ACTION OF γ-AMINOBUTYRIC ACID AND ITS PHENYL DERIVATIVE ON CENTRAL LINKS OF VASCULAR REFLEXES FROM AORTIC-CAROTID CHEMO- AND MECHANORECEPTORS*

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Experiments on decerebrate cats revealed an inhibitory effect of γ-aminobutyric acid (GABA; 100-200 μg/kg) and its phenyl derivative, phenyl-GABA (20 mg/kg), on depressor responses of the systemic arterial pressure and on inhibition of spontaneous electrical activity in the renal nerve arising in response to excitation of the carotid sinus mechanoreceptors and afferent fibers on the sinus and depressor nerves carrying impulses from mechanoreceptors. Pressor responses of the systemic arterial pressure and electrical activity evoked in the renal nerve by stimulation of the carotid sinus chemoreceptors were intensified after administration of the same doses of GABA and phenyl-GABA. The results are interpreted from the standpoint of the depriming action of GABA and its phenyl derivative on the paramedian reticular nuclei of the medulla.

KEY WORDS: aortic-carotid zone; γ-aminobutyric acid; phenyl-γ-aminobutyric acid; medulla.

Data on the effect of γ-aminobutyric acid (GABA) and substances similar to it in structure on the intrinsic reflexes of the cardiovascular system from chemo- and mechanoreceptors of the aortic-carotid zone are few in number and contradictory in nature [2, 4, 5]. Recent work has shown that reflexes from the chemo- and mechanoreceptors of this buffer zone differ in their central organization [11, 12].

The aim of this investigation was to study the action of GABA and its derivative β-phenyl-γ-aminobutyric acid (phenyl-GABA) on the bulbar link of reflexes from chemo- and mechanoreceptors of the aortic-carotid zone.

EXPERIMENTAL METHOD

Experiments were carried out on 32 decerebrate cats (listhenon; urethane–chloralose anesthesia) weighing 2-3.5 kg. Mechanoreceptors of the carotid sinus were stimulated by stretching the isolated sinus with warm physiological saline injected to a pressure of 200 mm Hg. Carotid chemoreceptors were stimulated with cytisine (50 μg in 0.2 ml physiological saline), injected into the right isolated sinus through the superior thyroid artery. Afferents of the aortic depressor and sinus nerves were stimulated electrically. Direct electrical activation (60 Hz, 0.1 msec, 150 μA) of the nucleus of the tractus solitarius was applied through insulated constantan microelectrodes (30 μ). GABA (5 μl of a 0.05 M solution) was injected directly into the region of the nucleus through a chemical electrode fixed to the microelectrode. The double-barreled electrode was inserted into the nucleus of the tractus solitarius in accordance with the coordinates

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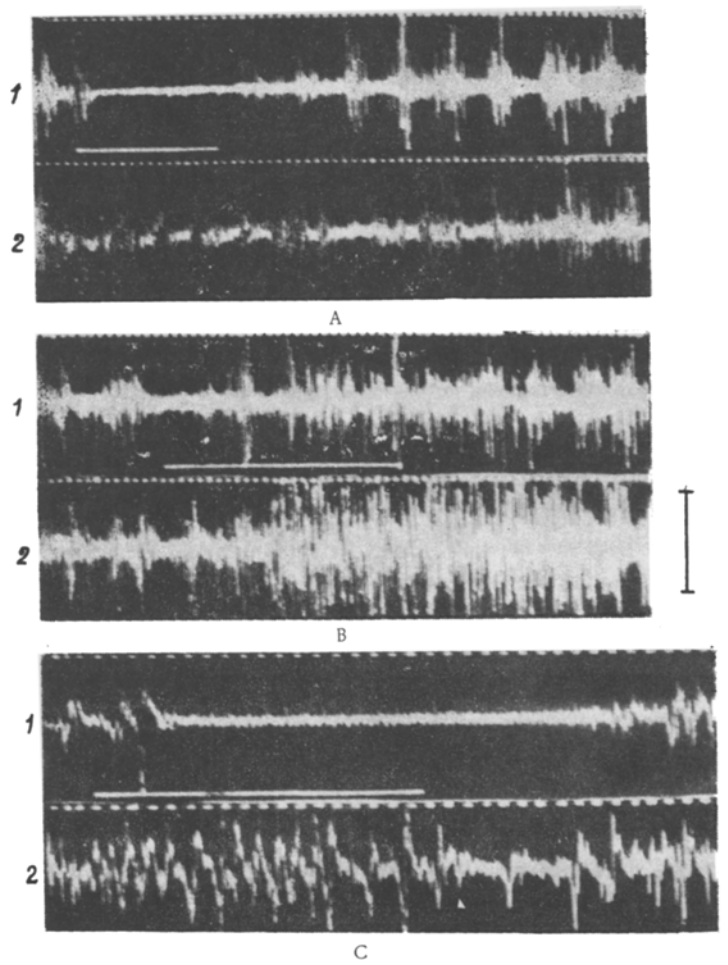

