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Effect of the Inhibition of Angiotensin I Converting Enzyme in Endotoxin and Hemorrhagic Shock[1] (37930)

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Renin is released when the circulating blood volume or the systemic arterial blood pressure drops suddenly. This homeostatic mechanism can cause vasoconstriction and may be in part responsible for the compensatory rise in the blood pressure (1). However, these reactions require the conversion of angiotensin I to angiotensin II by the converting enzyme (peptidyl dipeptide hydrolase). Thus, the converting enzyme may have an important function in shock. Various compounds inhibit this enzyme. Some of them are endogenous, such as glutathione or the B-chain of insulin (2), but some others have reecntly been synthetized (3). We used one of these peptide inhibitors in experiments designed to explore the role of angiotensin I converting enzyme in septic and in hypovolemic shock, the results of which were summarized at a recent meeting.[3]

Materials and Methods. Twenty-eight mongrel dogs of both sexes weighing 9.5–14 kg were prepared for the experiment by anesthesia with 30 mg/kg sodium pentobarbital. The systemic arterial blood pressure (SAP) and the respiration were recorded with a Grass polygraph as described previously (4, 5). The animals were shocked either by injection of *Escherichia coli* endotoxin (Difco) or by exsanguination (4, 5).

Sixteen dogs were shocked by the injection of 2 mg/kg of *E. coli* endotoxin given iv 5 min after injection of the inhibitor or saline. The same time interval was used in hemorrhagic shock. Twelve animals were shocked by rapid arterial bleeding into a reservoir to lower the SAP temporarily to about 40 mm Hg. The amount of blood collected varied from 190 to 300 ml.

The nonapeptide SQ 20881 (Pyr-Trp-Pro-Arg-Pro-Glu-Ile-Pro-Pro) was administered as a single injection before the induction of endotoxin shock. Ten milligrams was dissolved in 20 ml of saline and was injected over a 20-min period into the femoral veins of 6 animals. In hemorrhagic shock, 10 mg of the inhibitor in 10 ml of saline was injected in six animals over a 10-min period. Six animals served as controls in the first group and seven in the second group. They received saline only. Three dogs in the endotoxin study group received an additional 4 mg of inhibitor in 20 ml of saline infused within 30 min after endotoxin administration.

The blocking of angiotensin I conversion by SQ 20881 was established in each animal by the injection of equipotent doses of angiotensin I and II before and after the inhibitor was given. As expected from the published information, SQ 20881 blocked the transient vasopressor effect of angiotensin II (6).

Results. Septic shock. Figure 1 summarizes the reaction of 13 animals after injection of *E. coli* endotoxin. Of the 13 animals in

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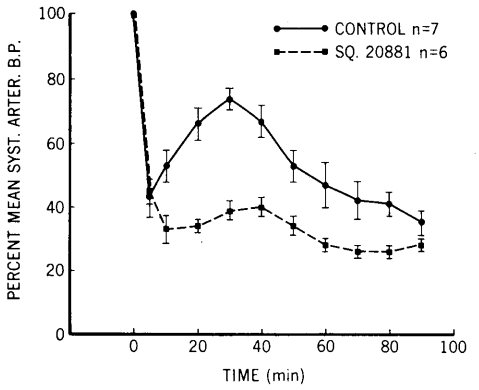

FIG. 1. The effect of inhibition of angiotensin I converting enzyme in endotoxin shock in dogs as reflected by alterations in systemic arterial blood pressure by pretreatment with SQ 20881.

endotoxin shock, 6 had been pretreated with SQ 20881. The cardiovascular reactions of the dogs to the i.v. injection of *E. coli* endotoxin were fairly uniform in the control group (4, 7, 8). The response consisted of two phases. In the acute phase, an immediate drop in SAP was followed by a compensatory rise toward the normal level. This acute phase lasted for about ½ hr and was followed by a steady, slower decline in the SAP during the second phase. During the period of hypotension, the animals showed a rapid, shallow pattern of breathing which reflected the changes in SAP. In the 6 animals treated with the inhibitor SQ 20881 5 min before the administration of endotoxin, the secondary compensatory rise was abolished or attenuated. The difference between treated and untreated animals was significant from 10 to 40 min postendotoxin ($P < 0.05$ after 10 min, $P < 0.01$ after 20 min, $P < 0.01$ after 30 min, and $P < 0.01$ after 40 min). In the control group, the SAP rose to 74% (±3.7 SE) of the preshock value within 30 min, compared to only 39% (±3.4 SE) in dogs in which the converting enzyme was inhibited.

