Hiroshima Journal of Medical Sciences
Vol.34, No.3, 281~290, September, 1985
HIJM 34-41

Blood Sugar in Relation to Endocrine Hormones During Hemorrhagic Shock in Dogs

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(Received May 15, 1985)

Key words: Blood sugar, Endocrine hormones, Hyperosmolality, Hemorrhagic Shock

ABSTRACT

Wiggers' standard method was used to induce hemorrhagic shock in eighteen anesthetized dogs by bleeding to a mean arterial pressure (MAP) of 50 mmHg for 2 hr and then to 30 mmHg for 1 hr, followed by reinfusion of the shed blood. The experimental protocol was designed to determine the sequence of changes in blood sugar during hemorrhagic shock and its relationship to variations in the underlying endocrine hormones, in particular the levels of insulin, catecholamines and cortisol. Venous blood samples were drawn from all experimental animals at specific regular time intervals for sugar and endocrine hormones determination. In early stages of hemorrhagic shock, blood sugar, catecholamines and cortisol were shown to be raised while insulin levels were not influenced by fluctuations in sugar levels. This suggested that, the effect of catecholamine inhibition on the synthesis of insulin is greater than the blood sugar stimulus on the secretion of insulin. Moreover pancreatic islet cells were shown to be intact at terminal stage by Electron microscopy. Corresponding elevated blood levels of sugar, catecholamines and cortisol were found to have a common goal towards increasing plasma osmolality to effect plasma refill. Persistent hypoglycemia in late stages of hemorrhagic shock was shown to be a major sign of failing neuroendocrine compensatory mechanisms against a shock insult. Electron microscopy revealed severe damage of the pituitary gland at the terminal stage.

Faced with aggression, any animal including human may respond by fleeing or by fighting, the dominant role being played by nervous system of relations. With a shock-inducing stimulus, the dominant role is usually played by the autonomic nervous system, the endocrine and metabolic system[25]. Whatever the initial etiological factor is, as soon as it exceeds the 'shock threshold' a particular generalized reaction is triggered urgently demanding that the entire organism, whose existence is endangered, should join the struggle. Therefore we should not forget that most of the phenomena of shock are in fact homeostatic attempts taking place in the organism for the purpose of serving its life. These attempts usually present as severe prolonged vasoconstriction, selective redistribution of fluids and anaerobiosis[25].

Glucose homeostasis disturbance has been reported to occur during hemorrhagic shock in all species studied including the dog, rat, guinea pig and man[22]. Claude Bernard (1877) first observed an initial hyperglycemia caused by hemorrhage and he attributed this to changes in carbohydrate metabolism in states of shock[3,28]. The occurrence of hyperglycemia in trauma, surgery and early stages of hemorrhagic shock has so-far been reported by many workers[4,5], which at one time led to the introduction of the term traumatic diabetes. Mobilization of hepatic glyco-

gen reserves in response to neuroendocrine stimulation is said to account for early hyperglycemia in hemorrhagic shock[22]. However, hypoglycemia has been observed by many investigators to occur in instates of prolonged hemorrhagic shock or endotoxin shock[6,8,28]. Reasons for the cause of hypoglycemia in late shock are many and complex to explain and as such many observers fail to decide whether shocked animals die of hypoglycemia or die in hypoglycemia. Recently, shock-induced impairment of high energy-linked hepatic mitochondrial function has been implicated as a cause of hypoglycemia[9,20,22,23].

Endocrine hormones are broadly accepted as circulating messengers. Hormonal discharge marks the start of the reaction against a shock stimulus and controls the totality of the circulatory and metabolic events[2]. In all states of shock the global endocrine response contains increased concentrations of adrenocorticotrophic hormone (ACTH), Cortisol, antideuretic hormone (ADH) and Aldosterone to which Catecholamines and angiotensin are added[2,10]. On the other hand the gonadotropic hormones are inhibited while insulin and glucagon present a varied behavior[1,2,4,18].

Circulating blood sugar is said to be the major source of fuel of all organ cells and in some (eg. brain and heart), the only possible one and that the liver is the vital crossroads of the energy producing mechanisms[6]. Therefore, a more detailed knowledge of the mechanisms which affect glucose homeostasis in shock is essential because this may be involved in the phenomenon of irreversibility. This study was undertaken to determine the sequence of changes in blood glucose during hemorrhagic shock and its relationship to variations in the underlying endocrine hormones, in particular the levels of insulin, catecholamines and cortisol.

