Effect of Stimulation of Hypothalamus and Reticular Activating System on Production of Cardiac Arrhythmia

By Houshang J. Attar, M.D., Mario T. Gutierrez, M.D., Samuel Bellet, M.D., and J. R. Ravens, M.D.

The role of the central nervous system in maintaining and modifying cardiac rhythmicity has been extensively studied\textsuperscript{1-5} by many investigators. Emphasis has been laid on the diencephalic region as a pathway for important neurovegetative fibers. Pitts et al.\textsuperscript{6} showed that from both sides of the hypothalamus, multiple pathways descend, over which impulses converge on a single preganglionic sympathetic neuron. Van Boogaert\textsuperscript{7} postulated that the diencephalic region serves as a passage of important neurovegetative fibers which connect with the medulla. Previous studies on the medulla oblongata\textsuperscript{7,8} have shown that centers that increase the blood pressure in these regions comprise an extensive zone within the lateral reticular formation, while the depressor center is located in the medial reticular formation. Likewise, stimulation of the reticular formation of the mesencephalon produces both depressor and pressor responses. The experiments of other workers\textsuperscript{9-12} showed the importance of the reticular formation and corticospinal tracts for the transmission of the sympathetic impulses from the hypothalamus. Weinberg and Foster\textsuperscript{13,14} postulated that the posteromedial hypothalamus exerts an effect chiefly upon the sinus node, whereas the lateral hypothalamus and subthalamus exert their influence principally upon the myocardium.

To clarify further the mode of action of the different areas of the hypothalamus and especially their relationships to the reticular activating system of the cerebral peduncle and pons on cardiac rhythmicity, a series of experiments were performed in cats. An analysis of changes in the blood pressure, heart rate, and electrocardiogram in relation to the site and intensity of stimulation of certain centers in the brain system was undertaken.

Methods

Twenty-three cats weighing between 2.6 and 3.2 Kg. were utilized in these experiments. Anesthesia was induced by injection of chloralose, 70 mg./Kg. intraperitoneally. The cat was then placed in the supine position for isolation of the femoral artery, and the blood pressure was recorded by the use of a Statham transducer, model P-23 Db. In addition, the electrocardiogram (lead II), 25 mm./sec, was simultaneously recorded on the Sanborn Twin-Viso. Two stainless steel electrodes (gauge 20) were coated with black Krylon quick drying enamel; the tips were then stripped of enamel about 2 mm. from the tip. The remainder of the electrodes (10 cm.) was checked for efficacy of insulation prior to each experiment by the use of an ohmmeter. The electrodes were then placed in the stereotaxic apparatus and calibrated on the horizontal, vertical, and frontal planes following the atlas of the diencephalon of the cat by Jasper and Maran.\textsuperscript{14} The zero line used for the horizontal plane was situated 1 cm. above the interaural line.

The stimulus employed consisted of a monophasic square wave current from a Grass Stimulator, 5 to 12 volts, with a 5-msec. pulse duration, at a frequency of 80 to 100 cycles/sec. The stimulation of each area was maintained for 30 to 120 seconds; each stimulus was applied three to five times in each of the areas studied. A period of recovery was permitted before a succeeding stimulus was applied. During stimulation, no struggling was noted in the cat, but occasionally the pupils were dilated on the side stimulated. At the end of the experiment, a D.C. current was applied to the electrodes in order to mark the
A. Effect of anterior hypothalamic stimulation. Note the increase in blood pressure from 90/60 to 200/150 mm. Hg and electrocardiographic changes (increase of T-wave inversion while normal rhythm is maintained). The electrocardiogram returns to the pre-stimulation pattern after two minutes. B. Coronal section of the brain of a cat through the anterior commissure showing a lesion in the left anterior hypothalamus. C. Coronal section of the brain of a cat through the anterior commissure to illustrate a lesion in the anterior hypothalamus of the left hemisphere. (Myelin sheath stain, Weil's method)
The brain was then fixed with 10 per cent formalin injected through the carotids while it was still in the skull, and after an hour, it was removed and placed in 4 per cent formalin for hardening and later morphological study.

Samples of the brains of 15 cats were investigated following transverse coronal section from the frontal to the occipital pole and horizontal sections through the brain stem and cerebellum. The areas of the lesions were selected for frozen section, and these areas (sections) were imbedded in paraffin and celloidin. The staining methods used to localize the lesions consisted of: (1) for myelin sheath (Weil's method); (2) for nerve cells and fibers, Lugol-fast blue stain (Kluver-Barrera's method); (3) for nerve cells, blood vessels, and neuroglial components, cresyl-violet stain.

