Interrelation Between Central and Peripheral Mechanisms Regulating Blood Pressure

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Changes in heart rate and blood pressure induced by electrical stimulation of the diencephalon were first demonstrated by Karplus and Kreidl in 1909. About 25 years later, Kabat et al. stimulated 7,700 points in the diencephalon and catalogued those producing elevation or depression of blood pressure. In these studies, the changes in heart rate were reported to be slight. Bronk and his associates established that electrical stimulation of selected diencephalic areas increases the sympathetic discharge to the heart. These authors suggested that the diencephalon "affects" the cardiovascular system by influencing excitability of medullary centers. Implicit in this suggestion is the assumption that the sympathetic discharge directly reflects only the activity of medullary centers.

In experiments with indwelling gauges, Rushmer observed, during exercise by healthy dogs, increases in the heart rate and left ventricular systolic pressure, usually accompanied by slight decrease in mean transverse diameter of the left ventricle (compared with a standing control) with either no change or a slight increase in its stroke diameter. Similar cardiovascular adjustments in "anticipation" of exercise were recorded as the animals became experienced in the experiment. More recently, complex responses closely simulating these adjustments to exercise have been produced by stimulation of a discrete diencephalic area in the region of the zona incerta near the H2 fields of Forel. The fact that effects of diencephalic stimulation mimic many of the effects of exercise on the cardiovascular system, together with the observation that anticipatory cardiovascular adjustments occur, suggested that central neural mechanisms may initiate coordinated cardiovascular adjustments and dominate the peripheral and medullary reflex systems. A study was therefore undertaken to evaluate the interrelation between these diencephalic areas and the carotid sinus-medullary system in regulation of blood pressure.

Methods

In eight dogs under light chloralose anesthesia, the aortic and left ventricular pressures were recorded without opening the thorax by means of catheters introduced through the femoral artery. The heart rate was recorded with a tachometer, triggered by the pressure pulse. Respiratory activity was monitored by means of a pressure transducer connected to one arm of a T-tube tracheal cannula.

In six dogs, the carotid sinus was partially isolated by clamping the common carotid artery and ligating all the major arterial branches except the internal carotid artery. This technique allowed oxygenated blood to circulate through the capillaries of the carotid body and arterial walls at the bifurcation of the common carotid artery; it was designed to avoid undesirable activation of chemoreceptors. Two polyethylene catheters were placed in the common carotid artery. A small catheter was passed to the vicinity of the carotid sinus to monitor the magnitude of carotid pressure, which was rendered nearly nonpulsatile by partial isolation of the carotid sinus. Fluctuations in carotid-sinus pressure were induced through a larger catheter. A small volume (5 to 15 ml.) of the dog's arterial blood was allowed to pass slowly through this catheter into a syringe. Small increments (1 ml.) of this blood were then manu-
Changes recorded in dog during electrical stimulations as the electrode tip approached, in 1-mm. steps, the diencephalic area producing the maximum elevation of systemic arterial pressure. Cardiovascular adjustments are similar in direction to responses to exercise, although maximum pressure and heart rate are greater. In (C), note that blocking of myoneural junctions in respiratory and limb muscle did not affect cardiovascular responses. (Sharp peaks on record of heart rate are technical artifacts.)

To stimulate discrete points in the diencephalon, a nichrome coaxial electrode was directed dorsoventrally into the subthalamus by means of a stereotaxic instrument. As the electrode was advanced in 1-mm. steps, its position was identified in millimeters dorsal to the ear bars. The final location of the electrode was verified histologically.

The stimuli* were negative current pulses having a rise time of 18 \( \mu \)sec. and a duration of 100 \( \mu \)sec., at a frequency of 50 c.p.s., 1.5 ma., and 5 to 10 volts, according to the impedance of the tissues. When the electrode tip was in the location which produced the greatest increase in blood pressure, changing the stimulation frequency between 150 and 12.5 c.p.s. and the current between 2.5 and 0.5 ma. altered the amplitude of the changes in blood pressure and heart rate, but did not cause a reversal in sign (i.e., did not cause a reduction in pressure or heart rate).