MATERIALS AND METHODS

Eighteen healthy adult mongrel dogs of either sex weighing 8 — 12 kg and unselected by age were used in this experimental study. Base line hematocrit values and ^{131}I-RISA circulating blood volumes were determined. Dogs were first sedated with i.m. injection of 15 — 20 mg/kg Ketaral (2-0-methylamino-cyclohexanone-hydrochloride). Later, anesthesia was induced with Sodium pentobarbital (25 mg/kg, i.v.), trachea cannulated with a cuffed endotracheal tube and respiration maintained on Mark 7 respirator (Bird Corporation, Palm Springs, California). Every dog was fastened over night prior to the experiment and were given a small amount of water in its cage.

Cutdowns were performed to introduce polyethylene catheters into both femoral arteries and veins. Systemic mean arterial pressure in the abdominal aorta was monitored by a catheter placed via the right femoral artery. Catheter in the right femoral vein monitored central venous pressure. These intravascular pressures were recorded throughout the experiment on a multichannel direct ink-writing polygraph monitor oscillograph (Polygraph 142-8, San-Ei Instrument Company, Tokyo) through strain gauge transducers. Pulse rate was also recorded sequentially at 1-min intervals by means of a computer system connected to the monitor. Lead II of the electrocardiogram was monitored throughout the experiment. The left femoral artery was used for bleeding the animal and was connected to a reservior bottle containing about 100 ml of acid citrated dextrose anticoagulant solution in saline solution. The right femoral vein was cannulated for subsequent transfusion. Heparin, 200 U/kg was administered intravenously in every dog after placement of the catheters.

A thirty min control period of baseline measurements was allowed during which arterial and venous samples were drawn for control determination of PO_2, PCO_2 bases, blood sugar and three endocrine hormones (Insulin, Catecholamines and Cortisol). The pH, bases and blood gas partial pressures were measured on an acid-base analyser (Acid Base Laboratory, ABL_2, Radiometer A/S, Copenhagen). Insulin and cortisol were determined by means of radioimmunoassay (Bead Solid Method), whereas adrenalin and noradrenalin were determined by the THI method (Griffith's modified fluorometric method).

Hemorrhage in the dogs was initiated via the left femoral artery catheter at a rate of about 50 ml/min and collected in a plastic blood reservior bottle, according to Wiggers standard method[27]. Mean arterial pressure was lowered from control values to 50 mmHg and maintained at this level for 2 hr, not infrequently by means of additional small withdrawals of blood dur-

ing the early period. After this period, the mean arterial pressure was further lowered to 30 mmHg by careful phlebotomy and maintained at this level for a period of 1 hr. The administration of small blood infusions towards the end of this period sometimes was necessary. This three hr period of hypovolemia was considered as a period of oligemic shock. The total volume of blood withdrawn during this period ranged from 350 ml to 450 ml. The whole shell blood, maintained at room temperature, was reinfused via the left femoral vein at a rate of less than 50 ml/min. The mean arterial pressure returned almost to control values immediately after reinfusion. The animals were followed up for an additional period until the mean arterial pressure dropped between 20 mmHg to 30 mmHg. This end stage of normovolemia was termed the terminal stage of normovolemic shock, whereas the recovery period immediately after reinfusion was identified as the compensated stage. The experiment was terminated at the terminal stage. Catheters were irrigated with normal saline containing heparin, 50 U per ml at hourly intervals, to prevent blockade of the catheters by blood clot formation.

Venous blood samples (8—10 ml) were drawn from all experimental animals at specific regular time intervals for sugar and endocrine hormones determination. The blood was collected in plastic tubes at room temperature and centrifuged at 3,000 rpm for 10 min (KS-103: Kubota Seisakusho-Tokyo) after which the plasma was decanted and stored at freezing temperatures. Sampling blood loss was volumetrically replaced with irrigant, which compensated for blood volume loss as a result of sampling.

Each dog in this experiment served as its own control by using the pre-experimental measurements. Statistical analysis for the investigated parameters was done by using the Student t-test for paired groups with $p<0.05$ considered significant.

The dogs were sacrificed at the terminal stage and immediately autopsied. Tissue samples for histopathological and electron microscopic investigation were obtained from heart, lung, liver, kidney, adrenal, pituitary, pancreas, spleen, stomach, ileum and colon. Morphological findings for pituitary and pancreas are reported in this paper.

RESULTS

An attempt was made to relate blood sugar (BS) to selected endocrine hormones in hemorrhagic shock. Results are presented in the following way.