Results

Depending upon the localization of the stimulus (of equal intensities ranging between 5 and 12 volts, 5 msec., 80 to 100 cycles per second), the following results were obtained:

Group 1 (11 cats): Unilateral stimulation of the hypothalamus, anterior, lateral, and posterolateral regions (left or right side) revealed the following:

1. Stimulation of the anterior hypothalamus (four cats) on the right side or left side produced an average rise in blood pressure from 100/75 to 200/150 mm. Hg, which was sustained for an average of 45 seconds during the period of stimulation and returned to the prestimulation level two minutes after cessation of the stimulus. The heart rate decreased from a control average rate of 160 to 120 beats per minute. The electrocardiographic changes consisted of slight ST segment elevations and marked deepening of the T-wave inversions while sinus rhythm was main-

A. Effect of lateral hypothalamic stimulation. Note the arrhythmia observed immediately after stimu-
HYPOTHALAMUS AND CARDIAC ARRHYTHMIA

All of these changes returned to pre-stimulation pattern after a period of about two minutes (fig. 1A). The morphological examination of two brains in this group showed punctures on the vertex of the left hemisphere, at the junction of the anterior and middle third of the lateral gyrus. On coronal section, the lesion was found in the left anterior hypothalamus. The puncture goes through the anterior portion of the fornix (fig. 1B). The anatomical characteristic of the lesion at this level is shown in the photomicrograph (fig. 1C).

2. Stimulation of the lateral hypothalamus (three cats) on the right and left sides resulted in a rise of blood pressure from an average of 125/95 to 170/110 mm. Hg. This increase was maintained for almost 50 seconds after cessation of stimulation. The electrocardiographic changes consisted of transitory periods of auriculoventricular (A-V) dissociation with frequent premature ventricular systoles in spite of a relatively slight rise in blood pressure (fig. 2A). Coronal section through the posterior portion of the optic chiasma (fig. 2B) showed the puncture clearly demarcated and the lesion situated at the level of the lateral hypothalamus (two brains). The microscopic section shown in figure 2C confirms the site of the stimulated area.

3. Stimulation of the posterolateral hypothalamus (four cats) showed a rise in blood pressures from an average of 110/75 to 200/140 mm. Hg during the period of stimulation; this rise was maintained for an average period of 60 seconds after the stimulus was removed. The arrhythmias in this group consisted of the appearance of A-V nodal rhythms with aberrant ventricular conduction, frequent premature ventricular beats from different foci, and, in a few instances, fusion beats (fig. 3A). Two brains in this group illustrate, on coronal section through the middle portion of the thalamus and the anterior portion of the pineal gland, the lesion located in the posterior hypothalamus (fig. 3B, x).

Group II (12 cats): Stimuli applied on the reticular activating system (mesencephalic region) produced the following results:

1. The blood pressure rose from an average of 100/70 to 200/120 mm. Hg, remained elevated for almost 90 seconds after the period of stimulation, and gradually returned to the prestimulation levels in about three minutes.

2. The electrocardiogram taken immediately after the stimulation showed an average increase in the heart rate from a control of 150 to 170 beats.

The most conspicuous finding was a shift of the pacemaker from the sinus to the A-V node with the control of the ventricular rhythm by a lower, subsidiary pacemaker. Transitory A-V dissociation with multiple auricular premature beats and A-V nodal escapes were a common finding. Ectopic beats of ventricular origin from different foci, interrupted by A-V nodal rhythm, and fusion beats were also present. In some portions of the tracing, widening of the QRS complexes due to aberrant ventricular conduction was observed. Deep and symmetrically inverted T waves were also noted. These disturbances in rhythm and abnormalities in the QRS-T complex returned to the normal control pattern within about two to three minutes after cessation of stimulation (fig. 4A). Morphological study (two brains) revealed a puncture in the vertex of the right hemisphere at the level of the posterior third of the right lateral gyrus. These punctures were close to the lateral sulci, as illustrated in figure 4B. The terminal point of the puncture was located in the reticular formation between the nucleus ruber and substantia nigra. In the first of the two brains of this group, the terminal point of the puncture was located in the right inferior colliculus and reticular formation of the pons (fig. 4C, x, x').

Discussion

These findings demonstrate that stimulation of the anterior hypothalamus produced a bradycardia rather than a tachycardia, most likely because the parasympathetic tone is most predominant in this region. A rise in blood pressure in this group was never accompanied by arrhythmias although the slight
ST segment deviation and deepening of the inverted T waves were often observed.

