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Cyproheptadine Blockade of a Cardiogenic Hypertensive Chemoreflex (39722)[1]

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Introduction. Certain cardiac chemoreceptors are sensitive to serotonin (1) and their activation elicits immediate and complex reflexogenic responses within the autonomic nervous system. Components of this cardiogenic reflex include acute arterial hypertension, changes in cardiac contractile state, and profound chronotropic and dromotropic actions. Using a technique of selective perfusion of the sinus node artery and AV (atrioventricular) node artery with autonomic blocking drugs, it has been possible to analyze the multiple coexisting cardiac components of the reflex (1). Various drugs have been shown to be serotonin antagonists (2). It was the purpose of this study to determine whether some of those agents had an effect on the cardiogenic hypertensive chemoreflex.

Methods and materials. Sixteen adult mongrel dogs of either sex weighing 15-22 kg were studied. Twelve were anesthetized with sodium pentobarbital (30 mg/kg iv) and four were anesthetized with a combination of phencyclidine hydrochloride (2 mg/kg im) and α-chloralose (80 mg/kg iv). Ventilation with room air was maintained through a cuffed endotracheal tube with an intermittent positive pressure Harvard pump. The heart was exposed and the stellate ganglia were isolated by a bilateral thoracotomy. A lead-II ECG was recorded along with electrograms from bipolar electrodes sutured in the vicinity of the sinus node or left atrial appendage as well as from the midsurface of the right ventricular outflow tract or left ventricular free wall. The sinus node electrogram was used to trigger a tachograph and central aortic blood pressure was routinely recorded. Atrial and ventricular contractile forces were recorded with Walton-Brodie strain gauge arches sutured onto either right or left atrial appendage or a ventricular-free wall. All tracings were amplified and recorded on a Hewlett-Packard polygraph.

The cardiogenic hypertensive chemoreflex was induced by injection of serotonin (50-200 μg/ml; 2 ml) into the left atrium through a catheter advanced via a pulmonary vein. This amount of serotonin administered in this manner has been shown consistently to elicit the cardiogenic reflex (1). Cyproheptadine hydrochloride, methysergide maleate, and morphine sulfate (3) were dissolved in Ringers solution for intravenous administration. When parasympathetic blockade was required, atropine (0.2-0.5 mg/kg was administered intravenously (eight dogs). Right stellate ganglion stimulation was performed before and after administration of the serotonin antagonists, to test their possible effect on sympathetic efferent responses. Stimulation parameters were 10 Hz, 2 msec duration, supramaximal voltage.

Results. A. Components of the hypertensive cardiogenic chemoreflex. Injection of serotonin into the left atrium of an anesthetized dog induces an immediate profound increase in systemic blood pressure occurring within a few seconds after onset of injection. A simultaneous vagally mediated sinus bradycardia can be readily blocked by atropine selectively perfused into the sinus node artery (1) or by bilateral vagotomy which breaks the afferent (and efferent) neural routes of the reflex. This reflex sinus bradycardia is both more rapid in onset and of greater magnitude than the direct negative chronotropic action of serotonin on the sinus node (4). Concomitant with the bradycardia, there is an immediate vagally me-

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diated decrease in atrial contractile force which is not rate dependent since it is still readily demonstrable during cardiac pacing. These control responses were all similar and were observed in each of the animals studied.

Figure 1 illustrates the effect of systemic atropine on the cardiogenic hypertensive chemoreflex (left panel). There is an increase in aortic blood pressure, heart rate, and contractile force in response to serotonin administration. In four dogs pretreated with atropine and utilized in the cyproheptadine studies, systolic aortic pressure increased 87 ± 14 (SEM) mm Hg, and the diastolic pressure increased 64 ± 9 mm Hg. Simultaneously there was a prompt sinus tachycardia which averaged 40 ± 9 bpm. This positive chronotropic effect is normally obscured unless muscarinic blockade is present (1). The increased atrial force is also normally obscured unless local effect of acetylcholine is blocked with atropine. The positive inotropic effect is independent of heart rate changes (observed in paced preparations) and is prevented by β-receptor blockade with propranolol (0.5–1.0 mg/kg iv).