(a) Results on Fig. 1.

Five min after the mean arterial pressure (MAP) was brought to 50 mmHg from control values (average control MAP was about 120 mmHg) by hemorrhage, BS was observed to have a sharp rise (249.14 ± 71.6). As the MAP continued to be lowered from control levels through 50 mmHg to 30 mmHg, BS was seen to slightly decline but maintained an elevated level throughout the hemorrhagic period. One hr following reinfusion of the shed blood (4H), BS was observed to drop down below pre-experimental values (129.4 ± 94), and thereafter

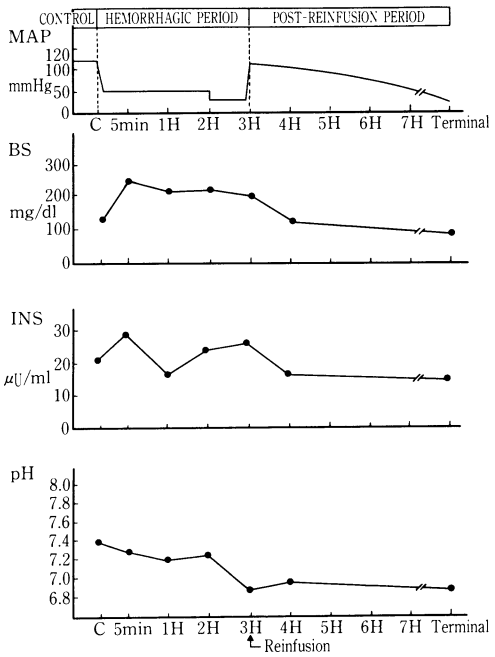

Fig. 1. Blood biochemistry as analysed in a series of anesthetized dogs subjected to Wiggers' standard method of hemorrhagic shock: This includes blood sugar (BS), Serum Insulin (INS) and blood pH. The upper most graph shows the control, hemorrhagic, and postreinfusion period. It also represents the experimentally controlled mean arterial pressure (MAP) and the expected behaviour of MAP after reinfusion.
Each values is a mean. C = control and H = hour.

a gradual fall in BS continued to be noted until terminal stage when it was significantly below control levels ($p<0.05$). Seven dogs were used in this part of the study. Two dogs died one hr after reinfusion. One of the two dogs died with BS well above control levels while the other one had BS below control values at the time of death.

Serum insulin (INS) rose slightly 5 min after hemorrhage (mean = 28.8 μU/ml) when the MAP was lowered to 50 mmHg. One hr after with MAP at the same level, INS dropped to a mean value of 16.6 μU/ml. While MAP still at 50 mmHg during the second hr (2H), INS was seen to rise again and by the third hr (3H) when MAP was 30 mmHg, INS had a mean value of 26.8 μU/ml. During the postreinfusion period, INS underwent a steady decrease in value and was 14.8 μU/ml as a mean by the terminal stage. Five dogs were used in this experiment and all reached the terminal stage.

On relating INS to BS during hemorrhagic period it was revealed that, at one hr after hemorrhage (1H), INS level dropped down despite elevated levels of BS at the same point in time. This suggested that INS levels were not elevated in response to hyperglycemia in hemorrhagic shock. There are probably other factors influencing pancreatic insulin release during hemorrhagic shock.

pH values were found to undergo a significant drop (6.9 ± 0.5, $p<0.05$) by the third hr of hemorrhage (3H) when MAP was 30 mmHg. Reinfusion could not restore the values to pre-experimental levels after which a gradual fall in pH was noted which continued up to the terminal stage.

(b) Results on Fig. 2.

Blood sugar (BS) in shown here for correlation purpose against endocrine hormones below. Results description is as given for Fig. 1.

The pre-experiment mean value of blood epinephrine was 1.4 ng/ml in the two dogs which were used in this experiment. Epinephrine (Adrenalin) concentration in peripheral blood increased rapidly in the hemorrhagic period reaching a maximum value of 13.1 ng/ml 5 min after hemorrhage when MAP was 50 mmHg. This high concentration of epinephrine gradually fell during the next two hr of hemorrhagic period with MAP still at 50 mmHg. After additional

