Significance of increased blood uric acid following extensive hemorrhage

CARL E. JONES, JACK W. CROWELL, AND ELVIN E. SMITH

Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

Hemorrhagic shock was induced in 30 mongrel dogs by the reservoir technique. Oxygen consumption was recorded continuously in all dogs, and oxygen debts were calculated. The blood uric acid level was determined periodically in all dogs; blood pentose and D-ribose were determined in 14 dogs. Following hemorrhage, the pentose level increased 2.9 (±1.0 SD) mg/100 ml, and D-ribose increased 2.0 (±0.7 SD) mg/100 ml. The uric acid level also increased; the magnitude of the increase was inversely related to the time required to produce a lethal oxygen debt. Also, the dogs which produced the oxygen debt more rapidly exhibited reversal of blood flow more rapidly. These findings suggest that degradation of adenine nucleotides during hemorrhagic hypotension may be an important stage in the processes leading to irreversibility. The increases in uric acid could account for only an extremely small fraction of total tissue ATP.

irreversible hemorrhagic shock; oxygen debt; adenine nucleotides; blood pentoses; hypoxia; blood D-ribose

The tissue hypoxia resulting from hemorrhage is widely accepted as one of the primary factors leading to the development of irreversible shock and ultimately to death. However, the metabolic derangement, or derangements, by which tissue hypoxia contributes to the death of the animal is less well known. One phase of metabolism studied extensively in this connection involves the adenosine high-energy phosphate system, a system which obtains energy primarily through oxidative processes and uses this energy to drive various cellular functions.

It has been well established by Imai et al. (10), Sanders et al. (16), and others (1, 8, 14, 15) that hypoxia to a tissue causes a marked reduction in the tissue adenosine triphosphate (ATP) level; presumably this is due to a reduction in the rate of oxidative phosphorylation.

Received for publication 31 August 1967.

This work was supported by NIH Grant HE-02494 from the National Institutes of Health.

Graduate Fellow, National Institutes of Health Fellowship 5-F1-GM-30,621-03.
INCREASED BLOOD URIC ACID FOLLOWING HEMORRHAGE

Oxygen consumption was recorded throughout the experiment using a Guyton continuous oxygen-usage analyzer (9) and a Grass recorder. Oxygen debts were obtained by integrating the difference between the oxygen consumption before hemorrhage and the oxygen consumption during the 30 mm Hg hypotensive period.

A blood sample (2 ml) was taken before hemorrhage, at 15-min intervals before reversal of blood flow, and at 30-min intervals thereafter via a catheter inserted into a femoral vein. The blood proteins of each sample were precipitated by the Folin Wu tungstic acid method (17), and the filtrate was used for the determination of uric acid, total pentose, and D-ribose. Total pentose and D-ribose were determined in 14 dogs, and uric acid was determined in all 30 animals. Because of its simplicity, Benedict’s direct colorimetric method (17) was used for the determination of uric acid in all dogs. But since the specificity of this method for uric acid is questionable, in five experiments uric acid was determined simultaneously by the uricase method of Blauch and Koch (3) which is absolutely specific. Comparison of the results of the two methods in these five experiments served as an indication of the accuracy of the direct method. Total pentose was determined by the von Dische modification of the orcinol reaction after incubating the filtrate with glucose oxidase as described by Nagle (13) to remove interfering glucose. D-ribose was isolated by ascending paper chromatography using Whatman no. 1 chromatographic paper and a solvent consisting of isopropanol, acetic acid, and water (3: 1: 1). After development of the chromatogram, D-ribose was eluted from the paper with water and determined colorimetrically using the von Dische modification of the orcinol reaction.

RESULTS

Figure 1 shows the results of a typical experiment. After hemorrhage and reinfusion, arterial pressure returned to a normal level but thereafter declined, and the dog died. Oxygen consumption fell sharply after hemorrhage and stayed at a subnormal level throughout the 30 mm Hg hypotensive period. It rose slightly after reinfusion but then again declined. Note that the blood uric acid level increased rapidly and reached a peak at approximately the time of reversal. Note also that the concentrations of total pentose and D-ribose rose markedly and that most of the increase in total pentose can be attributed to the increase in D-ribose.

The average prehemorrhage concentrations of total pentose and D-ribose, in the 14 experiments in which these metabolites were determined, were 7.4 (± 2.1 SD) mg/100 ml and 5.7 (± 1.7 SD) mg/100 ml, respectively. The average increase in total pentose during the 30 mm Hg hypotensive period was 2.9 (± 1.0 SD) mg/100 ml, and the average increase in D-ribose was 2.0 (± 0.7 SD) mg/100 ml. Although variable, the average increases in both total pentose and D-ribose were significant (P < 0.05).

The average prehemorrhage uric acid level of the five dogs in which the uricase method was used was 0.32 (± 0.06 SD) mg/100 ml by this method and 0.47 (± 0.04 SD) mg/100 ml by the direct colorimetric method. Thus, the direct method is not sufficiently specific for the normal blood uric acid content. However, the increase in the blood uric acid level following hemorrhage was nearly the same using either method; the increase as given by the uricase method averaged 95 (± 2 SD) % of that given by the direct method. Therefore, the direct method was considered sufficiently specific for detecting the increase in blood uric acid following hemorrhage.

