intensified and intravascular leakage occurs. The best indices of specific alterations are demonstration of factor XIII loss, thrombocytopenia and reduction of the maximal amplitude in thromboelastography. Loss of factor VIII and V activity and hypofibrinogenemia are additional valuable analytical criteria of hypocoagulability of consumption coagulopathy. Interstitial hemorrhage is seen diffusely and uncontrollable hemorrhage and coagulation difficulty following DIC develop[3].

B) Humoral pathophysiological responses

We studied the difference in organ perfusion in controlled hypotension using various kinds of vasodilators in anesthesia and in various types of shock[1,4–10].

ECG, direct arterial pressure, pulse rate, organ perfusion represented by renal cortical circulation, C.V.P., and cardiac output were monitored during a shock experiment on dogs. Humoral factors such as epinephrine, norepinephrine, plasma renin activity, angiotensin II, histamine, and prostaglandin E were measured. Blood gas and acid-base balance were also periodically checked throughout the experiment.

The same grade of arterial hypotension was induced either by controlled pharmacological methods or hemorrhagic, endotoxin, and cardiogenic shock. After discontinuation of controlled hypotension, blood pressure recovered in 2 hours while shock groups precipitated themselves into irreversible shock as shown in figure 1. Correspondent renal cortical flow shows a completely different pattern in both categories of hypotension. In controlled hypotensive anesthesia groups,

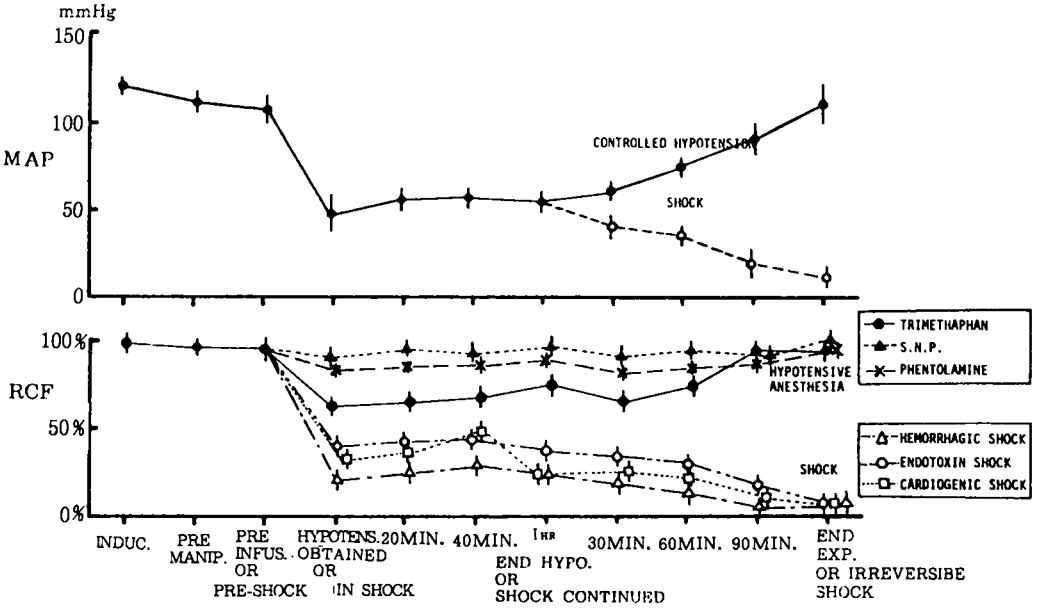

Fig. 1. Mean arterial blood pressure and renal cortical flow during controlled hypotensive anesthesia and shock in dogs. The figure shows the difference of renal cortical flow in various types of shock and controlled hypotensive anesthesia in dogs. Mean arterial blood pressure was lowered to 40 mmHg rapidly and then kept at 50 mmHg for 1 hour as shown in the upper panel. After 1 hour of shock or controlled hypotensive anesthesia, animals in shock were left without any treatment while controlled hypotension was discontinued and blood pressure returned to the original normal level. As in the lower panel, decrease of renal cortical flow in hypotensive anesthesia groups is much less than that in the groups in shock at the same blood pressure. In groups in shock renal cortical flow decreased significantly, and renal ischemia persisted with the progress of shock and irreversible shock resulted because of the failure of organ perfusion.

of course, there are certain degrees of decrease in flow but the grades are less or moderate as shown in figure 1. In the groups in shock, the decrease in renal cortical flow is severe and critical without any sigh of recovery. Figure 2 shows the response of norepinephrine during controlled hypotensive anesthesia and in shock in dogs. Immediately after the initiation of hypotensive anesthesia and a shock level at the same grade of mean arterial blood pressure, norepinephrine increases in different ways. In various types of shock, norepinephrine markedly increased more than in controlled hypotensive anesthesia groups. The increase of norepinephrine in hypotensive anesthesia is small. Values for all groups of shock reached very high levels at the irreversible stage of shock.