In 15 cats, the thorax was opened to gain access to the splanchnic nerves, and activity in them was recorded as a measure of peripheral sympathetic responses to diencephalic stimulation. Aortic pressure was also recorded. Epinephrine was administered intravenously in one of two doses (1.6 \( \mu \)g./Kg. or 20 \( \mu \)g./Kg.), and its effects on splanchnic discharge and arterial pressure were observed before and during stimulation.

Results

The distinctive and reproducible cardiovascular and respiratory adjustments that resulted from diencephalic stimulation as the electrode tip approached the area most responsive in terms of production of elevated sys-
Interplay of diencephalic and baroreflex influences on systemic arterial pressure in dog. Artificial carotid pulses produced by alternately removing and reinjecting small amounts of blood through catheter in sinus. In (C) and (D), duration of stimulation is indicated by horizontal line on record of carotid pressure. In (D), induced carotid pulsations were begun at the peak of the pressor response.

Artificial respiration was begun and the diencephalic stimulus was repeated. Figure 1 (C) shows the resulting cardiovascular adjustments, which were the same as those with the previous stimulus.

During the control period of the experiments on interaction of the carotid-sinus reflex and diencephalic stimuli, mean pressure in the partially isolated segment of the carotid sinus was 20 to 40 mm. Hg lower than pressure in the aorta (fig. 2 A), and the carotid pulse pressure was very small. When pulsations with a pressure difference of about 60 mm. Hg and a rise time approximating that of the systemic arterial pulse were induced in the carotid sinus, bradycardia and decrease in the systemic arterial pressure occurred (fig. 2 B). The heart rate was exquisitely sensitive to very small pulsation pressures, on the order of 5 mm. Hg. Bradycardia occurred within one or two cardiac cycles after the first induced pulsation. Decrease in systemic arterial pressure lagged by 6 to 10 cycles. Carotid pressure pulsations...
induced during the maximum elevation of systemic arterial pressure resulting from diencephalic stimulation also caused bradycardia. It appeared within one or two cardiac cycles, as before, and was again followed by a decrease in arterial pressure (fig. 2 D). In other experiments, carotid pressure pulsations were induced prior to stimulation of the diencephalon. The pressor, cardioaccelerator response to the diencephalic stimuli was delayed for 20 to 30 seconds, then gradually became dominant.

Stimulation of a discrete volume of the diencephalon in the region just medial to the zona incerta and the fields of Forel caused reproducible cardiovascular adjustments of the type illustrated in figure 3. There were increases in heart rate, in systemic arterial diastolic, systolic, and pulse pressure, and in left ventricular systolic pressure. The change in heart rate began and reached its maximum earlier than the changes in systemic arterial pressure. The heart rate usually accelerated within one second after the beginning of stimulation and reached a maximum of about 200 per cent of control levels within 5 to 10 seconds. After cessation of stimulation, heart rate abruptly returned to control values. Systemic arterial pressure began to rise 2 to 3 seconds after onset of stimulation and usually reached a maximum in 8 to 12 seconds. Systolic pressure rose about 100 mm Hg. In a small proportion of the experiments, systolic arterial pressure was elevated in two stages, so that the maximum was reached only after considerable delay (see fig. 4 B). With cessation of the diencephalic stimulus, blood pressure returned to control values in less than

Figure 3
Effects of repetitive stimulation of diencephalon at a rate of less than one train of stimuli per second. Note that each train of stimuli produced an increase in aortic and ventricular pressure. (Sharp peaks on record of heart rate are artifacts.) Caudate nucleus (CAUD); fornix (F); anterior thalamic nucleus (ANT); medial thalamic nucleus (MED); fields of Forel (H, and H2); zona incerta (Z. I.); mammillary bodies (MAM).
A. CONTROL  B. Diencephalic STIMULATION  C. EPINEPHRINE (1.66 µg/kg.)  D. Diencephalic STIMULATION

**Figure 4**

Effects of diencephalic stimulation before and after intravenous injection of epinephrine in cat.

one minute. Stimulations repeated at intervals of less than one minute caused a succession of blood-pressure elevations with peaks which differed only slightly in magnitude.

