Prevention of the Negative Chronotropic Effect of Adenosine by Caffeine

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A constant pressure perfusion of the sinus node artery was performed in ten vagotomized dogs. The selective administration of adenosine, AMP, ADP or ATP into this artery caused a negative chronotropic effect which was not blocked by either atropine or tetrodotoxin, but was blocked by the continuous infusion of caffeine or theophylline. In the meanwhile atrial fibrillation was readily induced by acetylcholine.

Since Drury and Szent-Györgyi observed slowing of the heart induced by adenosine, many authors have verified the negative chronotropic effect of adenosine. Nichols and Walaszek reported the antagonism of the vasodepressor effect of adenosine by caffeine in chickens, rabbits, cats and dogs. De Gubareff and Sleator revealed that caffeine antagonized the powerful depressant effects of adenosine on contraction and action potentials of guinea-pig and human atrial muscle. In 1965, James, using a technic for direct perfusion of the canine sinus node artery in situ, studied the action of adenosine on the pacemaker activity of this node. He showed that adenosine had a negative chronotropic effect and this effect was not antagonized by atropine.

In the present study, the authors investigated the antagonism between caffeine and adenosine on the pacemaker activity of the sino-atrial node, using a method of the constant pressure perfusion of the sinus node artery. Ten mongrel dogs weighing 10 to 16 kg were anesthetized with intravenous sodium pentobarbital in 30 mg/kg and were tracheotomized for the artificial respiration. All animals were bilaterally vagotomized. The blood flow of the sinus node artery was $2.18 \pm 0.35$ (s.e.) ml/min at 100 mm Hg.

Adenosine, AMP, ADP or ATP (1 to 10 μg) injected into the sinus node artery always induced a negative chronotropic effect. Fig. 1 showed a negative chronotropic response to 0.1, 1 and 10 μg of adenosine. This negative chronotropic response was abolished by the infusion of caffeine or theophylline but not by atropine or tetrodotoxin in a dose adequate to block all events caused by excitation of peripheral nerve fibers. The fibrillatory response of the sino-atrial node to acetylcholine (ACh) was clearly enhanced during the treatment with
Fig. 1. Responses of the sino-atrial node to increasing doses of adenosine (ADE) injected into the sinus node artery. Upper and lower curves represent the systemic blood pressure and heart rate, respectively.

Caffeine as shown in Fig. 2. The details of pharmacological investigation will be described elsewhere.

Fig. 2. Prevention of the negative chronotropic response to adenosine (1 µg) and facilitation of the effect of ACh (0.1 µg) for the induction of atrial fibrillation during continuous infusion of caffeine (100 µg/min).

References

1) Drury, A.N. & Szent-Györgyi, A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J. Physiol. (Lond.), 1929, 68, 213–237.


