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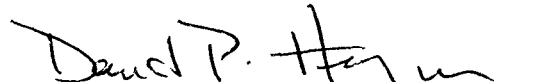
MECHANISMS INVOLVED IN
HEMORRHAGE-INDUCED
BRADYCARDIA IN THE RAT

STEVEN ARNOLD HAMBURGER

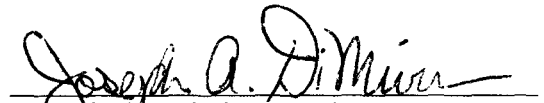
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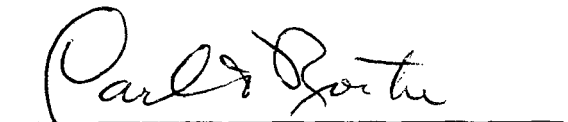
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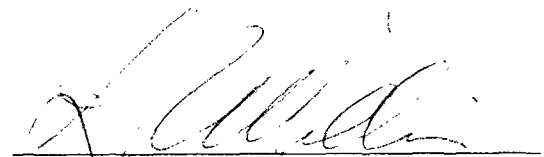
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MECHANISMS INVOLVED IN HEMORRHAGE-INDUCED BRADYCARDIA IN THE RAT

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

	<u>Page</u>
TITLE PAGE	i
SIGNATURE PAGE	ii
DEDICATION	iv
ACKNOWLEDGEMENTS	v
ABSTRACT	vii
TABLE OF CONTENTS	1
LIST OF FIGURES	4
LIST OF TABLES	8
LIST OF ABBREVIATIONS	9
1. INTRODUCTION	10
1.1 Experimental Hemorrhage Models	10
1.2 Changes of Heart Rate after Hemorrhage	12
1.3 Systems Implicated in Hemorrhage-Induced Bradycardia	13
2. STATEMENT OF PURPOSE	23
3. MATERIALS AND METHODS	24
3.1 Animals	24
3.2 Chemicals	24
3.3 Equipment	28
3.4 Tissue Extraction	28
3.5 Radioenzymatic Assays	29
3.5.1 Radioenzymatic Assay for Catecholamines	30
3.5.2 Radioenzymatic Assay for Tyramine	31
3.5.3 Radioenzymatic Assay for Histamine	33
3.6 Serum Constituent Determinations	34
3.7 Experimental Procedures	35
3.7.1 Description of the Hemorrhage Model	36
3.7.1.1 The Effect of Acute Hemorrhage on Blood Pressure and Heart Rate	37
3.7.1.2 The Effect of Nitroprusside on Blood Pressure and Heart Rate	37
3.7.1.3 The Effect of Hemorrhage on Serum Electrolytes and Indices of Tissue Function	37
3.7.1.4 The Effect of Hemorrhage on Plasma and Tissue Histamine	40

3.7.2	Involvement of Autonomic Nervous System in Hemorrhage-Induced Bradycardia	41
3.7.2.1	The Effect of Hemorrhage on Plasma and Cardiac Catecholamine Concentrations	41
3.7.2.2	The Effect of Vagotomy, Atropine Sulfate or Atropine Methyl Bromide on Hemorrhage-Induced Bradycardia and Hypotension	41
3.7.3	The Involvement of Adenosine, Opiates, Prostaglandins and Serotonin in Hemorrhage- Induced Bradycardia and Hypotension	42
3.7.3.1	The Effect of Pretreatment with Xanthine Amine Congener, an Adenosine-1 Antagonist, on Hemorrhage-Induced Bradycardia and Hypotension	44
3.7.3.2	The Effect of ICS 205-930, Naloxone, Atropine Methyl Bromide and Indomethacin Pretreatment on Hemorrhage-Induced Bradycardia and Hypotension	44
3.8	The Effect of Tyrosine on Plasma and Tissue Tyramine and Catecholamine Concentrations after Hemorrhage	44
3.9	The Effect of Yohimbine or Propranolol on Hemorrhage- Induced Bradycardia and Hypotension	45
3.10	Data Analysis	46
4.	RESULTS	47
4.1	Hemodynamic and Metabolic Effects of Hemorrhage in Urethane-Anesthetized Rats	47
4.1.1	The Effect of Intense Bleeding on Heart Rate and Blood Pressure	47
4.1.2	Alteration of Serum Constituents Following Hemorrhage	50
4.1.3	The Effect of Hemorrhage on Plasma and Tissue Histamine Concentrations	56
4.2	Assessment of Autonomic Nervous System Function after Hemorrhage	56
4.2.1	The Effect of Intense Acute Hemorrhage on Plasma and Cardiac Catecholamine Concentrations	56
4.2.2	The Effect of Vagotomy or Atropine on Hemorrhage- Induced Bradycardia and Hypotension	68
4.3	The Involvement of Adenosine, Opiates, Prostaglandins and Serotonin in Hemorrhage-Induced Bradycardia and Hypotension	78
4.3.1	The Effect of Pretreatment with Xanthine Amine Congener on Hemorrhage-Induced Bradycardia and Hypotension	78
4.3.2	The Effect of Pretreatment with ICS 205-930, Naloxone, Atropine Methyl Bromide or Indomethacine on Hemorrhage-Induced Bradycardia and Hypotension	84
4.4	The Effect of Administration of Tyrosine after Hemorrhage on Plasma and Tissue Catecholamine and Tyramine Concentrations, Blood Pressure and Heart Rate	89

4.5	Effect of Administration of Yohimbine or Propranolol on Hemorrhage-Induced Bradycardia and Hypotension	96
5.	DISCUSSION	99
5.1	Development of the Hemorrhage Model Used in These Studies	100
5.2	Characterization of the Hemorrhage Model Used in These Studies	105
5.3	Sympathetic Nervous System Response to Hemorrhage	111
5.4	Parasympathetic Nervous System Involvement in Hemorrhage-Induced Bradycardia	118
5.5	The Role of Serotonin, Opiates and Prostaglandins in Hemorrhage-Induced Bradycardia	120
5.6	The Role of Adenosine in Hemorrhage-Induced Bradycardia	125
	REFERENCES	128
	CURRICULUM VITAE	142