Hypothalamic Unit Response to Increases in Arterial Blood Pressure.* (30560)

D. T. FRAZIER,† CARLOS TAQUINI,‡ L. L. BOYARSKY AND M. F. WILSON§
(Introduced by Loren Carlson)
Department of Physiology and Biophysics, University of Kentucky College of Medicine, Lexington

Karplus and Kreidl(5) first demonstrated that electrical stimulation of the hypothalamus produced changes in blood pressure and heart rate. Since then, investigations were carried out in order to elucidate the participation of this area in the control of the cardiovascular system. Kabat, Magoun and Ranson(4) extensively catalogued the hypothalamic points which on stimulation caused either an elevation or depression of the blood pressure. From both stimulation and ablation experiments, Smith *et al*(7) showed that the hypothalamus has an important influence on the coordinated cardiovascular response to environmental stimuli. It is the purpose of this paper to report experiments designed to examine the cardiovascular influence on the hypothalamus. The changes in unit activity from selected hypothalamic areas were correlated with induced alterations of arterial blood pressure.

Methods. Fourteen cats (2 to 4 kg) were anesthetized with nembutal (25 mg/kg). Tracheotomy was performed in all animals but artificial respiration was not employed. The carotid and femoral arteries were exposed and cannulated with polyethylene tubes. An incision in the right side just below the 12th rib and 2 cm from the midline was performed. Through this exposure the abdominal aorta was liberated and a piece of umbilical tape placed around it. After reflecting the cranial skin, the head of the animal was fixed in a Lab-Tronics, stereotaxic apparatus. The skull was opened and an incision of the dura was made in an appropriate locus.

The experimental procedure consisted of 2 parts. In the first, a bipolar stimulating electrode insulated to each tip was introduced into the posterior hypothalamus. The position of the electrode was determined from stereotaxic coordinates. A square wave stimulating pulse of 9 volts with a duration of 2 msec was delivered at 60 cps from a Grass S-4 stimulator and isolation unit. This procedure was used to locate areas which on stimulation produced a significant elevation in blood pressure.

In the second part of the experiment a tungsten wire recording electrode was placed in those areas showing maximal blood pressure responses to stimulation. The rationale of this procedure is to ensure a greater likelihood of obtaining hypothalamic neurons sensitive to blood pressure changes. It is not implicit in the method, however, that the neurons responsive to stimulation are necessarily identical with those from which unit recordings are obtained. The recording electrode was connected to a cathode follower from which the signal passed through a Grass P5 preamplifier to be displayed on a Tektronix 502 dual beam oscilloscope. Unit responses were recorded throughout the entire experiment on a Magnecord 2-channel tape recorder (band width 30-18,000 cps). The tape was then replayed into the oscilloscope and segments of the record were photographed with a Grass kymograph camera. These segments included intervals of 15 to 20 seconds during the control period, during the period that the pressure was elevated and after the pressure returned to control levels. Each period was divided into 3 intervals of 3 seconds duration and the frequency (no./sec) was determined from the number of

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† Present address: Dept. of Physiology, Univ. of New Mexico School of Med., Albuquerque.

‡ Fellow from Consejo Nacional de Investigaciones Cientificas y Technicas, Republica Argentina. Present address: Centro de Investigaciones Cardiologicas, Buenos Aires, Arg.

§ Present address: Dept. of Physiology, West Virginia Univ., Morgantown.

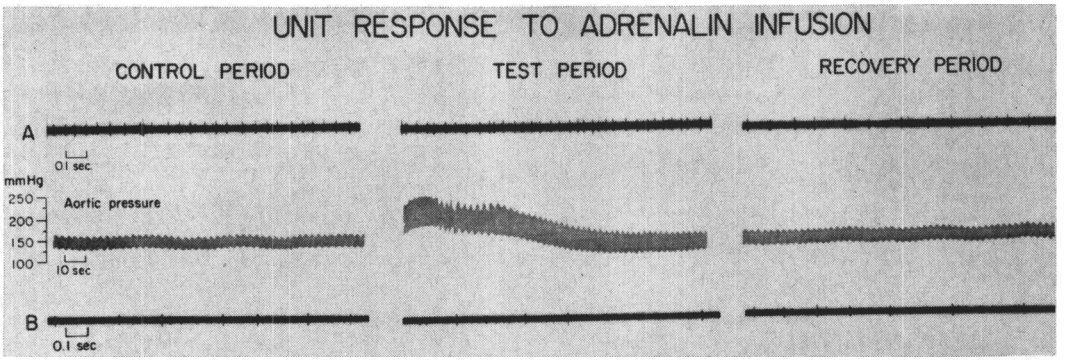

FIG. 1. Response of 2 hypothalamic units to an increase in blood pressure following infusion of 2 μg/kg of adrenalin. A) A unit showing increased rate of discharge during test period. B) A unit showing decreased rate of discharge during test period. Middle tracing shows level of arterial blood pressure during each period.

