ments, plasma ADH concentration one hour after vagotomy averaged slightly higher than that found in normal dogs, but the difference was not significant statistically ($P>0.5$). The absence of ADH release in dogs with vagi intact can be explained on the basis of the inhibitory influence on ADH release carried by some vagal afferents. Such inhibitory influence may be tonic and keeps the hypothalamico-hypophyseal system in a low state of excitability. Or alternatively, the inhibitory influence in vagal afferents may be operative in a phasic manner. For example, it may be triggered by the rise in systemic arterial pressure occurring during carotid occlusion. When the inhibitory influence, be it tonic or phasic, in afferent vagi is removed by vagotomy, occlusion of common carotid arteries resulted in a release of ADH.

Summary. In bilaterally vagotomized dogs, occlusion of common carotid arteries caused an increase in plasma ADH concentration, which averaged 264% of control at 2 minutes after beginning the occlusion. This increase in ADH was not observed in normal dogs with vagi intact or in dogs with efferent vagi blocked by atropine. It is concluded that the afferent vagal fibers exert some inhibitory influence on the supraoptico-hypophyseal system and that carotid occlusion results in ADH release when the vagal inhibition is removed.

The authors wish to thank Dr. Wilbur H. Sawyer for his advice on the technic for bioassay of ADH and Dr. William W. Walcott for his help in building the equipment for bioassay.

1. Gregersen, M. I., Rawson, R. A., *Physiol. Rev.*, 1959, v39, 307.
2. Reeve, E. B., Allen, T. H., Roberts, J. E., *Ann. Rev. Physiol.*, 1960, v22, 349.
3. Farrell, G., Taylor, A. N., *ibid.*, 1962, v24, 471.
4. Rydin, H., Verney, E. B., *Quart. J. Exp. Physiol.*, 1938, v27, 343.
5. Usami, S., Chien, S., *The Physiologist*, 1961, v4, 125.
6. Weinstein, H., Berne, R. M., Sachs, H., *Endocrinology*, 1960, v66, 712.
7. Gauer, O. H., Henry, J. P., Sieker, H. O., *Progress in Cardiovascular Diseases*, 1961, v4, 1.
8. Sawyer, W. H., *Methods in Medical Research*, 1961, v9, 210.
9. Share, L., Levy, M. N., *The Physiologist*, 1961, v4, 107.
10. Share, L., *Endocrinology*, 1961, v69, 925.
11. Cohen, G., Goldenberg, M., *J. Neurochem.*, 1957, v2, 58.
12. Perlmutt, J. H., *Fed. Proc.*, 1962, v21, 207.
13. Heymans, C., Neil, E., *Reflexogenic Areas of the Cardiovascular System*. Little, Brown & Co., Boston, 1958.
14. Berger, E. Y., Dunning, M. F., Steele, J. M., Jackenthal, R., Brodie, B. B., *Am. J. Physiol.*, 1950, v162, 318.
15. Morales, P. A., Crowder, C. H., Fishman, A. P., Maxwell, M. H., Gomez, D. M., *ibid.*, 1950, v163, 454.

Received June 21, 1962. P.S.E.B.M., 1962, v111.

The Reflex Nature of Release of Antidiuretic Hormone upon Common Carotid Occlusion in Vagotomized Dogs.* (27742)

SHU CHIEN, BRANKO PERIC† AND SHUNICHI USAMI
Department of Physiology, College of Physicians and Surgeons, Columbia University, New York City

In experiments reported in an accompanying paper(1), it was found that bilateral occlusion of common carotid arteries in vagotomized dogs elicited the release of antidiuretic hormone (ADH). The present experiments are designed to investigate whether such ADH release is due to a reflex originating from receptors in the common carotid arteries and their bifurcations or to the effect of reduced cerebral blood flow on the hypothalamico-hypophyseal system.

Methods. Healthy mongrel dogs apparently in normal hydration were used in these experiments. Food was withheld from the ani-

* Aided by research grants from Nat. Inst. Health, U.S.P.H.S.