B. Effects of cyproheptadine on the hypertensive cardiogenic chemoreflex. Intravenous administration of cyproheptadine (0.25 mg/kg) attenuates the chemoreflex. Increasing the cyproheptadine dose to 1.0 mg/kg (Fig. 1, right panel) abolished the cardiogenic chemoreflex in 9 of 10 dogs. In these dogs serotonin produced only minimal or insignificant changes in blood pressure, heart rate, or contractile force. The degree of blockade of the serotonin reflex wanes with time, but is still partially apparent for up to 2 hr.

C. Sympathetic neural effects before and after cyproheptadine. Possible β-receptor blocking actions of cyproheptadine (known to have a minor atropine-like property (5)) were tested by right stellate ganglion stimulation before and after cyproheptadine 1.0 mg.kg iv. Stellate stimulation induced the same positive chronotropic and inotropic effects before or after cyproheptadine in each of six dogs so tested (Fig. 2).

D. Surmounting the cyproheptadine block. Although cyproheptadine (1 mg/kg) effectively blocked the maximal response of the chemoreflex when 100 μg/ml of serotonin was used (2 ml), this blocking effect could be overcome in each of the three dogs so tested by a 10-fold increase in the serotonin concentration (Fig. 3). Bilateral cervical vagotomy, however, abolished the hypertensive chemoreflex elicited by 1000 μg/ml of serotonin (2 ml). Such "reversal" of the cyproheptadine blockade suggests that serotonin and cyproheptadine may compete for receptor sites in initiation of the reflex.

E. Lack of effects of methysergide and morphine on the hypertensive cardiogenic chemoreflex. Intravenous administration of

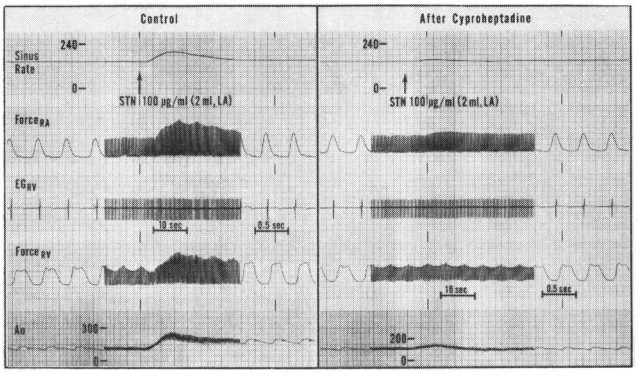

FIG. 1. *Left*: A characteristic example in an anesthetized, atropinized dog of the cardiogenic hypertensive chemoreflex elicited by administration of serotonin. $Force_{RA}$, right atrial contractile force from a Walton-Brodie strain gauge; EG_{RV}, right ventricular electrogram; $Force_{RV}$, right ventricular (conus) contractile force with a Walton-Brodie strain gauge; Ao, central aortic pressure. *Right*: Cyproheptadine (1.0 mg/kg iv) has virtually abolished the cardiogenic hypertensive chemoreflex.

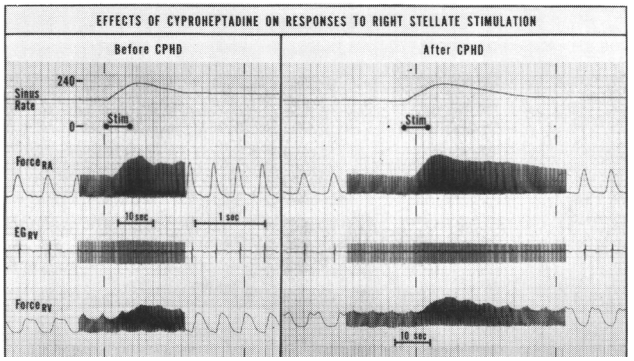

FIG. 2. Comparison of the cardiovascular effects of right stellate ganglion stimulation before (left) and after (right) 1.0 mg/kg of cyproheptadine (CPHD).

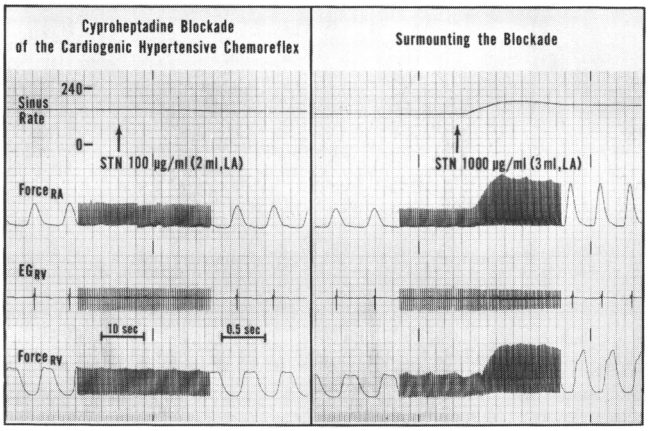

FIG. 3. Cyproheptadine blockade of the chemoreflex (left panel) can be surmounted with a 10-fold increase in the concentration of serotonin (right panel). The original response to serotonin in the standard test concentration (100 µg/ml) is shown for this same dog in Fig. 1.

