I am presenting this manuscript on the topic of the brain and its relation to control of the heart rhythm, which was published in the Journal of Integrative Neuroscience, *with the hope that you, as our reader, will react in any way you feel appropriate, via Letters to the Editor. The manuscript was sent to Dr. Michael E. DeBakey last fall with a request that he review it and comment to the author. Dr. DeBakey, in turn, referred it to me. I now, refer it to our general audience for your reaction. Let me know what you think about the concept - good, bad or indifferent. I will then report in a future issue what you have to say. Permission has been received from the author and the* Journal of Integrative Neuroscience *for publication in our journal.*

- William L. Winters, Jr., M.D., Editor-in-Chief, journal of the Methodist DeBakey Heart Center

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INTEGRATION OF THE HEART RHYTHMOGENESIS LEVELS: HEART RHYTHM GENERATOR IN THE BRAIN

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We propose that along with the intracardiac pacemaker, a generator of cardiac rhythm exists in the central nervous system - in the efferent structures of the cardiovascular center of the medullar oblongata. Signals in the medulla oblongata arise as a result of the hierarchic interaction of the brain structures. Neural signals originating there in the form of bursts of impulses conduct to the heart along the vagus nerves and after interaction with cardiac pacemaker structures, cause generation of the cardiac pulse in exact accordance with the frequency of "neural bursts". The intrinsic cardiac rhythm generator (the sinus node) is a life-sustaining factor that maintains the heart pumping function when the central nervous system is in a stage of deep inhibition, (e.g., under anesthesia or during unconsciousness). The brain generator is the factor that provides heart adaptive reactions in behaving organism. The integration of the two levels of rhythmogenesis in the brain and heart provides reliability and functional perfection of the cardiac rhythm generation system in the whole organism.

Keywords: Heart rhythm; duplicated control; cardiorespiratory synchronization; heart rhythm generator in the brain.

INTRODUCTION

The generally accepted ideas about the mechanisms of cardiac rhythm generation consist of the following: the cardiac rhythm arises in the heart itself, in its specialized structures (intracardiac rhythm generator), which have pacemaker properties: the autonomic nervous system exerts a modulating effect on the cardiac rhythm. In particular, the sympathetic nerves accelerate the heart rate, the parasympathetic ones decelerate it. Experiments in which these nerves were cut and subsequently electrically stimulated, provided the basis for these ideas. It has been established that the increase in heart rate produced by sympathetic nerve stimulation is due to accelerated depolarization of the pacemaker cells whereas parasympathetic vagal stimulation causes slowing of pacemaker depolarization.[1,7,16] However, the changes in heart rate so produced, cannot provide the whole spectrum of cardiac adaptive reactions in the whole organism. Recently obtained data allowed us to reevaluate critically the facts and ideas about the mechanisms of heart rhythm generation.

A classical phenomenon observed when stimulating the peripheral end of the cut vagus nerve, resulting in deceleration of the heart rate even up to a cardiac arrest, cannot be an adequate model for understanding the processes of heart rhythm neural regulation. First, an abrupt inhibition of heart activity is not observed in the process of natural regulation. Indeed, all efferent fibers of the vagus nerve are never excited simultaneously in natural conditions, as it happens under artificial suprathreshold electrical stimulation of the nerve. Moreover, the experimental nerve stimulation usually consists of a continuous train of impulses, whereas in natural conditions, impulses are grouped in "bursts", synchronized with the heart beat.[2,8]

The newly obtained data allowed us to formulate principally novel ideas about the mechanisms of cardiac rhythm generation in the whole organism. We have provided evidence that along with the existence of an intracardiac generator of the cardiac rhythm, a separate generator exists in the central nervous system in the efferent structures of the cardiovascular center in medulla oblongata. Originating there, nervous signals in the forms of bursts of impulses travel to the heart along the vagus nerves, thereby entraining the cardiac pacemaker in exact accordance with the frequency of the bursts.[8] The entrainment is accompanied by characteristic electrophysiological changes in the intracardiac pacemaker.

RESULTS

The experimemal findings leading to the formulation of the above stated hypothesis may be divided into 2 groups. The first group consists of data obtained during electrical stimulation of the peripheral end of the cut cervical vagus with repetitive bursts of impulses. The second group is represented by data demonstrating the ability of the heart to follow the rhythm of bursts of impulses formed in the central nervous system.

REPRODUCTION BY THE HEART OF THE RHYTHM OF ELECTRICAL STIMULI APPLIED TO THE VAGUS

During stimulation of the vagus with burscs of impulses applied wich a gradually increasing frequency the heart rate slows. When the frequency of bursts and che heart rate become equal, the vagal and cardiac rhythms synchronize in a 1:1 ratio. Now the heart responds to every burst of vagal impulses by a single comraction, occurring after a certain delay.5•15,19,21 For each set of burst characteristics (e.g., number of impulses in the individual burst), there is a range of burst frequencies within which the hearc rare follows precisely the rhythmicity imposed by the vagus nerve stimulation (Fig. 1).