Following posterior hypothalamic stimulation, the various types of arrhythmias were obtained in spite of a smaller rise in blood pressure as compared to that of anterior hypothalamic stimulation. Similarly, Weinberg and Foster observed that stimulation of the lateral and posterior hypothalamus produced T-wave changes, bigeminy, trigeminy, A-V

ventricular conduction, premature auricular systoles, and occasional fusion beats and return to prestimulation pattern two minutes after stimulation. B. Coronal section of the brain of a cat through the middle of the thalamus to show a lesion of the lateral posterior hypothalamus in the right hemisphere (x). (Myelin sheath stain, Weil's method)
dissociation, ventricular tachycardia, and even complexes resembling those of the Wolff-Parkinson-White syndrome. These results indicate the diversity of effect of stimulation of different areas of the hypothalamus. It is a well-established fact that the property of rhythmicity of the heart resides in the sinus node; however, this may be influenced by extracardiac factors. A transitory depression of the sinus node due to stimulation of the cardiovascular neurovegetative nerves in the hypothalamus is the important factor in establishing a
ATTAR, GUTIERREZ, BELLET, RAVENS

subsidiary pacemaker and ectopic foci of auricular and ventricular origin. The P wave changes in the electrocardiogram frequently encountered in this group of experiments are evidences of such transitory sinus node depression. The explanation why the anterior hypothalamus causes only myocardial abnormality rather than arrhythmias cannot be elucidated by the above statements.

The similarity of the arrhythmias observed following stimulation of the reticular formation of the cerebral peduncle and pons with those observed following stimulation of the posterolateral hypothalamus suggest the presence of similar functional activity of these two areas. The efferent pathways emanating from the reticular formation to the upper cerebral neurons have been extensively investigated. The afferent pathways of the reticular formations are described as multiple relay systems between the hypothalamus, medulla, and spinal cord; however, their interrelationships have not been well established. Harris describes the reticular formation as multiple neuron relays from the tegmentum of the medulla and midbrain up to the cerebral cortex via the hypothalamus and thalamus.

Previous experience has shown the importance of the reticular formation and the corticospinal tract for the transmission of sympathetic impulses from the hypothalamus. It seems that in regard to arrhythmias observed, the function of the reticular formation is intimately related to the function of the hypothalamus, especially the posterolateral area. Marked disturbances following stimulation of the mesencephalic reticular formation as observed in these experiments and the similarity of responses with those of stimulation of the posterolateral hypothalamus confirm the above hypothesis. The presence of multisynaptic transmissions occurring in the ascending and descending pathways of the reticular formation indicate the integrating role of the latter. Consequently we are inclined to believe that the hypothalamus serves as a pathway for cardiac neurovegetative stimuli, probably via the reticular formation, producing predominantly sinus node depression; (2) the posterolateral hypothalamus and reticular formation have similar functions in the production of cardiac arrhythmia.

Summary and Conclusions

Changes in blood pressure and the electrocardiogram were studied before and after the stimulation of the hypothalamus (anterior, lateral, and posterior) and the reticular formation of the pons in anesthetized cats.

The stimulation of the anterior hypothalamus produced a rise of blood pressure and usually bradycardia; tachycardia was rarely observed. Arrhythmias were not observed, and the electrocardiographic changes consisted only of slight ST elevation and deepening of the T waves. Stimulation of the lateral hypothalamus produced a rise in blood pressure of a lesser magnitude than that of the anterior hypothalamus but was associated with a transitory phase of A-V dissociation and frequent premature systoles. Stimulation of the posterolateral hypothalamus resulted in the same rise in blood pressure as that of stimulation of the lateral hypothalamus and was accompanied by nodal rhythms, aberrant ventricular conduction, and fusion beats. Stimulation of the reticular formation produced a rise in blood pressure similar to stimulation of the lateral and posterolateral hypothalamus and was associated with slight tachycardia, widening of the QRS complexes, transitory A-V dissociation with nodal escapes and ectopic beats of ventricular origin, and fusion beats.

These findings suggest that: (1) the hypothalamus serves as a pathway for cardiac neurovegetative stimuli, probably via the reticular formation, producing predominantly sinus node depression; (2) the posterolateral hypothalamus and reticular formation have similar functions in the production of cardiac arrhythmia.

References

Effect of Stimulation of Hypothalamus and Reticular Activating System on Production of Cardiac Arrhythmia

HOUSHANG J. ATTAR, MARIO T. GUTIERRÉZ, SAMUEL BELLET and J. R. RAVENS

doi: 10.1161/01.RES.12.1.14

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/12/1/14

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/