† International Postdoctoral Fellow, Nat. Inst. Health, U.S.P.H.S.

TABLE I. Effects of Common Carotid Occlusion on Plasma ADH Concentration of 4 Vagotomized and Sinus-Denervated Dogs.

	ADH conc. (μU/ml)	Heart rate (per min.)	Arterial pressure (mm Hg) Systolic / Diastolic
Control (mean $\pm$ S.E.$_m$)	95 ($\pm$ 15.0)	209 ($\pm$ 14.3)	157 ($\pm$ 30.1) / 103 ($\pm$ 14.4)
Occlusion* (mean $\pm$ S.E.$_m$)	96 ($\pm$ 22.7)	205 ($\pm$ 14.1)	156 ($\pm$ 29.3) / 103 ($\pm$ 14.4)
Change	+1	−4	−1 / $\pm$0
P value (t test)†	> .9	> .2	> .7 –

* Values obtained at 2 min. after beginning occlusion.
† Applied to changes observed in individual dogs.

mals for about 18 hours prior to experiments. Free access to water was allowed. The animals were anesthetized with intravenous injection of sodium pentobarbital (33 mg/kg), and small doses of the latter were given intraperitoneally during the experiments to keep a relatively constant degree of anesthesia. Three groups of experiments were performed. In one group of 4 experiments (Group A), the common carotid arteries were exposed low in the neck. The carotid sinus nerves were sectioned bilaterally. In a second group of 7 experiments (Group B), the external and internal carotid arteries were isolated above the carotid sinus areas without disturbing the sinus nerves. In a third group of 4 experiments (Group C), the common carotid arteries were isolated just below the sinus areas and above the thyrocarotid junctions (the points at which the superior thyroid arteries branch from the common carotid arteries). In this group, the sinus nerves were also intact. In all 3 groups of animals, the vagus nerves were sectioned bilaterally in the neck. A femoral artery was cannulated for the recording of arterial pressure and for sampling. For the recording of arterial pressure, Sanborn pressure transducer and recorder were used. All operative procedures were concluded at least one hour before any sample was taken for ADH determination. The samples were taken from the femoral artery before and at various time intervals after the occlusion of common carotid arteries or their branches. ADH concentration in the plasma was determined by bioassay technics in rats as described in the accompanying paper(1).

Results. A. *Common carotid occlusion after sinus denervation.* In sinus-denervated and vagotomized dogs, the control plasma ADH concentration averaged 95 μU/ml (S.E.$_m$ 15.0). During the occlusion of both common carotid arteries, plasma ADH concentration remained essentially unchanged from the control. ADH concentrations at 2 minutes after beginning the occlusion averaged 101% of control (Table I) and showed no statistically significant difference from control values ($P>0.9$). During carotid occlusion, arterial pressure and heart rate did not increase from the control.

B. *Occlusion of external and internal cartotid arteries.* In vagotomized dogs, occlusion of external and internal carotid arteries gave essentially the same results as common carotid occlusion after denervation of the sinuses. There was no increase in plasma ADH concentration, arterial pressure and heart rate. The plasma ADH concentration at 2 minutes after beginning the occlusion averaged 107% of the control, and there was no statistically significant difference from control values ($P>0.3$). The systolic pressure actually decreased during the occlusion of external and internal carotid arteries (Table II).

C. *Occlusion of carotid arteries between thyrocarotid junction and carotid sinus.* In vagotomized dogs, occlusion of common carotid arteries above the thyrocarotid junctions caused a marked increase in arterial pressure. Plasma ADH concentration increased in every experiment. At 2 minutes after beginning the occlusion, plasma ADH concentration averaged 341% control values (Table III). The difference from the control was significant ($P<0.001$).