spikes within each interval. The mean frequency during a period of 9 seconds was also determined from these data. The percentage change from control of this mean for each test period was calculated and, with these values, the bar graphs were constructed (Fig. 2, 4, 6).

Arterial pressure was monitored with a Gilson direct-writing recorder by means of a Statham P23AA transducer connected to the catheter previously placed in the carotid artery. In order to correlate pressure changes with unit activity, the timing of the different experimental maneuvers was marked on the tape (voice channel) as well as on the pressure trace. Adrenalin (2 μg/kg) was injected into the abdominal aorta *via* a catheter inserted into the femoral artery and pushed proximally. The period of injection varied from 40 seconds to one minute.

At the end of the experiment, the stimulating electrode was reinserted and a 6 ma direct current was applied. The brain was fixed with a solution of one per cent potassium ferrocyanide in 10% formalin and the positions of the tip and tracks were identified. In one animal, the reflex effects of both carotid and aortic baroreceptors were eliminated by injecting 10% formalin into the adventitia of the bifurcation of the carotid artery and by severing both vagi. As an extra precaution, the common carotid below the bifurcation and both internal and external carotid arteries were clamped.

Results. In all 14 animals, stimulation of areas in the posterior hypothalamus elicited an increase in arterial blood pressure that ranged from 60 to 150 mmHg. The coordinates used in the study ranged from vertical 6.5 to 8.5, anterior 8 to 9 and lateral 1 to 15(8). All action potentials consisted of spontaneous extracellular unit activity. Units that were stable during the control period but were lost with the infusion of adrenalin or on occlusion were not included among the data. Thirty-four units were found that maintained activity throughout one complete experiment, *i.e.*, during the control period, during the test period when the blood pressure was elevated with adrenalin or occlusion of the aorta, and during the recovery period. The elevation of the mean blood pressure with occlusion or administration of adrenalin ranged between 25 to 50% of the control value. No attempt was made to correlate frequency of unit firing with the magnitude of the blood pressure change. Control records of units taken for the same time period as the experimental showed less than 5% variability in frequency of firing. For the purpose of these experiments, changes in frequency greater than 10% were considered significant.

Response to adrenalin: The injection of 2 μg/kg of adrenalin intra-arterially either increased or decreased the frequency of firing of individual units. An example of both types of responses is shown in Fig. 1 in which both units were recorded from the same animal. In the upper tracing, there

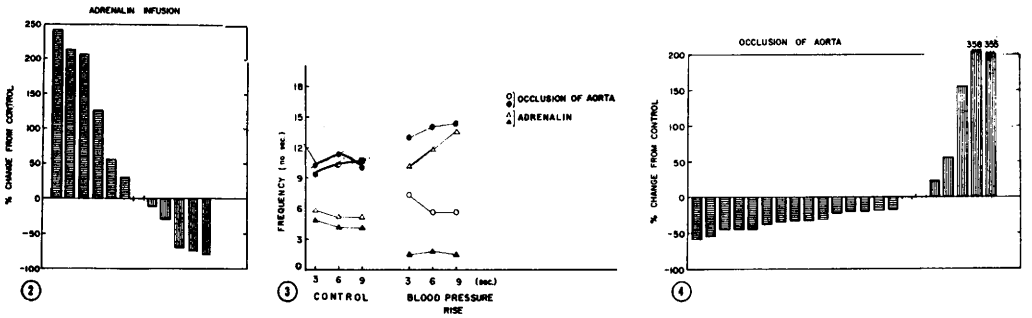

FIG. 2. Percentage change in frequency from control after the intra-arterial infusion of 2 μg/kg of adrenalin. Each bar represents response of one unit.