The rate of rise and peak increase in uric acid during the 30 mm Hg hypotensive period were highly variable and appeared to be dependent on the magnitude of the reduction in oxygen consumption. This is illustrated in Fig. 2 which shows the relationship between reversal time, increase in uric acid, and time required to produce an oxygen debt of 120 cc/kg as determined in all 30 dogs. This oxygen debt was chosen since Crowell and Smith (6) have shown that it is the lD50 oxygen debt.

FIG. 1. Shows the changes which occurred in mean arterial pressure, oxygen consumption, and the blood concentrations of uric acid, total pentose, and D-ribose during the course of a typical experiment.
Note particularly that the dogs which produced the oxygen debt more rapidly showed a larger increase in uric acid and exhibited reversal of blood flow more rapidly. The average increase in uric acid in each 15-min interval was significant ($P < 0.05$).

**DISCUSSION**

We propose that the increase in the blood uric acid level during hemorrhagic hypotension is due to increased production, but the possibility that it is due to decreased removal of uric acid from the blood must be considered. The renal shutdown resulting from extreme hypotension could cause an increase in blood uric acid, but since Miller et al. (12) have shown that the urinary excretion of uric acid in the mongrel dog is only approximately 4.5 mg/kg body weight per day, complete renal shutdown cannot nearly account for the increase in blood uric acid observed in this study. In the mongrel dog uric acid is rapidly destroyed by the enzyme uricase found in liver, and the blood uric acid level is maintained relatively low. But the increase in uric acid cannot be attributed to decreased uricase activity since the work of Cowaert et al. (4) has shown that uricase is very active during hemorrhagic hypotension. Likewise, it may be conjectured that the reduction in hepatic blood flow which occurs following hemorrhage would cause a decrease in uric acid destruction. However, it is likely that this would cause an equal decrease in uric acid formation.

LePage (11) reported a correlation between an increase in the blood pentose level and a reduction in tissue ATP levels during hemorrhagic shock, and we found that the concentration of blood pentoses increases simultaneously with the increase in the blood uric acid level following hemorrhage (Fig. 1). Since the increase in blood pentoses is due primarily to an increase in D-ribose, it appears that not only tissue nucleotides but also tissue nucleosides are degraded. Because of this finding, and in view of the rapid breakdown of tissue adenine nucleotides during hypoxia as reported by other investigators (1, 10, 15, 16), we feel the assumption is justified that the increase in the blood uric acid level during hemorrhagic hypotension is due primarily to degradation of adenine nucleotides and their functional derivatives in hypoxic tissues.

It is particularly interesting that the rate of rise and peak increase in the blood uric acid level during the 30 mm Hg hypotensive period were generally directly related to the magnitude of the reduction in oxygen consumption and, therefore, inversely related to the time required to produce an oxygen debt of lethal magnitude (Fig. 2). The smaller increases in uric acid occurring over longer periods of time do not necessarily mean that less uric acid is produced in these cases, but that it is produced at a slower rate so that its formation does not greatly exceed its destruction. It should be noted that the animals which produced the oxygen debt more rapidly and showed a greater increase in blood uric acid also exhibited reversal of blood flow more rapidly. The significance of this relationship is not certain. But since reversal of blood flow serves as a statistical indication that an animal has developed irreversible shock (18), this relationship supports the view that the hypoxia resulting from hemorrhage is a primary factor initiating the metabolic processes leading to irreversibility. And since there are indications that the increase in blood uric acid reflects increased degradation of tissue adenine nucleotides, it may be speculated on the basis of this relationship that a reduction in tissue ATP levels is an important stage in these processes.

The conversion of functional purine derivatives to uric acid is irreversible (2). Therefore, the question arises as to whether sufficient uric acid is produced during hemorrhagic hypotension to represent a detrimental loss of functional purine derivatives. In an attempt to answer this question, it should be noted that the normal ATP content of the various tissues is in the approximate range of 2-5 μmoles/g wet weight (1, 8, 10, 16) which is equimolar to approximately 300-800 mg uric acid/kg tissue. It is very evident that increases in the blood uric acid level of the general magnitude found in this study (Fig. 2) can account for only an extremely small fraction of the total tissue ATP. Furthermore, data concerning a correlation between reduced tissue ATP levels and depression of cellular function show that a 50% reduction in myocardial ATP is associated with a significant reduction in contractile force (8), a 40% reduction in liver ATP drastically depresses protein synthesis (16), and a 50% reduction in brain ATP represents the critical level for viability (15). In view of these findings,
it also seems unlikely that the relatively small increases in blood uric acid concentration found in this study represent a sufficient reduction in tissue ATP to cause any functional damage. On this basis, this study does not indicate that during the hypoxia of hemorrhage functional purine derivatives are converted to uric acid in quantities large enough to severely limit resynthesis of ATP.

REFERENCES


