MECHANISMS INVOLVED IN HEMORRHAGE-INDUCED BRADYCARDIA IN THE RAT

STEVEN ARNOLD HAMBURGER

Submitted to the faculty of the Graduate School
in partial fulfillment of the requirements
for the degree
Doctor of Philosophy
in the Department of Pharmacology and Toxicology
Indiana University

March 1989

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

David P. Henry, M. D.
Chairman

Joseph A. DiMicco, Ph.D.

Carl F. Rothe, Ph.D.

Lynn R. Willis, Ph.D.

MECHANISMS INVOLVED IN HEMORRHAGE-INDUCED BRADYCARDIA IN THE RAT

Steven Arnold Hamburger

Irrespective of the species studied, bradycardia may occur after hemorrhage. I examined some regulators of heart rate in relation to this bradycardia because all mechanisms responsible for hemorrhage-induced bradycardia have not been elucidated. To develop and characterize a model of hemorrhage-induced bradycardia, rats were anesthetized with urethane, and were hemorrhaged 16.5 or 20.0 ml/kg within 5 minutes. I observed elevations of serum phosphorus and glucose concentrations after hemorrhage. Increases in serum concentrations of certain enzymes, indicative of tissue failure, were not changed.

The role of catecholamines and tyramine in the bradycardia were evaluated. Elevated plasma epinephrine concentration was an indicator of the volume of blood removed during acute hemorrhage (five-fold elevation by 5 minutes); increased plasma norepinephrine and dopamine concentrations were late indicators of the duration of the hemorrhage (two-fold by 120 minutes). Plasma tyramine concentrations were also elevated after hemorrhage (two-fold by 30 minutes), suggesting that some of the increases in plasma norepinephrine concentrations might be mediated by mechanisms other than sympathetic stimulation. A greater decline in heart rate was observed in hemorrhaged animals pretreated with propranolol than in those untreated. Therefore, the bradycardia occurred in spite of elevations of circulating catecholamines and the

sinoatrial node was still capable of responding to catecholamines thereby offsetting an even more severe bradycardia.

The roles of acetylcholine, serotonin, opiates, prostaglandins and adenosine in the bradycardia were evaluated using specific receptor antagonists or synthesis inhibitors. The bradycardia occurred at times when the parasympathetic nervous system was inactivated by atropine or vagotomy. Thus, mechanisms independent of classical autonomic nervous system function were apparently involved in the bradycardia that occurs after blood loss. ICS 205-930 (a serotonin-3 receptor antagonist), naloxone (an opiate receptor antagonist), indomethacin (a prostaglandin synthesis inhibitor) or xanthine amine congener (an adenosine-1 receptor antagonist) administered before hemorrhage increased heart rate towards pre-hemorrhage values. At 5 minutes after hemorrhage, the heart rates of animals pretreated with atropine and/or indomethacin were significantly higher than those of other treatment groups. At 15 to 75 minutes, heart rates of all drug-treated animals were significantly higher than those of saline-treated animals. However, after 150 minutes, heart rates of all animals were significantly decreased (-120 bpm) compared to pre-hemorrhage values. The blood pressures in all treatment groups were similar, suggesting that differences in heart rate were not secondary to differences in blood pressure. These findings suggest that hemorrhage-induced bradycardia was mediated by several complex mechanisms involving acetylcholine, serotonin, prostaglandins, opiates and adenosine.

TABLE OF CONTENTS