

Effect of Pyrrolidone-Pyroglutamic Acid Composition on Blood Flow in Rat Middle Cerebral Artery

G. A. Semkina, D. D. Matsievskii, and N. R. Mirzoyan

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We compared the effects of a pyrrolidone-pyroglutamic acid composition and nimodipine on blood circulation in the middle cerebral artery in rats. The composition produced a strong effect on blood supply to the brain, stimulated blood flow in the middle cerebral artery (by $60 \pm 9\%$) and decreased blood pressure (by $25.0 \pm 2.7\%$). The cerebrovascular effects of this composition differed from those of nimodipine. Nimodipine not only increased middle cerebral artery blood flow, but also decreased cerebral blood flow in the early period after treatment.

Key Words: cerebral blood flow; middle cerebral artery; pyrrolidone; pyroglutamic acid; nimodipine

A composition of pyrrolidone and pyroglutamic acid possesses neuroprotective activity during local and global cerebral ischemia and protects nervous tissue from structural, metabolic, and functional disturbances [3,5].

Here we compared the effects of a composition containing pyrrolidone and pyroglutamic acid and cerebrovascular Ca^{2+} channel blocker nimodipine on blood circulation in the middle cerebral artery.

MATERIALS AND METHODS

Experiments were performed on 30 male Wistar rats weighing 250-300 g. General anesthesia was produced by intraperitoneal injection of sodium ethaminal in a dose of 40 mg/kg. Blood flow was measured using Doppler ultrasound devices [2]. An opening was made in the right side of the skull to study blood flow in branches of the middle cerebral artery. The brain region supplied by the middle cerebral artery was verified using a contact transducer. The location of the blood vessel was esti-

mated by recording the sound signal of blood flow. The use of an ultrasound sensor (size 0.5-0.7 mm, operating frequency 38.5 MHz) allowed us to study low-rate blood flow (mm/sec) in branches of the middle cerebral artery with a diameter $\leq 100 \mu$.

For blood pressure measurements and drug administration a polyethylene catheters were introduced into the femoral artery and vein. The data were transferred from blood flow probes and pressure sensors to an analog computer of ultrasound devices (online and continuous recording of the resistance in the middle cerebral artery).

A composition of pyrrolidone (Schuchardt Munchen) and pyroglutamic acid (Fluka) in a dose of 20 mg/kg was infused intravenously over 3 min (0.3 ml). Nimodipine (Nimotop, Bayer) in a dose of 20 mg/kg was infused intravenously (0.3 ml). The results were analyzed by Student's *t* test.

RESULTS

Intravenous infusion of the composition significantly increased blood flow in the middle cerebral artery (by $60 \pm 9\%$, $n=20$). In most animals blood flow progressively increased and reached maximum 60-90 min after treatment. Blood flow decreased in the follow-up period and did not differ

Laboratory for Pharmacology of Cerebrovascular Disorders, V. V. Zakusov Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow. **Address for correspondence:** cerebropharm@mail.ru. N. R. Mirzoyan

from the baseline level after 2-3 h. Eight rats exhibited an earlier and less continuous increase in blood flow in response to administration of the test drugs (5-30 min after treatment). It should be emphasized that the increase in blood flow in these animals was not necessarily significant. The composition had no effect on the middle cerebral artery blood flow in 5 of 20 animals.

The mixture in the specified dose decreased blood pressure by $25.0 \pm 2.7\%$. These changes were observed immediately after treatment and developed over 5 min. Blood pressure returned to normal 10-15 min after administration of pyrrolidone and pyroglutamic acid.

Middle cerebral artery resistance decreased by $21 \pm 7\%$ immediately after administration of the composition. This decrease was most pronounced 60-120 min after the start of treatment. Middle cerebral artery resistance decreased by $73.0 \pm 9.6\%$ after infusion for at least 2 h. The observed decrease in middle cerebral artery resistance suggests that this composition has a direct effect on the tone of cerebral vessels.

In 8 of 10 animals intravenous infusion of the reference drug nimodipine in a dose of 0.03 mg/kg decreased middle cerebral artery blood flow by 20%. This effect developed over 3-5 min after treatment. The next phase was observed 10 min after administration of nimodipine (increase in middle cerebral artery blood flow by $65 \pm 4\%$). Two rats did not exhibit the first phase of nimodipine-induced changes and were characterized by an increase in middle cerebral artery blood flow.

In all experiments blood pressure decreased by $35.0 \pm 2.4\%$ immediately after administration of nimodipine and remained low over 10-15 min. The resistance in the middle cerebral artery little varied in the early period after administration of nimodipine: it decreased 15-20 min after nimodipine administration and attained the minimum on minutes 60-90 min. Middle cerebral artery resistance decreased by $66.0 \pm 8.2\%$. In our experiments blood flow was measured in small branches of the middle cerebral artery with a diameter not exceeding 100 μ . Our findings are consistent with the results of previous experiments on large branches of the middle cerebral artery. These data indicate that nimodipine improves blood supply to the brain [4].

Our results are consistent with published data that this composition modulates microcirculation in rat brain cortex [1].

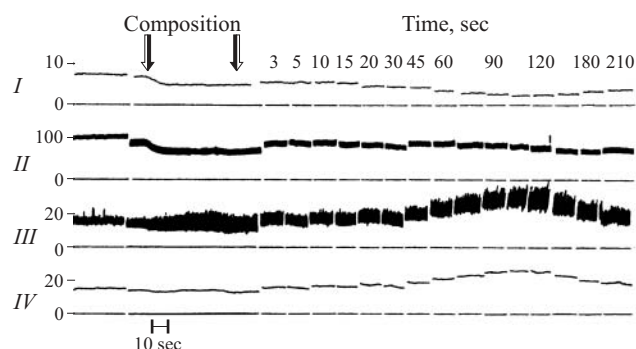


Fig. 1. Effect of the composition containing pyrrolidone and pyroglutamic acid on blood flow, middle carotid artery resistance, and blood pressure in the rat. Arrows: administration of the composition. Here and in Fig. 2: right middle cerebral artery resistance (mm Hg/mm/sec; I); blood pressure (mm Hg; II); pulse (III) and mean blood flow in a microvessel of the middle cerebral artery (IV, mm/sec).

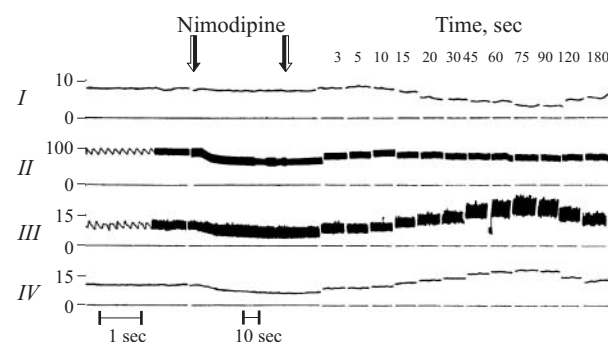


Fig. 2. Effect of nimodipine on blood flow, middle carotid artery resistance, and blood pressure in the rat. Arrows: administration of nimodipine.

We conclude that the composition of pyrrolidone and pyroglutamic acid significantly increases blood flow in the middle cerebral artery and produced a direct effect on the vascular tone. It should be emphasized that blood supply to the brain is not impaired in the early period after administration of this composition (as differentiated from nimodipine).

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