PHARMACOLOGY AND TOXICOLOGY

Effect of Nimodipine on the Circulation in the Midbrain and Carotid Arteries of Rats

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It is found that nimodipine induces biphasic changes in the circulation in the midbrain artery: an initial slight and transient reduction gives way to a considerable and long-term increase of the circulation. Nimodipine also boosts the circulation in the common and internal carotid arteries, which coincides in time with, but is shorter than, the first phase of changes in the hemodynamics in the midbrain artery. The findings are not consistent with the common view on the selectivity of the cerebrovascular effect of nimodipine.

Key Words: *nimodipine; ultrasound method; cerebral circulation; midbrain artery*

According to published data nimodipine (ND), dihydropiridine calcium antagonist, possesses a selective cerebrovascular activity. Experiments on various animal species (rats, rabbits, monkeys) and with the use of discrete experimental methods have demonstrated the ability of ND to increase the cerebral circulation [1,5-9]. For a characterization of the vascular effect of ND it is important to study the dynamics of ND-induced changes in the cerebral circulation. Such an approach will advance our understanding on the mechanism of the cerebrovascular effect of ND and will promote both a more judicious use of the preparation in neurological patients and a targeted search for new cerebrovascular preparations. The aim of the present study was to study the effect of ND on the circulation and the vascular tonus in the system of the midbrain artery in comparison with the circulation in the common and internal carotid artery in rats.

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MATERIALS AND METHODS

The experiments were carried out on 30 male Wistar rats weighing 250-300 g under general anesthesia (Nembutal, 40 mg/kg, intraperitoneally). The circulation was measured using the ultrasound Doppler technique [2]. Band transducers calibrated in units of the voluime rate of circulation were placed on the right common and internal carotid arteries. The circulation in the right midbrain artery was measured using an ultrasound transducer, which was previously used for a study of the coronary circulation in rats [3]. To this end an openning was made on the right side of the head, the midbrain artery was located by the sound signal, and the optimal position of the transducer was determined. Arterial pressure was measured and the preparation was injected through polyethylene cath-

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eters introduced into the femoral artery and vien. The data from the transducers were fed into an analog computer which calculated in real time the resistance and assessed the dynamics of redistribution of the circulation in the vascular bed of the above regions. In some experiments cardiac output was measured using an intravascular transducer inserted through the femoral artery to the ascending aorta [4]. ND (Bayer) was injected intravenously in a dose of 0.03 mg/kg in a volume of 0.3 ml during 3 min. The results were processed statistically using the Student t test.

RESULTS

First, we studied the effect of ND on the circulation in the common and internal carotid arteries. The experiemnts revealed that ND in a dose of 0.03 mg/kg i.v. led to a marked increase (54±4.4%) in the volume rate of the circulation in the common carotid artery, the linear rate also being increased during diastole. The vascular resistance dropped by 51±3% (Fig. 1). The vascular effect of ND was noted immediately after injection and attained the maximal value after 3-5 min. Simultaneously, immediately after ND injection arterial pressure (AP) dropped and 3 min later it constituted 30±3.4% of the initial value. Thirty to 50 min after injection of ND the circulation in the common carotid artery and AP returned to the initial level. At the same time as the circulation was recorded in the common carotid artery, the cardiac output was measured using a miniature transduced inderted into the ascending aorta through the femoral artery. The cardiac output was shown to be slightly increased under the action of ND, this increase accounting for 18% on average at the 3rd min postinjection.

In the second experimental series, together with the circulation in the common carotid artery, we recorded blood flow through the internal carotid artery to the brain. ND in the above dose was shown to induced a marked increase of the circulation, which attained the maximal value (45±6.4%) at the 5th min postinjection. The vascular resistance in the system of the internal carotid artery dropped immediately after injection of the preparation and after 3 min constituted 50±4.5%. The initial tonus of the internal carotid artery was regained 45-60 min after administration of ND (Fig. 1).

