

Effects of GABA Derivative TZ-50-2 on the Autonomic Nervous System

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 129, No. 2, pp. 189-193, February, 2000
Original article submitted November 23, 1999

GABA derivative TZ-50-2 (4-oxy-3-benzylamino-N-benzylbutanamide hemisuccinate) with pronounced neurotropic (anticonvulsive and local anesthetic) and cardiotoxic (antiarrhythmic and antianginal) activities produced a transient facilitation followed by a long-term inhibition of nerve transmission in the parasympathetic and, especially, sympathetic ganglia in acute experiments on cats. TZ-50-2 reduced sensitivity of adrenal chromaffin cells and cholinergic receptors of the carotid glomeruli to cytisine.

Key Words: *autonomic nervous system; γ -aminobutyric acid; neurotropic effect*

Many pharmacological preparations acting on different parts of the central and peripheral nervous system, and cardiovascular system exhibit also pronounced effects on the autonomic nervous system, which extends the range of their pharmacological activities [4,8,10,12].

We have previously shown that GABA derivative TZ-50-2 (4-oxy-3-benzylamino-N-benzylbutanamide hemisuccinate) exhibits high anticonvulsant [9], local anesthetic [11], antiarrhythmic [6], and antianginal [5] activities.

Our aim was to study the effects of TZ-50-2 on the autonomic nervous system.

MATERIALS AND METHODS

Experiments were performed on 40 male and female cats weighing 2.8-4.2 kg narcotized with intraperitoneal urethane (1.0-1.3 g/kg) [7].

The effects of TZ-52-2 (10 and 15 mg/kg, intravenously) on sympathetic (superior cervical) and parasympathetic (cardiac) ganglia were studied [12]. In additional experimental series nicotinic cholinergic receptor stimulator cytisine (0.025 ml/kg) was injected intravenously. Changes in systemic blood pressure

(SBP) in response to carotid artery occlusion were measured. We also studied the influence of TZ-52-2 on the nicotinic action of acetylcholine (2 mg/kg, intravenously) after blockade of muscarinic receptors with atropine (2.6 mg/kg, intravenously). SBP in the common carotid artery, pneumogram, and mechanogram of the third eyelid were recorded. The functional state of peripheral cholinergic and adrenergic structures was assessed by responses of SBP and of the third eyelid tonus to intravenous injection of acetylcholine (10 μ g/kg) and epinephrine (25 μ g/kg) [1,3].

The data were analyzed by routine statistical methods [2].

RESULTS

TZ-50-2 in a dose of 10 and 15 mg/kg produces a moderate hypotensive effect (6.1 ± 0.49 and 11.6 ± 1.72 mm Hg, respectively, $p < 0.05$) persisting for 1.3 ± 0.11 and 1.8 ± 0.09 min, respectively ($p < 0.05$). It also enhanced respiration during 0.8 ± 0.08 and 0.6 ± 0.06 min, respectively ($p > 0.05$), which was followed by a period of slight inhibition (2.2 ± 0.11 and 3.6 ± 0.54 min, respectively, $p < 0.05$).

TZ-50-2 (10 and, especially, 15 mg/kg) inhibits propagation of impulses in parasympathetic efferent pathways. This effect persisted for 13.2 ± 1.07 and 23.4 ± 1.28 min, respectively ($p < 0.05$) and manifested in a less pro-

