Chinese Journal of Physiology 34(4):399-412, 1991

Neurons in the Medullary Gigantocellular Reticular Nucleus Mediate Cardioinhibition in Cats

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Su, C.K., C.T. Yen, C.Y. Chai, and J.S. Kuo, *Neurons in the medullary gigantocellular reticular nucleus mediate cardioinhibition in cats.* Chinese J. Physiol. 34(4): 399-412, 1991. The cardioinhibitory mechanisms (bradycardia) of the gigantocellular reticular nucleus (GRN) of medulla was studied in chloralose-urethane anesthetized cats by means of microinjection of sodium glutamate (0.5 M, 100 nl) and single neuron recording. Microinjection of glutamate excited the GRN neurons and produced the bradycardiac responses. The rostral GRN (rostral to the caudal superior olivary nucleus) had higher proportion of bradycardiac loci than the caudal GRN. This suggests that the density of cardioinhibitory neurons in GRN is higher in the rostral than the caudal level. Seventy-eight GRN neurons were recorded extracellularly. Activities of 60 neurons were tested if they were correlated with cardiac rhythm or systemic arterial blood pressure (SAP) changes following intravenous norepinephrine or nitroglycerin. Among these neurons 45% (27/60) exhibited changes related to SAP and 25% (15/60) related to cardiac rhythm. Sixty-one GRN neurons were tested by antidromic activation to determine whether they have axonal projection to the dorsal motor nucleus of vagus and nucleus tractus solitarius (DMN/NTS). Eighteen percent (11/61) of them had axonal projections to the DMN/NTS. These findings suggest that: (i) In GRN there are neurons which mediate cardioinhibition. (ii) These neurons may receive baroreceptor inputs. (iii) They may decrease heart rate through the DMN/NTX.

Key Words: gigantocellular reticular nucleus, dorsomotor nucleus of vagus, nucleus tractus solitarius, vagal bradycardia, cardioinhibition

Our previous studies have shown that the cardioinhibitory responses following activation of the gigantocellular reticular nucleus (GRN) in chloralose-urethane anesthetized cats were mediated through a descending pathway via the dorsal motor

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nucleus and/or nucleus tractus solitarius (DMN/NTS) (13), and that GRN may modulate the baroreceptor reflex through this pathway (6). In these experiments, GRN was electrically activated. Therefore, it was possible that not only perikarya but also passing fibers in or around the GRN area were activated. In addition, whether there is a direct axonal projection from GRN to DMN/NTS was not explored. Thus, it is necessary to re-evaluate the nature of cardioinhibitory mechanism in GRN. Specifically, the present study attempts to examine the following questions: (i) the existence of cardioinhibitory neurons in GRN; (ii) their electrophysiological characteristics, especially their responses to baroreceptor input and (iii) the pathway which mediates cardioinhibitory output from GRN to DMN/NTS.

Materials and Methods

General Procedures

Twenty-two cats of either sexes, weighing 1.2 – 3.0 kg, were anesthetized intraperitoneally with a mixture of chloralose (40 mg/kg) and urethane (400 mg/kg). Preparation of the animal, including keeping the rectal temperature at 37 ± 0.5°C, intubation of the trachea for artificial ventilation, cannulation of the right femoral vein for infusion and the right femoral artery for systemic arterial blood pressure (SAP) and heart rate measurements were described previously (13). Cats were paralyzed with pancuronium bromide (initial dose: 100 μg/kg, i.v., additional dose: 40 μg/kg per 30 min) during the course of recording the electrical activity of GRN neurons. All recordings were made on a Grass 79D polygraph.