Adjacent ranges partially overlap, determining the global range of a precisely controlled heart race (132 bpm to 66 bpm in Fig. 1). The above-described phenomenon was studied in different animals species (monkey, cat, rabbit, dog, rat, guinea pig, coypu, pigeon, duck, frog). It has been reproduced in all tested animals and this similarity supports its general biological significance.16.[17] These faces demonstrate the existence of a robust general biological phenomenon by which bursts of impulses applied to the vagus nerve entrain the sinoatrial node and chus, che heart rate to the frequency of the bursts.

Electrophysiological mechanisms underlying the cardiac rhythm control phenomenon have been tested in experiments in animals with a computer mapping of che sinoatrial node region. Bioelectric activity has been simultaneously recorded from 64 points and isochronous maps of origin and spread of excitation in the sinoatrial node region have been analyzed. Ir was established that in control and also during bradycardia caused by traditional (continuous) stimulation of the vagus nerve, the area of early depolarization constituted a single focus. However, when the heart was forced to follow the frequency of the repetitive burst vagal stimulation, the area of early depolarization became wider and included not l bur 2-11 of the mapped points. Thus, an eleccrophysiological marker of the reproduction by the heart of the rhythm of signals coming via the vagus nerves, appeared to be a pronounced widening of che area of early depolarization in the sinoatrial node.12

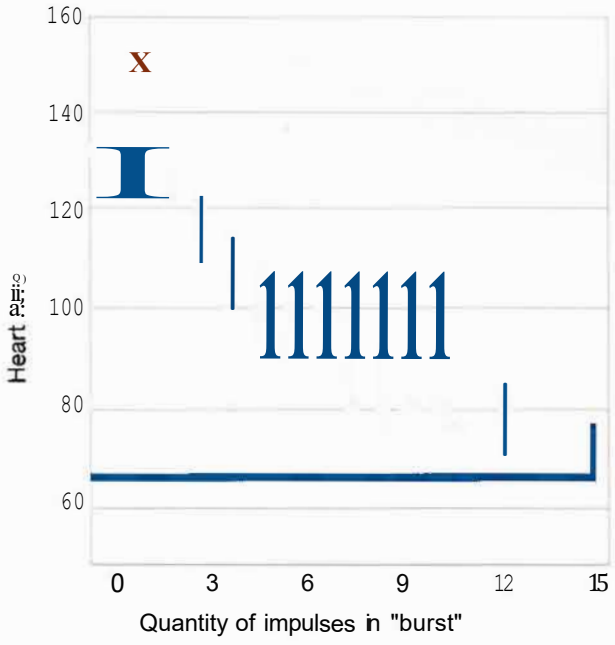

Figure 1. Synchronization of the heart rate and vagus nerve rhythm, stimulated by bursts of impulses. X-d - quantity of impulses in the burst. Y-d - heart rate, and also the bursts' frequency per 1 min, x - heart rate initial level (172.9±5, 8 contractions per 1 min). Vertical lines on the graf - frequencies' range within which acceleration or deceleration of the bursts of impulses' frequency initiates heart rate synchronous changes. Horizontal lines bound the limits of the total range of a precisely controlled heart rate.

REPRODUCTION BY THE HEART OF THE RHYTHM OF SIGNALS GENERATED IN THE CENTRAL NERVOUS SYSTEM

In order to study the above-mentioned phenomenon in the whole organism, we developed methods that allowed us to observe the formation of the cardiac rhythm under the influence of signals generated in the central nervous system and passed to the heart via vagus nerves. For this purpose, the well known functional relationships between the respiratory rhythm generator and che cardiovascular center in the medulla oblongata proved useful.

The uniformity of the cardiac and respiratory rhythmogenesis mechanisms is so considerable that one of the well-known investigators of central mechanisms of respiratory rhythmogen-

esis Koepchen (1983) published a work titled: "Respiracory and cardiovascular "centers": functional entirety or separate structures? "4

It has been shown in our investigations that one and the same medullary neuron in the efferent nucleus of the vagus can have an impulse activity pattern corresponding occasionally to the breathing rhythm or to the cardiac rhyrhm. During inhalation, the neuron's activity is synchronized with diaphragm contraction; during exhalation, it is synchronized with the heart beat.14

The breathing rate in both humans and animals is usually lower than the heart rate. At the same time, respiration, among all other autonomic functions, possesses a unique feature - the ability of voluntary control. In order to achieve the predetermined level of heart rate acceleration, the volunteers were asked co breath in synchrony with phoco-scimulator's light bulb, the frequency of which was sec to exceed the initial heartbeat frequency by 5-10%. After a transitional period of 20-30 cardiac cycles, the cardiac and respiratory rhythms synchronized.11 The range over which the heart beat could be synchronized to the respiracory cycle was 10-20 bpm.

