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Differential blood pressure and heart rate responses to supramedullary brain stimulation in cats

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The purpose of this study was to compare the cardiovascular responses to electrical stimulation of different supramedullary brain regions. Arterial blood pressure (BP) and heart rate (HR) effects were elicited by electrical stimulation of the lateral hypothalamus (LH), mammillary bodies (Mm), substantia nigra (SN), globus pallidus (GP), and the subthalamic nucleus (Sub) in conscious, freely moving cats. Pressor responses were obtained from all of these regions. The higher intensity of stimulation the higher increase in BP and HR was obtained. However, clear-cut differences occurred in the effects both during and after the termination of stimulations. Namely, a continuous increase in BP and HR was obtained from the LH and SN. In contrast, the initial increase in BP and HR was followed by a reduction compared to the peak value of the effects of stimulation in the GP and the Sub. However, the BP and HR never reduced to the pre-stimulation level during the stimulation. Also the changes following the cessation of stimulation at the different brain loci were dissimilar. The BP and HR either returned gradually to the pre-stimulation level, or long-lasting oscillation occurred. The electrical activity of the nucleus of the solitary tract (NTS) and the vagus nerve co-varied with the changes in BP and HR. It is concluded that the supramedullary stimulations produce differential cardiovascular effects, and these effects are modified by the baroreflexes that are activated by the electrically elicited rise in blood pressure.

Keywords: basal ganglia, blood pressure, electrical stimulation, heart rate, hypothalamus, nucleus of the solitary tract, vagus nerve

There is a wealth of experimental evidence demonstrating that supramedullary brain stimulations are able to modulate the arterial blood pressure (BP) and heart rate (HR) (1–7, 11–14, 16–19, 21). However, the functional role of these supramedullary

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mechanisms in the cardiovascular control is not well understood. It has been suggested that supramedullary mechanisms adjust the cardiovascular functions to the actual metabolic demands of the organism by producing cardiovascular changes as part of complex behavioural responses (2, 6, 8–10, 13, 15). However, it is not clear up to now that supramedullary brain mechanisms initiate complex patterns of response (e.g. pressor response) or BP and HR responses are modulated separately. Furthermore, what are the characteristics of the effects obtained from the different brain regions? Because the commonly employed anaesthetics affect the circulatory control (20), it is also an important question that the electrically elicited cardiovascular effects were studied in conscious, unrestrained animals or under anaesthesia. The reason of the present study was to compare the electrically elicited cardiovascular effects from various supramedullary brain structures that are able to modulate cardiovascular functions. The experiments were performed on conscious, freely moving animals, except the recording of the electrical activity of the vagus nerve.

Materials and Methods

Animals

Fifteen adult cats, weighing 2–4 kg, were used.

Surgery

Under pentobarbital sodium (iv. 40 mg/kg) anaesthesia bipolar electrodes were implanted chronically in the lateral hypothalamus (LH), mammillary bodies (Mm), substantia nigra (SN), globus pallidus (GP), subthalamic nucleus (Sub), and the nucleus of the solitary tract (NTS). The surgery has been described in details in our previous studies (2–4). In five cats bipolar electrodes were placed on the cervical vagus nerve under Chloralose anaesthesia.

Stimulations

Rectangular pulses at 100 Hz and 0.3 ms pulse width were used. The stimulus intensity was determined by the behavioural effects, and varied between 0.1 and 1 mA. The intensity producing the first visible change in behaviour was regarded as threshold. The intensity eliciting localised movements (e.g. head-turning, elevation of the leg) served as medium, and that intensity evoking locomotion (e.g. circling) was regarded as high intensity. The duration of stimulation was varied between 1 and 10 seconds.

Recordings

Polygraphic recordings were done. In freely moving animal, except the recording of vagal nerve activity that was recorded from anaesthetised cat. BP was recorded by a cannula inserted into one of the common carotid arteries and connected to a Statham

(P23Db) pressure transducer placed on the top of the experimental chamber. (*The occlusion of one of the carotid arteries caused no visible change in the behaviour of the animal*!) The polygraph was connected to a computer through an interface for automatic evaluation of the signals.

Anaesthesia for recording vagal nerve activity

Chloralose (0.08 g/kg).

Statistical analysis

BP and HR values were calculated as an average value measured over 10-s epochs derived from the BP recordings during a 10-s period immediately before stimulation, during a 10-s stimulation period, and again 10 s immediately after stimulation. All statistical comparisons were made using a standard Student's *t*-test. The BP and HR obtained from the pre-stimulation period served as controls and were considered as 100%.

