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Cardiac Alpha Receptors and Arrhythmias

THERE IS NO LONGER any doubt that there are alpha-adrenergic receptors in the heart, but we are far from certain about their function. A number of recent findings point to a connection with cardiac arrhythmias developing under a variety of conditions. The report by Maze, et al.[1] in this issue concludes that the alpha-adrenergic receptor is to blame for halothane–epinephrine arrhythmias. It is based on the antiarrhythmic effects of droperidol, a rather nonspecific drug acting at many receptors including the alpha-1 receptor, and of doxazosin, a relatively specific alpha-1 receptor blocker, and adds to a previous report by the same group, which used prazosin as a specific blocker. Others have demonstrated a role for this receptor, for example, in arrhythmias seen in the infarction-reperfusion model.[2] These results are exciting, but our enthusiasm at having found an "arrhythmogenic receptor" must be tempered by our knowledge that many types of drugs, among which we can count the antihistaminics, the beta-receptor blockers, and of course the antiarrhythmics, are also highly effective in preventing epinephrine arrhythmias in sensitized hearts.

Data on the antiarrhythmic effects of alpha-blockers first were obtained in 1948 by Moe et al., who showed dibenamine and some of its derivatives to be effective in sensitized dogs[3] and who first showed that blood pressure played a role. Much work has been done since, especially as concerns the role of heart rate and the blood pressure in causing the arrhythmias, their mechanism, and the localization of their origin. Too little attention has been paid to the fact that epinephrine-induced arrhythmias differ in detail not only between sensitized versus nonsensitized preparations (in which vagotomy blocks arrhythmias and fibrillation never occurs), but also as a function of the manner in which sensitization is studied. The early work from my own laboratory used cyclopropane as the anesthetic agent primarily because it caused "pure" sensitization with no chance of cardiac depression associated with chloroform, its close congeners, or halothane.[4] The animals were routinely induced with thiopental—several years passed before we found the difference this made. The data were clear: cyclopropane–epinephrine arrhythmias due to low doses of epinephrine were due to reentry rather than increased automaticity and were completely dependent on blood pressure. Mechanical changes in blood pressure changed the "minimal arrhythmia," defined by us as a constantly coupled bigeminy, to either sinus rhythm or multifocal tachycardia but never to fibrillation. The nonfatal arrhythmias could be abolished by stimulation of the vagus nerve. Several series of experiments were required to show that this effect of the vagus was not totally due to its effect on sinus rate.[5,6] Our study with halothane[6] was an attempt to summarize the observations of many years, as well as to confirm that halothane sensitization did not materially differ from that caused by cyclopropane. Further, we were able to confirm by direct recordings that the site of origin of the abnormal beat of the typical bigeminal rhythm was the intraventricular septum, a conclusion reached less directly in cyclopropane-anesthetized dogs.[7]

The properties of the arrhythmia change considerably when thiopental induction is omitted from the protocol. Larger doses of epinephrine are now required to cause any given severity of ventricular arrhythmia.[8,9] Particularly noteworthy is the observation by Atlee and Malkinson[9] that atrial arrhythmias, regularly observed to precede ventricular arrhythmias as graded doses of epinephrine are administered, are not potentiated by thiopental and therefore can no longer be observed with regularity. Bigeminal rhythm may not occur at all[8] or occurs less regularly.[9] The exquisite sensitivity to the level of systolic blood pressure can no longer be observed.[1] In short, the halothane-anesthetized animal behaves quite differently from the thiopental-induced preparation.

Nothing is known about the mechanism of this action of thiopental. The site of action corresponds to the site implicated in the origin of the bigeminy. As little as 200 ng to 200 μg injected into the circumflex coronary artery

cause potentiation, while milligrams injected into the anterior descending artery do not.[8]

Few things are simple in this world, and the mechanism of sensitization has never even been claimed to be simple. We are seeing impressive data associating cardiac alpha receptors with cardiac arrhythmias. I suggest, however, that close attention must be paid to the different types of preparations. Maze *et al.* have worked with pure halothane anesthesia, a good model. Clinical anesthetists are more likely to work with a different model: thiopental–halothane anesthesia. Although there is no reason to believe that cardiac alpha-receptors do not play a role in this model as well, one must await further results that demonstrate this under conditions of strict control of blood pressure and heart rate. I predict that, as usual, no single cause is likely to be found for what is almost surely a pluricausal phenomenon.

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