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Blocking Effects of Cyproheptadine and Methysergide upon Two Different Cardiovascular Responses to Serotonin[1] (40998)

GILBERT R. HAGEMAN, THOMAS N. JAMES, AND FERDINAND URTHALER

Departments of Medicine and of Physiology and Biophysics, University of Alabama Medical Center, Birmingham, Alabama 35294

Abstract. There are several different types of receptors which mediate responses by the cardiovascular system to serotonin. In this study we utilized 16 anesthetized dogs to compare the effects of cyproheptadine and methysergide upon two different cardiovascular responses to serotonin. Injection of serotonin (50–200 μg) into the right atrium produced pulmonary vasoconstriction during which the mean pulmonary artery pressure increased from 14 (±2) to 20 (±2) mm Hg ($P < 0.05$). As the same serotonin later reached the coronary circulation, a cardiogenic hypertensive chemoreflex is activated, causing systemic hypertension in which the mean aortic pressure promptly increases from 104 (±7) to 179 (±10) mm Hg. Administration of either cyproheptadine or methysergide eliminated the pulmonary hypertension, but only cyproheptadine was effective in blocking the cardiogenic hypertensive chemoreflex. The differential blocking effectiveness of these two serotonin antagonists suggests an important difference in physiological characteristics of the serotonin receptors involved.

Since the work of Gaddum and Picarelli over 20 years ago (1) there has been continuing interest in the number, types, and location of serotonin receptors. Such receptors have been demonstrated in the brain (2, 3), peripheral nerves (4, 5), gastrointestinal tract (1), and circulation (6, 7).

Activation of a coronary chemoreceptor by serotonin (8) coincides with demonstrable onset of traffic in its afferent nerve (9). The efferent component of this reflex induces sympathetic and parasympathetic discharge, the hemodynamic consequences at which include virtual doubling of aortic pressure within 4 to 6 sec, alterations in peripheral flow patterns (10, 11), and changes in cardiac rate, rhythm, and contractile force (8–10). This cardiogenic hypertensive chemoreflex is eliminated by intravenous administration of cyproheptadine, concomitant with which the afferent neural traffic disappears (9, 12).

Although several vascular beds promptly constrict during the cardiogenic hypertensive chemoreflex, the pulmonary vasculature does not (10, 11). Since the direct pulmonary vascular constricting effect of serotonin is well known (13), sparing of this same circulation during the cardiogenic hypertensive chemoreflex is conspicuous. In the present study we examined the responses to serotonin by the pulmonary vasculature and by the coronary chemoreceptor before and after administration of two serotonin antagonists, cyproheptadine and methysergide.

Methods. Sixteen adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg iv). Positive-pressure ventilation was maintained through a endotracheal tube and ventilatory volume was adjusted according to end-tidal CO_2 concentration (LB-2 Beckman). Central aortic and main pulmonary artery pressures were measured with transducers attached to catheters placed via the femoral artery and right ventricular outflow tract, respectively. Following thoracotomy, a catheter was placed in the right atrium via the azygous vein. A standard lead II electrogram and heart rate were routinely monitored. Serotonin (5-hydroxytryptamine) creatinine sulfate, cyproheptadine hydrochloride, and methysergide maleate were prepared in Ringer's solution. The serotonin was pre-

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pared in concentrations ranging from 25 to 100 μg/ml. One or two milliliters was administered within 2 sec. Administration via the azygous vein catheter was with the lowest concentrations first followed by higher concentrations with a minimum of 5 min between injections. The serotonin antagonist methysergide was prepared at a concentration of 1 mg/ml and administered in 100 μg/kg increments until the serotonin-induced effects were blocked or until toxic complications (cardiac arrhythmias) were noted. Cyproheptadine was administered in 500 μg/kg increments until the cardiogenic hypertensive chemoreflex was blocked (12). Four dogs received cyproheptadine alone (following serotonin challenges) while 12 dogs received either methysergide alone or methysergide followed no sooner than 30 min later by cyproheptadine. Results are expressed as means ± 1 SEM. The significance of differences was assessed by Student's *t*-test (unpaired), significance being $P < 0.05$ (14).