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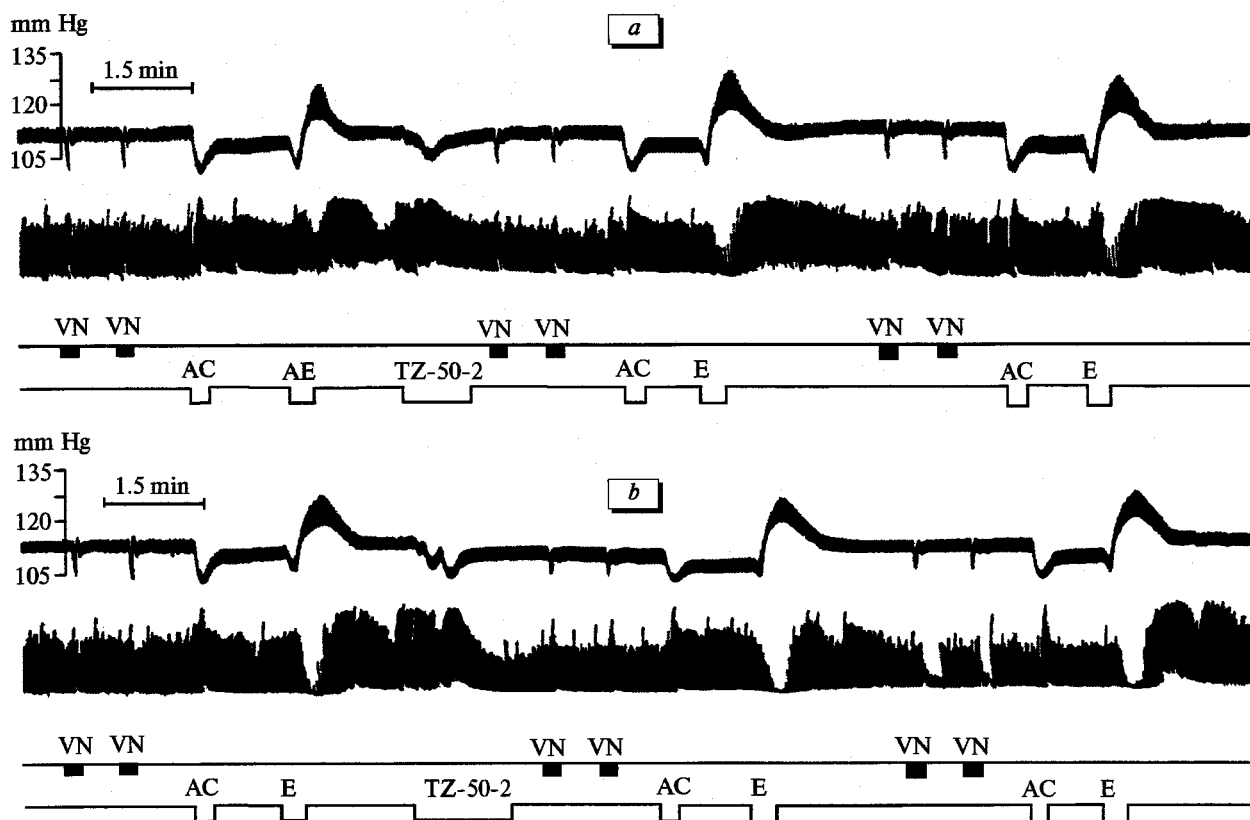


Fig. 1. Effect of TZ-50-2 in a dose of 10 (a) and 15 µg/kg (b) on the amplitude of SBP and respiratory responses to electrical stimulation of the cervical part of the vagus nerve and to injection of acetylcholine (AC, 10 µg/kg) and epinephrine (E, 25 µg/kg) in cats. From bp to bottom: blood pressure, pneumogram, electrical stimulation of the vagus nerve (VN).

nounced decrease in SBP (by 8.8 ± 0.64 and $46.4 \pm 2.15\%$, respectively, $p < 0.05$) in response to electrical stimulation of preganglionic vagal fibers. At the same time, TZ-50-2 in both doses did not influence epinephrine-induced pressor response and inhibition of respiration (Fig. 1).

In a dose of 10 mg/kg TZ-50-2 reduced the amplitude of third eyelid response, which implies its inhibitory action on the transmission of efferent signals to postganglionic sympathetic fibers. This effect lasted for 39.4 ± 2.15 min and peaked 23.8 ± 1.72 min post-injection ($93.8 \pm 1.5\%$). A slight contraction of the third eyelid observed during the injection of TZ-50-2, or immediately after it possibly points to facilitation of transmission in sympathetic ganglia (Fig. 2, a).

In a dose of 15 mg/kg, the preparation diminished respiratory response to cytisine, which indicated partial block of excitation in the carotid reflexogenic zone. The amplitudes of vasoconstrictor and third eyelid responses also decreased by $86.4 \pm 1.72\%$ and $76.8 \pm 1.93\%$, respectively, which suggests inhibition of signal transmission in sympathetic ganglia and celiac nerve endings innervating the adrenal medulla. In this series, injection of 15 mg/kg TZ-50-2 also induced slight contraction of the third eyelid (Fig. 2, b).

TZ-50-2 (10 mg/kg) reduced pressor and respiratory responses to occlusion of the common carotid

artery for a short period (8.20 ± 0.64 min), which suggest its inhibitory effect on mechanoreceptors of the carotid zone (Fig. 3, a).

In atropinized cats, injection of 10 mg/kg TZ-50-2 suppressed nicotinic effect of acetylcholine, enhanced depressor and reduced pressor components of SBP response, and inhibited respiration (Fig. 3, b).