Discussion. If the increase in plasma ADH in vagotomized dogs after common carotid occlusion(1) is a reflex phenomenon due to changes in excitation of the receptors in the sinus area, then the removal of sinus nerves should abolish such response. This is demon-

TABLE II. Effects of Occluding External and Internal Carotid Arteries on Plasma ADH Concentration of 7 Vagotomized Dogs.

	ADH conc. (μU/ml)	Heart rate (per min.)	Arterial pressure (mm Hg) Systolic / Diastolic
Control (mean ± S.E.$_m$)	105 (± 22.7)	173 (± 10.4)	150 (± 9.7) / 93 (± 9.3)
Occlusion* (mean ± S.E.$_m$)	112 (± 26.5)	172 (± 9.7)	132 (± 10.9) / 83 (± 9.7)
Change	+7	−1	−18 /−10
P value (t test) †	> .3	> .8	< .01 > .05

* Values obtained at 2 min. after beginning occlusion.
† Applied to changes observed in individual dogs.

TABLE III. Effects of Occluding the Common Carotid Arteries Above the Thyrocarotid Junctions in 4 Vagotomized Dogs.

	ADH conc. (μU/ml)	Heart rate (per min.)	Arterial pressure (mm Hg) Systolic / Diastolic
Control (mean ± S.E.$_m$)	64 (± 9.2)	168 (± 13.3)	172 (± 5.7) / 114 (± 4.9)
Occlusion* (mean ± S.E.$_m$)	218 (± 26.2)	184 (± 9.3)	239 (± 13.4) / 168 (± 7.1)
Change	+154	+16	+67 /+54
P value (t test) †	< .001	< .05	< .01 < .001

* Values obtained at 2 min. after beginning occlusion.
† Applied to changes observed in individual dogs.

strated in the first group (A) of experiments. Furthermore, in the vagotomized dogs, when the external and internal carotid arteries were occluded above the bifurcations (Group B), there was no increase in plasma ADH. Thus, in order to elicit ADH response, carotid occlusion must be made below the sinus area, where the receptors involved in classical vasomotor and respiratory reflexes are known to be located. These findings clearly indicate that the release of ADH after common carotid occlusion is due to alteration in the state of excitation of receptors in the carotid sinus area and depends on the ensuing changes in afferent impulses traveling in the sinus nerves. At the same time, the results in these experiments (Groups A and B) seem to have eliminated the alteration in cerebral blood flow as a possible mechanism for release of ADH after common carotid occlusion.

Recently, the junction between common carotid artery and superior thyroid artery has been found to contain receptors sensitive to changes in arterial pressure(2). There is evidence that these receptors and the afferent fibers arising from them are related to the regulation of aldosterone secretion(3). In our experiments on vagotomized dogs, occlusion of common carotid arteries below(1) and above (Group C) the thyrocarotid junction resulted in essentially the same degree of ADH release (Fig. 1). Hence the carotid sinus area rather than the thyrocarotid junction was responsible for the reflex release of ADH after common carotid occlusion.

When the common carotid arteries are occluded, the decrease in intraluminal pressure in the carotid sinuses reduces the stretching of baroreceptors(4), but at the same time the reduction in blood flow through the carotid bodies decreases the pO_2 at the chemoreceptors and causes the stimulation of the latter (5). Whether the reduction of stretching of baroreceptors or the stimulation of chemoreceptors caused the release of ADH after common carotid occlusion in vagotomized dogs cannot be answered from our experiments. A reduction in the stretching of baroreceptors decreases the afferent impulses from these receptors(6), whereas stimulation of chemoreceptors increases the afferent impulses from these latter receptors(5). For each of these receptors to be responsible for the ADH release, the baroreceptor impulses would have to be inhibitory to ADH release and the chemoreceptor impulses would have to be excitatory. Since it has been shown that stimulation of the central end of glossopharyngeal nerve could result in an increase of the femoral arterial pressure of viviperfused isolated-