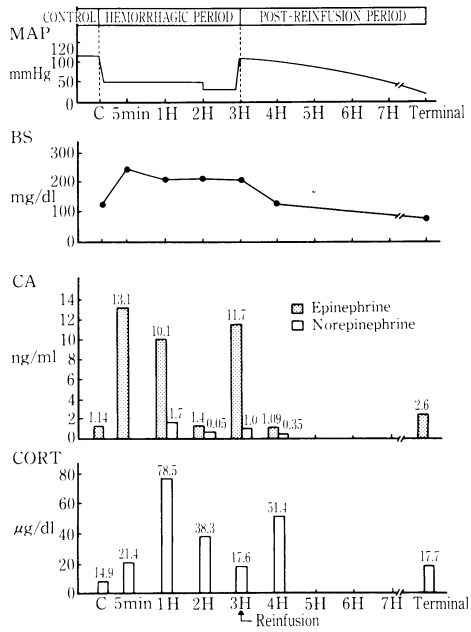

Fig. 2. Blood biochemistry as analysed in a series of anesthetized dogs subjected to Wiggers' standard method of hemorrhagic shock. This includes BS, Catecholamine (CA) and Cortisol (CORT). The upper most graph shows the control, hemorrhagic and postreinfusion period. It also represents the experimentally controlled MAP and the expected behaviour of MAP after reinfusion. Each value is a mean.
C = control and H = hour.

bleeding when MAP was brought to 30 mmHg, epinephrine levels rose again to a concentration of 11.7 ng/ml by the end of the third hr (3H). Following complete reinfusion, blood epinephrine levels declined markedly and became somewhat lower than control values. At the terminal stage of normovolemic shock in the postreinfusion period, blood epinephrine levels were slightly increased.

Unlike epinephrine, norepinephrine was not detectable before hemorrhage. However, a small amount of norepinephrine appeared in blood as MAP was lowered through 50 mmHg to 30 mmHg and in the first hr (4H) of the postreinfusion period. At the terminal stage, norepinephrine was undetectable in the circulating blood.

Before hemorrhage, mean value of blood cortisol (CORT) levels was 14.9 ± 0.3 μg/dl. Two dogs were used in this experiments. Five min after hemorrhage when the MAP was brought down to 50 mmHg, CORT levels rose slightly to 21.4 ± 5.5 μg/dl, and by the end of the first hr of hemorrhagic period (1H) with MAP at the same level of 50 mmHg, CORT was elevated to a maximum value of 78.5 ± 0.98 μg/dl. In the second hr (2H) with MAP still at the same level, CORT was decreased considerably to 38.3 ± 18.2 μg/dl. On further lowering the MAP to 30 mmHg by hemorrhage, CORT further decreased to 17.6 ± 5.8 μg/dl by the end of the third hr (3H). One hr after reinfusion (4H), mean value of CORT rose again to 51.4 ± 13.6 μg/dl. At terminal stage, CORT was found to have decreased to 17.7 ± 2.5 μg/dl.

On trying to correlate BS to catecholamines (CA) and CORT, it can be easily seen from the figure that the three parameters have a corresponding behavior during hemorrhagic shock. All of them tend to have elevated levels during the early stages of hemorrhagic shock (hemorrhagic period) and then in the late stage of shock (post-reinfusion period), their blood levels tend to decline with progression of shock towards the terminal stage. These three blood chemicals could probably have a common goal towards compensatory mechanisms against a shock insult (so called nature's first aid) which usually takes place during the early stages of hemorrhagic shock.

(c) Ultrastructural changes of adenohypophysis and pancreatic islet cells (Fig. 3a and 3b).

The cells of adenohypophysis were more or less injured at the terminal stage of hemorrhagic shock. Swelling of mitochondria and dilatation of smooth and rough endoplasmic reticulum were usually recognised in all kinds of the secretory cells, i.e., somatotrophs (growth hormone (GH) cells), thyrotrophs (thyroid