Fig. 1. Effect of GABA and phenyl-GABA on change in electrical activity of renal nerve in response to mechanical, chemical, and electrical stimulation of carotid sinus. A) Inhibition of spontaneous electrical activity in renal nerve in response to raising pressure in carotid sinus (200 mm Hg) before (1) and 15 min after injection of GABA in a dose of 200 mg/kg (2). B) Change in activity in renal nerve in response to chemical stimulation of isolated carotid sinus (50 μg cytisine) before (1) and 20 min after injection of GABA in a dose of 200 mg/kg (2). C) Appearance of high-amplitude discharge in renal nerve during stimulation of high-threshold afferents of sinus nerve before (1) and 20 min after injection of phenyl-GABA in dose of 20 mg/kg (2). Calibration: time 20 msec, amplitude 50μV. Marker of stimulation applies both to initial response and to response after injection of compound.

of Crill and Reis' atlas [9]. After the experiments the location of the electrode was verified. The systemic arterial pressure (BP), the ECG (lead II), and the electrical activity in the left renal nerve were recorded.

GABA (100-200 mg/kg) and phenyl-GABA (20 mg/kg) were injected intravenously. In some experiments solutions of GABA or phenyl-GABA were injected into the fourth ventricle and into the vertebral canal through polyethylene cannulas.

EXPERIMENTAL RESULTS AND DISCUSSION

The depressor vascular response to electrical stimulation of the sinus and depressor nerves was considerably (on the average by 66.5%) reduced 10-20 min after intravenous injection of GABA and phenyl-GABA. The depressor response of the BP to stimulation of the carotid sinus mechanoreceptors was depressed on the average by 63.6% after injection of the same doses of GABA and phenyl-GABA.

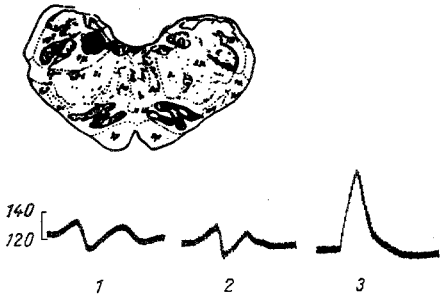

Fig. 2. Effect of GABA on response of BP to electrical stimulation of nucleus of tractus solitarius: 1) before injection of GABA; 2) 10 min after microinjection of 5 μl 0.05 M GABA solution into nucleus of tractus solitarius; 3) 30 min after intravenous injection of GABA in dose of 200 mg/kg.

During electrical stimulation of the sinus and depressor nerves and also during distension of the isolated carotid sinus spontaneous activity in the renal nerve disappeared, indicating the inhibitory character of the afferent stimuli. Inhibition of tonic activity in the renal nerve in response to electrical stimulation of the sinus and depressor nerves or to elevation of the pressure in the carotid sinus was abolished 10-15 min after the injection of GABA or phenyl-GABA (Fig. 1A).