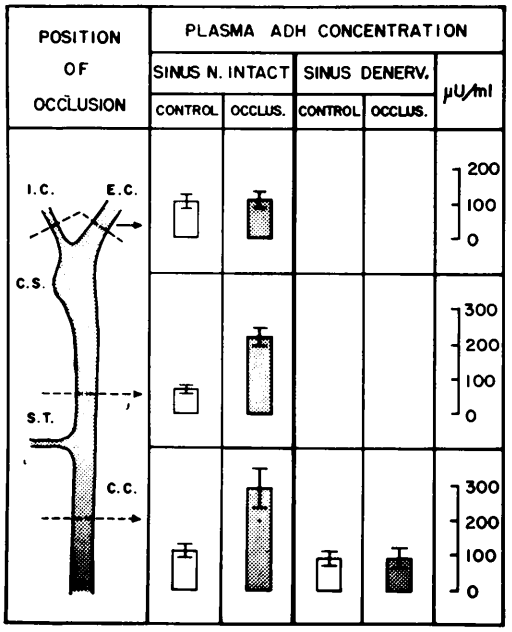

FIG. 1. Summary of effects of occluding the common carotid arteries or their branches on plasma ADH concentration of vagotomized dogs. Ordinates on extreme right indicate ADH concentration in μU/ml plasma. Lines above and below each bar represent one stand. error of mean. In preparations with the sinus nerves intact, an increase in ADH was obtained by occluding the carotid arteries either below or above the thyrocarotid junctions, but not by occluding the branches above the sinus areas. I.C., internal carotid artery; E.C., external carotid artery; C.S., carotid sinus; S.T., superior thyroid artery; C.C., common carotid artery.

head dogs(7), it is likely that this nerve carries some excitatory fibers for the release of vasopressin. If this is the case, then the ADH release on common carotid occlusion could be due to stimulation of carotid chemoreceptors.

Whether the baroreceptors or chemoreceptors are responsible for the ADH release on common carotid occlusion, the afferent fibers for these receptors travel in the glossopharyngeal nerves, which enter the brain at the level of medulla oblongata. Recently, there is evidence that the stimulation of certain areas in the midbrain(8) and the posterior hypothalamus(9) can result in ADH release. These findings offer a central pathway for the connections between the sinus nerves and the supraoptico-hypophyseal system.

Summary. In vagotomized dogs, there was no increase in plasma ADH concentration following (A) common carotid occlusion if the carotid sinuses had been denervated, or (B) occlusion of external and internal carotid arteries above the bifurcation. Hence the release of ADH in vagotomized dogs during common carotid occlusion was a reflex phenomenon due to the alteration in the state of excitation of receptors in the carotid sinus area and the ensuing changes in afferent impulses traveling in the sinus nerves. In vagotomized dogs, occlusion of common carotid arteries above and below the thyrocarotid junction caused similar increases in plasma ADH, indicating that the nerves of the thyrocarotid junction do not play a significant role in such ADH release.

1. Usami, S., Perić, B., Chien, S., PROC. SOC. EXP. BIOL. AND MED., 1962, v111, 189.

2. Green, J. H., *J. Physiol.*, 1953, v122, 70.

3. Bartter, F. C., Mills, I. H., Gann, D. S., *J. Clin. Invest.*, 1960, v39, 1330.

4. Euler, U. S. von, Liljestrand, G., *Skand. Arch. Physiol.*, 1936, v74, 101.

5. Chungcharoen, D., Daley, M. deB., Neil, E., Schweitzer, A., *J. Physiol.*, 1952, v117, 56.

6. Bronk, D. W., Stella, G., *J. Cell. Comp. Physiol.*, 1932, v1, 113.

7. Huang, J. J., *Chinese J. Physiol.*, 1941, v16, 277.

8. Sharpless, S. K., Rothballer, A. B., *Am. J. Physiol.*, 1961, v200, 909.

9. Fang, H. S., Liu, H. M., Wang, S. C., *ibid.*, 1962, v202, 212.

Received June 21, 1962. P.S.E.B.M., 1962, v111.