In shock the defense system of a living body tries to stabilize itself by mobilizing the autonomic nervous system and endocrine responses. If there is an overreaction such as an excess secretion of catecholamine, plasma renin activity, angiotensin II, ADH, histamine, bradykinin, autacoids, and other numerous shock products, an aggravation of vascular constriction will result.

Increased vascular permeability causes decreased circulatory blood volume, decreased venous return, and decreased cardiac output. The vicious cycle leads to cardiogenic shock, and eventually irreversible shock occurs.

2. Endocrine Responses in Shock

A) Thyrotropin-releasing hormone (TRH)

Naloxone has an antishock action since β-endorphin aggravates the state of shock both in central and peripheral nervous system[11,12]. Holaday and Faden also noticed the antishock action of thyrotropin-releasing

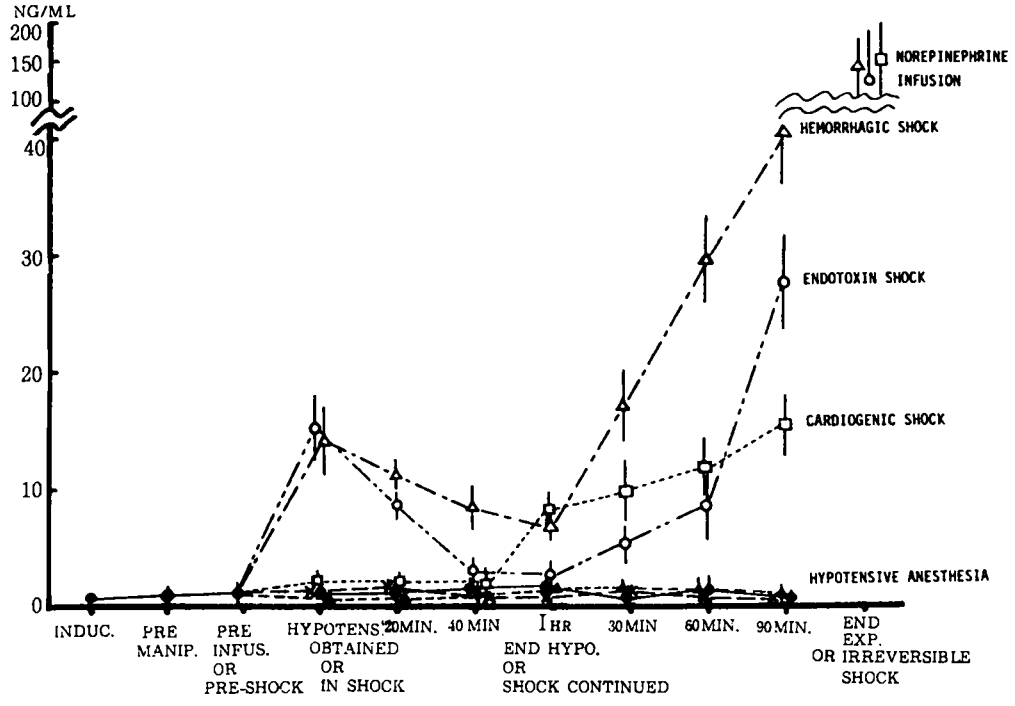

Fig. 2. Changes of norepinephrine level during various types of shock and controlled hypotensive anesthesia in dogs. The figure shows the difference of norepinephrine levels in shock and controlled hypotensive anesthesia in dogs. Mean arterial blood pressure was lowered to 40 mmHg and then kept at 50 mmHg for 1 hour. After 1 hour of shock or hypotensive anesthesia, shock animals were left without any treatment while controlled hypotension was returned to the original normal level. Serum norepinephrine was measured at each stage of experimental procedure. Hypotensive anesthesia was induced with trimethaphan (-•-), sodium nitroprusside (-▲-), and phentolamine (-x-). Three types of shock were induced by Wigger's original and modified by Elliot and Paton's reservoir method of hemorrhagic shock (-△-), endotoxin shock by an injection of 3 mg/kg of *Escherichia coli* endotoxin manufactured by Difco Co. (-○-), and cardiogenic shock made by occlusion of left coronary artery (-□-), respectively. Immediately after the initiation of hypotensive and a shock level at the same mean arterial pressure, norepinephrine increased in both groups. In various types of shock, norepinephrine markedly increased more than in controlled hypotensive anesthesia groups. The increase in norepinephrine in hypotensive anesthesia was small. In hemorrhagic and endotoxin shock, it reached 14 and 15 ng/ml, respectively. In cardiogenic shock it increased after 40 min in shock. Values of all groups of shock reached very high levels at the irreversible stage of shock. Extremely high levels in shock groups at the last stage indicate high norepinephrine levels during norepinephrine infusion treatment. Norepinephrine levels throughout the shock process are significantly higher than those on controlled hypotensive anesthesia even at the same low level of mean arterial blood pressure.