Thus, TZ-50-2 (10 mg/kg and 15 mg/kg) produces a transient hypotensive effect, stimulates respiration, inhibits transmission in parasympathetic and, especially, in sympathetic ganglia, and reduces sensitivity of adrenal chromaffin cells and nicotinic cholinergic receptors in the carotid glomeruli. At the same time, the preparation does not influence pressor reflex and respiratory response induced by epinephrine. TZ-50-2 exhibits a biphasic action on cholinergic structures: short-term activation followed by long-term moderate inhibition. It can be concluded that the transient hypotensive effect of TZ-50-2 is due to both excitation of cardiac and vascular muscarinic receptors and inhibition of efferent transmission in ganglia.

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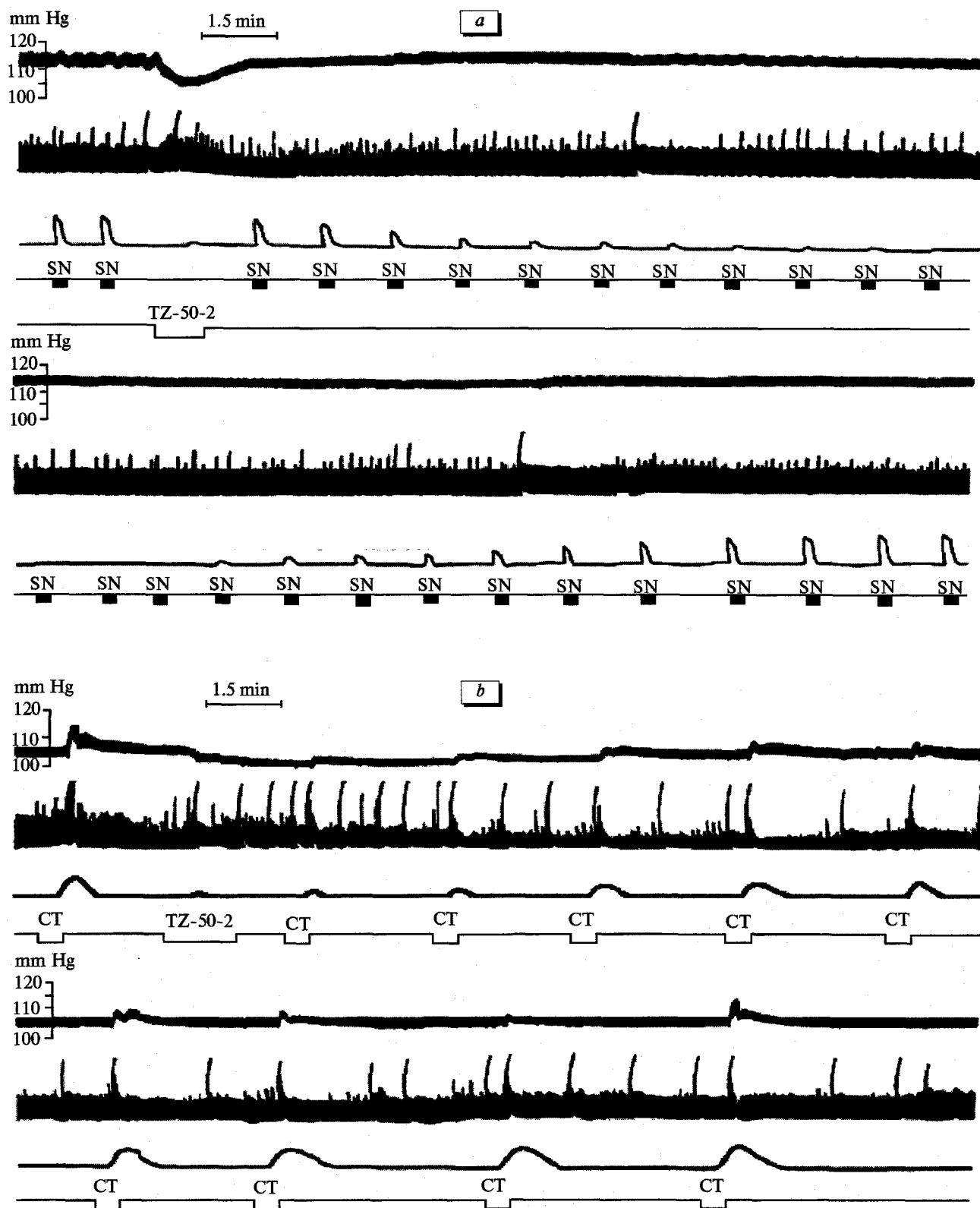


Fig. 2. Effect of TZ-50-2 in a dose of 10 (a) and 15 µg/kg (b) on blood pressure, respiratory, and third eyelid responses to electrical stimulation of the cervical sympathetic chain and injection of cytosine (CT, 0.025 ml/kg) in cats. From top to bottom: blood pressure, pneumogram, third eyelid mechanogram, and electrical stimulation of the sympathetic trunk (SN).