Neural Recordings

The head of the animal was immobilized with a David-Kopf stereotaxic instrument. The dorsal medulla was exposed by removing portions of the occipital bone and cerebellum. The obex was used as a surface landmark for insertion of the recording electrode. Action potentials of GRN neurons in the medulla, at levels 6 – 8 mm from the obex, were recorded extracellularly with a tungsten microelectrode (1 – 5 μm tip diameter; impedance: 4 – 11 megaohm at 1000 Hz) by means of a stepping hydraulic microdrive (Narishige Instruments). A platinum reference electrode was placed on the muscle near the parietal bone. A set of preamplifier, amplifier, and filter (Neurolog: NL104, NL105, NL106) with a band pass filter of 0.3 – 5 KHz were used. Biphasic action potentials, peak-to-peak amplitude greater than 0.2 mv and duration greater than 1 ms were considered to be derived from neuronal somata rather than from passing axons (8, 21). After amplification, signals were monitored by an audio-monitor and displayed on an oscilloscope (Tektronix 5113) for observation and photographing. Signals, including the arterial pressure, the neural activities were stored in an FM magnetic tape

recorder for later analysis.

Two methods were used to determine if a GRN neuronal activity was affected by baroreceptor inputs. First, baroreceptor-reflex activation or inactivation were accomplished by increasing or decreasing the arterial pressure following an intravenous (i.v.) infusion of norepinephrine bitartrate (1 – 2 μg/kg) or nitroglycerin (5 – 10 μg/kg), respectively. By means of a window discriminator (NL200) and a Log Display (NL700), the firing rates of the neurons were then correlated with the change of the arterial pressure. Second, with the aid of an averager (NL750) the histograms triggered by arterial pulse wave were constructed and the relationship between spontaneous activity of GRN neurons and cardiac cycles were analyzed. Each sweep time was set for 1000 ms to assure that more than two arterial pulse-waves were displayed and each sampling bin was 4 ms.

Dorsal Motor Nucleus of Vagus/Nucleus Tractus Solitarius (DMN/NTS) Stimulation

The DMN/NTS was stimulated electrically (rectangular pulses, 0.2 ms, 40 Hz and 200 μA) through a bipolar co-axial electrode (Rhodes Medical Ins., NEX-100) stereotaxically inserted to the brain at an angle of 34 degree from the vertical axis. A bradycardiac (cardioinhibitory) response greater than 60% with little change of arterial pressure (see Fig. 5D) was taken as a criterion for a correct positioning of the electrode.

The DMN/NTS was stimulated by a higher intensity (500 μA) pulses at 1 pulse/sec while moving the recording microelectrode at the GRN area to search for neurons that responded with a constant onset latency. Two additional criteria were used to identify the antidromic response: (i) while a 100 Hz stimulation was applied at the DMN/NTS region, the action potentials occurred following each stimulus artifact in a constant latency; and (ii) time-controlled collision of the spontaneous action potentials with the stimulus-evoked action potentials (16).

Glutamate Stimulation

The cardioinhibitory neurons in GRN were activated by sodium glutamate (100 nl, 0.5 M, in artificial CSF containing 1% fast green, pH 7.4) through a system of 30 G needle tubing (also served for monopolar stimulation) and Hamilton syringe as described previously (3).

Histology

Upon completion of each experiment, the medulla was removed and fixed in 10% buffered formalin for 10 – 20 days. Frontal sections in 40 μm thickness were made by cryostat and stained with cresyl violet. Sites of stimulation or recording were identified by the green marks produced by fast green or by ion deposit from electrolysis (200 μA, 20 sec, anodal DC).

Statistical Analysis

The results were placed in a 2 x 2 table and Chi-square test was used to determine the significance level of ratio of occurrence.

Results

Mapping of GRN Cardioinhibitory Neurons

A total of 145 microinjections of glutamate were made in the GRN. Forty-four reduced the heart rate greater than 10% of the resting rate. These were defined as bradycardiac response. The sites of injection are shown in Fig. 1. Eighty-one injections were in the level rostral to caudal superior olivary nuclei. Among them, 32 injections produced bradycardiac response. Sixty-four injections were made in the caudal GRN adjacent to the facial nucleus, only 12 produced bradycardiac response. The ratio is significantly higher ($p < 0.01$) in the rostral (32/81, 39.5%) than that in the caudal GRN (12/64, 18.8%).