After injection of 15 mg GABA or phenyl-GABA (in 0.1 ml physiological saline) into the vertebral canal in the region of the thoracic segments of the cord no decrease in the depressor responses of BP and no inhibition of spontaneous activity in the renal nerve as the result of stimulation of the sinus and depressor nerves were observed. However, injection of 3-5 mg GABA or phenyl-GABA into the fourth ventricle at once abolished these responses. It thus follows that the point of application of the action of GABA and phenyl-GABA on the central links of the vascular reflexes from the aortic-carotid zone is in the structures of the rhombencephalon.

A pressor response of BP was observed to injection of cytisine directly into the isolated carotid sinus in these experiments. Meanwhile, recording from the renal nerve showed volleys of high-frequency discharges of high amplitude. GABA and phenyl-GABA potentiated the pressor responses of BP and increased the frequency and amplitude of the discharges arising in the renal nerve (Fig. 1B) as a result of excitation of the carotid sinus chemoreceptors.

In some experiments GABA or phenyl-GABA reversed the depressor response of BP to activation of the sinus nerve into pressor, the amplitude of which gradually increased to reach a maximum 30-40 min after injection of the compounds. Sometimes disappearance of electrical activity in the renal nerve in response to maximal electrical stimulation of the sinus nerve was preceded by a volley of high-amplitude evoked discharges, attributable in their origin to excitation of nonmedullated C-afferent fibers carrying impulses from chemoreceptors [10]. In these cases, instead of disappearance of spontaneous activity in the renal nerve, an increase in amplitude of the discharges recorded from it was observed after injection of GABA (Fig. 1C).

The principal relay point for primary afferents of the aortic-carotid zone is considered to be the nucleus of the tractus solitarius and adjacent bulbar structures at the level of the obex [1, 3, 6, 9, 14], a location described as the "intermediate" zone [8].

In these experiments subthreshold direct electrical stimulation of the nucleus of the tractus solitarius evoked a pressor–depressor response of BP (Fig. 2:1). The appearance of pressor and depressor components of the BP response to electrical stimulation of the nucleus of the tractus solitarius can probably be attributed to the fact that primary afferents carrying information from mechano- and chemoreceptors are directed into this region of the medulla. Secondary sensory neurons of both modalities also are located there [11].

Stimulation of carotid sinus chemoreceptors gave a pressor effect, later masked by a depressor effect.

After microinjection of the GABA solution through the chemical electrode directly into the region of the nucleus solitarius stimulated electrically, the ensuing depressor response of BP remained unchanged (Fig. 2:2). If, however, GABA was injected intravenously the depressor component of the pressor–depressor response of BP to electrical stimulation of the nucleus of the tractus solitarius disappeared, whereas the pressor component of the vascular response was more than doubled (Fig. 2:3). This indicates that neurons of the "intermediate zone" of the medulla are not the region of action of GABA and phenyl-GABA on reflexes from chemo- and mechanoreceptors of the aortic-carotid zone. Disappearance of the depressor reflexes from the mechanoreceptors observed after injection of GABA and phenyl-GABA, it will be noted, was accompanied by facilitation of reflexes from the chemoreceptors. This action of GABA and phenyl-GABA on reflexes from the aortic-carotid zone resembles the effect of destruction of the paramedian reticular nuclei. As a result of destruction of the medullary paramedian nuclei the de-

pressor vascular response to stimulation of mechanoreceptor myelinated afferent fibers is abolished and the pressor response to excitation of the carotid sinus chemoreceptors is facilitated [11].

The action of GABA and its phenyl derivative on the central links of the intrinsic vascular reflexes from the mechano- and chemoreceptors of the aortic-carotid zone is thus evidently aimed at neurons of the paramedian nuclei. The decrease in their excitability may be due to hyperpolarization of the neuron membrane by GABA [7, 13] or phenyl-GABA. This leads to inhibition of the depressor response to excitation of the myelinated mechanoreceptor afferent fibers of the sinus and depressor nerves. Facilitation of vascular responses to excitation of the carotid sinus chemoreceptors can be explained by the presence of reciprocal relations between the depressor and pressor reflexes from the carotid sinus zone [11].

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