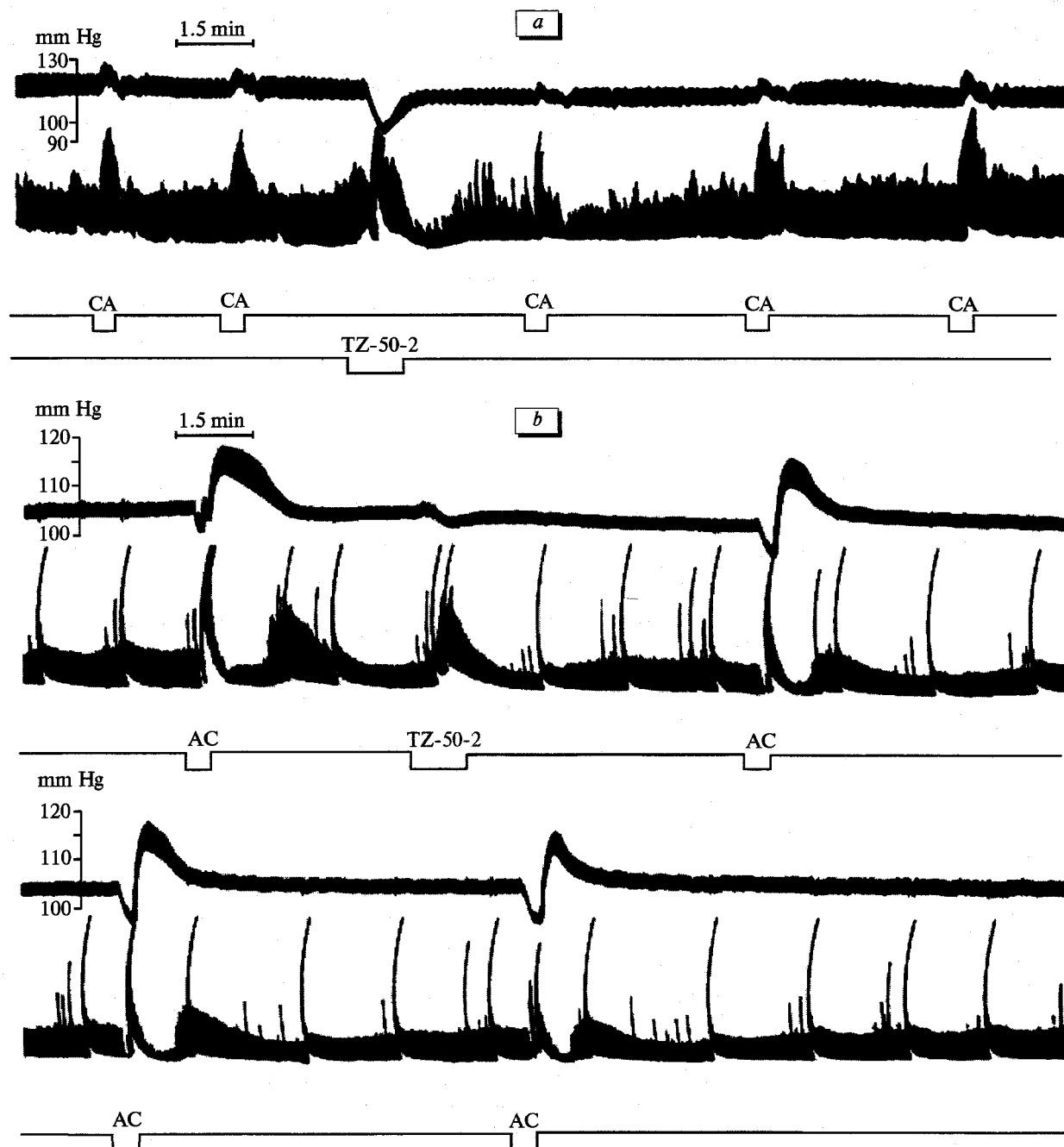


Fig. 3. Effect of TZ-50-2 (10 μ g/kg) on blood pressure and respiratory responses to occlusion of the carotid artery (a) and injection of acetylcholine (AC, 2 μ g/kg, b) in atropinized cats. From top to bottom: blood pressure, pneumogram, occlusion of the carotid artery (CA).

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