EFFECT OF γ-AMINOBUTYRIC ACID, NICOTINOYL-γ-AMINOBUTYRIC ACID, AND ITS ETHYL ESTER ON CENTRAL VASOMOTOR REFLEX FORMATION

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In experiments on cats γ-aminobutyric acid (GABA), nicotinoyl-GABA, its ethyl ester, and the γ-aminobutyrate of nicotinic acid were found to have a depriming effect on tonic activity in the sympathetic nerves of the heart and kidneys and on reflex responses from group A and C afferents of somatic and visceral nerves, identified with the aid of the afferent neurogram. The most active of these substances as regards inhibition of the sympathetic and vasomotor tone were nictoinoyl-GABA and its ethyl ester. The difference between the activity of GABA and its nicotinoyl derivatives is due to differences in the ability of these compounds to penetrate into the brain through the blood-brain barrier. An important role in the mechanism of action of these compounds of vasomotor regulation is played by the presynaptic component of inhibition of primary afferents of spinal somatic and visceral nerves.

γ-Aminobutyric acid (GABA) has been ascribed an important role in central inhibitions [14, 16-17]. A link has been established between GABA and adrenergic processes in the brain [5, 10] and its participation in the regulation of vascular tone and vasomotor reflexes has been postulated [10, 11]. Because of the important role of the sympathetic system in nervous control of vascular tone, it was decided to use these properties of GABA in order to correct disturbances affecting the systems of central control of the circulation. Japanese workers have suggested the GABA preparation gammalon for this purpose [19].

However, the practical use of GABA is complicated by the fact that it penetrates poorly through the blood-brain barrier. It is for this reason that for many years investigations have been going on in order to test GABA metabolites and derivatives, of which sodium hydroxybutyrate, β-phenyl-γ-aminobutyric acid, and succinic acid semialdehyde have been shown to pass through the blood-brain barrier and to have a sedative, hypnotic, and anesthetic effect [6, 7, 12, 13, 20].

The same problem was tackled in rather a different way by Halpern and Neck [18], who suggested combining GABA with nicotinic acid as the γ-aminobutyrate salt of nicotinic acid, in order to terminate vascular spasms of neurogenic origin. To increase the activity of this compound (to improve its penetration through the blood-brain barrier), nicotinoyl-GABA and its ethyl ester also were synthesized (L. M. Shmuilovich and V. M. Kopelevich).

The object of the present investigation was to compare the effects of the above-mentioned nicotinoyl derivatives of GABA on intracentral processes of regulation of sympathetic and vasomotor tone.

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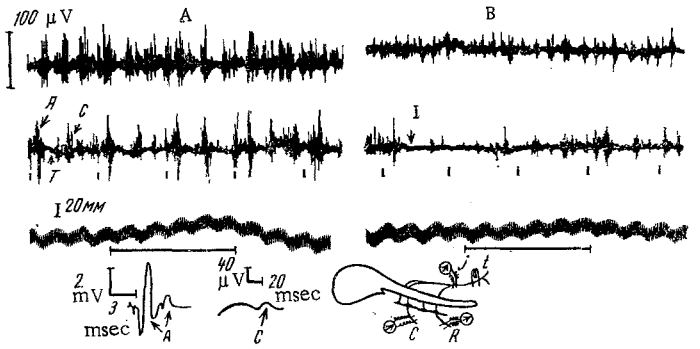

Fig. 1. Effect of nicotinoyl-GABA (60 mg/kg) on tonic activity in inferior cardiac nerve, reflex responses from group A and C afferents of the tibial nerve, and postactivation inhibition (I). A) Before injection of compound (control); B) 15 min after intravenous injection of nicotinoyl-GABA. In A and B, above: tonic activity in inferior cardiac nerve, reflex responses (groups A and C), and postactivation inhibition of tonic and reflex activity (I), marker of electrical stimulation of afferent fibers of tibial nerve (7 V, 1 msec, 1 cm/sec), pressor vasomotor reflex, marker of stimulation (10 sec, frequency 10 cm/sec). Below: waves of excitation of A and C afferents of tibial nerve in neurogram of sciatic nerve; scheme of experiment – stimulation of tibial nerve (t), afferent neurogram recorded in sciatic nerve (j), and reflex responses recorded in sympathetic nerves (C and R).

EXPERIMENTAL METHOD

Experiments were carried out on 45 cats anesthetized with chloralose (30 mg/kg) and urethane (400 mg/kg), maintained on artificial respiration and heating.

Tone of the sympathetic nervous system and central processes of vasomotor reflex formation were assessed by electroneurographic recording of tonic activity in the sympathetic nerve of the heart and kidneys and of reflex responses from group A and C afferent fibers of somatic and visceral nerves [4, 8]. Reflex responses from the various groups of afferents were identified by recording the afferent neurogram [15].

The arterial pulse pressure and pressor vasomotor reflexes were recorded simultaneously on the mingograph-81 (Elema) and the Cossor instrument (Disa Electronic). To localize the action of GABA and its nicotinoyl derivatives on the afferent and efferent components of the spinal reflex arc, reflex responses in the sympathetic nerves were compared with responses evoked by stimulation of the lateral column of the spinal cord [2].