Other endocrine, humoral, and chemical mediators' responses such as release of epinephrine, renin-angiotensin II, histamine, ADH, autacoids, and kinin groups were also measured at the same time. Those responses in shock are far more serious than in other physiological states and greatly influence organ perfusion.

hormone (TRH), a tripeptide, and since then the action of TRH has been intensively investigated[13–17]. TRH is known to have various actions within the central nervous system (CNS), in addition to its endocrine functions[15,18]. In a pathophysiological state such as various types of shock, administration of TRH has been shown to have therapeutic effects mainly by improving the cardiovascular function in experimental animals[15,19–21]. Recently, a number of experimental studies suggested that TRH is involved in central cardiovascular control[11,20] probably by increasing sympathetic outflow[20,22], and/or by stimulating the release of vasopressin or other pressor substance[23]. In various types of shock, centrally as well as peripherally administered TRH has been shown to elevate blood pressure and survival rate[13,19,24,25]. However, the mechanism by which TRH exerts its action on the central cardiovascular regulatory system remains speculative. Also, systemically administered TRH may have a direct peripheral action[13]. TRH was found to be a stimulating hormone of secretion of thyrotropin, TSH, at first. Since then, its distribution was confirmed at not only hypothalamus but also in other parts of the brain and liver, and now it is known as a neuropeptide which has various actions of physiological activity as above described.

TRH is the tripeptide which consists of three amino acids. Intravenously or intracerebroventricularly administered TRH is rapidly decomposed through the metabolic pathway and eventually is pooled in each composed amino acid. Intermediate metabolites, deamide-TRH and histidyl-proline diketopiperazine have different physiological activities.

B) TRH and Vasopressor action

Okuda et al. investigated the interaction between intracerebroventricularly administered TRH with some of the central neurotransmitter pathways involved in controlling blood pressure. The vasopressor action of intravenously administered TRH was also studied[26–30]. Okuda et al. also examined whether or not such central cardiovascular regulatory systems play a major role in the pressor effect by intravenously administered TRH.

Male Wistar rats were used for our experiments. Under sodium pentobarbital anesthesia, the animals were placed on a stereotaxic device and stainless steel guide cannulas aimed at the fourth ventricle were implanted and cemented to the skull. Within one week after the surgery, the animals were anesthetized again. The right femoral artery and vein were cannulated with PE10 (5 cm). The distal ends were connected to PE50 tubing (40 cm). These cannulas were compactly coiled and fixed on the neck. The animals were allowed to recover for one or two days while placed individually in their cages. They were conditioned to controlled lighting and temperature, and laboratory chow and tap water were given. In same rats, adrenal glands were removed by the dorsal approach, and they were maintained on physiological saline and received subcutaneous injection of 1 mg/kg of corticosterone once a day until the morning of the experiment. All measurements were performed in conscious and freely moving rats. Arterial cannulas were extended and further shielded with vinyl tubes, which were then connected to a pressure transducer coupled with a polygraph for measurement of blood pressure, Heart rate was measured with a cardiotachometer triggered from the blood pressure. Intracerebroventricular injection of TRH increased arterial blood pressure in proportion to the dosage in a range from 0.1 to 100 μg in conscious and freely moving rats. Either intracerebroventricular or intravenous administration of TRH produced a rapid increase in blood pressure and the peak value was obtained within one minute, which was followed by a gradual return to the base-line level. The increase in blood pressure lasted for more than 2 hours and was accompanied by tachycardia in most of the rats that received high doses (10–100 μg). This increase in blood pressure was greatly diminished after adrenalectomy as well as after pretreatment with 5 mg/kg of intravenously administered mecamylamine, a ganglionic blocker, or with 0.6 mg/kg of intra-

venously administered phentolamine, an α-receptor blocker. TRH-free acid (TRH-OH) and histidylproline diketopiperazine, metabolites of TRH, or saline did not change the blood pressure in these animals. Pretreatment with 50 μg of intracerebroventricularly administered atropine, a muscarinic receptor antagonist, 5 min before the injection of TRH significantly suppressed the enhancement of blood presure by TRH administered through either an intravenous or intracerebroventricular route. Haloperidol, a dopaminergic receptor antagonist, also suppressed the rise in blood pressure 20 min after TRH injection, but not that occurring 1 min after, while bicuculine, γ-aminobutyric acid (GABA) receptor blocker reduced the latter but not the former. Propranolol and naloxone, which are β- and opioid receptor antagonists, respectively, had no significant effects during this observation period. Fifty μg of intracerebroventricularly administered hemicholinium-3, an inhibitor of choline uptake, caused prolonged suppression of blood pressure increase induced by TRH as did atropine. Figure 3 shows the representative interaction with these cholinergic drugs and TRH. Although these intracerebroventricularly administered cholinergic drugs changed blood pressure and heart rate temporally, they returned to almost the base-line levels when TRH was injected.