Histology

The position of the electrode tips was examined on serial transverse sections of the brain stained with cresyl violet and Luxol fast blue.

Results

The results obtained from stimulations with histologically verified electrodes in the target sites were evaluated in this study. Eight electrodes were localized in the SN and GP, six in the LH and Mm, and five in the Sub.

The electrical stimulation of the LH, Mm, SN, Sub and GP produced regular changes in the BP and HR. The results obtained from medium intensity stimulations are shown in Figure 1. The characteristics of the cardiovascular effects depended on the stimulus parameters and on the site of stimulation. The higher the stimulus intensity the higher amplitude effects were obtained. The duration of stimulation also affected the pattern of cardiovascular responses. Short pulse-train (1.0 s) stimulation elicited an increase both in BP and HR followed by long-lasting post-stimulatory effects (Fig. 2). Two kinds of changes occurred after the cessation of stimulation depending on the site of stimulation. [1] In cases of SN and LH stimulations the BP and HR returned gradually to the pre-stimulation level. [2] In the post-stimulation effects of Mm, Sub and GP stimulation long-lasting oscillation appeared in BP and HR. Also long pulse-train (10 s) stimulations produced differential effects (Fig. 3). SN and LH stimulation elicited a continuous rise in BP and HR during stimulation, and a gradual return to the pre-stimulation level after turning off the stimulation.

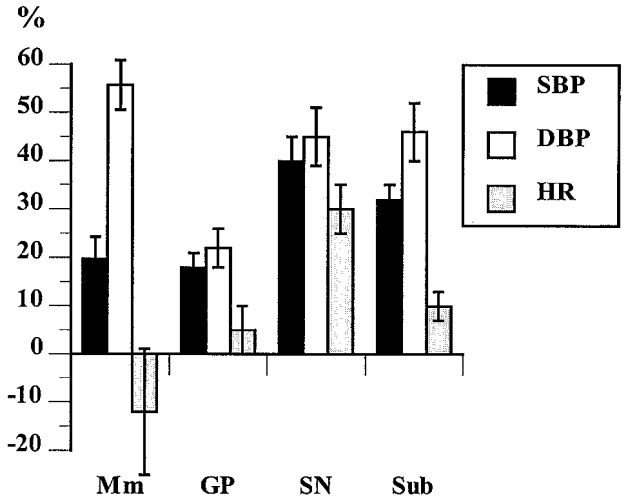

Fig. 1. Systolic (SBP) and diastolic (DBP) blood pressure, and heart rate (HR) effects (mean ± SE) elicited from the mammillary bodies (Mm), globus pallidus (GP), substantia nigra (SN) and subthalamic (Sub) stimulation. The values are given in percent of the pre-stimulation level

The Mm stimulation produced rise in BP and slowing in HR during stimulation, and oscillation in BP and HR following the termination of the stimulation. Characteristic changes appeared in BP and HR responses to GP and Sub stimulation. In cases of GP stimulation the initial rise in BP and HR was followed by bradycardia after a latency of 1.5–2.5 s. As a consequence of bradycardia the pulse pressure increased because of the fall in diastolic blood pressure (Fig. 3). The typical BP response to Sub stimulation showed an initial rapid increase after which the BP remained elevated on relatively steady high level, or increased more slowly as in the initial phase. The termination of the stimulation was followed by bradycardia and oscillation in BP and HR.

Stimulations repeated with identical parameters at the same site elicited similar effects; neither the magnitude nor the characteristics of the BP and HR effects changed significantly during the later (>30 s) stimulations.

The vagal electrical activity was recorded simultaneously with BP in five anaesthetized cats. The hypothalamic stimulation with medium intensity elicited pressor responses. The cessation of stimulation was followed by bradycardia. At the same time high amplitude waves appeared in the electrical activity of the vagus nerve (Fig. 4).

In a series of experiments on five cats the BP and HR responses were recorded simultaneously with the electrical activity of the nucleus of the solitary tract (NTS). The electrical stimulation of the supramedullary brain loci elicited small amplitude fast activity interrupted by sharp waves of high amplitude. The appearance of the high amplitude waves in the electrical activity of NTS coincided with the increase in BP (Fig. 2).