GABA, nicotinoyl-GABA, its ethyl ester, and the γ-aminobutyrate of nicotinic acid were injected intravenously and intraperitoneally in increasing doses from 10 to 200 mg/kg body weight. In some experiments the compounds were injected into the lateral ventricles.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that GABA and nicotinic acid evoked a hypotensive response starting from relatively low doses. However, this response was not accompanied by any corresponding changes in tonic activity in the sympathetic nerves of the heart and kidneys. In 2 of 10 cases, on increasing the dose of GABA from 10 to 100 mg/kg, a slight and transient weakening of tonic activity in the sympathetic nerves and a decrease in amplitude of reflex responses from group A and C afferent fibers of the tibial and greater splanchnic nerve were observed. The depriming effect of GABA on sympathetic and vasomotor tone was clearly revealed when the compound was injected into the lateral ventricles (1-10 mg). This effect was characterized by inhibition of responses from slow-conducting afferent fibers of groups A_δ and C and by

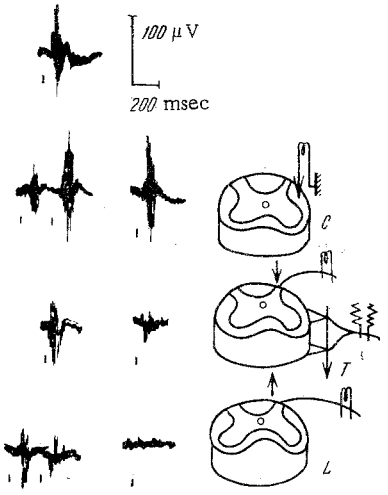

Fig. 2. Effect of GABA and the ethyl ester of nicotinoyl-GABA on reflex responses in the sympathetic nerve of the kidney from group A afferents of the tibial and splanchnic nerves and responses to stimulation of lateral columns of the spinal cord. From left to right: responses in renal nerve before injection of compounds (control), responses in renal nerve after injection of GABA and ethyl ester of nicotinoyl-GABA, scheme of experiment. Legend, from top to bottom: left – response in renal nerve evoked by stimulation of lateral columns of spinal cord (5V, 0.2 msec); reflex response and postactivation inhibition in renal nerve to stimulation of tibial nerve, no change in response evoked by stimulation of lateral columns during postactivation inhibition (paired stimuli, interval 240 msec); reflex response in renal nerve to stimulation of splanchnic nerve (7V, 0.5 msec); reflex responses (paired stimuli 10V, 1 msec, interval 240 msec) and postactivation inhibition in renal nerve (inhibition of second response compared with first) to stimulation of tibial nerve. Right – response in renal nerve evoked by stimulation of lateral columns of spinal cord after injection of GABA (1 mg into cerebral ventricles) and of ethyl ester of nicotinoyl-GABA (80 mg/kg, intravenously); reflex response to stimulation of splanchnic nerve 10 min after injection of GABA; reflex response to stimulation of tibial nerve 10 min after injection of ethyl ester of nicotinoyl-GABA. On scheme, from top to bottom: stimulation of lateral columns of spinal cord (C), stimulation of splanchnic nerve and recording of reflex responses in renal nerve (T), stimulation of tibial nerve (L).

an increase in the intensity of postactivation inhibition of tonic activity in the sympathetic nerves in response to impulses from A_β afferents. Under these conditions a parallel was observed between the development of the hypotensive response and the decrease in tonic and reflex activity in the sympathetic nerves.

It can accordingly be concluded that the hypotensive effect of GABA and nicotinic acid when injected intravenously is due principally to the spasmolytic properties of the compounds. Where marked penetration of GABA into the brain took place in the blood-brain barrier (after intraventricular injection) its central depriming effect on the sympathetic and vasomotor tone was observed.

By contrast with GABA, nicotinoyl-GABA, its ethyl ester, and γ-aminobutyrate of nicotinic acid, when injected intravenously and intraperitoneally, had a marked inhibitory action on tonic activity in the renal and inferior cardiac nerves, and also on reflex responses to electrical stimulation of group A and C afferent fibers of the somatic and visceral nerves (Fig. 1). These compounds inhibited pressor vasomotor reflexes on the average by 60-80% for 40-60 min. Of the three compounds, nicotinoyl-GABA and its ethyl ester were most active. The threshold doses of these substances were 20-40 mg/kg. The γ-aminobutyrate of nicotinic acid [18] was less active. It caused appreciable inhibition of tonic and reflex activity only in doses of 100-200 mg/kg. A characteristic feature of the action of these compounds, like that of GABA, was that they intensified postactivation inhibition of tonic activity in the sympathetic nerves in response to impulses from group A afferent fibers (Fig. 1B). Reflex responses in the sympathetic nerves were significantly inhibited (by 80-90%), whereas responses evoked by stimulation of the lateral columns showed no significant change (Fig. 2). This process evidently has a marked presynaptic inhibitory component, like the effects of GABA and sodium hydroxybutyrate [9, 14], aimed at primary group A afferents (Ia, Ib, II cutaneous and muscle afferents, and also terminals of primary afferent fibers of the splanchnic nerve). This hypothesis is confirmed by results obtained previously showing that the postactivation inhibitory response is antagonized by picrotoxin, which blocks presynaptic inhibition at the segmental level [3]. The presynaptic character of the inhibition was also demonstrated by the prolonged dynamics of the process. Unlike the familiar types of postsynaptic inhibition, whose duration does not exceed 50 msec [9], the duration of the postactivation inhibition measured by the writers previously averaged 500-1000 msec after appropriate stimulation of intact animals and 100-200 msec after stimulation of spinal animals [1, 2].

All three nicotinoyl compounds of GABA can thus penetrate into the brain across the blood-brain barrier

and there exert a depriming effect on intracentral processes of formation of sympathetic tone and vasomotor reflexes. These experiments show that this effect is due to the inhibitory action of GABA or of its metabolites on the central component of the vasomotor reflexes. The more stable chemical bond between GABA and nicotinic acid in the first two compounds than in the γ-aminobutyrate of nicotinic acid evidently allows freer penetration of GABA into the brain, and this explains the much higher level of their activity.

It can be postulated on the basis of these results that the nicotinoyl compounds of GABA studied in these experiments may prove useful in the treatment of cardiovascular diseases and, in particular, those of neurogenic origin.

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