Holaday et al. reported that intravenously administered TRH produced prolonged cardiovascular effects, probably through central mechanisms[21]. Thus, they recommended the use of this peptide in shock instead of other pressor substances that are known to act at peripheral sites and transiently elevate blood pressure. Although blood-brain barrier permeability to TRH is extremely low[31], there may be passage of some intact TRH by a nonspecific pathway through the choroid plexus into cerebrospinal fluid followed by diffusion in the extracellular space of nervous structure adjacent to the ventricles[32]. The present findings support this idea since the pressor effects of peripherally as well as of centrally injected TRH were blocked by the pretreatment with centrally administered atropine. Although TRH is thought to be rapidly degraded in the brain and plasma[33], the pressor effect seems to be exerted by TRH itself rather than by its metabolites. However, the possibility that these metabolites have some other beneficial effects in the treatment of shock can not be excluded[19].

In the CNS, there are TRH receptors which may account for the biological and pharmacological actions of TRH, including those on the cardiovascular system. Some of the pharmacological effects of TRH have been reported to be induced by interactions with other neuronal systems in the CNS. For example, the mesolimbic dopaminergic system is suggested to be involved in the increase of spontaneous motor activity induced by TRH[34]. In the analeptic actions of TRH, such as the antagonism of pentobarbital induced sleep, an interaction of TRH with central cholinergic systems have been suggested[35,36]. Okuda et al. found that the pressor response to TRH was greatly diminished in pentobarbital anesthetized rats[27]. It is becoming apparent that various central neurotransmitters such as catecholamine[37], acetylcholine[34], GABA[38], and opioids[39] are involved in central regulation of the cardiovascular system. As above mentioned, Okuda et al. found that intracerebroventricularly given atropine and hemicholinium-3 diminished the pressor effects of TRH throughout the time course observed, whereas intraventricularly administered 50 μg to 100μg of mecamylamine reduced only the peak response to TRH. Since hemicholinium-3 is known to inhibit the uptake of choline into cholinergic nerve terminals and thereby depletes acetylcholine stores[40], it appears that TRH exerts its pressor effect by increasing the release of acetylcholine from cholinergic neurons. Central muscarinic receptors are involved in the prolonged pressor effect of TRH, while nicotinic receptors appear to have only a minor, if any, role in it. Okuda et al. and other investigators[20,22], have shown that TRH increases sympathetic nerve activity. Physostigmine, a cholinesterase inhibitor, that can enter the CNS, evokes a pressor