The bradycardiac responses evoked by glutamate injections at two points symmetrically located on either side of GRN are illustrated in Fig. 2. In this particular case, the right GRN was first stimulated by glutamate while both sides of the vagus nerves were

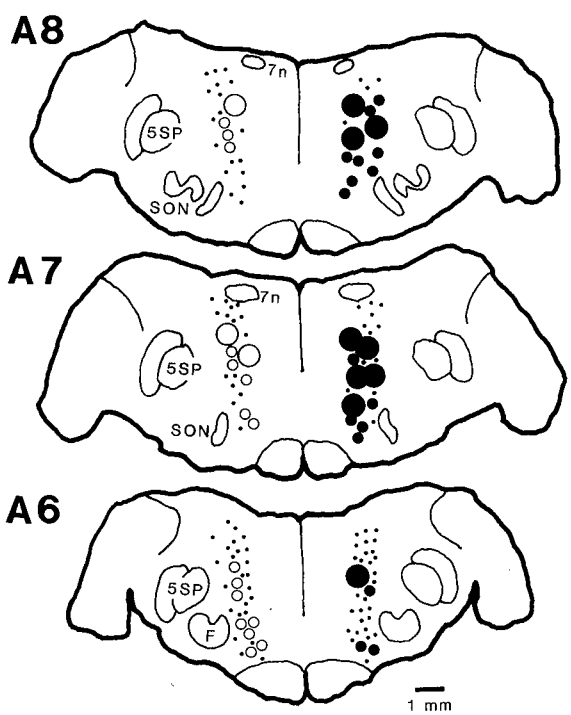

Fig. 1. Locations of 145 Loci in medulla responded to sodium glutamate (0.5 M, 100 nl). Large circles: bradycardiac response greater than 40%. Small circles: response in the range of 10 – 39%. Dots: the response was less than 10%. Right side: solid circle, obtained when both vagi remained intact. Left side: open circle, loci after section of the left vagus nerve. Abbreviations: 7n, genu of facial nerve; F, facial nucleus SON, superior olivary nucleus 5SP, trigeminal nucleus of the spinal tract.