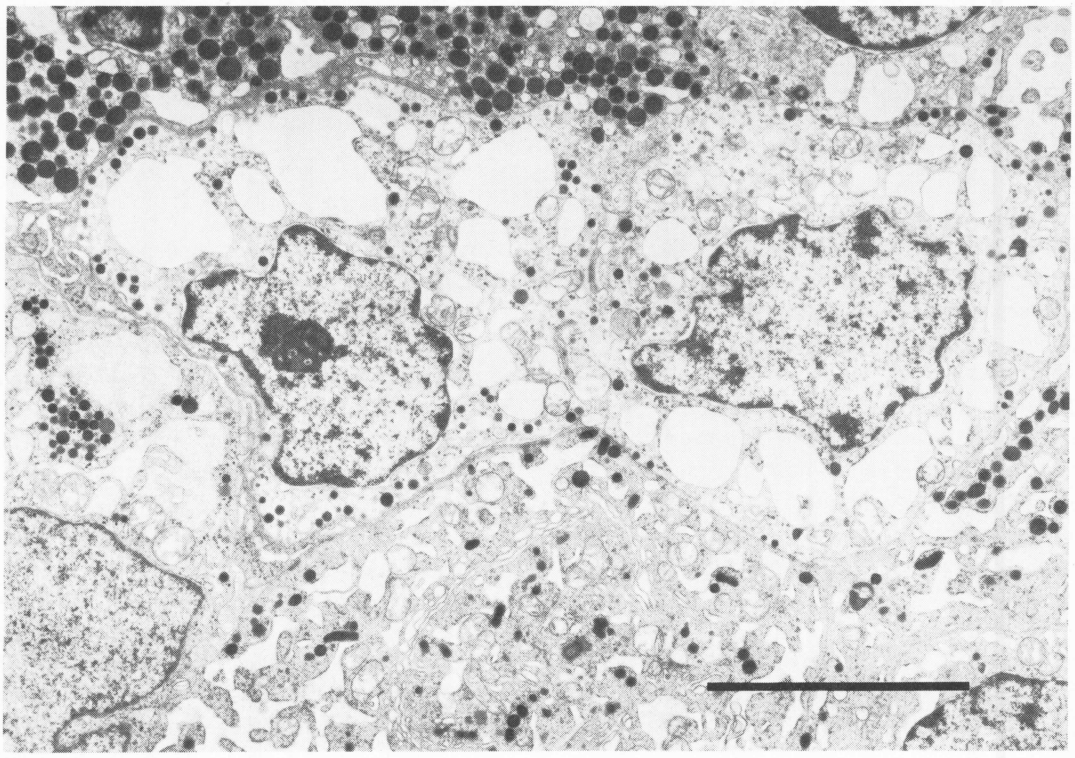

Fig. 3a. Electron micrograph of adenohypophysis at the terminal stage of the normovolemic shock (Dog No. 11). Dilatation of the mitochondria are observed in somatotrophs, mammotrophs and other types of cells. × 8700. Calibration mark on the micrograph is 5 μm.

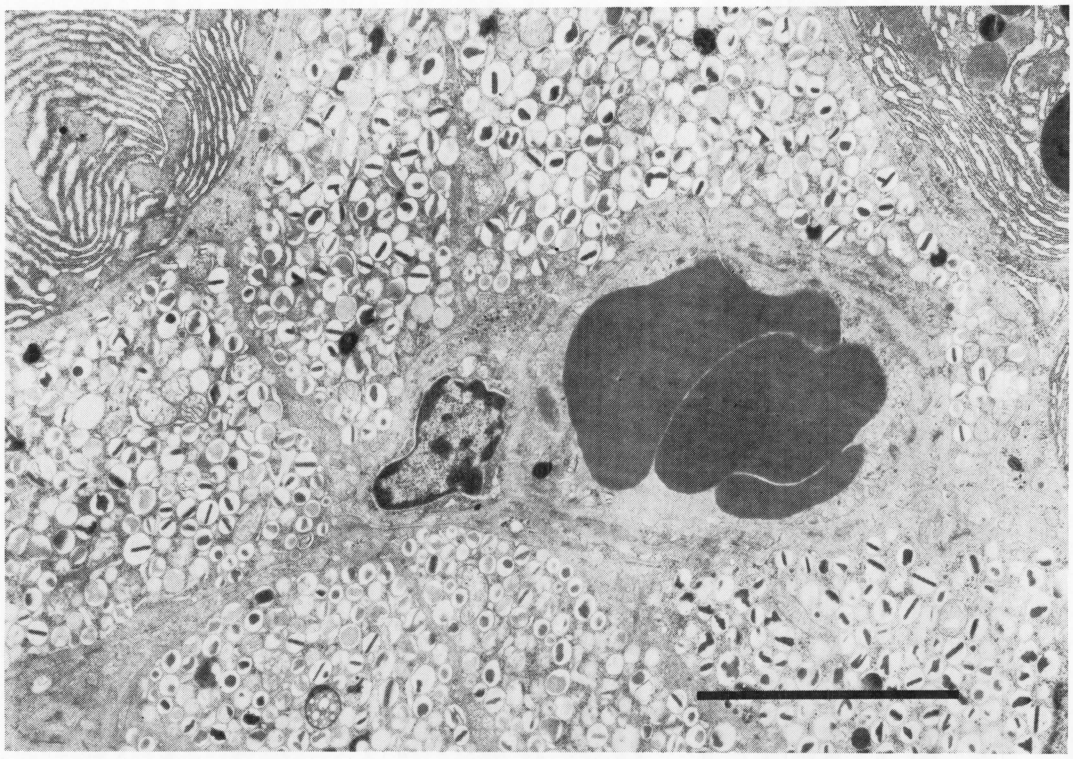

Fig. 3b. Electron micrograph of pancreatic islet cells of the same experimental animal (Dog. No. 11). Pancreatic beta cells are relatively well preserved in the terminal stage of the normovolemic shock. × 8700