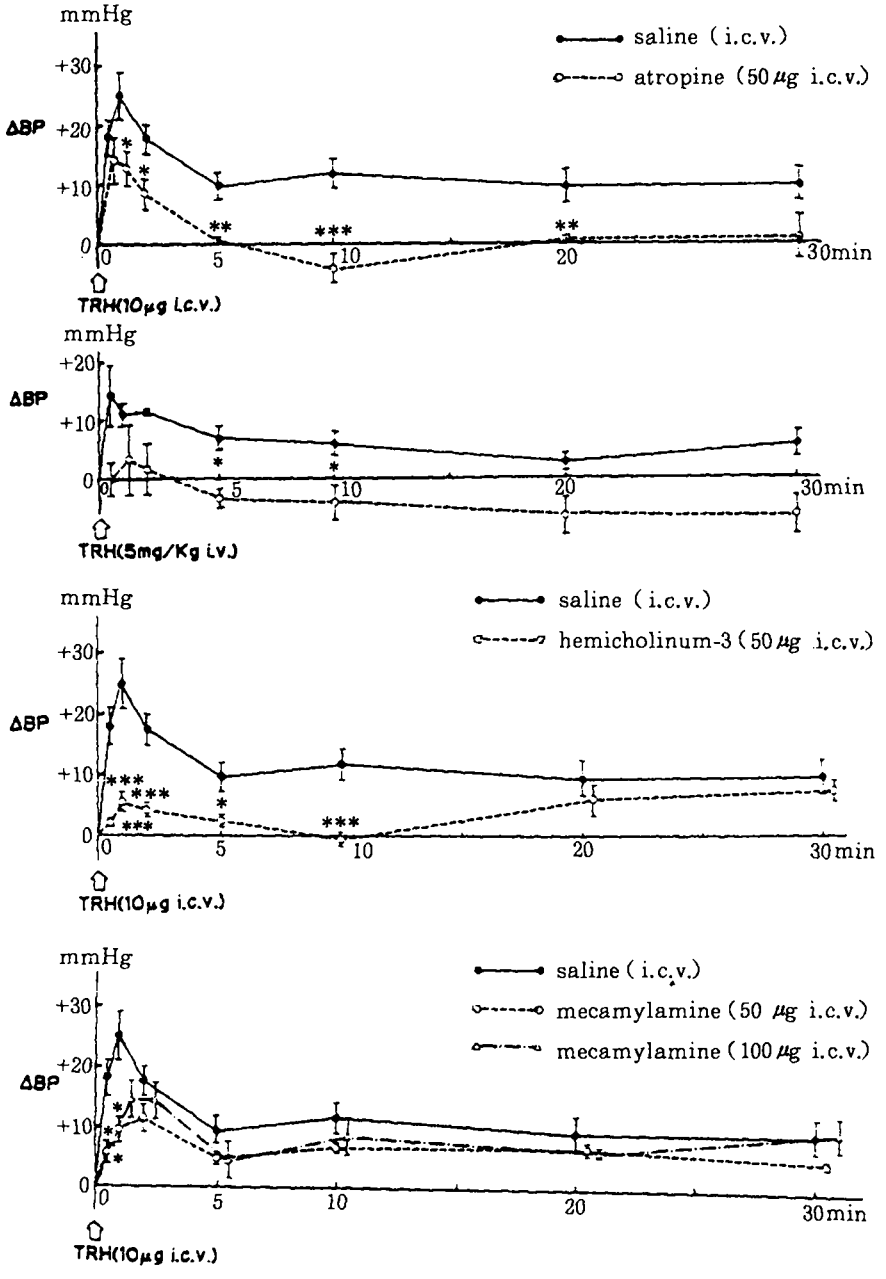

Fig. 3. Effect of various cholinergic drugs pretreatment on blood pressure response to TRH (10 μg, intracerebroventricularly), or (5 mg/kg, intravenously). Uppermost panel: Atropine (50 μg/rat) was injected i.c.v. 5 min before TRH administration (10μg i.c.v.).

Second panel: Atropine (50 μg/rat) was injected i.c.v. 5 min before TRH administration (5 mg/kg i.v.).

Third panel: Hemicholinium-3 (50 μg/rat) was injected i.c.v. 10 min before TRH administration (10 μg i.c.v.).

Bottom panel: Mecamylamine (50 μg and 100 μg/rat) was injected i.c.v. 5 min before TRH administration (10 μg i.c.v.). Comparisons were made to the control group injected with saline. Each value represents the mean ± S.E.M. obtained from 3–8 rats. * $P<0.05$; ** $P<0.01$; *** $P<0.005$.

response by increasing central acetylcholine, which in turn acts on central muscarinic receptors and peripherally increases sympathetic activity[22]. In addition to cholinergic drugs, haloperidol and bicuculline, dopaminergic and GABAergic receptor blockers respectively, have been found to partially reduce the response to TRH. Figure 3 shows the effects of main cholinergic pretreatments on blood pressure response to TRH. It is necessary to further investigate the relationship between cardiovascular effects and analeptic actions of TRH, since the central cholinergic pathway appears to be involved in both actions.

C) TRH and hemorrhagic shock

Although the blood-brain barrier permeability to TRH as well as other peptides is very low[31], as shown in a previous section the prolonged pressor action of TRH is produced mainly through a central cholinergic mechanism[29]. TRH is known to be distributed widely throughout the CNS and it is thought to act as a neurotransmitter or neuromodulator. Although the functional significance of TRH in various parts of the brain is still speculative, the involvement of the peptide in central autonomic regulation is suggested by the existence of TRH-positive neural structures and/or its receptors in the areas where exogenous TRH was microinjected and exerted its effects on autonomic functions such as circulation[11,20], respiration[11,15,25], and thermoregulation[20,41]. However, there is little information about the regulation between the functional changes of autonomic nervous system and the biochemical changes in the endogenous TRH in the central nervous system. Therefore, Mizobe et al. investigated the alteration of brain TRH contents during hemorrhagic shock to investigate whether or not the brain TRH may play a physiological role in the shock.

Male Wistar rats were used in a conscious state. Mean arterial pressure was maintained at 40–70 mmHg for 60 min by withdrawing a total of 8ml of blood intermittently. Fifty per cent of circulatory blood volume was withdrawn. Plasma lactate, blood gas, and acid-base status were measured during and 60 min after the end of the hemorrhage. The shock was considered reversible if the animal survived 24 hours after the hemorrhage. The plasma lactate levels at 60 min after the end of the hemorrhagic period of the survived rats were 0.8–2.3 mEq/1, and the levels were significantly lower than those of the animals that died witihin 24 hours and showed the levels of 3.5–14.2 mEq/1.

