Effect of Synthetic Angiotonin on the Carotid Sinus

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Natural decapeptide or synthetic octapeptide angiotonin was ineffective in lowering arterial pressure or decreasing the carotid occlusion response when injected into the carotid sinus adventitia. Injection of synthetic octapeptide angiotonin into the lumen of the carotid sinus after tying its branches decreased the carotid occlusion response but the effect depended on dosage many times the pressor activity of 1/γ of norepinephrine which elicited a comparable effect.

Heymans and Delaunois showed that constriction of the carotid sinus wall is responsible for the increased baroreceptor stimulation leading to hypotension and diminution or loss of the carotid occlusion reflex when epinephrine or norepinephrine is applied locally. Other vasoconstrictor agents such as serotonin, synephrine and Pitressin have since been shown to have the same effect (for review see Heymans). The local effect of angiotonin on the carotid sinus has not been measured. This report describes the relatively weak activity of both highly purified natural decapeptide angiotonin (converted by a circulating enzyme to the vasoactive octapeptide) and synthetic octapeptide angiotonin (Bumpus, Schwarz and Page). A summary of experiments is presented below.

METHODS

Adult mongrel dogs were anesthetized with morphine 2 mg./Kg. and sodium pentobarbital 15 mg./Kg. In the first group of experiments test drugs were injected in volume of 0.05 or 0.10 ml. into the adventitia of one carotid sinus after sectioning the other carotid sinus and the vagus and aortic nerves. In the second group of experiments all branches of one common carotid and carotid bifurcation were tied, care being taken not to damage the carotid sinus nerve; the other carotid sinus and the vagus and aortic nerves were sectioned. Drugs were injected directly into the lumen of the carotid sinus in volumes of 0.1 ml. through a small needle inserted through the wall of the common carotid directly below the bifurcation. The external carotid artery and external jugular vein were cannulated and connected by plastic tubing to ensure adequate circulating blood supply. The tubing was clamped when drugs were injected; a T-tube permitted flushing drugs from the sinus so that they did not enter the systemic circulation. Test drugs were norepinephrine and Pitressin, dosages given below, and highly purified natural decapeptide angiotonin and synthetic octapeptide angiotonin. Dosage of angiotonin is expressed in units, one unit having approximately 1/γ of the pressor activity of 1/γ of norepinephrine in normal adult mongrel dogs anesthetized with sodium pentobarbital. Solutions of all test drugs were adjusted to pH 6-7.

Arterial pressure was measured from a cannulated femoral artery by a mercury manometer writing on a smoked drum. The carotid occlusion reflex was measured before and after application of each test drug.

Results and Discussion

Extrasinus Injection. Angiotonin in decapeptide form (40 units) was injected into the carotid sinus adventitia in two experiments and synthetic octapeptide angiotonin (40, 40 and 55 units) in 3 experiments. There was no decrease in the carotid occlusion reflex in any experiment, and the injection of these large doses caused small to moderate sustained rises, rather than falls, in average arterial pressure levels (fig. 1). In contrast with the lack of effect of angiotonin on the occlusion reflex and its lack of depressor effect, norepinephrine in doses of 50 or 100 γ into the adventitia in 4 of the same experiments caused moderate to marked fall in systemic arterial pressure and elimination of the occlusion reflex. Figure 1 illustrates a typical effect.

Pitressin (2 or 3 units) caused small fall in arterial pressure in 3 experiments and approximately 50 per cent reduction in the carotid occlusion reflex (fig. 1).
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Intrasinus Injection. The more powerful effect of norepinephrine compared with Pitressin might have been due to the larger molecular size of the latter agent acting to hinder its diffusion into the muscular layer of the arterial wall. This would also apply to angiotonin since its molecular weight is approximately equal to that of Pitressin. To enable the test drugs possibly better to permeate the arterial wall they were injected into the lumen of the carotid sinus. The injected drugs were trapped in this area for 3 or 4 min. by occluding the shunt from external carotid artery to jugular vein; other vessels from the common carotid and bifurcation were tied.

Injection of large dosage of synthetic octapeptide angiotonin (50 units) was followed by a small sustained rise in arterial pressure in 2 of 3 experiments—as after injection into the adventitia in the first group of experiments. The carotid occlusion response, however, was reduced by 25, 35 and 55 per cent respectively and the effect was sustained for long periods after flushing the sinus of injected angiotonin. Figure 2 shows the most marked effect observed. That injected angiotonin was not quickly inactivated is indicated by the sustained rise in arterial pressure due to absorption of some of the agent into the systemic circulation. That it was not completely absorbed was
indicated by a maximum, prolonged pressor response when the sinus was purposely flushed into the systemic circulation after 4 min. in 1 experiment.

Norepinephrine was effective in reducing the occlusion reflex when injected in much smaller dosage. One gamma was sufficient to cause sharp and sustained reduction in the occlusion reflex though there was little lasting effect on average arterial pressure (fig. 2). Only small amounts of norepinephrine were absorbed or inactivated since, when the sinus was purposely flushed into the systemic circulation, the pressor response was approximately equal to that produced by injection of 1 γ of norepinephrine into the femoral vein. This observation would seem to support the suggestion of Palme4 and Kezdi5 that small amounts of norepinephrine released by the sympathetic nerve supply to the carotid sinus might play an important role in regulating baroceptor function.

The effect of one unit of Pitressin injected into the carotid sinus was equal to, or slightly greater than, the effect of 2 or 3 units injected into the adventitia. It produced moderate fall in arterial pressure and reduction of the carotid occlusion response by 50 per cent or more.

SUMMARY

Injection of highly purified natural decapeptide angiotonin or synthetic octapeptide angiotonin into the adventitia of the carotid sinus did not lower arterial pressure or decrease the carotid occlusion reflex, contrasting with the effect of Pitressin and norepinephrine.

Injection of synthetic octapeptide angiotonin into the lumen of the carotid sinus after tying its branches caused diminution of the occlusion reflex, but this effect depended on dosage many times the pressor activity of 1 γ of norepinephrine which elicited a comparable effect.

It is concluded that angiotonin shows a higher degree of specificity for arteriolar than for carotid arterial smooth muscle, and that even very high concentrations of circulating angiotonin probably do not modify baroceptor function through a direct action on the wall of the carotid sinus, at least over short periods of time.

SUMMARIO IN INTERLINGUA

Le injection de altemente purificate angiotonina decapeptidic natural o de angiotonina octopeptidic synthetic a in le adventitia del sino carotic non reduceva le pression arterial e non diminueva le reflexo carotic de occlusion. Su effecto assi contrasta con illos de Pitressina e de norepinephrina.

Le injection de synthetic angiotonina octopeptidic a in le sino carotic post le ligation de su brancas causava un diminution del reflexo de occlusion, sed iste effecto requireva un dosage con un activitate pressori multe vices plus grande que le activitate de 1 μg del dosage de norepinephrina requirite pro evocar un effecto comparabile.

Nos conclude que angiotonina monstra un plus alte grado de specificitate pro le musculo lisie arteriolar que pro le musculo lisie carotic, e que probabilmente etiam multo alte concentrationes de angiotonina circulante non modifica le function baroceptor per action directe super le parietes del sino carotide, al minus non in le curso de breve periodos de tempore.

REFERENCES

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