stimulating hormone (TSH) cells), gonadotrophs (follicle stimulating hormone (FSH) and luteinising hormone (LH) cells), mammotrophs (luteotrophic hormone (LTH) cells) and corticotro phs (ACTH cells) (Fig. 3a).

In contrast to the cells of adenohypophysis, pancreatic islet cells were well preserved until terminal stage of the hemorrhagic shock. Alpha and beta cells contained a number of secretory granules (Fig. 3b). Mitochondria and endoplasmic reticulum showed no remarkable change.

DISCUSSION

The biphasis behavior of blood sugar (BS) observed in our experiments during hemorrhagic shock and similar observations reported by many other workers[22,28-30] have prompted us to divide the whole hemorrhagic shock course into two major stages for discussion purposes. The first stage occurred in the early stage of hemorrhagic shock during the hemorrhagic period and was designated *the stage of hyperglycemia.* This was found to last from 5 min to 3 hr though not very specific (See Fig. 1). The second stage occurred in the late or terminal stage of hemorrhagic shock during the post-reinfusion period and was termed *the stage of hypoglycemia.* This lasted from 3 hr to terminal stage of the experimental animal (See Fig. 1).

(1) Early stage of hemorrhagic shock (Stage of hyperglycemia).

From our study it was found that, blood levels of sugar, catecholamine and cortisol were all raised during this stage. Similar results have been reported by others[1,9,11,14,19,22]. The authors suspect that, resemblance in behavior of these three biochemical parameters in early hemorrhage might have a common aim towards protecting the organism against a shock inducing stimulus. It is a well established fact that immediately following hemorrhagic hypovolemia,

the body tries at all costs to protect its circulating blood volume and especially blood flow to the brain and heart. The hyperglycemia observed in our experiments and that reported by others is mainly due to the part played by endogenous catecholamine and cortisol following a neuroendocrine reaction[6,25,26]. Hyperglycemia in early hemorrhage has been reported to cause plasma hyperosmolality which can play an important role in the cardiovascular compensatory adjustments by restoring the plasma volume via a transcapillary osmotic absorption of fluid from the extravascular space[5,29,30]. Hyperglycemia is also essential for fuel supply to vital organs in shock especially the central nervous system and the heart[3].

Elevated levels of catecholamines in shock states and their participation in restitution of blood volume after hemorrhage through vasoconstrictive effects is well documented[14,15,28]. The vasoconstriction in the microcirculation causes a decrease in intravascular hydrostatic pressure allowing the plasma colloid osmotic pressure to draw additional extravascular fluid into the circulation to aid in restoration of the circulating blood volume[8,15]. This phenomenon is an autotransfusion process. Furthermore, during the process of adaptation following an acute stress, catecholamines have been reported to accelerate glycogenolysis in the liver by activation of the enzyme phosphorylase[6,26]. Hyperglycogenolysis results into increased blood glucose and thus causing plasma hyperosmolality with its subsequent effects towards restoration of blood volume (See Fig. 4). Catecholamines are also reported to inhibit the formation of cAMP during the process of insulin synthesis[7,13,18]. Therefore, insulin insufficiency reduces the transfer of glucose into the cell across the cell membrane. In our study, indeed changes in serum insulin levels were not related to the fluctuations in blood sugar levels (See Fig. 1). However, our results showed a high correlation between blood level changes of sugar and catecholamines (compare Fig. 1 and Fig. 2). On the other hand, some workers have reported that, the detection of