methylsergide, 10 to 100 µg/kg, failed to block or attenuate the serotonin induced cardiogenic reflex in five of seven dogs. Increasing the methysergide concentration to 1–2 mg/kg in two dogs also failed to affect the chemoreflex but produced hypotension. This hypotension may be attributable to the ergot alkaloid nature of methysergide (2).

Intravenous morphine sulfate [known to block serotonin in some preparations (6)] was administered in increments of 500 µg/kg doses in three dogs. Even at a total concentration of 2 to 3 mg/kg morphine failed to prevent the serotonin induced cardiogenic hypertensive chemoreflex.

Discussion. Cyproheptadine (but not methysergide or morphine) effectively blocks all components of a hypertensive cardiogenic chemoreflex regularly elicitable with serotonin. The blockade appears to be competitive in nature and at the site of initiation of the reflex since it can readily be surmounted by an appropriate increase in the concentration of serotonin. Because the cyproheptadine blockade can be overcome with greater concentration of serotonin, it is unlikely that central nervous system depression by cyproheptadine played an important role in the blockade of the serotonin reflex. Furthermore the results indicate cyproheptadine has no significant antiadrenergic nor β-receptor blocking effects.

Any human counterparts to this experimental hypertensive cardiogenic chemoreflex remain to be defined, although the histological similarity of chemoreceptor tissue near the main left coronary artery of both human and canine hearts supports the possi-

bility of a similar reflex in man. Clinical circumstances in which this chemoreflex may participate include the severe hypertension sometimes observed in patients with angina pectoris or acute myocardial infarction. If further studies support this speculation, clinical trial of cyproheptadine to treat such hypertensive crises merits consideration.

Summary. A cardiac chemoreceptor can be activated by serotonin to cause a complex autonomic reflex which includes acute hypertension, changes in cardiac contractile force, and alteration of rhythm and conduction. In 16 anesthetized dogs blood pressure, heart rate, and contractile force (Walton–Brodie strain gauges sutured on atria and ventricles) were continuously measured during serotonin-induced reflexes before and after intravenous administration of cyproheptadine and/or methysergide or morphine. Cyproheptadine in concentrations of 0.2–0.5 mg/kg attenuated the reflex responses, and higher concentrations (1.0 mg/kg) abolished the reflex (9 of 10 dogs). The responses to right stellate ganglion stimulations before and after cyproheptadine were identical, indicating that cyproheptadine had no effect on neural release of norepinephrine nor any significant β-receptor blocking action. Cyproheptadine blockade was readily surmounted by a 10-fold increase in serotonin concentration. The serotonin reflex progressively recovered in time after the administration of cyproheptadine. Central nervous system depression accounting for this abolishing effect of cyproheptadine is unlikely because of the surmounting effects of larger concentrations of serotonin. Methysergide and morphine had no significant effect in preventing the serotonin reflex. Cyproheptadine most likely interferes with the effect of serotonin at the site of initiation of the reflex within the cardiac chemoreceptor.

1. James, T. N., Isobe, J. H., and Urthaler, F., Circulation **52,** 179 (1975).
2. Douglas, W. W., *in* "The Pharmacological Basis of Therapeutics" (L. S. Goodman and A. Gilman, eds.), p. 590. MacMillan, New York (1975).
3. Urthaler, F., Isobe, J. H., and James, T. N., Chest **68,** 222 (1975).
4. James, T. N., J. Pharmacol. Exp. Ther. **146,** 209 (1964).
5. Stone, C. A., Wenger, H. C., Ludden, C. T., Stavorski, J. M., and Ross, C. A., J. Pharmacol. Exp. Ther. **131,** 73 (1961).
6. Jaffe, J. H. and Martin, W. R., *in* "The Pharmacological Basis of Therapeutics" (L. S. Goodman and A. Gilman, eds.), p. 245. MacMillan, New York (1975).

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