Is There a Serotonin-Induced Hypertensive Coronary Chemoreflex in the Nonhuman Primate?

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SUMMARY. The purpose of this study was to investigate the nature of the serotonin-induced coronary chemoreflex in the conscious monkey. Ten chronically prepared and four acute monkeys were used in this study. Five chronically prepared animals had catheters in the left atrium, ascending aorta, descending aorta, and, bilaterally, in the common carotid arteries. In addition, Silastic catheters were placed next to both vagi to permit vagal block with 2% lidocaine. Serotonin was injected (12-200 μg/kg) into the left atrium, ascending aorta, descending aorta, or, bilaterally, into the carotid arteries while blood pressure, heart rate, and respiratory movements were recorded. Injections of serotonin were associated with hypertension and bradycardia followed by tachycardia, all of which were preceded by a cough response. Atropine blocked the bradycardia, whereas atropine and phentolamine eliminated the cardiovascular components of the reflex. Vagal blockade eliminated the bradycardia but otherwise did not alter the response to left atrial serotonin. Three monkeys were prepared with aortic and left atrial catheters. Subsequently, they were subjected to sinoaortic deafferentation. Serotonin injected into these animals did not alter blood pressure or respiration. The results of this study show that serotonin injected into the left atrium of the conscious monkey produces respiratory and cardiovascular alterations by its effect on aortic and carotid chemoreceptors, and that there is no coronary chemoreflex in the conscious monkey. *(Circ Res 52: 312–318, 1983)*

Methods

Our study involved the use of eight chronically prepared monkeys and four acutely prepared monkeys (five Rhesus, five stump-tails, and two fascicularis). After the chronic monkeys had been conditioned for 1-2 weeks to sit quietly in a primate restraint chair, they were anesthetized with sodium pentobarbital (15 mg/kg iv) and prepared for sterile surgery. The chest was opened at the 5th intercostal space, and Silastic catheters were placed in the ascending aorta, descending aorta, or carotid arteries. Specially prepared Silastic catheters were bilaterally placed alongside the vagus nerve and the Silastic catheter. This permitted the infusion of 0.5 ml 2% lidocaine around the vagus nerve to produce vagal block. The effectiveness of the lidocaine block was determined by injecting veratridine into the left atrium, which produces a vagally mediated Bezold-Jarisch reflex (Krayer and Meilman, 1977). Failure to observe the Bezold-
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Jarisch reflex after lidocaine would indicate the presence of afferent vagal block. All measured parameters were recorded on an eight-channel Sanborn recorder. Blood pressure was recorded with a Millar pressure transducer. A pneumograph and a Millar transducer were used to record respiration. Heart rate was obtained by using the blood pressure pulse to trigger a Gould cardiotach.

In three animals, the aortic arch, and 1 to 2 cm of the brachiocephalic and subclavian arteries were stripped of their adventitia. Extreme care was taken not to damage the vagus, cardiac sympathetics, phrenic, or other major nerves in the area. In a later surgery, the carotid sinuses and associated vessels were stripped. Sinoaortic deafferentation was confirmed by recording heart rate while decreasing blood pressure with hemorrhage or nitroprusside. When blood pressure was decreased from 131 ± 20 to 55 ± 9 mm Hg, heart rate increased from 176 ± 16 to 177 ± 15.

In the initial experiments, atropine (0.1 mg/kg) and phenolamine (2 mg/kg) were given to determine the components of the reflex. Acetylcholine (50 µg into the left atrium) and phenylephrine (20 µg) were used to determine the effectiveness of the autonomic blockade. Serotonin was injected into the left atrium, ascending aorta, bilateral carotid arteries, and the descending aorta in doses of 12–200 µg/ml. The doses were varied to determine whether there was a difference in the threshold to serotonin when injected into the different sites. Since those injections previously used in dogs (Zucker and Cornish, 1980) employed 100–200 µg/1–2 ml, we felt that 50–100 µg/1 ml would be most comparable. The injections of serotonin were made at 5-minute intervals to avoid tachyphylaxis and to allow time for all variables to return to control.

Injections of nicotine (0.8 µg/kg) into the left atrium, ascending aorta, and, bilaterally, into the carotid arteries were also used to determine the similarity of the serotonin response to an agent which is known to stimulate primarily chemoreceptors (Zimpfer et al., 1981).

The data were analyzed by means of a randomized block for analysis of covariance. This analysis takes into consideration the variation for error and the variation among animals. The F ratio for treatment was determined as the

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F = \frac{\text{MS between groups}}{\text{MS within groups}}
\]

where the error term took into consideration the treatment effect, the animal effect, and the error effect. When the F ratio indicated that there was a significant effect due to treatments, multiple comparisons were done using Duncan’s new multiple range test. Since the statistical analysis was performed on the normalized data, i.e., percent of control, there were only minimal effects of the animal’s variation. A P value of less than 0.05 was considered significant. The data are expressed as the mean ± SEM.