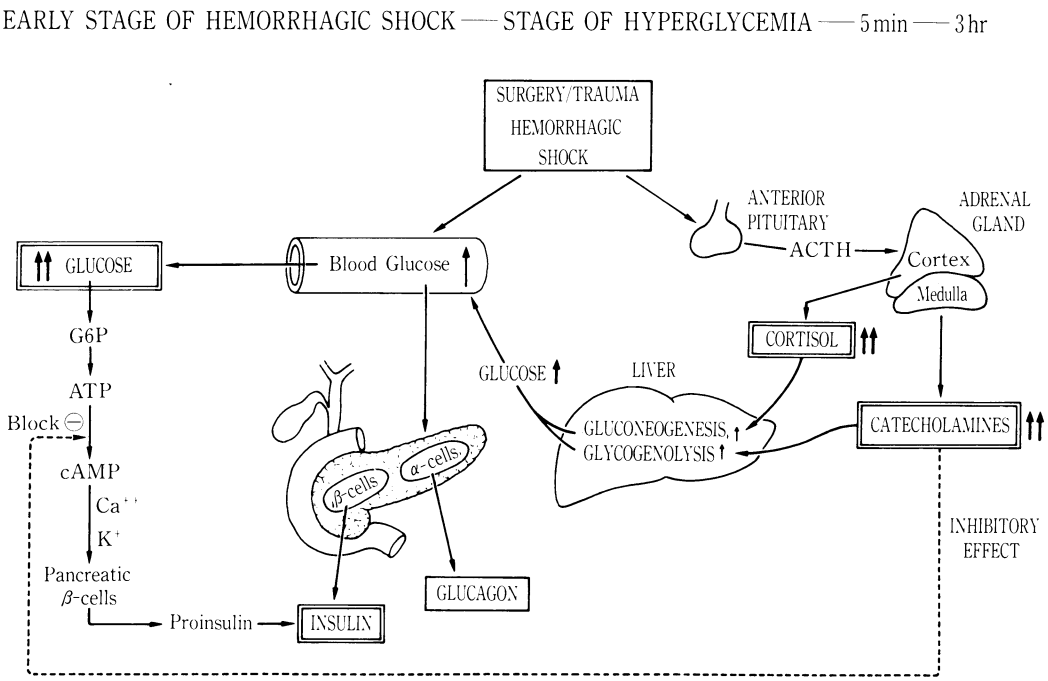

Fig. 4. A simplified representation of interrelated complex neurohormonal mechanisms taking place in early hemorrhagic shock aimed at restoration of blood volume via beneficial effects of plasma hyperosmolality. The liver is shown here as a major metabolic crossroads. The calcium-dependent insulin secretion process is also shown with the point of inhibition in the formation of cAMP. G6P = Glucose-6-Phosphate, ATP = Adenosine triphosphate, cAMP = Cyclic adenosine monophosphate.

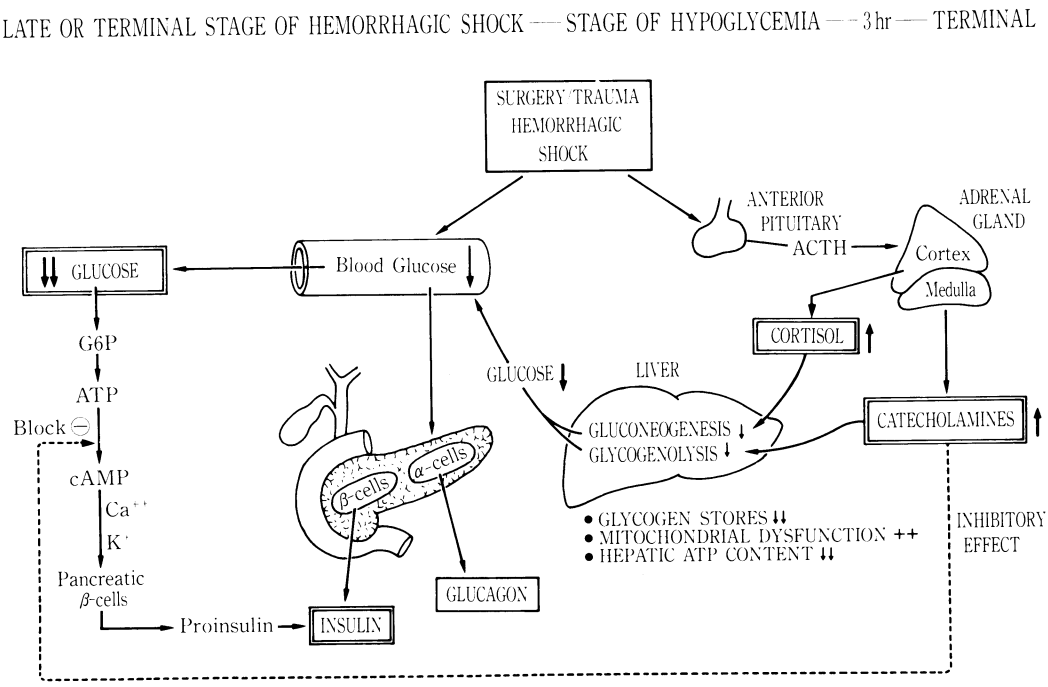

Fig. 5. A simplified representation of interrelated complex neurohormonal mechanisms taking place in late hemorrhagic shock. The mechanisms seem to be failing to raise the osmotically active agent glucose. Compare the arrows with those on Fig. 4.