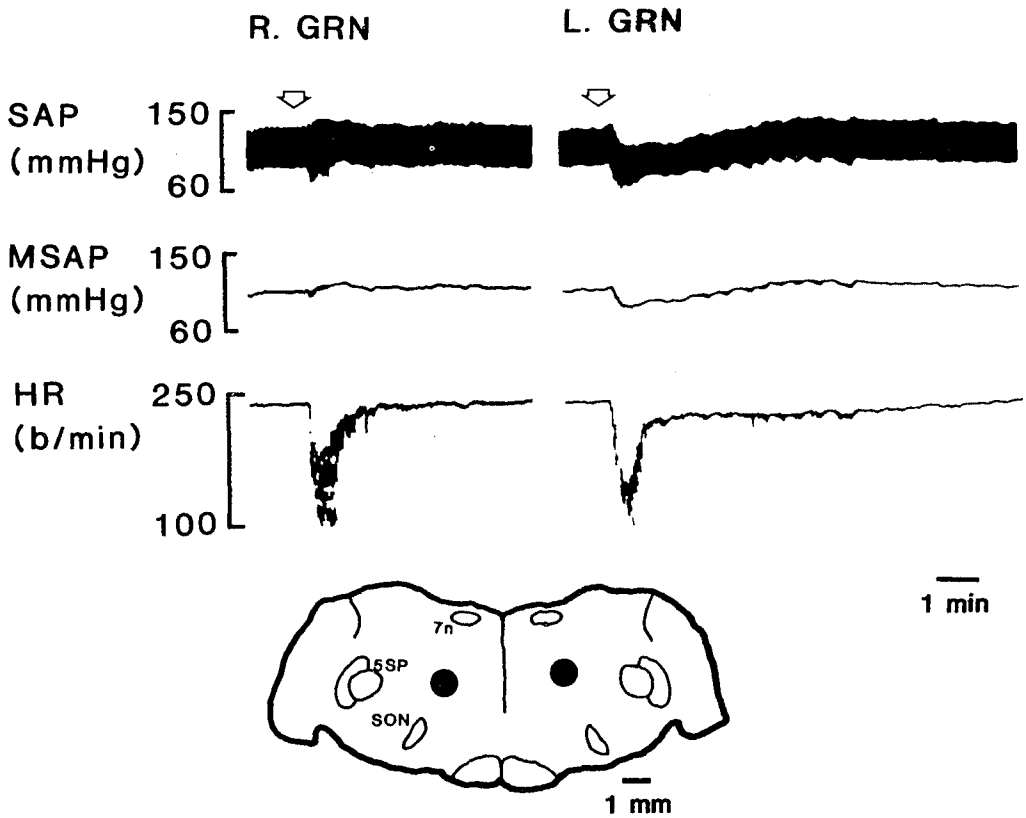

Fig. 2. The bradycardiac responses elicited by sequential injection of sodium glutamate (0.5 M, 100 nl) into two symmetrical loci (solid circles) in the GRN. After stimulation of the locus in the right GRN, the left vagus nerve was cut and then the locus in the left GRN was stimulated. Note the similar magnitude between the two bradycardiac responses suggesting the existence of a contralateral bradycardiac pathway. In this and the following figures abbreviations are: SAP, systemic arterial blood pressure MSAP, mean systemic arterial blood pressure; HR, heart rate.

intact. Then the left vagus nerve was cut and glutamate was injected into the left GRN. The latter injection produced bradycardiac responses in a magnitude similar to that of stimulating the right GRN. This suggests the existence of a contralateral projecting pathway from the GRN neurons to produce the cardioinhibitory action.

Baroreceptor Inputs to the GRN Neurons

Seventy-eight GRN neurons were recorded. They were classified into three categories according to the firing pattern in relation to cardiac rhythm and/or the change of SAP after i.v. infusion of norepinephrine or nitroglycerin.

(i) Arterial pressure related neurons. Responses of 27 (45%) out of 60 GRN neurons (from the 78 neurons) were related to the change of SAP. They are classified

延腦巨大細胞網狀核引發心跳變慢作用的神經細胞機構

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在氯醛醣及氨甲酸乙酯麻醉的貓，在其延腦的巨大細胞網狀核用0.5M胰氨酸鈉作微量(100nl)注射，觀察其心跳變慢情形，並在該地區行神經細胞外電位活動記錄，以進一步探討巨大細胞網狀核細胞的神經性心跳變慢機構。

結果發現，在巨大細胞網狀核分佈注射胰氨酸鈉能引發心跳變慢反應，其引發心跳變慢的效果，以在該核的頭端（在上橄欖核之頭端）較尾端爲佳，暗示該神經核具有能引發心跳變慢的細胞，而這些細胞又以存在於頭端較多。

在巨大網狀核行細胞外電記錄，一共觀察到78個細胞。在60個巨大網狀核的神經細胞中、曾對其電活動情形與心律，及由靜脈注射正腎上腺素、或三硝酸甘油酯所引起的血壓上升或下降之間的關係加以探討，發現其中45％(27/60)細胞，其電活動情形與血壓之升降相關，而2.5％(15/60)細胞則與心律相關。61個巨大網狀細胞中，曾用逆向激發方法探測其是否有向迷走神經背核及獨孤核作軸突投射，結果發現18％(11/60)之細胞、其細胞電活動能因迷走神經背核及獨孤二核被刺激所激發，亦即巨大網狀細胞之軸突有向迷走神經背核及獨孤核投射情形。

由上所得到的結果，推論：1.在巨大細胞網狀核中具有抑心作用的細胞存在。2.這些神經細胞可能是經由迷走神經背核及獨孤核之感壓反射機構，產生心跳變慢反應。

into 4 types. Type I (N = 13, 22%), the change of firing rate of a neuron was in the same direction as the change in SAP; that is, the firing rate increased when SAP increased and vice versa (Fig. 3A). Type II (N = 5, 8%), the change of firing rate of a neuron was in the opposite direction to the change of SAP (Fig. 3B). Type III (N = 6, 10%), the firing rate of a neuron decreased when SAP either increased or decreased (Fig. 3C). Type IV (N = 3, 5%), the firing rate of a neuron increased when SAP either increased or decreased (Fig. 3D).