Results

Typical responses to serotonin injections of 50 µg, observed in conscious monkeys, are shown in Figure 1. Serotonin injected into the left atrium of the monkeys caused initial coughing, which was associated with a concomitant short bradycardia, followed by moderate tachycardia and an increase in blood pressure. This response was also observed to a lesser degree when serotonin was injected into the ascending aorta, bilaterally into the common carotid arteries, or into the descending aorta. Reducing the amount of serotonin injected did not result in a response which could be isolated only to the left atrium and, thus, the coronary circulation. The mean data for the five conscious monkeys are presented in Figure 2. There was a significant difference in the blood pressure responses to ascending aortic, bilateral carotid, and descending aortic injections, compared to left atrial injections, with no detectable difference in the latency of response. Bilateral carotid injections caused a greater bradycardia, while there was less bradycardia with descending aortic injections when compared to the left atrial response. There were no significant differences in the observed tachycardia.

Figure 3 shows the responses to left atrial serotonin alone, with atropine, and with atropine and phenolamine. The bradycardia observed with left atrial injections was completely eliminated by atropine, whereas atropine potentiated the tachycardia and the increase in blood pressure. Both the hypertensive and tachycardic responses were significantly attenuated by the combined treatment of atropine and phenolamine; however, the respiratory response was not altered. The infusion of lidocaine bilaterally around the vagi attenuated the blood pressure response to

![Figure 1. Blood pressure, heart rate, and respiratory responses in the conscious monkey resulting from the injection of serotonin into the left atrium (LA Ser), ascending aorta (AA Ser), bilateral carotids (BC Ser), and the descending aorta (DA Ser).](image-url)
left atrial serotonin but did not eliminate it. Vagal block substantially reduced and, in many instances, completely eliminated the bradycardia resulting from serotonin injections, while, at the same time, it increased control heart rate (197 ± 1.6 to 208 ± 5) and blood pressure (113 ± 2.5 to 121 ± 8). However, vagal block did not alter the respiratory component. When serotonin was injected into the left atrium of the monkeys whose aortic arch and carotid sinus areas had been stripped of adventitia, it failed to stimulate respiration, elicit a bradycardia, or cause the typical abrupt increase in blood pressure. However, they did continue to show a delayed increase in blood pressure and an increase in heart rate. The increase in pressure probably was due to the serotonin-induced release of adrenal catecholamines as well as the direct vasoconstrictor effect of serotonin. To document the denervation procedure, nitroprusside was injected to lower blood pressure. The absence of a tachycardia (panel A, Fig. 4) indicated baroreceptor denervation. Figure 4 shows the response observed in two sinoaortic denervated (SAD) monkeys to left atrial serotonin. Figure 5 shows the mean data for these interventions.

To determine the competency of the vagal pathways, we first injected veratridine into the ascending aorta. Without waiting for any tachyphylactic effects to wear off, we made a second injection into the left atrium. Since the aortic injections did not induce a Bezold-Jarisch reflex, we concluded that the aortic catheters were placed far enough away from the coronary orifice to prevent drug injections from reaching the coronary circulation. The second veratridine injection caused a pronounced Bezold-Jarisch reflex. If the first injection had reached the coronary circulation, the animal probably would have been tachyphylactic to the second injection (Zucker and Cornish, 1981). After we had waited for possible tachyphylaxis to wear off, vagal block was produced, and veratridine was again injected into the left atrium. In each instance, the Bezold-Jarisch reflex was completely eliminated by the vagal block. When veratridine was injected into the left atrium of the SAD animals, they displayed a bradycardia and hypotension typical of the Bezold-Jarisch reflex, indicating that both the afferent and efferent vagus are intact. These data are presented in Figure 6.

Figure 7 demonstrates the effect of vagal block upon the responses to serotonin and veratridine. After blockade, there were no differences in the responses to left atrial or bilateral carotid injections of serotonin. When serotonin was injected into the left atrium...
and ascending aorta of the pentobarbital anesthetized, open-chest animal, a significant pressor response was noted. The pressor responses were not significantly different from each other when left atrial injections were compared to ascending aortic injections. In addition, the hypertension evoked by left atrial serotonin in the anesthetized monkey was not significantly different from that observed in conscious monkeys (Fig. 8).

Figure 9 shows a record of the effects of 0.8 μg/kg of nicotine into the left atrium, ascending aorta, and

![Figure 4](image)

**Figure 4.** Effect of injecting nitroprusside into the left atrium of a chronically sinoaortic denervated monkey (panel A). Panel B shows the effect of serotonin injected into the left atrium of the same monkey, whereas panel C is the response to serotonin in a second sinoaortic denervated monkey. Injections were made at the vertical bar in each panel.

![Figure 5](image)

**Figure 5.** Data obtained from the conscious monkey after autonomic blockade with atropine, or atropine and phentolamine, after vagal block with lidocaine (10 experiments, 5 monkeys) or after chronic sinoaortic denervation (6 experiments, 3 monkeys). The control values are presented for comparative purposes. *P < 0.05; **P < 0.01.

