Effects of Vagotomy and of Carotid Constriction on Corticosteroid Secretion in the Dog.* (29085)

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(Introduced by R. H. Egdahl)
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It is well known that hemorrhage leads to increased secretion of 17-hydroxycorticosteroids (17OHCS)(1,2) but the mechanisms underlying this increase are poorly understood. Constriction of the thoracic inferior vena cava(3) and systemic hypotension produced pharmacologically(4) are also effective stimuli to secretion of 17OHCS. This suggests the possibility that at least a part of the 17OHCS response to hemorrhage might be mediated through hypotension in the heart or great vessels. The present experiments are consistent with this hypothesis, and identify two previously undescribed stimuli to 17OHCS secretion.

Methods. Experiments were performed on dogs anesthetized with pentobarbital. On the day prior to experiment, each dog underwent adrenal vein cannulation by the method of Hume and Nelson(1). In addition, chokers were placed about each common carotid artery low in the neck, and loose silk ligatures were passed about each vagus nerve. The vagi were dissected free from the carotid arteries for a distance of several centimeters, so that they might be pulled up without distorting the vessels.

Following induction of anesthesia on the day of experiment, cannulas were inserted in the femoral artery and vein, and in some cases in lingual arteries as well. Pressures were monitored continuously by means of Sanborn 267 transducers and a Sanborn recorder. Each dog received one liter of normal saline intravenously during the next 2 hours. Surgical anesthesia was maintained to permit secretion rates of 17OHCS to return toward basal levels. After 2 hours, control timed adrenal venous blood samples were collected. Some animals then underwent bilateral vagotomy, effected by pulling up the ligatures about the vagi to expose the nerves, and dividing the nerves. In other animals, designated "sham-vagotomized," the nerves were pulled up and dropped back in place without being cut. Samples were collected 10, 30 and 60 minutes after this procedure. Some animals from each group then underwent bilateral constriction of the carotid arteries, effected by tightening the chokers, without applying any pull on the arteries, until mean femoral arterial pressure rose 20mm Hg. Lingual arterial pressure fell with constriction and was not monitored after early experiments, to minimize manipulation of the animals on the day of the experiment. Other animals from each group, designated "sham-constricted," did not undergo carotid constriction at this time. Adrenal venous samples were again collected at 10, 30 and 60 minute intervals. All animals then received 5 units of ACTH intravenously, and an additional sample was collected 5 minutes later. Blood lost by collection was replaced with equal volumes of 6% dextran in saline. Samples were analyzed for 17OHCS by the method of Peterson(5), and secretion rates were calculated from concentration of 17OHCS and adrenal blood flow. No animal who did not have a control secretion rate of 17OHCS of less than 8 μg/min and who did not respond to ACTH with a secretion rate in excess of 8 μg/min was included in the study, in order to exclude those animals who were stimulated non-specifically, as well as those who were unable to respond to stimulation.

Results. Bilateral cervical vagotomy led to a prompt increase of secretion of 17OHCS to maximum levels (not significantly different

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from the response to 5U ACTH). Secretion rates remained high 30 minutes after vagotomy, but fell to levels not significantly different from control at 60 minutes. In contrast, sham-vagotomy was without effect on 17OHCS secretion. Results of vagotomy and of sham-vagotomy are summarized, compared and analyzed statistically in Fig. 1. The differences between the responses to vagotomized and to sham-vagotomy are significantly different at 10 and 30 minutes.

Bilateral carotid constriction in sham-vagotomized (intact) animals was without effect on 17OHCS secretion, despite the ability of the animals to respond to ACTH. In contrast, bilateral carotid constriction in vagotomized animals led to a prompt increase of secretion of 17OHCS to maximum levels. Secretion rates remained high 30 and 60 minutes after constriction, though there was a tendency for the secretion rate of 17OHCS to decrease gradually with time. Results of carotid constriction in vagotomized and in intact animals are summarized, compared and analyzed statistically in Fig. 2. The differences in responses of the 2 groups to carotid constriction are significantly different at 10, 30 and 60 minutes. Vagotomy without carotid constriction did not lead to increased 17OHCS secretion at the same time intervals. Results of carotid constriction and of sham-constriction in vagotomized animals are summarized, compared and analyzed statistically in Fig. 3. The differences in responses of these 2 groups are significantly different at 10, 30 and 60 minutes after constriction or sham-constriction.

