Title: THE MECHANISM OF ACTION OF α_1-ADRENOCEPTOR AGONISTS IN SENSITIZATION OF HEART BY HALOTHANE

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Introduction. It has been reported recently that α_1-adrenoceptors in the heart play an important role in halothane-epinephrine arrhythmias[1], whereas, elevated blood pressure has also been regarded as an important factor to induce arrthythmias during halothane anesthesia.[2] The present study was undertaken to clarify the mechanism of action of α_1-adrenoceptor agonists to induce arrhythmias during halothane anesthesia, i.e, in inducing arrhythmias whether they directly act on the α_1-adrenoceptors in the heart or contribute by elevating blood pressure through α_1-adrenoceptors in the blood vessels.

Methods. Fifteen mongrel dogs of either sex were anesthetized with halothane, 1.3 MAC at end-tidal concentration. The dogs were intubated endotracheally and mechanically ventilated to maintain end-tidal Pco_2 at 35-40 torr. A femoral artery catheter was placed for intra-arterial pressure monitoring and blood sampling. A femoral vein was canulated for the administration of drugs and fluids. Lead II of the electocardiogram was monitored continuously. The esophageal temperature was maintained at 36.5-38.0 C. Arterial gas analysis and measurement of serum electrolytes were carried out frequently to maintain them within normal range. Phenylephrine (PHE) or angiotensin II (ANG II) was administered intravenously by continuous infusion for more than 3 minutes and the systolic blood pressure was controlled at 140, 150, 160, 170 or 180 mmHg. When ANG II was administered, prazosin was simultaneously given at the dose which blocked α_1-adrenoceptors completely. With maintaining blood pressure at each level, arrhythmogenic dose (AD) of isoproterenol (ISP) was determined by bolus injection. ISP was given at logarithmically spaced increasing doses with a minimum 10-min recovery periods until the AD was reached. The AD of ISP was defined as the dose that produced four or more premature ventricular contractions within 15 sec. The AD of ISP was obtained at each level of blood pressure maintained by PHE and ANG II. All values have been expressed as mean ± SEM. Data were analyzed by Student's t test. Statistical significance was defined as $P < 0.05$.

Results. No arrhythmia was induced by PHE, ANG II or ISP when each drug was administered independently. Fig. 1. shows ISOBOLS plotting the AD of ISP against the systolic blood pressure indicating a synergistic interaction of ISP and blood pressure. At 140 mmHg of systolic pressure, the AD of ISP was significantly lower in the presence of PHE than in the presence of ANG II. At the systolic pressure 150, 160, 170 and 180 mmHg, there was no significant difference in the AD of ISP between in the presence of PHE and in the presence of ANG II.

Discussion. The results show that blood pressure elevation and the stimulation of myocardial ß -adrenoceptors are important factors to induce arrhythmias during halothane anesthesia, especially at higher levels of blood pressure (150 mmHg or more). However, at a lower blood pressure (140 mmHg), α_1 -adrenoceptors in the heart would possibly contribute to potentiate the arrhythmogenicity of myocardial ß -adrenoceptor stimulation during halothane anesthesia.

Reference.

1. Maze M, Smith CM: Idendification of receptor mechanism mediating epinephrine-induced arrhythmias during halothane anesthesia in dogs. Anesthesiology 59:322-326, 1983

2. Reynolds AK: On the mechanism of myocardial sensitization to catecholamines by hydrocarbon anesthetics. Can J Physiol Pharmacol 62: 183-198, 1984

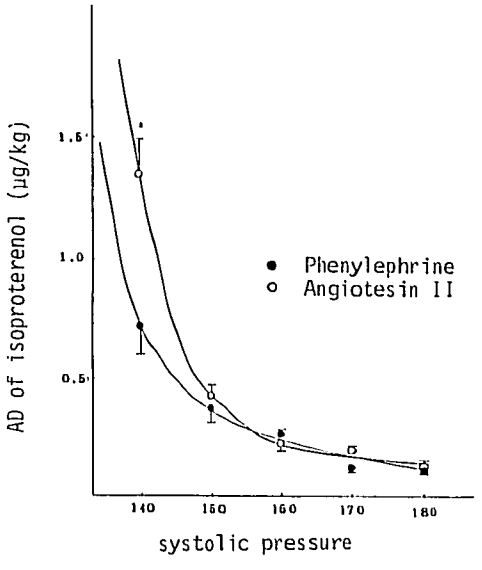

Fig. 1. Interaction of isoproterenol and phenylephrine and angiotesin II-induced increase in blood pressure (mean±SEM). Each value represents at least 5 experiments. *P<0.05 phenylephrine vs angiotensin II