Change in Baroreceptor Sensitivity by Angiotensin

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It was demonstrated in the dogs with sustained hypertension produced by infusion of angiotensin into the vertebral arteries arterial pressure rose during sleep (1). The same phenomenon was previously reported in the dogs with experimental neurogenic hypertension produced by section of the carotid sinus nerves and aortic depressor nerves (2). Therefore, it may be interesting to test the possibility that angiotensin given centrally can influence the central nervous system to modulate afferent stimuli exercised from the reflexogenic area.

Fourteen mongrel dogs weighing 12 to 20 kg were used. Anesthesia was induced with intramuscular injection of morphine (2 mg/kg) and intravenous injection of α-chloralose (100 mg/kg). Unilateral carotid sinus nerve was exposed and laid on a bipolar silver electrode for electrical stimulation. In most cases the contralateral carotid sinus nerve was intact. Bilateral vertebral arteries were exposed through incisions in supraclavicular areas. A catheter was placed into each vertebral artery in a way not to disturb the vertebro-basilar circulation. The other end of the catheter was connected to an infusion pump. Arterial pressure was measured through a cannula inserted into the femoral artery by a strain-gauge transducer.

Angiotensin II (Hypertensin, Ciba) was dissolved into isotonic saline at a concentration of 100 ng per ml. The solution was infused with a syringe infusion pump (Sweden Inc.). To stimulate the carotid sinus nerve, a 0.1 msec rectangular wave form was used. The frequency was set at 50 pulses per second and the amplitude (2.0–6.0 Volt) was adjusted at the beginning of the experiment to cause a fall of about 20 mmHg in mean arterial pressure in each dog. A cardiograph, triggered by R-R interval of ECG, was provided for instantaneous records of heart rate. Pulsatile pressure, mean pressure, heart rate and ECG (standard limb lead II) were recorded simultaneously on a multichannel pen recorder.

Effect of angiotensin on depressor response to CSN stimulation

In control study, 30 sec stimulation of the carotid sinus nerve produced an average maximum decrease in mean arterial pressure of 21.0 ± 2.7% (mean ± SE) from initial pressure. The pressure began to decrease within the first 5 sec of the stimulation and reached the lowest level at 20 sec, began to return toward the control level during the later 10 sec of the stimulation and recovered by 30 sec after cessation of the stimulation. Infusion of angiotensin into vertebral arteries was made at a rate of 3.0 ng/kg/min, that caused little rise in systemic arterial pressure. The stimulation during the infusion of angiotensin produced the same type of response but the maximum decrease of mean pressure was less than that of control (P<0.01); it was 13.0 ± 1.8% and appeared 20 sec after starting the stimulation. The recovery was shortened and required 20 sec following discontinuation of the stimulation.

Effect of angiotensin on bradycardia produced by CSN stimulation.

In control a 30 sec period of the carotid sinus nerve stimulation induced bradycardia. A maximum decrease in heart rate, 30.4 ± 2.7% from the initial value, was obtained 5 sec after starting the stimulation. It recovered gradually and

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returned to the control value 5 sec after withdrawal of the stimulation. During vertebral artery infusion of angiotensin, the stimulation produced also an immediate fall in heart rate. However, the maximum decrease of 18.5 ± 3.6% was significantly smaller than that of the contral (P<0.01). Recovery of heart rate was more rapid and it returned to the initial value 15 sec after induction of the stimulation while arterial pressure was still decreasing.

Hypotension and bradycardia in response to carotid sinus nerve stimulation were summarized in 8 dogs and shown in the figure 1.

**Influence of angiotensin on carotid occlusion response.**

Occlusion of a common carotid artery was performed for 20 sec before and during infusion of the same doses of angiotensin into vertebral arteries. A change in arterial pressure responding to this procedure was not significantly affected by the infusion.

Before infusion of angiotensin the carotid occlusion caused a rise of mean arterial pressure 18.6 ± 1.3% (Mean ± SE, N = 7) from the initial value. During the infusion it was 19.1 ± 0.7%.