Discussion. These experiments demonstrate that bilateral cervical vagotomy increases secretion of 17OHCS in the dog. This increase does not result from non-specific trauma incident to nerve section, since sham-vagotomized animals showed no increase in secretion of 17OHCS. However, these experiments do not exclude the possibility that nerve section may stimulate secretion of 17OHCS, regardless of what nerve is sectioned. The case for the specificity of

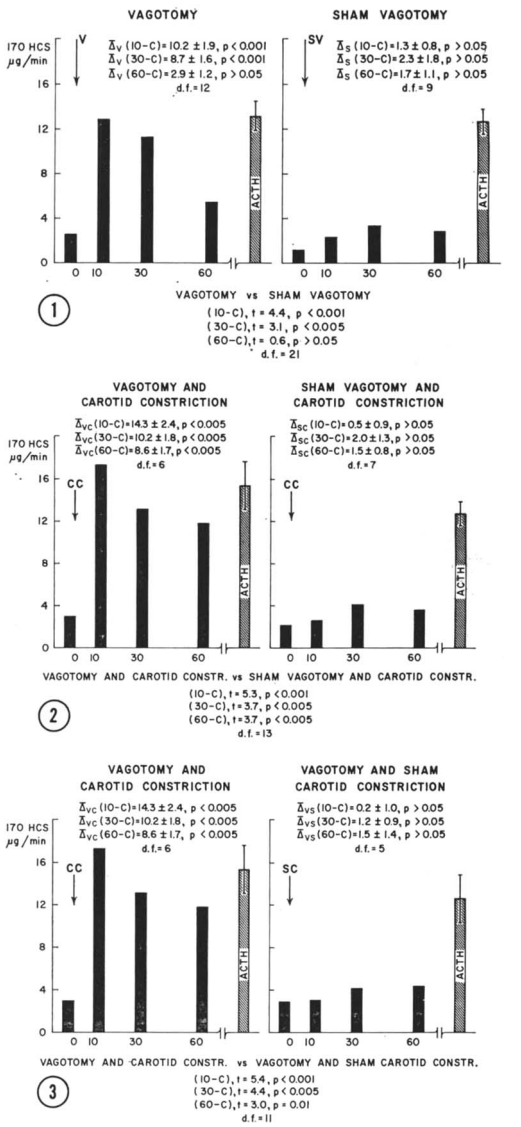

FIG. 1. Effects of vagotomy (V, left), of sham vagotomy (SV, right) and of 5U ACTH (hatched bars) on secretion of 17OHCS. Abscissa, time in min. Δ = mean difference (paired values, time after stimulus-C=control) $\pm$ standard error. d. f. = degrees of freedom; t = student's t; V = vagotomized; S = sham-vagotomized. Below the figure Δ_V and Δ_S are compared for each time interval.

FIG. 2. Effects of carotid constriction (CC), and of 5U ACTH on secretion of 17OHCS in vagotomized (left) and sham-vagotomized (right) dogs. Data are plotted as in Fig. 1. VC = vagotomized, carotid constriction; SC = sham-vagotomized, carotid constriction.

FIG. 3. Effects of carotid constriction (CC, left), of sham carotid constriction (SC, right) and of 5U ACTH on secretion of 17OHCS in vagotomized dogs. Data are plotted as in Fig. 1. VC = vagotomized, carotid constriction; SC = vagotomized, sham carotid constriction.

vagotomy as a stimulus rests ultimately upon the demonstration that constriction of the carotid arteries, which is without effect in the intact dog, is a potent stimulus to secretion of 17OHCS in the vagotomized dog. The results shown in Fig. 2 indicate that vagotomy is a prerequisite to a response of secretion of 17OHCS to carotid constriction, while those shown in Fig. 3 indicate that the increased secretion is not merely a late effect of vagotomy, but depends upon carotid constriction.

If vagotomy is a specific stimulus to 17OHCS secretion, it might act by changing the level of activity in the reticular system, which is thought to play a major role in control of ACTH release(6,7,8). In this view, vagotomy might lower the threshold for other stimuli, and thus permit carotid constriction to be an effective stimulus to 17OHCS secretion. Alternatively, impulses in the vagi, arising from atrial or aortic arch receptors, may inhibit tonically the release of ACTH. Such receptors, sensitive to stretch, are known to exist(9). The participation of atrial stretch receptors in the control of secretion of 17OHCS is suggested by the results of Anderson, McCally and Farrell(10). Atrial receptors have also been implicated in control of secretion of aldosterone(10,11,12) and of antidiuretic hormone (ADH)(13).

