PHARMACOLOGY AND TOXICOLOGY

Effect of Glycine on Microcirculation in Pial Vessels of Rat Brain

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Single application of glycine in a final dose of 40 mg/kg to the surface of the parietal area of rat brain produced a potent vasodilatory effect. The diameter of arterioles increased to 250% from the baseline level 1-3 min after treatment. These changes persisted for 5-10 min. In the follow-up period the diameter of vessels progressively decreased to the baseline level. Repeated application of glycine in the same dose also induced dilation of arterioles. Application of physiological saline under similar conditions did not produce these changes.

Key Words: *glycine; cerebral vessels; microcirculation*

Glycine is extensively used in the treatment of patients with neurological disorders. This preparation has a positive therapeutic effect in patients with ischemic stroke [3]. At the molecular level, the neuroprotective effect of this amino acid is mediated by one or several general biological mechanisms. Glycine possesses protective activity during ischemia and reperfusion of the liver, kidneys, and skeletal muscles [7]. The question arises whether glycine directly modulates microcirculation or its protective effect is mediated by indirected mechanisms. Impaired blood supply to brain regions underlies pathogenesis of ischemic stroke. The effect of medicinal preparations used for the therapy of this disorder should be evaluated with relation to the recovery of microcirculation. There is no direct evidence that glycine improves blood flow in the brain.

Here we studied the effects of glycine on cerebral arterioles were using the methods of biomicroscopy.

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MATERIALS AND METHODS

Experiments were performed on 30 male Wistar rats weighing 180-200 g. The animals were intraperitoneally anesthetized with 400 mg/kg chloral hydrate. Glycine (1 M) was dissolved in physiological saline and applied (0.1 ml) to the surface of the parietal area after craniotomy. The dura mater was removed or remained intact. The final dose of glycine was 40 mg/kg. Control animals were treated with physiological saline. The dura mater provided physiological conditions, but decreased the rate of glycine transport to microvessels by 2-3 times. After removal of the dura mater, vascular reaction (constriction or dilation) was observed 1-3 min after application of glycine. Visual monitoring of the microcirculatory bed involved a Philips video camera and was performed at the intervals varying from several seconds to 3 min. Images of microvessels were obtained with a surface-contact objective (×10). In this case, the integrity of the dura mater was not impaired. The method allowed us to obtain images at a 100-fold magnification [1,2]. The state of microcirculation in pial vessels of the brain was estimated by the diameter of arterioles (20-200 μ).

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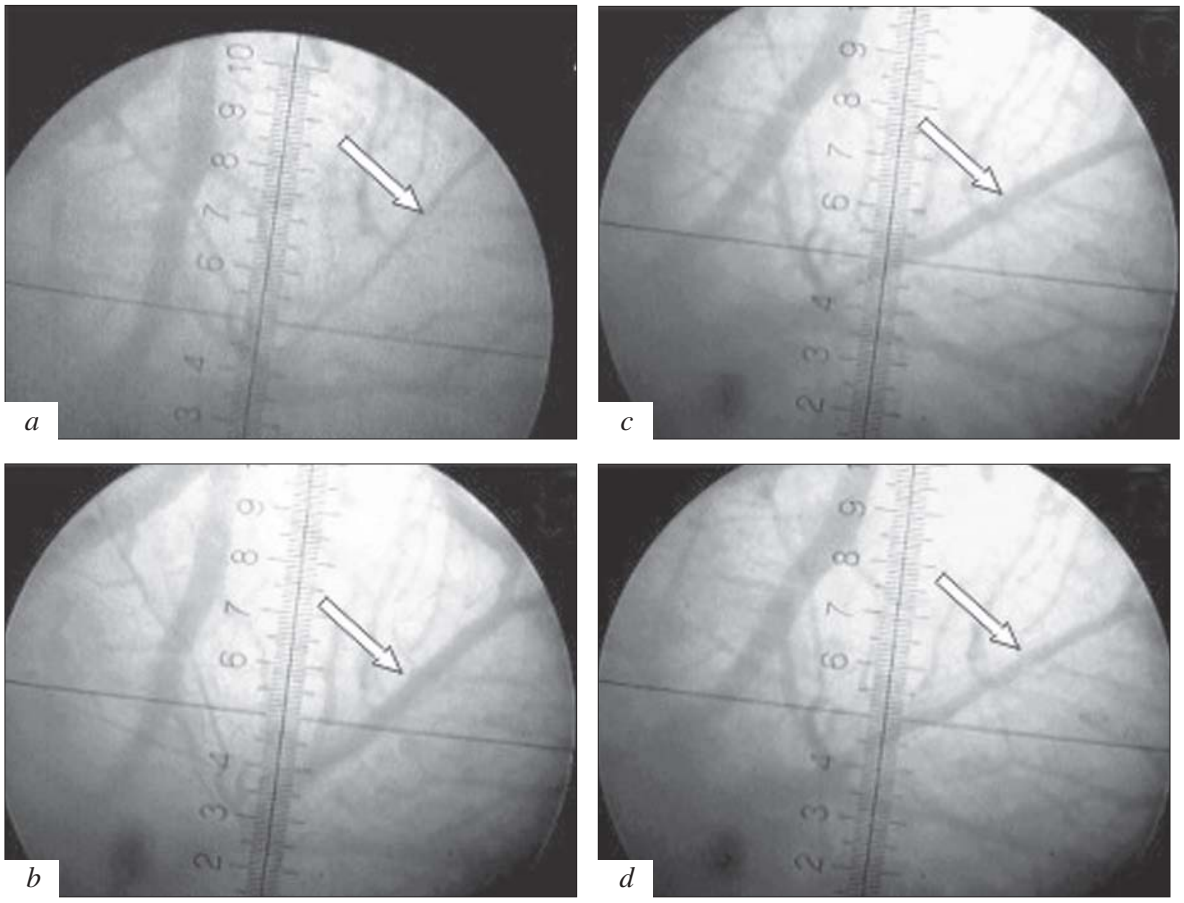