Here; it was demonstrated clearly that carotid sinus nerve stimulation in the morphine-chloralose anesthetized dog resulted in a reduction in arterial pressure and heart rate; during infusion of angiotensin into vertebro-basilar circulation in the doses of little or no effect on systemic arterial pressure, the stimulation of identical intensity and duration in the same dog resulted in a lesser degree of arterial hypotension and bradycardia; the time required for recovery of heart rate and arterial pressure was also shortened.

The carotid sinus baroreceptors reflexly control sympathetic vasomotor discharges. The relationship of the carotid sinus nerve discharges and the inhibition of the sympathetic impulses is reciprocal. Although the pattern of activation of carotid sinus nerve employed differed from the sinus nerve discharges which occurs physiologically, the qualitative responses were considered to be identical. It was demonstrated here that the electrical stimulation of the sinus nerve caused a lesser fall in arterial pressure and heart rate during the infusion of angiotensin. The result will be explained thus: angiotensin may activate directly the facilitatory adrenergic tracts in central nervous system, or suppress the tonic inhibition of afferent sinus nerve input. Parasympathetic nervous system would not largely be involved because bradycardia associated with the sinus nerve stimulation in anesthetized dogs was blocked by propranolol but not by atropine (3). The fact that carotid occlusion response was not affected by the infusion in this study possibly supports the latter mechanism rather than the former. The investigation will also be compatible

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with this hypothesis that a rise in arterial pressure induced by vertebral artery infusion of angiotensin was associated with initial augmentation in splanchnic nerve activity as determined electrophysiologically (4).

There are some evidences to suggest central modulation of the baroreflex; baroreceptor sensitivity can be changed during sleep, anesthesia (3) and hypoxia (5). Thus, it is indicated that angiotensin may act on vasomotor centre and modulate baroreceptor function reflex, resulting in an increase of central sympathetic outflow.

Discussion:

Dr. IIZUKA: In 1969 we similarly injected suppressor doses of angiotensin into the dog’s vertebral artery. By this procedure, the pressor effect of electrical stimulation of the posterior hypothalamus was significantly augmented. However, pressor responses to stimulation of the medulla oblongata or carotid occlusion were not influenced. Which do you think is the cause of the phenomenon you observed, a change of gain or a resetting?

Dr. FUKIYAMA: I do not know. Therefore, I used such a noncommittal term as “sensitivity”. Dr. KANEKO: The mechanism Dr. Fukiyama proposed for the central action of angiotensin is interesting, since veratram alkaloids are known to exert their hypotensive actions by the apparently opposite mechanism, that is, by stimulating the afferent nerve inhibition from baroreceptors. It would be interesting if you could show that angiotensin and veratram alkaloids have actually the opposite action in this respect. By the way, Dr. Fukiyama, if you are right, do you have any evidence suggesting that a fall in arterial pressure during sleep less in hypertensive patients in whom circulating angiotensin levels or plasma renin activity are elevated?

Dr. FUKIYAMA: According to Pickering, in hypertensive patients, the fall of arterial pressure in sleep is slight, if present at all.

Dr. SOKABE: The effect of angiotensin you reported would be an opposite direction to that of veratram alkaloids, but their sites of action are different. Veratram alkaloids primarily act on the baroreceptor area on peripheral blood vessels.

Dr. YAMORI: Your result that the central effect of angiotensin is an inhibition of the central inhibitory mechanism is consistent with the following two pieces of observation made by us. 1) The central effect of angiotensin is weaker in rats treated with 6-OHDA and SHR, which have abnormalities in the central noradrenergic inhibitory mechanism. 2) When pretreated with clonidine, a central stimulant, the central pressor effect of angiotensin is augmented. It is possible that the central pressor effect of angiotensin is an inhibition of the central inhibitory mechanism of possibility that the baroreceptor function is mediated by the central noradrenergic mechanism?

Dr. FUKIYAMA: I imagine that the abnerergic inhibitory tract is involved.

Dr. SOKABE: I would like to know the comparison of the effect of angiotensin on carotid sinus nerve stimulation with that of clonidine.

Dr. NAKAMURA (in answer to Dr. YAMORI): Recently it was found that Nucl. tractus solitarius contains the second neurons of the baroreceptor reflex. In the vicinity, the cell bodies of the baroreceptor reflex. In the vicinity, the cell bodies of the ventral NA neuron pathway are also present. Therefore, it is likely that the carotid sinus nerve is connected with the central NA neuron.