(ii) Cardiac rhythm related neurons. Responses of 15 (25%) spontaneously firing neurons were related to cardiac rhythm. The criteria of these neurons were: First, the firing pattern of a neuron must be locked with a specific phase of the cardiac cycle. Second, the maximum change of the firing rate was twice the spontaneous variations, namely, having a signal/noise ratio greater than 2. A typical response is shown in Fig. 4. Note that most of the action potentials were time-locked in the systolic phase of the cardiac cycle.

(iii) Neurons related to both arterial pressure and cardiac rhythm. A total of 50 neurons were examined for both SAP and cardiac rhythm correlation. Activities of 25 (50%) neurons were related to SAP changes (Table 1). Activities of 8 (32%) neurons were also related to cardiac rhythm. On the other hand, most (8/11, 72%) of the cardiac rhythm related units were also related to SAP changes. Table 1 also shows only portion of type I, II and III SAP related neurons were related to cardiac rhythm.

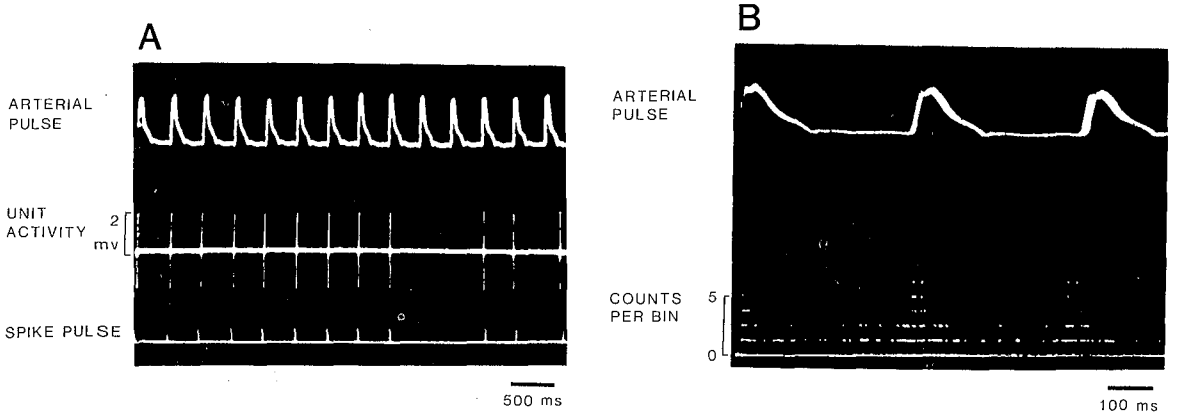

Fig. 4. Cardiac rhythm related GRN neuron. A, correlation between arterial pulse cycle and neural activity. Fourteen arterial pulse cycles are shown in the upper trace. Note the timing of appearance of the 12 spikes. Eleven spikes were time-locked in the systolic phase and one was in the diastolic phase. Note also the absence of spikes in two arterial pulse cycles. This suggests that the neural activity was not a consequence of artifact. B, Arterial pulse wave triggered histogram constructed from the output of a window discriminator (bottom trace of A). Sweep time: 1000 ms Sampling bin: 4 ms.

Table 1. Classification of 50 GRN neurons based on their correlation with cardiac rhythm and change of systemic arterial blood pressure (SAP).

Cardiac rhythm	SAP					Total
	related				not related	
	Type I	Type II	Type III	Type IV		
related	4	2	2	0	3	11
not related	8	2	4	3	22	39
Total	12	4	6	3	25	50

Axonal Projection between DMN/NTS and GRN

The neural connection of 61 GRN neurons were tested by electrical stimulation of the DMN/NTS. Thirty-one (51%) neurons were orthodromically activated while 11 (18%) neurons were antidromically activated. An example of collision test is shown in Fig. 5.