Of the three dogs which received an additional dose of SQ 20881 after endotoxin injection, one did not respond to the drug. The SAP rose to 79% of the initial value in 30 min, while in the two dogs it stayed at 36% and 56% of the preshock SAP.

Hemorrhagic shock. Blood loss in dogs caused a transient drop in systemic blood pressure that was followed by a compensatory rise (5). Concomitantly, the rate and depth of respiration increased. [This represents the well-known compensatory activation of the abdomino-thoracic pump mechanism triggered by arterial pressoreceptors (8)]. In six control animals in hypovolemic shock, the SAP rose from 32% (±4.0 SE), the lowest point of the preshock value, to 69% (±4.9 SE) in 30 min. This secondary rise was significantly delayed and lowered by pretreatment with SQ 20881 (Fig. 2). The SAP changes from 23% (±1.7 SE) to 49% (±3.5 SE) of the initial value in 30 min. The difference between the treated and untreated groups was statistically significant ($P < 0.02$ after 10 min, $P < 0.01$ after 20 min, and $P < 0.02$ after 40 min).

Discussion. The release of a variety of vasoactive substances in shock (such as histamine, bradykinin, and vasopressin) has been scrutinized by several investigators (9–11). Increased liberation of renin and

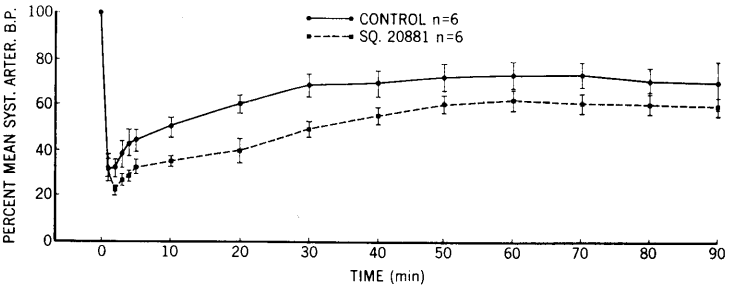

FIG. 2. The effect of inhibition of angiotension I converting enzyme in hypovolemic shock in dog as reflected by alterations in systemic arterial blood pressure by pretreatment with SQ 20881.

catecholamines can result in a rise in the level of circulating angiotensin II and catecholamines. These latter agents may contribute to the shock syndrome by causing vasoconstriction in some important vascular beds. Because of this α-adrenergic receptor blockers have been tested in shock both experimentally and clinically (13).

Our experiments indicated that the conversion of angiotensin I to angiotensin II is important in the initial recovery of SAP in the acute phase of shock. The compensatory rise of SAP, that followed the initial drop after endotoxin injection was blocked or considerably lowered in dogs pretreated with the converting enzyme inhibitor SQ 20881. Because the inhibitor could block the compensatory rise in endotoxin shock, any release of catecholamines may be a consequence of the liberation of angiotensin II during the first phase of shock. The animal that was resistant to the repeated administration of the inhibitor may be the exception to this.

The changes in SAP of the dog caused by hemorrhagic shock differ from those caused by injection of endotoxin. However, in hypovolemic shock as well, a compensatory rise follows the initial hypotension. This rise is significantly delayed and attenuated in the animals pretreated with the inhibitor. Our experiments (2) and those of others (14–17) indicate that the inhibitor may act in the first place on the converting enzyme located in the pulmonary circulation.

The angiotensin I converting enzyme (or kininase II) has several functions. It can either cleave His^9-Leu^{10} dipeptide from angiotensin I, and thereby release the vasopressor agent angiotensin II, or it can liberate Phe^8-Arg^9 from bradykinin (2, 15, 18). By the latter action, it inactivates a hypotensive peptide. Both of these reactions are inhibited by SQ 20881 (2, 14, 19). The administration of this agent to dogs, however, did not raise the concentration of the circulating bradykinin (20).

Because the converting enzyme metabolizes both vasoconstrictor and vasodilator peptides, its role in the regulation of blood pressure in other pathologic conditions is of interest. The presence of the enzyme in many different tissues, such as kidney, umbilical cord, mast cells (21), testes (14), etc., also suggests important functions.

Summary. We studied the role of the angiotensin I converting enzyme in shock Dogs were shocked by injection of *E. coli* endotoxin or by bleeding. The animals in the experiments were pretreated by iv administration of SQ 20881, the synthetic peptide inhibitor of the converting enzyme. The administration of the inhibitor blocked or attenuated the compensatory rise that followed the initial drop in systemic arterial pressure. In hypovolemic shock, as well, the inhibitor significantly delayed and decreased this compensatory rise in blood pressure. The results indicate that the enzyme has important function in shock.

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