Further analysis of the synchronization mechanisms of cardiac and respiratory rhythms was performed in experiments in dogs. Since animals cannot voluntarily speed up the breathing, we used overheating to induce hurried breathing (tachypnea) in dogs. For chat purpose, animals were placed in a thermo camera at 38C°. After 1-1.5 hours, the breathing frequency reached the heartbeat frequency and soon breaching and heartbeat rhythms synchronized at a rate of about 180 bpm. Later on during the test, the breathing frequency could increase or decrease leading to synchronous changes of the heartbeat frequency. The range over which the cardiac and respiratory frequencies could be synchronized was 50 bpm.

When the vagus nerves (which were previously exposed under the skin on the neck) were cut, the cardiorespiratory coordination was complecely disrupted. A similar effect was observed when the animal was injecred wich atropine, which interrupts the transmission of excitation from che vagal endings to the heart. Thus, synchronization of the heart beat to the respiratory cycle in a I:I relation was che result of signals coming to the heart by vagus nerves.10 The experiments in animals[10] and observations in humans[9,13] have shown chat at high breathing races, the cardiac efferent neurons in the medulla oblongata become entrained to the respiratory rhythm. The signals initially formed as bursts of impulses come to the heart via the vagus nerves and by interacting with the imracardiac pacemaker structures, cause excitation in exact accordance with the frequency of che bursts. From the above discussed model of cardiac and respiratory rhythm synchronization, it can be supposed that under normal conditions cardiac medullary centers have their own periodicity.

The multilevel system of the nervous system structures and mechanisms takes part in CRS (cardiorespiratory synchronism) developmem. The processes raking part in the humans' central nervous system during cardiac and respiratory rhythm synchronization could be schematically presented as follows: optic signal perception (phocostimulacor lamp flashes); processing and estimation of the opcic signal frequency; the formation of the task of the respiratory rate voluntary control; implementation of respiration in the ratio of I:I co the photostimulsacor flashes frequency; cardiac and respiratory centers interaction; synchronization of the rhythms generated by respiracory and cardiac centers; signal transferring in the form of impulse bursts along vagus; signals interaction with intracardiac rhythmogenesis structures; reproduction by the heart of the heartbeat frequency sec by voluntary breaching (cardiorespiracory synchronism developmem).

It has been proposed that bursts of vagus nerve impulses synchronous with the cardiac rhythm are caused by barorecepcor feedback.3 Nonetheless, we have demonstrated burst activity in the vagus center of the medulla oblongata at the frequency of the heart beat after complete baroreceptor deafferencation.20 For this purpose cardiac arrest was induced by intracoronary administration of KCL. The bursting activity of the neurons in the efferent nucleus of the vagus in the medulla oblongata continued for some time with the rhythm of the heart before its arrest.

These results indicate that medullary circuits are inherently capable of generating a rhythm in the range of the heart beat frequency in the absence of sensory feedback from the baroreceptors.

ELECTRO PHYSIOLOGICAL PROCESSES IN THE SINOATRIAL NODE IN HUMANS AND ANIMALS WHEN HEART CONTRACTIONS FOLLOW THE NATURAL SIGNALS COMING VIA VAGUS NERVES

As described above, we have demonstrated cwo observations. Firstly, a pronounced increase of the early depolarization area in the sinoacrial node during entrainment of the heart rhythm by electrically-evoked rhythmic bursts of signals coming to the heart via the vagus nerve. Secondly, the reproduction by the heart of che rhythm of signals arising in che efferent structures of the medulla oblongata which reach che heart via the vagus nerves (cardiorespiratory synchronization revealed in humans and animals). These observations provided the impetus for further investigations.

We have studied in chronic dogs the electrical activity in the sinoatrial node during synchronization of the brain and heart events. Mapping of che sinoarrial node area during the surgical stage of the experiment (under anesthesia) revealed an early depolarizarion area chat was represented by a single focus. After recovery from anesthe-

sia and during pose-operative activities (interacting with personnel, eating, etc), the early depolarization area widened. Importantly, atropinization of the animals or cutting of the vagus nerves reversed chis process so chat rhe region of depolarization was once again restricted to one focal point.

The face that the pronounced reduction in the area o fthe early depolarization of the sinoarrial node was exactly correlated with the ceasing of cardiac-related signals in the vagus nerves was also demonstrated in these animals during cardiorespirar cory synchronization caused by thermo-tachypnea. In these experiments, the early depolarization area in the sinoatrial node was abruptly increased during cardiorespiratory synchronization and this effect was reversed by the cutting of the vagus nerves or atropinization.