Seven out of the 11 antidromic neurons were evoked from ipsilateral DMN/NTS stimulation with an onset latency of 1.2 – 3.6 ms (average 2.6 ± 1.0 ms). The conduction velocity was 1.1 – 2.1 m/s (average 3.2 ± 1.6 m/s) for the ipsilateral projecting neurons. The other 4 antidromic neurons were contralaterally evoked. They had an onset latency of 1.6 – 6.0 ms (average 3.1 ± 2.1 ms) and conduction velocity of 1.4 – 5.3 m/s (average 3.7 ± 1.6 m/s).

Further analyzing the spontaneous activity of these antidromic neurons revealed that only one had a spontaneous firing rate greater than 1 Hz (2.5 Hz). The average firing rate of the remaining 10 neurons was 0.2 Hz.

In comparison, most of the non-antidromic neurons (39/50) had spontaneous firing rate greater than 1 Hz. There was a significant difference between the spontaneous firing rates of the antidromic neurons and those of the non-antidromic neurons ($p < 0.005$).

Discussion

In the present study, with the aid of glutamate which excites perikarya while spares axons (10), we have demonstrated the existence of perikarya of cardioinhibitory neurons

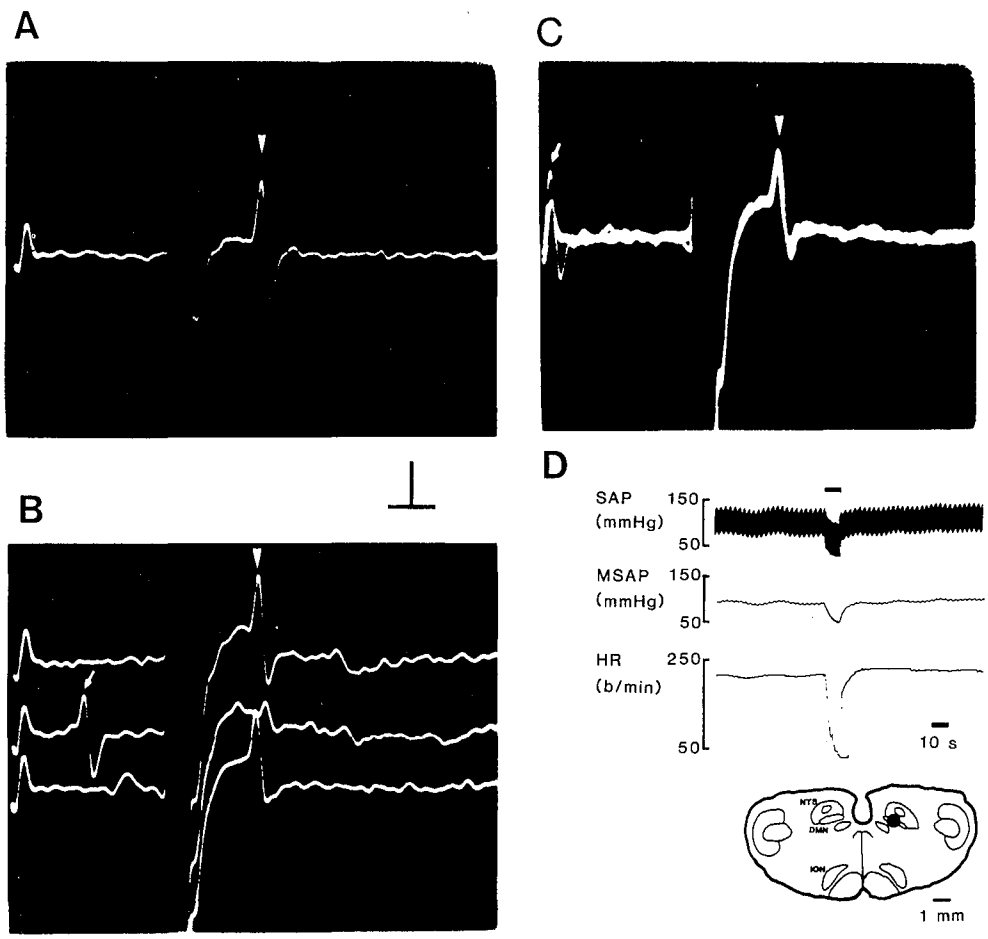

Fig. 5. Antidromic activation of GRN neuron by electrical stimulation of DMN/NTS. In A, B, or C, a single trace or 5 superimposed traces were displayed. Arrows mark the appearance of spontaneous spikes arrowheads mark the antidromic spikes. A, control antidromic response (onset latency, 3.6 ms) produced by DMN/NTS stimulation, 1.5 x threshold (75 μA). B, neuron failed to respond to antidromic stimulation (collision) when a spontaneous spike appeared within the critical period. C, neuron responded antidromically when the spontaneous spikes appeared outside the critical period. D, bradycardiac response by DMN/NTS stimulation (200 μA, 0.2 ms, 40 Hz). Dot in the frontal section of medulla marks the locus of stimulation.

in GRN. This is consistent with our previous findings using electrical stimulation (13) and a recent study using glutamate activation (24). The cardio-inhibitory neurons are located with higher density in the rostral GRN (Fig. 1). As demonstrated previously (13), the present study confirms the existence of both an ipsilateral (uncrossed) and contralateral (crossed) descending vagal bradycardia pathways from the GRN (Fig. 2).

At least part of the bradycardiac effect is mediated through the axonal projection

