PHARMACOLOGY

CONNECTION BETWEEN CENTRAL ACTION OF GLYCERYL TRINITRATE AND MONOAMINE METABOLISM OF THE BRAIN

N. V. Kaverina, N. B. Vysotskaya, Yu. B. Rozonov, and T. M. Shugina

We have previously shown that glyceryl trinitrate depresses reflex reactions of the coronary vessels and arterial pressure in response to stimulation of various reflexogenic zones and that this effect is due to the influence of the drug on the centers controlling the circulation [2, 3]. Comparison of these findings with observations of other authors showing that glyceryl trinitrate does not increase the blood flow in the vessels of the heart [7, 12] led to the suggestion that its clinical value may be determined by its central action. This hypothesis, however, indicates only in general features the properties of glyceryl trinitrate by virtue of which it remains even today the most reliable remedy for the treatment of angina pectoris.

The object of the present investigation was to continue the study of the mechanism of action of glyceryl trinitrate on processes of central regulation of vascular tone.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with urethane (200–300 mg/kg) and chloralose (20–50 mg/kg). Since constrictor reflexes acting on the coronary vessels are mediated through the sympathetic innervation of the heart [3], in order to judge the effect of glyceryl trinitrate on the central processes responsible for formation of these reflexes, the method of electroneurographic recording of tonic and reflex activity in the inferior cardiac nerve during electrical stimulation of the central end of the divided tibial nerve, with differentiation of responses to impulses in A and C groups of afferent fibers was used [6]. To judge the effect of glyceryl trinitrate on reflex inhibition of tonic activity in the sympathetic nerves of the heart, the mechanoreceptors of the carotid sinus were stimulated by raising the pressure. This was done by pumping blood from the peripheral end of the animal's divided carotid artery into the region of the carotid sinus, which was isolated from the systemic circulation, at assigned perfusion pressures.

In a special series of experiments the noradrenalin concentration was determined in various parts of the cats' brain by a spectrofluorometric method [11].

EXPERIMENTAL RESULTS AND DISCUSSION

These experiments showed that glyceryl trinitrate in a dose of 1 mg/kg depresses spontaneous electrical activity and reflex discharges in the inferior cardiac nerve. In some experiments selectivity of its action was observed in relation to reflex discharges from afferent C-fibers along which nociceptive impulses are known to be transmitted into the central nervous system. At the same time pressor vasomotor reflexes were depressed. The effect lasted for 30–35 min (Fig. 1).

An interesting fact revealed by our previous investigations was that similar changes in character of the reflex discharges in the sympathetic nerves develop under the influence of monoamines and of their precursors – DOPA and 5-hydroxytryptophan, and also of substances capable of liberating monoamines from tissue reserves: reserpine (in phase I of its action), analgesics, and MAO inhibitors [4]. These substances simultaneously caused a sharp increase in the intensity of reflex inhibition of tonic activity evoked by stimulation of the carotid sinus mechanoreceptors. The development of these effects coincides in time with the period of liberation of monoamines from reserves of the labile fraction [4, 5, 8, 13, 14]. After comparing these observations with the histochemical findings of Carlson and co-workers [9], who found a system of...
Glyceryl trinitrate, 1 mg/kg

Fig. 1. Effect of glyceryl trinitrate on tonic activity and reflex discharges in the inferior cardiac nerve in response to impulses from afferent fibers of A and C groups and vasomotor reflexes arising during electrical stimulation of afferent fibers of the tibial nerve. A) Tracing of tonic activity and reflex discharges in inferior cardiac nerve during electrical stimulation of central end of divided tibial nerve (3 V, 2 msec, 1 stimulus/sec); B) tracing of vasomotor reflexes arising during electrical stimulation of central end of divided tibial nerve (30 V, 1 msec, 30 stimuli/sec for 20 sec); 1) tonic activity and reflex responses in inferior cardiac nerve and vasomotor reflexes before injection of glyceryl trinitrate; 2) the same 5-7 min after injection of glyceryl trinitrate in dose of 1 mg/kg body weight; 3) the same 30 min after injection of the drug.

Effect of Glyceryl Trinitrate (1 mg/kg) on Noradrenalin Concentration (in \( \mu g/g \)) in Different Parts of the Brain Tissue in Cats*

<table>
<thead>
<tr>
<th>Time of observation</th>
<th>Hypothalamus</th>
<th>Medulla</th>
<th>Thoracic portion of spinal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.55±0.077</td>
<td>0.63±0.11</td>
<td>0.5±0.09</td>
</tr>
<tr>
<td>30 Min after injection</td>
<td>0.24±0.04</td>
<td>0.2±0.017</td>
<td>0.27±0.08</td>
</tr>
<tr>
<td>2 h after</td>
<td>0.29±0.04</td>
<td>0.3±0.05</td>
<td>0.37±0.006</td>
</tr>
<tr>
<td>4 h after</td>
<td>0.47±0.12</td>
<td>0.5±0.1</td>
<td>0.4±0.07</td>
</tr>
</tbody>
</table>

*Mean results of the series of experiments with standard error are shown in the table.

Inhibitory monoaminergic neurons descending from the vasodepressor region of the medulla in the posterolateral columns of the spinal cord, we were able to postulate that the observed effects are associated with activation of the inhibitory system of monoaminergic neurons by monoamines.

It was stated above that the character of the action of glyceryl trinitrate on tonic and reflex activity of the sympathetic nervous system is analogous to the effects of monoamines and of substances liberating their tissue reserves just described. However, this was not the only factor suggesting that central adrenergic mechanisms are concerned in the development of the effects of glyceryl trinitrate. This compound is known to abolish symptoms of excitation of the sympathetic nervous system arising during attacks of angina pectoris. The view is also held that its clinical efficacy is associated with its ability to abolish sympathetic influences on the myocardium and thereby to reduce the energy requirements of the heart [10, 15, 16].

The study of the action of glyceryl trinitrate in experiments in which injury to the myocardium was produced by injection of potassium chloride into the lateral ventricle of the brain showed that the drug abolishes the increased bioelectrical activity developing under these conditions in the sympathetic nerves of the heart and prevents accumulation of catecholamines in the myocardium [1]. On the basis of these findings, we postulated that adrenergic mechanisms may be concerned in the mechanism of action of