Electrical stimuli to the diencephalon produced immediate massive discharge along the splanchnic nerve (fig. 4). With cessation of the stimulus, splanchnic-nerve activity was abruptly reduced below the control level. In contrast, intravenous injection of a small amount of epinephrine (1.6 µg/Kg.) caused little change in splanchnic-nerve activity and produced bradycardia concomitant with the peak elevation of systemic arterial pressure. Diencephalic stimulation 10 minutes after administration of this amount of epinephrine, when the systemic arterial pressure had returned to its control level, produced the same kind of massive discharge over the splanchnic nerve, but cardiovascular response was greatly reduced. With larger doses (20 µg/Kg.) of epinephrine, the pressure elevation was followed by prolonged hypotension and reduced pulse pressure lasting about an hour. Stimulation of the diencephalon produced no cardiovascular response if delivered within a half hour after this dosage of epinephrine, and the response was still reduced at one hour in spite of massive splanchnic-nerve discharge.

**Discussion**

As Hess pointed out (see also Rothlin and Berde), electrical stimulation of an individual point in the diencephalon may elicit a coordinated response, such as elevation of arterial pressure and heart rate together with increase in respiratory activity. The question that remains to be answered, especially with respect to the cardiovascular system, concerns the relation between the complex adjustments induced from the diencephalon and the well-known peripheral mechanisms which affect some facet of cardiovascular function. In the example of a diencephalically initiated response complex studied here, the simple hypothesis that concurrent movements aroused peripheral mechanisms which adjusted cardiovascular function will not suffice, since
paralysis with decamethonium bromide did not affect the cardiovascular component of the complex.

The experiments designed to test the interplay between effects of diencephalic stimulation and pressure pulsation of a physiological size within the carotid sinus do demonstrate, however, that the carotid baroreceptor reflex is quite capable of breaking through a strong central sympathetic drive. There appeared to be no marked difference in the ease with which the baroreceptor reflex caused bradycardia and reduction of blood pressure in control and stimulation experiments in the same animal (see fig. 2). Thus, the sinus reflex may not be inhibited by diencephalic stimulation. In fact, these findings suggest that the diencephalic and carotid-sinus influences upon blood pressure are independent and may be algebraically summed.

The concept that circulating catecholamines play an important role in normal pressor responses is not supported by either the fact that diencephalic stimulation may cause coordinated cardiovascular adjustment beginning within three seconds, or the fact that repetitive stimulations at intervals of less than one minute produced large elevations of arterial and ventricular pressure with only a slight decrement in the maximum pressure attained (see fig. 3). The slight decrement in succeeding pressor responses and the large decrement in heart-rate responses remain unexplained.

Summary

Electrical stimulation of selected discrete sites in the diencephalon induced a profound and coordinated response consisting of increased respiratory activity, limb movements, and cardiovascular adjustments. The effects on the cardiovascular system were similar to those of exercise, although the increases in aortic pressure, left ventricular pressure, and heart rate were greater. Massive splanchnic-nerve discharge occurred immediately when the diencephalon was stimulated, but splanchnic activity abruptly fell below control levels with cessation of the stimulus. The increase in respiratory activity and the organized running movements seen during stimulation apparently did not contribute to the pressor and cardioaccelerator responses.

There appeared to be no marked difference between control and diencephalic-stimulation experiments in the ease with which induced pressure pulsations in the partially isolated carotid sinus caused bradycardia and blood-pressure depression. It may be that the influences of the diencephalon and carotid-sinus reflex upon blood pressures are independent and sum algebraically.

Experiments in which effects of epinephrine on splanchnic-nerve activity and systemic arterial pressure were measured before and during diencephalic stimulation did not support the concept that catecholamines have an important role in normal pressor responses.

References


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