Results. All serotonin injections were into the right atrium. When less than 30 μg of serotonin was injected, there was no more than 5 mm Hg alterations of pulmonary artery pressure, and there was no evidence (changes in cardiac rate or rhythm, or aortic hypertension) for activation of the cardiogenic hypertensive chemoreflex. All pressures measured in the pulmonary system are the peak responses which were obtained before activation of the cardiogenic hypertensive chemoreflex. Reflex activation of the cardiogenic hypertensive chemoreflex was determined by heart rate changes seen in the electrocardiogram. When over 50 μg (up to 200) serotonin was injected, there was first a significant increase in the mean pulmonary artery pressure from 14 ± 2 to 20 ± 2 mm Hg (Fig. 1), followed several seconds later by the reflexly induced systemic hypertension when the serotonin reached the coronary circulation. The mean aortic pressure then increased from 104 ± 7 to 179 ± 10 mm Hg (Fig. 2).

Cyproheptadine attenuated the pulmonary hypertensive response to serotonin (Figs. 1 and 3). Methysergide (100–500 μg/kg) also attenuated the pulmonary

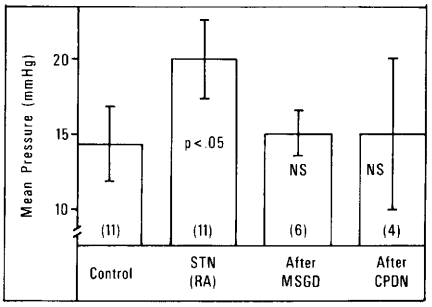

FIG. 1. These histograms illustrate the pulmonary vasoconstriction elicited by serotonin (STN). There is a significant increase from control following serotonin (50 to 200 μg). However, there is no significant effect by serotonin after either cyproheptadine (CPDN) or methysergide (MSGD). The mean pressure is not significantly increased above that of the control. The number of dogs is in parentheses.

hypertensive response to serotonin (Figs. 1 and 3). What pulmonary hypertension there was from serotonin after either blocking agent was uniformly delayed (Figs. 3 and 4) and unlikely due to a direct effect of serotonin within the pulmonary circulation. By contrast, although cyproheptadine effectively blocked the aortic hypertension reflexly produced by serotonin (Figs. 2 and 5), methysergide did not (Figs. 2 and 4).

Discussion. Serotonin has multiple complex and interrelated effects upon the

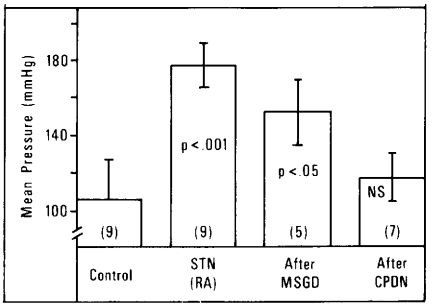

FIG. 2. These histograms illustrate the pressor component of a cardiogenic hypertensive chemoreflex. There is a significant increase above control with serotonin. This response is eliminated by cyproheptadine but not methysergide. Serotonin (50 to 200 μg) still elicits a significant ($P < 0.05$) increase in pressure following methysergide but not cyproheptadine (NS). There is no significant difference between the control hypertension and the hypertension following methysergide.

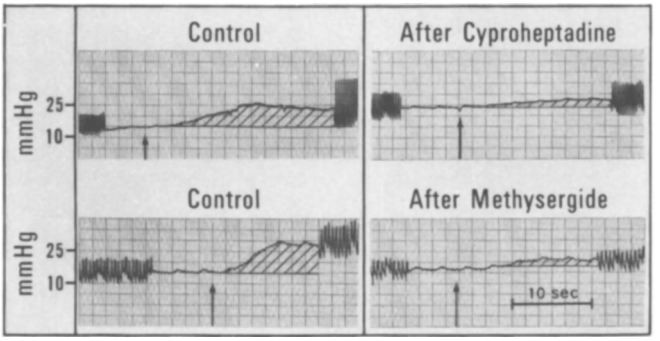

FIG. 3. These tracings from a representative experiment illustrate the increase (crosshatched area) in pulmonary artery pressure due to serotonin, and its attenuation by cyproheptadine or methysergide. Both pulsatile and average pressures are illustrated. Same paper speed is used throughout.