The mapping of the sinoatrial node region in the presence of the cenrral driving rhythm in humans fully reproduced the phenomena that were obtained in the chronic experimenrs in dogs. Figure 2 represenrs fragmenrs of the sinoatrial node region mapping which was done in order to reveal reestablishment of the central driving rhythm in a patienc undergoing cardiac surgery.

The sinoatrial node field recordings reached the computer from a probe containing 6 platinum abducent electrodes. The computer fixed the dynamics of the early depolarization area in the node by using a special program. Immediately after the operation, the mapping showed that the region of che early depolarization was limited to a single focus (A on Fig. 2). One day later, the early depolarization region covered an area between 2 electrodes (B on Fig. 2); rwo d_{ays} later 3 electrodes were covered in the morning (Con Fig. 2); 5 electrodes were covered in the afternoon (D on Fig. 2) and 6 electrodes were covered in the evening (E on Fig. 2). This demonstrated the switching-on of the central driving rhythm. The progressive increase in the area of early depolarization correlated with an improvement of a patient's common feeling and reestablishment of his ability to elicit cardiorespiratory synchronization during breaching, in rime with the light pulses emitted by rhe phorostimulator.

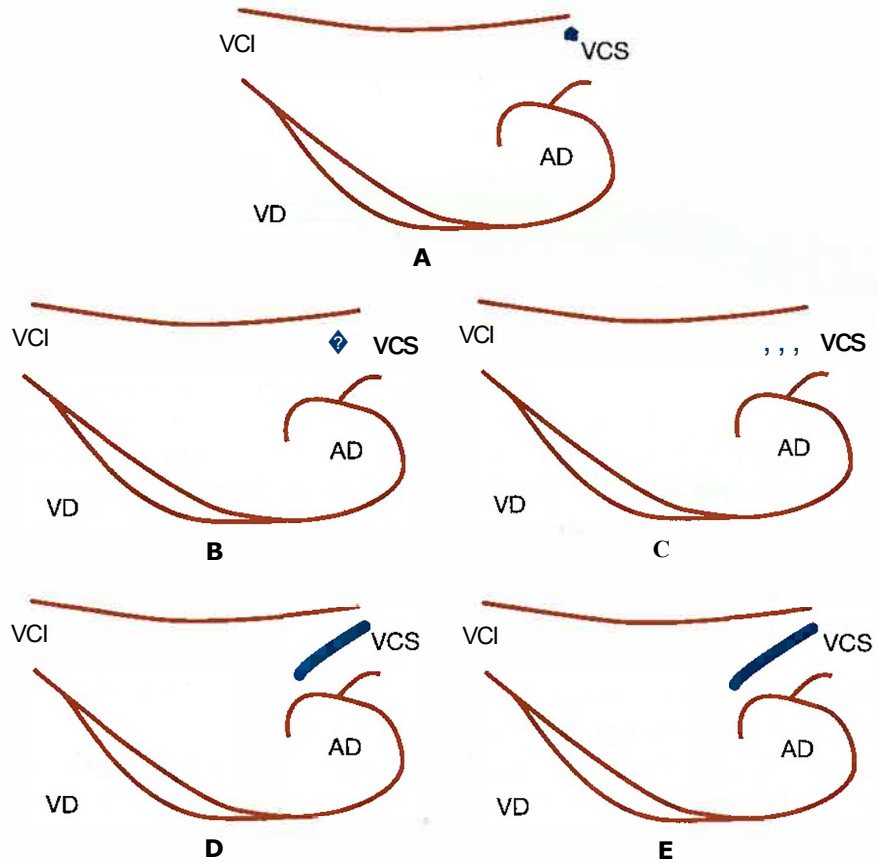

Figure 2. Dynamics of the zone of initiation of the excitement in the sinoatrial node in human (explanations are given in the text). On the scheme: AD, auriculum dexter; VCI, vena cava inferior; VCS, vena cava superior; VD, ventriculllm dexter.

CONCLUSION

In view of the above, rhe facts presented here demonstrate the existence of a rhythm generator in the central nervous system, along with the cardiac rhythm generator in the heart itself. The inrracardiac generator is a life-sustaining factor that assures the pump function of the heart when the central nervous system is in a stage of deep inhibition. The central generator forms the heart's adaptive reactions under normal conditions. The heart's $abili_{ty}$ to reproduce the central rhythm is based on the specificity of electrophysiological processes in the inrracardiac pacemaker. The integration of the two levels of rhythmogenesis in the brain and heart provides reliability and functional perfection of the cardiac rhythm generation system in the whole organism.

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