Discussion

The present results support the previous data that electrical stimulation of the supramedullary brain structures induces changes in the cardiovascular functions. The new information of this study is from [1] the assessment of the BP and HR effects of electrical stimulation in various supramedullary brain loci in conscious, freely moving animals, and, [2] the electrical activity of the NTS and the vagus nerve recorded simultaneously with the BP and HR responses.

Short pulse-train stimulations elicited pressor responses from all loci. It has been shown in our previous studies that the electrically elicited increase in BP failed to appear after pharmacological blockade of the α_1-receptors (4, 5). So, the pressor responses are mediated by sympathetic vasonconstrictor activation.

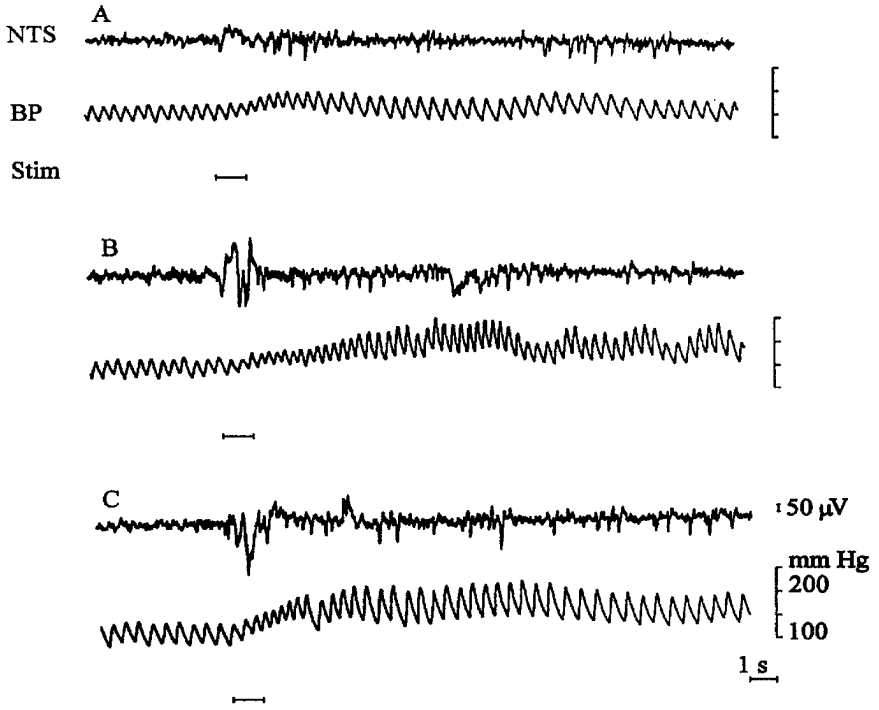

Fig. 2. Changes in the electrical activity of the nucleus of the solitary tract (NTS) and the arterial blood pressure (BP) elicited by electrical stimulation of the substantia nigra (A), mammillary bodies (B) and lateral hypothalamus (C)

