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Title : ANESTHETIC AGENTS, RENIN AND THE SYMPATHETIC NERVOUS SYSTEM

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Introduction. The peripheral sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) are thought to be important regulators of blood pressure when various anesthetics are administered. Both SNS and RAS now may be blocked through the use of specific inhibitors. Experiments were performed to examine the importance of the SNS and the RAS when three commonly used anesthetics were administered to rats.

Methods. 30 newborn Wistar rats received 50 mg/kg IM of guanethidine daily for the first twenty days of life. This method of treatment has been shown to produce a permanent peripheral sympathectomy while central nervous system catecholamine concentrations remain intact.[1] After drug treatment, the rats were allowed to grow to 250-300 gram size (12-15 weeks) before experiments were performed. All experiments were carried out in sympathectomized rats. Femoral arterial and venous cannulas were placed under ether anesthesia and the animal allowed to awaken in a restraining cage. The rats were divided into four groups: awake (A), halothane (H=1MAC), enflurane (E=1MAC), and ketamine (K=125 mg/kg IM). The protocol consisted of a two hour control awake period, one hour of stable anesthesia (one group received no anesthesia) and a one-half hour I.V. infusion of saralasin, a competitive inhibitor of angiotensin II. Arterial pressure was recorded continuously and plasma renin activity was determined at the end of the control period, after one hour of stable anesthesia and after the saralasin infusion. Arterial plasma renin activity was measured by radioimmunoassay. Cardiac norepinephrine concentrations (fluorescence analysis of trihydroxyindoles) were measured in eight randomly selected guanethidine-treated rats and in six normal rats. The data presented are the mean values ± standard error of the mean. Statistical significance of the results was determined using one-way analysis of variance among groups and Student's t-test for paired data. $P < 0.05$ was considered significant.

Results. The guanethidine-treated rats often showed evidence of diarrhea and ptosis. Cardiac norepinephrine concentrations for treated rats was 42.4 ± 5 ng/gm heart (n=8) as compared to 189.15 ng/gm heart (n=6) in normal rats. Mean arterial blood pressure, heart rate, and plasma renin activity was similar in all four groups during the awake control period. With the induction and maintenance of stable anesthesia, mean arterial pressure and heart rate decreased from the awake state but plasma renin activity was unchanged from control. Saralasin infusion caused an initial pressor response but blood pressure subsequently decreased significantly only in animals anesthetized with halothane. Similarly, plasma renin activity rose only in this group of animals anesthetized with halothane. The results for the 30 animals are summarized in the table.

Mean Arterial Pressure (torr)

	A (n=6)	H (n=8)	E (n=8)	K (n=8)
Awake	117±1	113±2	114±1	115±2
Anesthetized	118±2	82±2*	92±1*	103±2*
+ Saralasin	121±2	59±1*	86±2	104±2

Plasma Renin Activity (ng/ml/hr)

	A (n=6)	H (n=8)	E (n=8)	K (n=8)
Awake	1.2±0.2	2.1±0.8	1.3±0.2	1.6±0.3
Anesthetized	1.0±0.3	3.5±0.9	1.7±0.4	1.5±0.4
+ Saralasin	5.2±2.4	40.8±11*	11.4±7	5.1±2.3

*p<.05

Discussion. The experiments demonstrate that chronic guanethidine treatment to newborn rats offers a new approach to the study of the interaction of anesthetic agents and the peripheral sympathetic nervous system. The response to three commonly administered anesthetics was not unlike that previously reported in normal rats.[2] Plasma renin activity is not elevated after one hour of stable anesthesia. The initial pressor response to saralasin is due to the agonist effects of the drug rather than release of norepinephrine as some have speculated. The responses to saralasin demonstrate the importance of the renin-angiotensin system in supporting blood pressure during halothane anesthesia. The blood pressure response to saralasin differed in animals anesthetized with either halothane or enflurane. The mechanism responsible for the decrease in blood pressure with halothane and enflurane in the rat are different. Halothane decreases cardiac output while peripheral resistance remains normal. Enflurane's predominant effect is to decrease peripheral resistance. Therefore when angiotensin II is inhibited, blood pressure decreases more during halothane anesthesia because the peripheral resistance is little affected by halothane but is already markedly reduced by enflurane prior to angiotensin II inhibition. The peripheral sympathetic nervous system plays little role in the maintenance of blood pressure when halothane, enflurane or ketamine were administered under the circumstances of these experiments. This raises the possibility that other vasoactive substances may be important regulators of blood pressure with various anesthetic agents.

References.

1. Johnson EM, O'Brien F, Werbitt R: Modification and characterization of the permanent sympathectomy produced by the administration of guanethidine to newborn rats. European J of Pharm 37:45-54, 1976

2. Miller ED, Longnecker DE, Peach MJ: The regulatory function of the renin-angiotensin system during general anesthesia. Anesthesiology 48:399-403, 1978

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