form GRN to DMN/NTS. With respect to the spontaneous activity of these cardioinhibitory neurons we found that 45% were SAP related and 25% were cardiac rhythm related. This suggests that GRN neurons may receive baroreceptor input. This possibility was further supported by the observation that 51% of the GRN neurons tested showed orthodromic responses following electrical stimulation of the cardioinhibitory area in or around the DMN/NTS.

On the other hand, among the 50 spontaneous active GRN neurons examined for the correlation of SAP and cardiac rhythm, there were only 8 of the 25 SAP related GRN neurons whose spontaneous activities were also correlated with cardiac rhythm. This suggests that, in spontaneous state, only a small portion of the GRN neurons (8/50, 16%) examined were closely coupled with the baroreceptor inputs. In other word, only a small portions of neurons received spontaneous inputs from baroreceptors in resting condition. When the baroreceptor mechanism was strongly disturbed, i.e., after i.v. norepinephrine or nitroglycerin, most of the GRN neurons (25/50, 50%) were affected significantly by baroreceptor inputs, and their activities were related with the change of SAP. In fact, 17 SAP related GRN neurons, which did not clearly show activity related to cardiac rhythm, responded when the baroreceptor were strongly excited or inhibited. This again suggests that spontaneous activities of these neurons (17/50, 34%) were less closely coupled with the baroreceptor inputs. It is worthwhile to note that there were 3 cardiac rhythm-related GRN neurons whose activities were not SAP related. These neurons may have the character or a cardiac rhythm generator but independent of the baroreceptor inputs.

It has been a general practice by using pressor agents or by directly increasing the intra-carotid sinus pressure to determine whether the activities of neurons in the brain are affected by baroreceptor input (1, 5, 20). In the present study, we used both pressor (vasoconstrictor) and depressor (vasodilator) agents to alter the SAP. We found that 9 GRN neurons could be classified as type III or type IV. This finding was similar to that of Salmoiraghi (25), namely, neurons respond to arterial pressure were either more sensitive to the pressor effect than to the depressor effect or vice versa. We can not exclude, however, if these chemicals have direct action on the activities of such neurons.

Functions of GRN are not entirely clear. In addition to modulation of baroreceptor reflex (6, 15, 22, 26), GRN has been found to modulate respiration (7, 14, 17, 23), somatosensation (9), nociception and antinociception (2, 9, 11). It is possible that the SAP related type III and IV and SAP unrelated GRN neurons are related to functions other than baroreceptor mechanism.