Another group of rats were killed for the determination of the brain TRH contents. Brain TRH was measured by radioimmunoassay. TRH contents were significantly increased in the medulla oblongata and midbrain during the period of hemorrhage. At 60 min after the end of the hemorrhage, TRH contents were significantly decreased in the rats whose plasma lactate levels were as high as 4.0–18.3 mEq/1, whereas those in the animals having low plasma lactate levels of 2.0–2.9 mEq/1 remained at/or were higher than the control values of TRH contents in various brain regions including the medulla oblongata and midbrain. These results suggest that the brain TRH plays an important role in the course of recovery from hemorrhagic shock. The decrease in Pa_{CO_2} and increase in Po_2, and increased blood glucose during the hemorrhage, suggest that activation of the autonomic nervous system, especially of sympathetic tone, occurs throughout the hemorrhagic period in both reversible and irreversible groups. Since the autonomic reflex control centers for circulation and respiration are known to be located in the medulla oblongata, the increase in the TRH content, at least in it, may be directly induced by the activation of the TRH-containing neurons. It does not seem likely that the decrease of brain TRH was caused by the inhibition of the biosynthesis of TRH as a result of brain ischemia. Rather, brain TRH was probably decreased by increased consumption, probably by increased release from the nerve terminals of the TRH-containing neurons which were involved in various responses to the shock. In animals in the course of irreversible shock, the brain TRH may finally be exhausted and this may, whether directly or

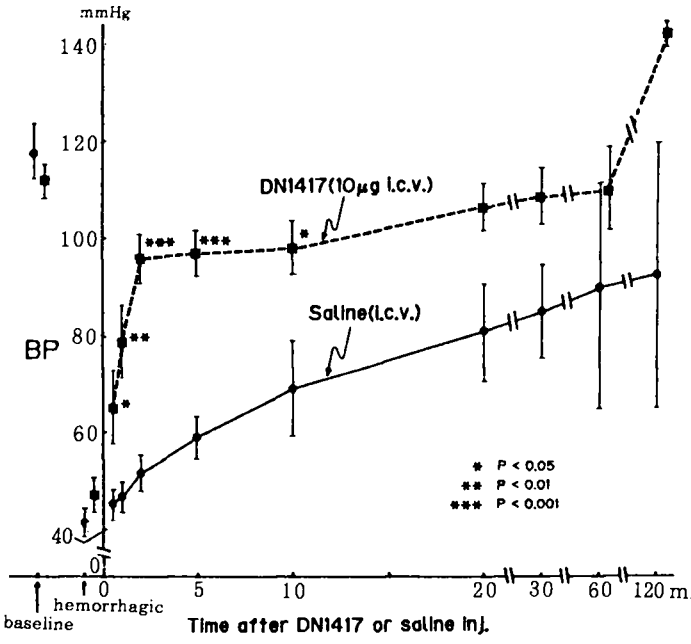

Fig. 4. Effect of saline (intracerebroventricularly administered) or DN-1417 (10 μg i.c.v.) on blood pressure after hemorrhagic shock. 44–47% of circulatory blood volume was exsanguinated from femoral artery of the rat and blood pressure was lowered to 40–50 mmHg. Each value represents the mean ± S.E.M. obtained from 7 rats.

indirectly, lead the central autonomic control to breakdown.

In the early stage of shock, the increase in TRH release may be rapidly compensated with the accelerated synthesis of the peptide, and it may continue after the hemorrhage in the rats recovering from the shock. This type of dynamic change of neurotransmitters has been reported to occur in the stress-induced reduction of catecholamine in the rat brain. The same phenomenon was seen in dogs during various types of shock as described in the previous section. The stress-induced mobilization of the catecholamine store was compensated more than enough by the increase of norepinephrine and dopamine synthesis[42]. Such a compensatory increase in endogenous TRH during hemorrhagic shock may participate in the course of recovery from the shock, as suggested by earlier studies and our study which indicated that exogenously administered TRH improves cardiovascular function and survival rate from hemorrhagic shock[15,16]. No significant changes were seen in the TRH content in the hypothalamus which is known to be the higher center of the autonomic nervous system. Hypothalamic TRH may not play such an important role as that in the brain stem in such rapid and fatal stress as shock. However, it seems necessary to further localize the areas where the changes in TRH contents occur for the detailed understanding of the role of the brain TRH in hemorrhagic shock.

D) Vasopressor action of TRH and its derivative DN-1417

How will TRH act in hemorrhagic shock? Rats were exsanguinated nearly 50% of their circulatory blood volume and blood pressure was lowered to 40 to 50 mmHg. Then 10 μg of TRH was given intracerebroventricularly. Compared with the saline injection (control), TRH markedly elevated blood pressure. The antishock vasopressor effect of TRH continued for at least 5 min. For the treatment of shock, we may use TRH as a vasopressor, but a related drug which decomposes more slowly, and thus with a longer lasting effect could be more valuable. DN-1417, a TRH derivative, γ-butyrolactone-γ-carbonyl-L-histidyl-L-prolinamide, has a more intense pressor action than TRH.