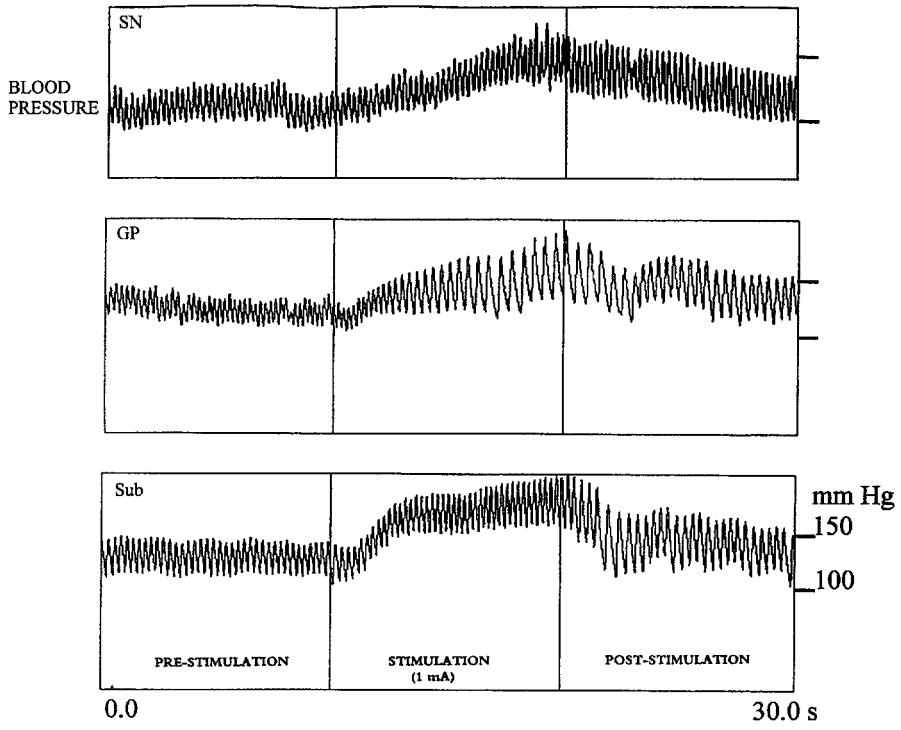

Fig. 3. Different blood pressure responses to electrical stimulation of the substantia nigra (SN), globus pallidus (GP) and subthalamic nucleus (Sub)

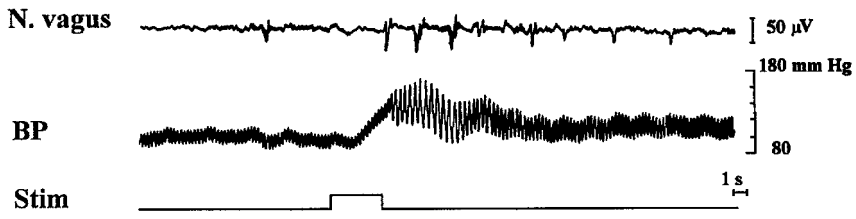

Fig. 4. Changes in the electrical avtivity of the vagus nerve and the arterial blood pressure produced by hypothalamic stimulation under chloralose anaesthesia

However, the long-lasting post-stimulatory effects that follow the termination of stimulation are not explainable uniformly. The continuous return of BP and HR to the pre-stimulation level follows the cessation of the activation of the brain mechanisms. However, there are two possibilities for the explanation of the oscillation in BP and HR: i) the increase in the arterial BP activates the baroreflexes that counteract with the central facilitation, ii) the supramedullary stimulation produces instability in central cardiovascular regulatory mechanisms. The instability occurs when a regulatory mechanism is working at the upper level of its regulatory range.

The first possibility is supported by the increase in the electrical activity of the vagus nerve and the NTS after the cessation of stimulation. A similar reflex bradycardia was obtained from hypothalamic stimulation in rabbit (16). The second suggestion is kept up by the regional differences, namely, by the fact that oscillation did not occur after stimulation at all sites despite the high BP. It was suggested that in addition to the sympathetic activation and the baroreflexes, also the ability of the vasculature to respond to sympathetic activity plays a role in determining the strength of oscillations (14).

It is reasonable to suppose that different mechanisms are responsible for the dissimilar effects of long-pulse train stimulations. Also in this case, the continuous rise in BP and HR during SN and LH stimulation might be caused by activation of the vasoconstrictor and cardioaccelerator sympathetic efferents. However, the characteristic changes in the effects of GP and Sub stimulation are produced by more complex mechanisms. The initial pressor responses are elicited similarly to the effects of SN and LH stimulations. The bradycardia and the increase in pulse pressure following the initial phase are produced by simultaneous activation of the central mechanisms and the baroreflexes. The long latency (1.5–2.5 s) of the bradycardia indicates the activation of the baroreflexes by the high BP. However, the baroreflexes cannot suppress the central sympathetic facilitation, therefore, the BP remains elevated. It means that the baroreflexes are effective on the impulse generation of the heart, but less effective on the vasoconstrictor activity under the effect of GP and Sub stimulations. There are evidences for the existence of opposing modulatory influences on the cardiovascular neurons in the medulla (1, 16, 21). These reports suggest the possibility that the simultaneous stimulation of excitatory and inhibitory pathways would cause the differential BP and HR effects observed in the present study. However, the delay between the increase in BP and the bradycardia indicates the activation of baroreflexes rather than the simultaneous activation of the excitatory and inhibitory pathways from the supramedullary loci.

In conclusion, the present results show that supramedullary brain mechanisms produce differential cardiovascular responses depending on the parameters and the locus of stimulation. The modulatory effect of brain stimulations is not restricted to the duration of stimulation but long-lasting post-stimulatory effects occur. Both during and after the stimulation the electrically elicited sympathetic activation and the baroreflexes are responsible for the changes in the cardiovascular functions.

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