elevated levels of serum immunoreactive insulin during hypovolemic shock may increase insulin resistance or may suppress release of insulin[4,18]. However, histopathological examination of the pancreas at terminal stage showed that, the pancreatic islet cells were well preserved at all stages of hemorrhagic shock during the experiment (See Fig. 3b). This meant that at any one time the pancreas was capable of releasing enough insulin to control the hyperglycemia observed in early stages of this experiment. Falling levels of insulin one hr after hemorrhage (See Fig. 1) could be due to the inhibitory effect of the persistently raised catecholamines on the formation of cAMP during insulin synthesis.

Increased levels of cortisol during hemorrhagic shock have also been reported to be involved in restitution of blood volume following hemorrhage via virious mechanisms[19,26]. Cortisol is said to accelerate gluconeogenesis in the liver by coordinated increase in the biosynthesis of key gluconeogenic enzymes[26]. Increased blood glucose levels by this way also add to the plasma glucose hyperosmolality (See Fig. 4). Plasma hyperosmolality has also been reported to occur following increases in plasma cortisol concentration per say after hemorrhage[19].

(2) Late or terminal stage of hemorrhagic shock (Stage of hypoglycemia).

During this stage of hemorrhagic shock (post-reinfusion period), our experiments showed a gradual decrease in blood levels of sugar, catecholamines and cortisol. But at terminal stage, blood levels of catecholamine and cortisol were slightly raised above pre-experimental values while sugar levels went below control readings. Our results agree with those reported by other investigators[6,10,13,14]. Persistent hypoglycemia in this stage reflects that the mechanisms involved in the production of glucose (i.e. glycogenolysis and gluconeogenesis) are either impaired or disturbed. Explanation given for impaired glucose production in late hemorrhagic shock are many but, the obvious reason as deduced from our results is that, as blood lev-

els of catecholamine and cortisol tend to be decreased, gluconeogenesis and glycogenolysis will also be reduced (See Fig. 5 compare arrows with Fig. 4). Other documented cause of hypoglycemia include depleted hepatic glycogen stores, impairment of high energy-linked mitochondrial ability to synthesize the glucose precursor phosphoenopyruvate, decreased hepatic adenosinetriphosphate (ATP) content, and depressed hepatic mitochondrial phosphorylative activities[20-23,29,30]. Furthermore, the anterior pituitary entirely depends on the hypophysial portal system for its blood supply and as such, hypovolemia brought about by hemorrhagic shock in the general circulation may cause hypoperfusion of the pituitary gland with resultant ischemic damage to the sinusoids of the pars distalis of the anterior pituitary. Histopathological assessment of the pituitary gland at terminals stage revealed that the corticotrophs (ACTH cells) were severely injured. This injury probably brought about a disturbance in the hormonal axis between pituitary gland and adrenal gland which led to the decreased levels of cortisol and catecholamine with subsequent hypoglycemia through depressed gluconeogenesis and glycogenolysis.

pH was measured in the experiment in order to reflect carbohydrate metabolism in shock. pH values were gradually and constantly decreased with prolonged shock. This meant that, the anaerobic glycolytic cycle (Embden-Meyerhof pathway) could not enter the aerobic tricarboxylic acid cycle (Kreb's Cycle) due to hypoxemia and this led to accumulation of lactic acid and low ATP production[24]. However, the effects of lactic acidemia on the heart are very well known in the field of shock.

The late stage of hemorrhagic shock usually depicts the failure of compensatory mechanisms to serve the animal from a shock insult. Hypoglycemia in this stage shows the failure of neuroendocrine mechanisms to maintain plasma refill. Our earlier studies on hemorrhagic shock also showed major cardiorespiratory and hepatic dysfunction during this stage[16,17]. We therefore suggest that, any shock therapy should always be aimed at not allowing the victim to enter this stage of shock otherwise the chances of irreversible shock are very high as multiple organ involvement tends to supervene.

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