Absence of Chronotropic Effects of Dibutyryl Cyclic Adenosine 3',5'-Monophosphate on the Dog S-A Node

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The effects of catecholamine on the heart have been postulated to result from an increase in the intracellular level of cyclic AMP (adenosine 3', 5'-monophosphate) produced by activation of adenyl cyclase. Many investigators failed to elicit positive chronotropic or inotropic response with exogenously administered cyclic AMP in the isolated or intact heart. Recently, Skelton et al. (1970) reported that dibutyryl cyclic AMP caused a concentration-dependent increase in isometric tension and rate of tension development, the threshold concentration being $5 \times 10^{-4} \text{M}$, using isolated cat right ventricular papillary muscles.

In the present experiments, we made an attempt to study effects of dibutyryl cyclic AMP on S-A nodal pacemaker activity, using direct perfusion of the sinus node artery of the in situ dog heart.

Six mongrel dogs weighing 10 to 13 kg were anesthetized with intravenous sodium pentobarbital in 30 mg/kg and artificial respiration was maintained. All animals were bilaterally vagotomized. The flow rate of the sinus node artery was $1.90 \pm 0.3 \text{ (mean \pm s.e.) ml/min at 100 mm Hg}$. Adenosine, AMP, ADP and ATP injected into the sinus node artery always induced a negative chronotropic effect as reported previously (James 1965). However, cyclic AMP or dibutyryl cyclic AMP never induced any chronotropic effect at doses from 100 $\mu$g to 1 mg. Table 1 shows effects of adenosine, cyclic AMP and dibutyryl cyclic AMP.

Sutherland et al. (1968) reviewed that an alteration in the intracellular level of cyclic AMP is reasonably established as the mechanism by which effects of
catecholamine are produced in the heart.

From the present results, we could not show the possible role of cyclic AMP in mediating the positive chronotropic response to catecholamines. The explanation for the absence of chronotropic response to dibutyryl cyclic AMP is unknown, but it may be related to organ and species specificities with respect to ability of dibutyryl cyclic AMP to penetrate cell membranes.

References