FIG. 3. Effects of increasing blood pressure, by injection of adrenalin or occlusion of abdominal aorta, on frequency of firing of hypothalamic cells. Each point represents the mean frequency in number of spikes per second, for intervals of 3 sec, during control and test periods. Symbols represent 4 different experiments.

FIG. 4. Percentage change from control in frequency of hypothalamic unit activity following elevation of blood pressure by occlusion of abdominal aorta. Each bar represents response of one unit.

is an increase in frequency during the period that the pressure is elevated, while in the lower one a decrease in frequency is shown during the same period. The blood pressure response was essentially identical in both magnitude and time course during both procedures; therefore, only one trace is presented.

The maximum increase in frequency obtained for any unit with this treatment was 244% and the maximum decrease was 78% (Fig. 2). The mean percentage change for the increase was 146% and for the decrease 51%. No relation existed between the magnitude of the control frequency and the direction of the response. Fig. 3 shows 2 units with almost the same control frequency that responded in opposite directions after the infusion of adrenalin. Frequently at this moment there was a generalized increase of the activity of the area, as indicated by the appearance of multiple units in the record.

Fig. 2 summarizes the responses to adrenalin. Of 12 units, 6 showed an increase in the frequency of firing, 5 a decrease and, in one, no change occurred. After the pressure returned to control levels, most of the units whose frequency had been altered during the period that the blood pressure was elevated, approached control levels. In 4 of the units, however, the level of activity obtained during the experimental period was maintained throughout the recovery phase.

Response to occlusion: The abdominal aorta was occluded in order to increase the blood pressure in the brain without introducing a pharmacological substance into the circulation. Twenty-two units were studied in their response to this treatment. In 2 units no change in frequency occurred during the occlusion, in 15 units there was a significant decrease and in 5 a significant increase (Fig. 4). The maximal increase for this series of experiments was 358% and the maximal decrease was 58%. Fig. 5 shows the results for two units that responded in opposite directions during the period of occlusion.

The mean percentage change in all the occlusion experiments was 160 for the increase in frequency and 31 for the decrease. For this series also, there was no relation between the control frequency and the direction of the response, as shown in Fig. 3. When the occlusion was released and the pressure returned to control levels, there was an increase in frequency in 19 of the units while in one a decrease was found, and in 2 others no change occurred with respect to the frequency during the occlusion period (Fig. 6). The magnitude of the increase in rate of firing after the release of the occlusion was not related to the magnitude or direction of change found during the occlusion period.

The effects of the baroreceptors were eliminated in one animal, to evaluate the possibility of this reflex influence on the unit

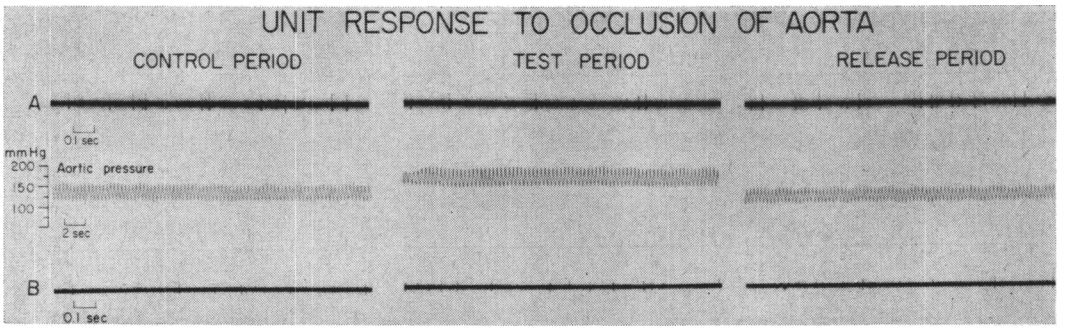

FIG. 5. Response of 2 units to an increase in blood pressure following occlusion of abdominal aorta. A) A unit showing a decrease in frequency of firing. B) A unit showing an increase in frequency of firing. Middle tracing shows level of arterial blood pressure for the 3 periods.

responses. In this animal, 4 units were studied in their responses to occlusion of the abdominal aorta. In 2 units, an increase in frequency of 89 and 14% took place, in one a decrease of 56% and in the other no change occurred.

Discussion. The above results demonstrate that changes in arterial blood pressure, caused by occlusion of the abdominal aorta or by infusion of adrenalin, elicited changes in the frequency of neuronal activity over a fairly wide area of the posterior hypothalamus. In the experiments in which adrenalin was injected, the possibility that other factors than blood pressure could be involved in evoking unit responses was not ruled out.