Fig. 1. Reaction of pial microvessels to glycine application. Initial state (*a*); 7 (*b*), 11 (*c*), and 15 min (*d*) after application of glycine. Arrows: arterioles (×100).

This parameter is the major characteristic of blood flow in vessels. The diameter of arterioles was measured using a graded scale (minimum scale mark 16 μ) projected on the image of microvessels.

RESULTS

Application of glycine was followed by pronounced dilation of arterioles. The diameter of arterioles increased by 150-250%, which depended on the initial diameter of vessels. This effect developed 1-3 min after application (Fig. 1). The amplitude of vasodilation was in inverse proportion with the diameter. The diameter of 20-40-μ arterioles increased by 200-250%. Large vessels (50-80 μ) were dilated by 150-200%. The diameter of vessels returned to normal 50-10 min after application of glycine. Repeated application of glycine produced similar increase in vessel diameter (Fig. 2). These changes were not observed after application of physiological saline. The diameter of venules remained practically unchanged.

Our study revealed a new effect of glycine on microcirculation in cerebral vessels. Glycine causes dilation of pial vessels by several mechanisms. Glycine activates endothelial nitric oxide (NO) synthase, which is followed by stimulation of NO production

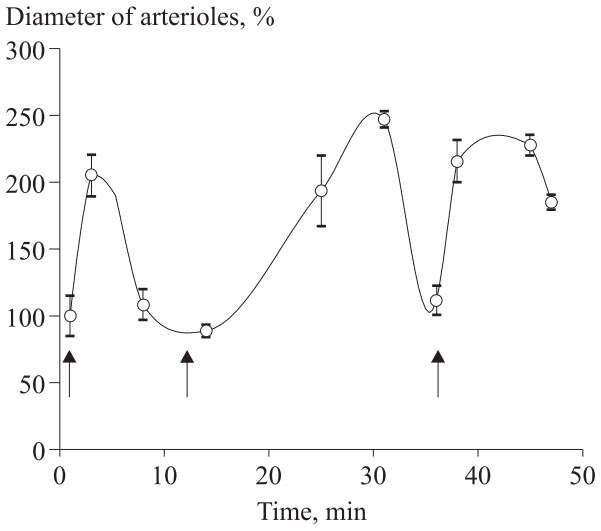

Fig. 2. Typical changes in the diameter of rat pial microvessels (arterioles) under the influence of glycine (% of the baseline level). Arrows: glycine application.

and relaxation of the smooth muscle wall in vessels. Published data show that the improvement of blood flow in rat kidneys under physiological conditions is mediated by the NO-dependent mechanism [5]. The protective effect of glycine is associated with compartmentalization of calcium ions in the cell [4]. It cannot be excluded that improvement of microcirculation is related to a direct effect of glycine, which serves as the inhibitory neurotransmitter [6]. The effect of glycine on microcirculation can be associated with blockade of α_1-adrenoceptors on smooth muscle cells in the wall of arterioles. These changes should be followed by the reduction of vascular tone (vasodilation). The *in vivo* effect of glycine can be realized via several molecular mechanisms. The prevalence of some mechanism is determined by metabolic activity of neurons and glial cells.

Our findings suggest that the increase in local glycine concentration improves microcirculation. Therefore, glycine should be used as a neuroprotector for the therapy of patients with ischemic stroke and other vascular disturbances in the brain.

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