Figure 4 shows the effect of saline of DN-1417 on blood pressure after hemorrhagic shock. DN-1417 shows about the same degree of vasopressor effect as TRH has but its

pressor effect persists longer.

3. Metabolism and Amino Acids in Shock

Breakdown of the energy production system is one of the most serious causes of irreversible shock. The concept of energy charge proposed by Atkinson is a useful tool to study the prognosis of shock[43]. Ozawa classified his patients into 4 groups by blood ketone body ratio which is the ratio of acetoacetic acid and β-hydroxy butyric acid. The metabolic state of the patients, which is the liver mitochondrial activity, was clarified by this method. The decrease in the blood ketone body ratio is well correlated with the increase of amino acids in blood and in brain.

A) Energy charge and blood ketone body ratio

Energy charge is expressed by the following formula.

$$\text{Energy charge} = \frac{(\text{ATP}) + 1/2(\text{ADP})}{(\text{ATP}) + (\text{ADP}) + (\text{AMP})}$$

This formula indicates the balance of energy production and consumption in the cell. Energy charge is 0.85–0.90 in normal state. If it decreases, glycolysis and activation of TCA cycle occurs and ATP is rapidly produced. Thus the energy charge stays in a good balanced condition. A persistent decrease of energy charge means that serious metabolic impairment is progressing in cells.

In a state of shock, the energy charge decreases significantly in liver and kidney, while it stays unchanged in the brain, heart, and muscle. Severe decrease of energy charge in liver has a serious effect on the course of shock, and will contribute to the development of multiple organ failure.

Ozawa et al. studied the relationship between liver energy charge, ATP production of liver mitochondria, redox state of liver mitochondria, and total amount of ketone body in endotoxin shock[44–47,48]. At the beginning, only a slight decrease of energy charge is noted while ATP production of mitochondria markedly elevated. This indicates that increased metabolic overload by endotoxin is compensated for by the increased ATP production.

Meanwhile ketone body formation in the liver increases, which suggests increased mitochondrial function due to increased β-oxidation of fatty acid. Blood ketone body ratio greatly decreases for the first 30 min of hemorrhagic shock and gradually recovers in 90 min. Hepatic energy charge also decreases for the first 30 min of shock and stays at about the same level throughout the state of shock. Hepatocellular ketone body ratio decreases for the first 30 min but rapidly recovers to the preshock level after 120 min from the beginning of shock. The relationship between energy charge and blood ketone body ratio, which is the ratio of acetoacetic acid and β-hydroxy butyric acid, shows a high positive relationship. The decrease in the blood ketone body ratio indicates a decrease in energy charge, and is one of the most important signs of multiple organ failure. Ozawa classified his surgical cases into 4 groups according to the postoperative blood ketone body ratio, group A which had a blood ketone body ratio of over 0.7 and showed an uneventful course, group B which had a blood ketone body ratio of between 0.7 and 0.4 and showed moderate pulmonary complication, coagulopathy, and unconscious disturbances transiently, but still recovered by intensive care therapy, group C which had a blood ketone body ratio of between 0.4 and 0.25 and had serious complication of liver and brain, with a survival rate of only 14%, and group D which had a blood ketone body ratio below 0.25 and eventually died because of serious multiple organ failure.

Substrate of liver mitochondria changes according to the decrease in blood ketone body ratio. In group A, the liver can utilize glucose. The patients in group B cannot use glucose effectively, but ATP is produced by fatty acid oxidation. The patients in group C cannot use either glucose or fatty acid as an energy substrate, and the mitochondria becomes starved. Group D has practically no liver function at all. Intensive conventional treatment is necessary in group A and B. The cases in group C need metabolic

liver support, which means an artificial liver device by extracorporeal circulation.

B) Amino acids in shock

Ozawa examined the relationship between several amino acids and blood ketone body ratio[47]. There exists a good correlation between the increase in amino acids and the decrease in ketone body ratio. Alanine, proline, phenylalanine, and tyrosine increased markedly when the ketone body ratio decreased. In shock, blood ketone body ratio decreased and catabolism progresses, and destruction of muscular protein is aggravated. A decrease in blood ketone body ratio means NADH accumulation in the liver mitochondria, suppression of the activity of citrate synthesis and blockage of TCA cycle. This results in the increase of unmetabolized alanine, proline, phenylalanine, and tyrosine. Unbalanced blood amino acid composition causes a hepatic coma as the symptom of the last stage of shock.