Baust *et al*(1), recording from the posterior hypothalamus, found that infusion of adrenalin increased the frequency of firing in 90% of the units studied. This was attributed to the increase in blood pressure. However, in our study elevation of blood pressure by occlusion of the abdominal aorta resulted in a decreased firing rate in 75% of the units responding. The difference in results may possibly be accounted for by the fact that they recorded from a small area which may represent a single population of cells. Supporting this possibility is the finding that when they recorded over a wide area of the mesencephalic reticular formation they obtained changes in pressure-sensitive cells in agreement with those reported here, namely, a decrease in the firing rate of most cells following the elevation of blood pressure by occlusion(2). Adrenalin, however, had the same effect as occlusion, a result differing from our findings in the hypothalamus.

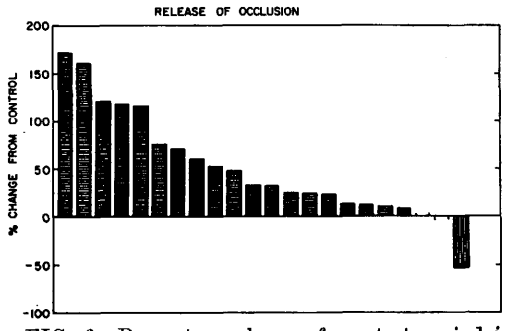

FIG. 6. Percentage change from test period in frequency of firing of hypothalamic cells after release of occlusion of the abdominal aorta. Each bar represents response of one unit.

Wilson (unpublished results), in mapping the responses of various cardiovascular parameters to stimulation of discrete points throughout the hypothalamus, obtained an increase or decrease in blood pressure from closely approximated stimulation points one millimeter apart. Such results, as well as those reported here, can be interpreted as resulting from two different populations of cells. That is to say, one population whose response is a decrease in frequency to an induced blood pressure rise and an elevation of blood pressure to electrical stimulation. The second population would have an opposite response to both treatments. In the posterior hypothalamic areas selected for our investigations, 75% of the cells which responded to an elevation of blood pressure, had a decrease in frequency of their unit activity. According to the above hypothesis, it would be this population of cells that elicits the increase in blood pressure when elec-

trically stimulated. Salmoiraghi(6), recording from the pons and medulla, found units that responded in opposite directions to the blood pressure changes induced by noradrenalin and histamine. He named these different units "population one neurons" and "population two neurons." These seemed to be influenced by the carotid and aortic baroreceptors pathways.

The origin of the pressure sensitive cells which caused the hypothalamic unit responses to blood pressure changes is obscure. The experiment in which the baroreceptor reflex pathways were eliminated suggests that baroreceptors are not necessary to obtain the changes in the unit response, since the 4 units studied showed the same type of response as units in the intact animal. This was also pointed out by Baust(1) who, in addition, showed that after isolation of the posterior hypothalamus by different sections, the response was not altered(3).

The evidence suggests that the cells of the posterior hypothalamus are influenced in their frequency of firing by alterations in arterial blood pressure. Whether there is a direct chemical effect upon the cells in the response to infusion of adrenalin is not clear. Nevertheless, the fact that with occlusion of the abdominal aorta frequency changes occurred is evidence that the units can respond to alterations in blood pressure. This response of the hypothalamic units appears to be independent of the baroreceptor activity. The mechanism(s) by which these cells respond to arterial blood pressure elevations, and the pathways through which this frequency change may act upon the regulation of the blood pressure remains to be established.

Summary. The responses of hypothalamic unit activity to changes in arterial blood pressure were studied in 14 cats under nembutal anesthesia. Areas of the posterior hypothalamus were stimulated in order to determine the points from which maximal increases in blood pressure could be obtained. A tungsten recording electrode was placed at these points and a single unit activity recorded. Arterial blood pressure was increased by infusion of 2 μg/kg of adrenalin intra-arterially and by occlusion of the abdominal aorta. With infusion of adrenalin, there was an increase in the frequency of firing in 55% of the cells, whereas with occlusion of the aorta there was a decrease in 75%. A direct effect of adrenalin was not ruled out. These results were interpreted as resulting from two different populations of pressure-sensitive cells in the posterior hypothalamus.

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