![Figure 6](image)

**Figure 6.** Data obtained from injecting veratridine into the left atrium of the conscious monkey before and after vagal block (20 experiments, 5 monkeys) and in the conscious, sinoaortic denervated monkey (6 experiments, 3 monkeys). The data for veratridine delivered into the ascending aorta are presented for comparison.
carotid arteries in the conscious monkey. The responses were very similar to those obtained with serotonin (Fig. 1). The animals displayed a rapid increase in respiratory rate and depth, bradycardia, and hypertension. The responses were similar when injections were made in the left atrium, ascending aorta, or, bilaterally, into the carotids; however, the response was most pronounced with bilateral carotid injections. The mean data for the monkeys that received nicotine are shown in Figure 10.

Discussion

The effect of serotonin on receptors located in the proximal portion of the coronary circulation has been reported to increase blood pressure in the anesthetized dog or to decrease blood pressure in the conscious dog (Zucker and Cornish, 1980). The heart rate response in both conditions is predominantly a bradycardia. This reflex is also closely associated with a pronounced stimulation of respiration. Injections of serotonin into the ascending aorta, carotid arteries, or the descending aorta do not elicit this reflex in the dog (James et al., 1975; Zucker and Cornish, 1980). However, Urthaler et al. (1978) have shown that serotonin does have a direct effect on the adrenal medulla to release catecholamines, which accounts for the delayed pressure response that is seen in the dog.

When serotonin is injected into the left atrium of the conscious monkey, the response is not dissimilar to that seen in the anesthetized dog. There is an initial bradycardia, followed by a tachycardia, both of which are associated with a substantial increase in blood pressure. There is also a respiratory component which is a cough, rather than the "gasp" heard in the dog. However, there are differences between the two species. Serotonin injected into the ascending aorta and the carotid arteries produces essentially the same response as that observed with left atrial injections.

The afferent pathway in the dog has been reported to be predominantly in the vagus nerve (James et al., 1979); however, bilateral vagotomy in the anesthetized dog does not completely eliminate it (Zucker and Cornish, 1980). We therefore concluded that part of the afferent pathways was outside the vagi, perhaps in cardiac sympathetic nerves. When the vagi of the monkey were infiltrated with lidocaine, the veratridine-induced bradycardia and hypotension was completely eliminated. Lidocaine around the vagi also eliminated the bradycardia induced by serotonin injections, indicating an effective efferent block. In spite of this vagal block, the injection of serotonin into the left atrium of the monkey still produced a substantial increase in blood pressure (Fig. 5). If serotonin is stimulating specific cardiac receptors, they either have an afferent pathway other than the vagus nerve, or they have afferent pathways in addition to the vagus. Whereas vagal lidocaine eliminates the vagal efferent component, it has little effect on the major components of the reflex, thus differing significantly from
that hypertensive coronary chemoreflex initially reported for the dog (James et al., 1979). When serotonin was given into the left atrium of the anesthetized monkey, the response was not different from that obtained by injections into the ascending aorta (Fig. 8). Except for the lack of evoked bradycardia, the response observed in the anesthetized monkey was essentially the same as that seen in the conscious monkey. These data are also significantly different from those reported in the dog (Zucker and Cornish, 1980), since the response observed in the conscious dog is characterized by pronounced bradycardia and either a hypotension or mild hypertension, whereas the anesthetized dog responds to serotonin injections with a pronounced hypertension.

**Figure 8.** Data obtained by injecting serotonin into the left atrium and ascending aorta of open-chest anesthetized monkey. The control data obtained in the conscious monkey are presented for comparison.

**Figure 10.** Responses to nicotine injected into the ascending aorta, left atrium, and bilateral carotids. Open bars are the bradycardia; shaded bars represent the observed change in blood pressure (*P < 0.05; **P < 0.01).
The response to serotonin injections appeared to be similar to that elicited by stimulation of chemoreceptive tissue. For this reason, nicotine was given so that the serotonin response could be compared to the response obtained by chemoreceptor stimulation. Even though the magnitudes were different for the various injection sites, the responses to the two substances were essentially the same. When the chemoreceptors of the aortic arch and carotid bodies were denervated, left atrial serotonin failed to elicit either a stimulation of respiration or an increase in blood pressure (Fig. 4), even though vagal pathways were intact. From these data, we would conclude that serotonin is stimulating chemoreceptor tissue which is primarily associated with respiratory control. These data do not support the existence in the nonhuman primate of a receptor in the coronary circulation which is specifically stimulated by serotonin.

K.G. Cornish was supported by Nebraska Heart Association Grant-in-Aid.

I.H. Zucker was a recipient of an Established Investigatorship award from the American Heart Association.

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Received March 12, 1982; accepted for publication December 30, 1982.

References


INDEX TERMS: Serotonin • Chemoreflex • Hypotension • Coronary circulation
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Circ Res. 1983;52:312-318
doi: 10.1161/01.RES.52.3.312

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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