To study the changes of acitivity in central nervous system, Mizobe et al. measured the amino acids in brain using a push-pull cannula and cerebral perfusion method. The push-pull cannula consisted of double needles of 23G and 30G was inserted in various parts of the brain, and artificial cerebrospinal fluid was perfused by a syringe pump. The inner needle was used for injection and outer needle was used for suction. The model and method of hemorrhagic shock were about the same as previously described. Cerebrospinal perfusion of intact rat was used as a control. Amino acids in perfused fluid were measured by a Beckman System 6300E acid analyzer.

Alanine increased after one hour of shock and stayed at a high value. Tyrosine revealed marked increase after 20 min and then kept a significantly higher value than the control level for over two hours. Phenylalanine showed same significant increase after 20 min and the value decreased at the end of the experiment. Fisher et al. have suggested that the plasma amino acid pattern, known to be deranged in hepatic encephalopathy, may be related causally. The ratio of (valine + leucine + isoleucine)/(phenylalanine + tyrosine) showed an excellent correlation with the grade of encephalopathy. When this ratio, previously 1.0 in shock in the presence of encephalopathy, returned to the normal value of 3.0 to 3.5, encephalopathy improved. An excellent correlation was obtained between the ratio of amino acids and the grade of encephalopathy and was dose related as well. These results suggest that manipulation and normalization of plasma amino acids in animals with hepatic failure may be efficacious in providing adequate nutrition while minimizing hepatic encephalopathy[49–52].

Our study on increased aromatic amino acids in perfused cerebrospinal fluid suggests derangement of the cerebral status at the terminal stage of shock. There is a close relationship between increased aromatic amino acids and irreversibility of shock. These experiments may shed some light on the mechanism of irreversible shock in the central nervous system.

4. Summary of Approaches to Pathophysiology of Shock

The recent developments in three categories of shock research were discussed. Organ perfusion and pathophysiological responses were the first problem studied. The cause of fatal shock is always ischemia, tissue hypoxia, and resulting cell damage and abolishment of mitochondrial function[53]. Microscopic findings of mesenterial circulation reveal progressive changes in tissue perfusion. Retardation of venular blood flow, stasis, decrease in arterial flow velocity, increased blood viscosity, opening of arteriovenous anastomosis and shunt of peripheral circulation, capillary constriction, then tissue hypoxia occur. Destruction of wall of vessels occurs while DIC is proceeding, and diffuse coagulation difficulty appears.

The body reacts promptly by mobilizing sympathetic activity and neurotransmitters. Thus all chemical mediators start to increase for the protection against stress invasion. However, increased catecholamines, plasma renin activity, angiotensin II, histamine, bradykinins, and autacoids also aggravate systemic circulation and normal cell metabolism.

The research in endocrinology of shock has recently shown particular progress. Holaday and Faden found that naloxone has an antishock action. They also noticed an antishock action of thyrotropin-releasing hormone. We also examined the vasopressor actions of TRH. Both centrally and peripherally administered TRH had pressor effects mediated by central cholinergic mechanisms, probably by activating cholinergic neurons. TRH and its derivative DN-1417 revealed good vasopressor action on hemorrhagic rats. Distribution of TRH in the brain in shock was also investigated and a localized increase in TRH in medulla oblongata and midbrain was noticed in reversible shock. TRH contents in brain decreased in the rats that showed high levels of blood lactate and that were in irreversible shock. The peptides that have been understood as endocrine regulators have another action of antishock and sympathetic nervous regulation when the body is exposed to stress such as shock.

Breakdown of energy metabolism is one of the gravest factors in precipitating irreversible shock. Energy charge proposed by Atkinson is a useful method to study the prognosis of shock. Ozawa classified his surgical cases that needed intensive care treatment into 4 groups by blood ketone body ratio, which is the ratio of acetoacetic acid to β-hydroxy butyric acid levels, to define the metabolic state of the patients, namely liver mitochondrial activity. Then Ozawa decided the prognosis and treatment of his patients in shock. Decrease in blood ketone body ratio is well correlated with the increase in amino acids in blood. Using push-pull cannula perfusion method, we found that the amounts of alanine, tyrosine, and phenylalanine in the brain increased with the progress of hemorrhagic shock.

These studies all shed light on the mechanism of the pathophysiology of shock.

Acknowledgments: This work was supported in part by a Grant-in Aid for Scientific Research (No. 56570527 1981–1982, No. 58480322 1983–1985, No. 61440067 1986–1989, No. 61570746 1986) from The Ministry of Education, Science and Culture, Japan. The paper was presented as the plenary lecture of International Symposium of Role of Divalent Metals in Critical Care Medicine of American Society For Magnesium Research on June 24, 1987.

(Received Jan. 19, 1988, accepted for publication Jun. 11, 1988)

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