The effect of carotid constriction on secretion of 17OHCS in the vagotomized dog suggests the participation of carotid baroceptors in the control of secretion of 17OHCS. The specific receptors which may be involved have not been identified by the present experiments. The effect of carotid constriction on release of ACTH might be mediated directly by nervous pathways, or might result from reflex hemodynamic changes which activate in turn an unidentified peripheral receptor. The present results suggest the former interpretation, since carotid constriction in the intact animal did not affect secretion of 17OHCS, despite the fact that it led to qualitatively the same reflex hemodynamic changes (*e.g.*, increased peripheral arterial pressure) as did constriction in vagotomized animals. The possibility that carotid constriction is a non-specific stimulus so mild that its effect is unmasked only after vagotomy cannot be excluded. However, the sustained response to carotid constriction in the vagotomized dog makes this seem unlikely.

The relationship between response to carotid constriction and prior vagotomy is not immediately apparent, and is evidently complex. According to our current working hypothesis, central nervous mediation of ACTH release is inhibited tonically by impulses arising from carotid baroceptors and by impulses arising from carotid baroceptors and by those carried by the vagi, arising either from the aortic arch or from the atria. Vagotomy stimulates secretion of 17OHCS by release of inhibition. However, the transient rise in blood pressure following vagotomy increases inhibition of ACTH release through carotid receptors, which buffer the increase in a manner analogous to the buffering of the transient hypertension which follows vagotomy(9). Accordingly, 17OHCS secretion returns to control levels. Carotid constriction also releases inhibition of ACTH release. However, carotid constriction increases reflexly aortic arch(9) and atrial(14) pulse pressures, which in turn increase vagal inhibition of release of ACTH. Thus, there is no effect on secretion of 17OHCS. On the other hand, vagotomy interrupts the reflex arc, so that carotid constriction in the vagotomized animal serves only to release inhibition of release of ACTH and thus to increase secretion of 17OHCS. The preliminary nature of this hypothesis must be emphasized.

The results of these experiments are qualitatively identical to those of Share and Levy (15) in which the responses of levels of ADH to vagotomy and carotid constriction were studied, in that vagotomy increased ADH, and carotid constriction was effective in increasing ADH only in animals vagotomized previously. The remarkable parallel of these results and those of the present experiments suggest that a common receptor system may mediate release of both hormones in response to hemodynamic stimuli.

It has been reported that carotid constriction in intact animals increased secretion of

17OHCS(16), a finding not confirmed by the present experiments. The discrepancy may be explained by the fact that the experiments of Biglieri and Ganong were performed on acutely prepared animals and involved only a small number of animals. Increase in secretion of 17OHCS was observed after carotid constriction in only one of 16 other intact dogs prepared 24 hours before the experiment(4).

Summary. Changes in secretion of 17OHCS were measured in dogs with chokers about both carotid arteries and isolated vagus nerves, one day after operative preparation. Vagotomy stimulated secretion of 17OHCS; sham vagotomy did not. Carotid constriction stimulated secretion of 17OHCS in vagotomized, but not in intact, animals. These findings suggest that the adrenal cortical response to hypotension may be mediated in part by vagal pathways and by carotid baroceptors.

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Differences in Interferon Content in Tissues of Mice of Various Ages Infected with Coxsackie B1 Virus.* (29086)

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The work to be reported here was undertaken in an attempt to explain why the infant mouse almost universally succumbs to infection with Coxsackie viruses, whereas the older animal responds with the production of antibody but displays no symptoms of illness. Through the study of this convenient model, information might be obtained that would further our understanding of the factors that influence the pathogenesis of viral infections and their relative importance in the immature and the mature host. The Coxsackie virus model acquires additional interest since newborn infants infected with group B strains may develop a fatal infection characterized by myocarditis and encephalitis that is reminiscent of the disease in mice.

Previous investigators have tended to ascribe the severity of Coxsackie virus infection in the infant mouse to the failure of the immature animal to form antibody. The observations upon which these tentative conclusions were based include the demonstration that younger animals developed antibody at a later time after infection than did older mice(1), and that the virulence of the

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