Only one of the 11 antidromic GRN neurons had spontaneous firing rate greater than 1 Hz. The spontaneous activity of this neuron was correlated with arterial pulse and its activity changed in the same direction as that of SAP. Therefore, it is a type I and cardiac rhythm related neuron. The spontaneous firing rates of the remaining 10 antidromic neurons were too slow to correlate with the change of SAP or arterial pulse wave. This low activity may be due to the effect of anesthetics. Kunze (12) and McAllen & Spyer (18) reported that the tonic activity of cardiac vagus nerve was low in anesthe-

tized animals.

Activities of the cardioinhibitory or sympathoinhibitory neurons are well correlated with arterial pulse and SAP. McAllen & Spyer (19) reported that 59% of ambiguus neurons which have axonal projections to the cardiac vagus nerve exhibiting cardiac rhythm. When homocysteic acid was applied electrophoretically to the vicinity of these neurons, 83% of such stimulations induced bradycardiac response. Morrison and Gebber (20) also demonstrated that some cardiac rhythm related neurons in raphe nucleus increased their firing rates when the baroreceptor mechanism was excited. Among these neurons 30% have axons projected to the intermediate lateral column of the spinal cord. In addition, electrical stimulation of the raphe neurons could evoke sympathoinhibitory response. Using a similar approach, we provide three lines of evidences to suggest that the neuron, which is type I, cardiac rhythm related and antidromically activated from electrical stimulation of DMN/NTS, is a cardioinhibitory neurons. First, glutamate microinjection, which excited GRN neurons, produced bradycardiac responses. Second, when baroreceptors were excited by norepinephrine, the firing rate of these neurons increased and the cardiac response were similar to that of glutamate stimulation in GRN. Third, some of these neurons have axonal projections to the cardioinhibitory area in DMN/NTS.

In summary, this study provides evidences that GRN neurons receive baroreceptor input and have axonal projection to DMN/NTS. These neurons may be cardioinhibitory in nature. However, whether there is an axonal projection from GRN to ambiguus nucleus, which also mediates cardioinhibition (4), remains to be determined.

Acknowledgements

The authors thank Mr. G.T. Chen for preparation of the illustrations and Ms. J.J. Pan for handling the manuscript. Special thanks are due to Dr. S.H. Ngai of Columbia University for reading the manuscript and for providing advice. Part of materials of this work have been submitted by C.K. Su for partial fulfillment of the requirements of a Master of Science Degree in National Taiwan University. This study was supported in part by Grants from the National Science Council, No. NSC78-0412-B001-09 Shih-Chun Research Fund, and from the Foundation of Biomedical Sciences (1991).

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延腦巨大細胞網狀核引發心跳變慢作用的神經細胞機構

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在氯醛醣及氨甲酸乙酯麻醉的貓，在其延腦的巨大細胞網狀核用0.5M胰氨酸鈉作微量(100nl)注射，觀察其心跳變慢情形，並在該地區行神經細胞外電位活動記錄，以進一步探討巨大細胞網狀核細胞的神經性心跳變慢機構。

結果發現，在巨大細胞網狀核分佈注射胰氨酸鈉能引發心跳變慢反應，其引發心跳變慢的效果，以在該核的頭端（在上橄欖核之頭端）較尾端爲佳，暗示該神經核具有能引發心跳變慢的細胞，而這些細胞又以存在於頭端較多。

在巨大網狀核行細胞外電記錄，一共觀察到78個細胞。在60個巨大網狀核的神經細胞中、曾對其電活動情形與心律，及由靜脈注射正腎上腺素、或三硝酸甘油酯所引起的血壓上升或下降之間的關係加以探討，發現其中45％(27/60)細胞，其電活動情形與血壓之升降相關，而2.5％(15/60)細胞則與心律相關。61個巨大網狀細胞中，曾用逆向激發方法探測其是否有向迷走神經背核及獨孤核作軸突投射，結果發現18％(11/60)之細胞、其細胞電活動能因迷走神經背核及獨孤二核被刺激所激發，亦即巨大網狀細胞之軸突有向迷走神經背核及獨孤核投射情形。

由上所得到的結果，推論：1.在巨大細胞網狀核中具有抑心作用的細胞存在。2.這些神經細胞可能是經由迷走神經背核及獨孤核之感壓反射機構，產生心跳變慢反應。