TITLE: HALOTHANE DECREASES ARRHYTHMOGENIC THRESHOLD FOR EPINEPHRINE THROUGH α AND β ADRENOCEPTOR MECHANISMS

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Introduction: Halothane sensitizes the myocardium to the arrhythmogenic properties of exogenously administered catecholamines. If the mechanism of this interaction was understood, rational pretreatment measures could be devised to eliminate this hazard. Previous attempts to define the mediating receptor mechanism have been flawed by (i) use of non-selective adrenergic blocking agents, (ii) omission of an α-adrenergic blocking agent for comparison (iii) the use of excessively high doses of propranolol, at which its membrane stabilizing effect on myocardium, rather than its receptor blocking action may predominate in abolition of ectopy and (iv) concurrent use of other anesthetic agents which may sensitize the myocardium by a separate mechanism. The advent of the new adrenergic blocking agents, α_1, prazosin, or β_1, metoprolol, facilitates specific assessment of which adrenergic receptor mechanism mediates sensitization by halothane of the arrhythmogenic effects of epinephrine.

Methods: Anesthesia was induced and maintained in 6 dogs with halothane in oxygen. After tracheal intubation, ventilation was controlled to maintain end-tidal CO^2 at 5% (Beckman LB-2). Catheters were placed percutaneously for continuous arterial pressure monitoring and for intravenous fluid and drug administration. Arterial blood pressure, end-tidal CO_2, inspired and end-tidal halothane concentration and the cardiac rhythm (lead II) were recorded. After 45 min at an end-tidal concentration of 1% halothane (1.2 MAC for dogs), the arrhythmogenic dose of epinephrine (ADE), defined as that dose in $\mu g.kg.^{-1}.min^{-1}$ which produced 4 or more premature ventricular contractions within 15 seconds during a three minute infusion, was determined. If the ADE was not achieved with the first infusion, the dog was allowed 10 minutes to recover and the next higher dose was tested until the ADE was reached. Determination of the baseline ADE was repeated 3 times after which the animal was treated with either prazosin, 100 $\mu g.kg^{-1}$, i.v., (α_1 blockade) or metoprolol, 0.5 $mg.kg^{-1}$, i.v., (β_1 blockade) and the ADE again determined. The other adrenergic blocker was administered on a subsequent day so that each animal served as its own control. In the metoprolol treatment experiments, the dog first received D-metoprolol 0.5 $mg.kg^{-1}$ i.v., a stereo-isomer devoid of receptor blocking properties, after which the ADE was assessed. In subsequent experiments, the dogs received both prazosin and L-metoprolol simultaneously and the ADE assessed. The data were analyzed using paired one-tailed t tests.

Results: The mean arrhythmia dose for epinephrine (ADE^B) in the presence of 1.2 MAC halothane was 2.15 $ug.kg.^{-1}min^{-1}$. This threshold was enhanced 13 times by prazosin treatment (ADE^P=27.4). There was a modest but statistically significant increase in the ADE following the D-metoprolol treatment (ADE^D=5.5) and a further increase after infusion of the receptor blocking isomer, L-metoprolol (ADE^L=15.3). The increase in threshold in the presence of both α_1 and β_1 blockade exceeded that for either drug when given alone (ADE^{P+L}=53.3).

Discussion: The most important finding in this study is that the threshold for epinephrine induced arrhythmias was increased to a greater extent by α_1 blockade than by specific β_1 blockade. This is evidence that mediation of the sensitization by halothane is predominantly due to an α_1 adrenergic receptor-effector mechanism. The heightened responsiveness could be due to an up-regulation of α_1 adrenoceptors on the target organ, or to the stimulation of the effector response which for the α adrenoceptor is not well recognized. The role of the specific β adrenergic receptor antagonist in elevating the threshold, is confirmed. Recently, the existence of a presynaptic β adrenergic receptor on the post-ganglionic sympathetic neurone has been recognized. In response to stimulation by its agonist, epinephrine, it facilitates further norepinephrine release and thus an increased biological response at the target organ. This effect is aborted by β-blockade and may well be the mechanism by which L-metoprolol increases the ADE.