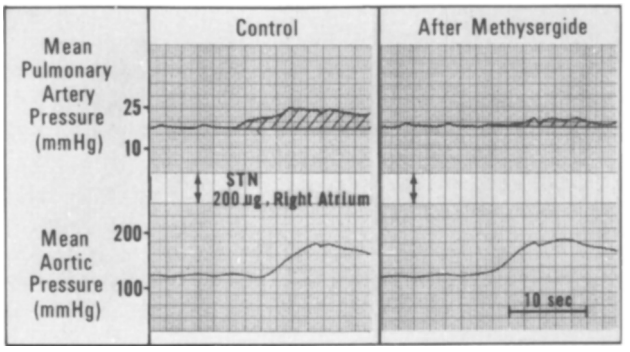

FIG. 4. These tracings from a representative experiment illustrate the blocking effects of methysergide upon the pulmonary artery pressure response (direct) but not upon the systemic hypertension (reflex).

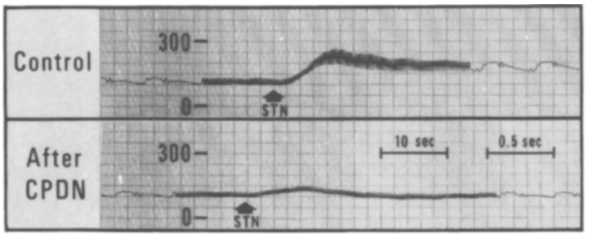

FIG. 5. These tracings illustrate the reflex changes of the aortic blood pressure to serotonin (100 µg/ml, 2 ml), before (control) and after cyproheptadine (CPDN) in an animal pretreated with atropine (0.5 mg/kg iv). Aortic pressure is calibrated in millimeters of Hg.

cardiovascular system (4, 6–13, 15–17). Among other factors, variability of responses depends upon the species tested, amount of serotonin given, route of administration, and status of the nervous system. The vasoconstrictive effects of serotonin upon the pulmonary vascular bed are thought to be a direct action upon its smooth muscle (13). It has been reported (7, 15) that several different canine arteries possess a D (musculotropic)-type serotonin receptor (1) which is competitively blocked by cyproheptadine and methysergide. The canine saphenous vein, however, possesses

an unusual serotonin receptor which is noncompetitively blocked by cyproheptadine but is actually stimulated by methysergide (7, 15). The pulmonary vascular smooth muscle thus appears to contain D-type serotonin receptors which are easily blocked with musculotropic antagonists. The serotonin receptor which modulates norepinephrine release from the presynaptic sympathetic neuron appears to be an M (neural)-type receptor (1) and is not blocked by cyproheptadine (16). In the central nervous system both methysergide and cyproheptadine antagonize serotonin in the hippocampus (2).

We have now found (as previously (12)) that the cardiogenic hypertensive chemoreflex is regularly blocked by cyproheptadine but not by methysergide, whereas in the same animals both of these serotonin antagonists are effective in blocking the direct effect of serotonin on pulmonary vessels. The effects upon the pulmonary vasculature in our study were assessed at the highest concentration of the agonist (serotonin) and the final concentrations of the antagonists (cyproheptadine and methysergide). While the coronary chemoreceptor is blocked by the D-type (musculotropic) serotonin antagonist, cyproheptadine, it is not activated by methysergide and is therefore different from the saphenous vein serotonin receptor (7, 15). According to Gyermek (18) additional serotonin receptors should be identified. The actual segregation of serotonin receptor subtypes could be based upon their physiological effects, their anatomical location, or their susceptibility to blockade by various antagonists (relative binding affinity studies (19)).

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