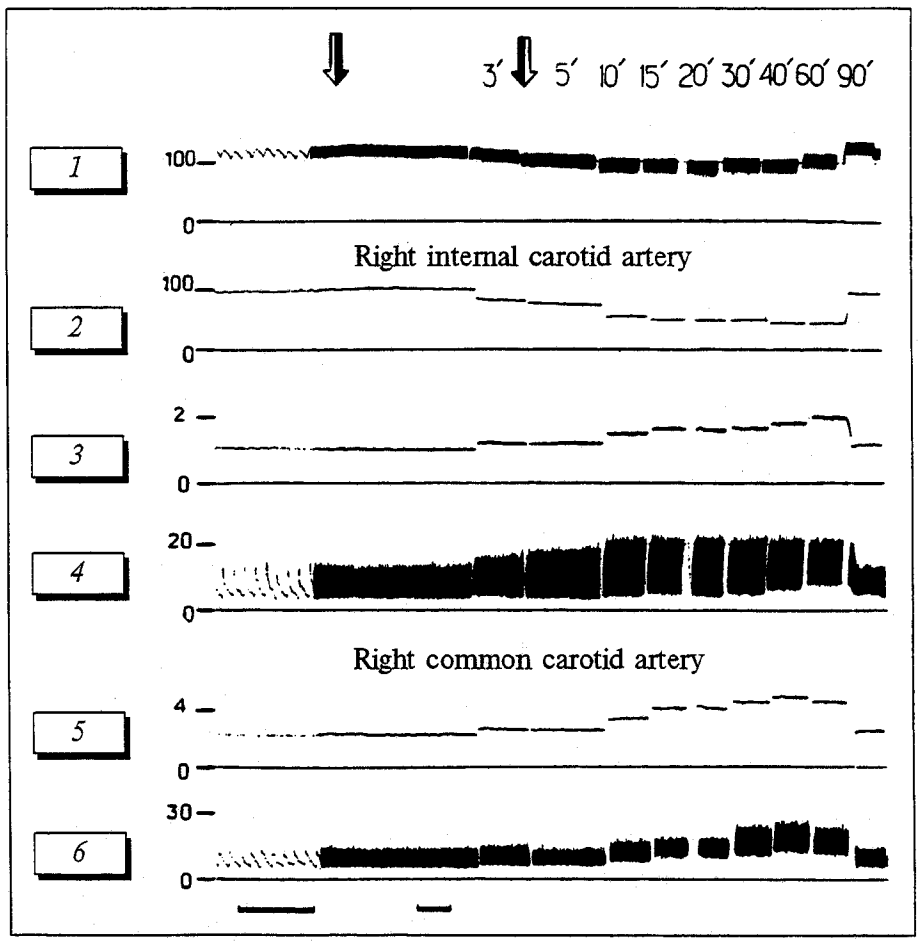

Fig. 1. Effect of ND (0.03 mg/kg, i.v.) on circulation and vascular resistance in the common and internal carotid arteries of rats. *1*) arterial pressure, mm Hg; *2*) vascular resistance, mm Hg/ml/min; *3*, *5*) volume blood flow, ml/min; *4*, *6*) pulse blod flow, cm/sec. Here and in Figs. 2 and 3: arrows indicate time of ND injection, min. Time scale 1 and 10 sec.

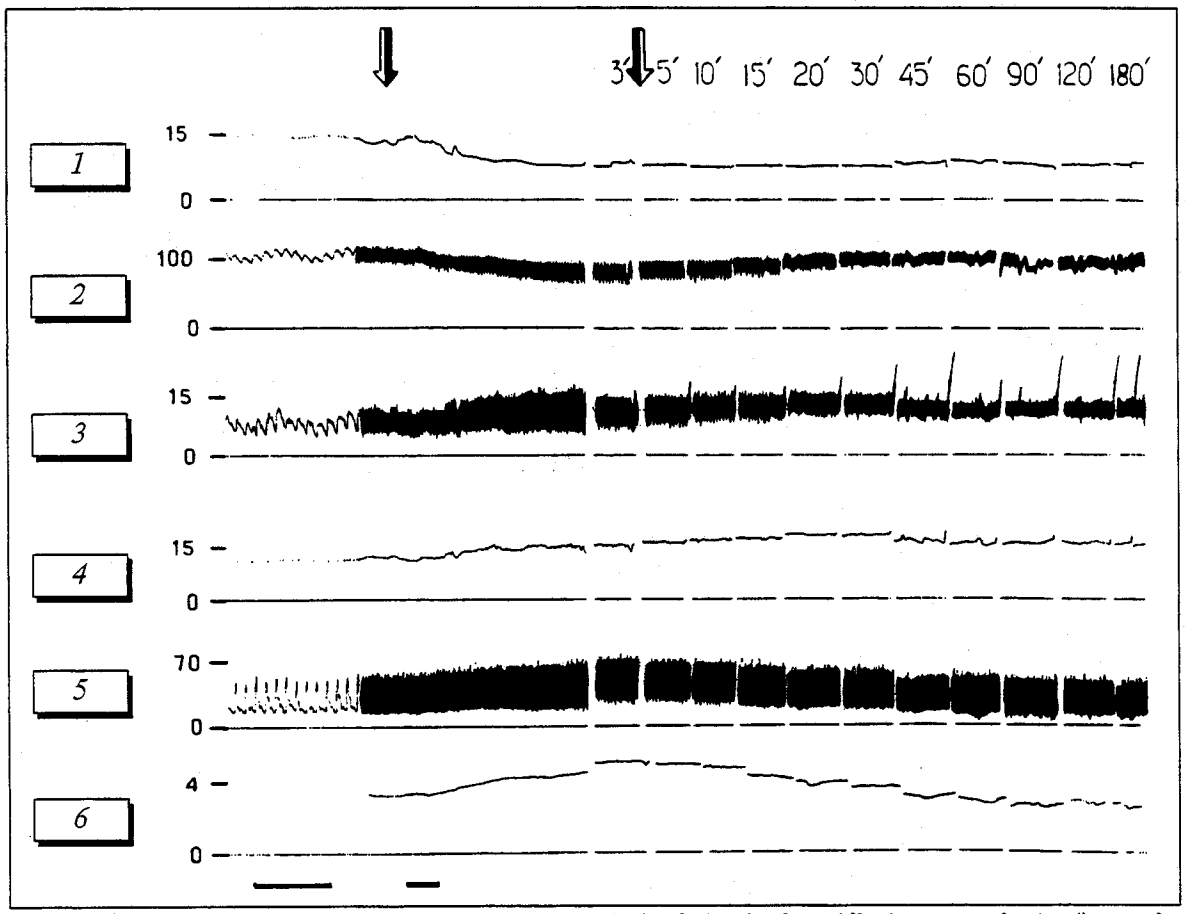

Fig. 2. ND—induced changes in vascular resistance and circulation in the midbrain artery of rats. *1*) vascular resistance in the right midbrain artery, mm Hg/cm/sec; *2*) arterial pressure, mm Hg; *3*) pulse blood flow in the right midbrain artery, cm/sec; *4*) averaged blood flow in the right midbrain artery, cm/sec; *5*) pulse blood flow in the right carotid artery, cm/sec; *6*) volume blood flow in the right common carotid artery, ml/min.

For direct evaluation of the state of the brain circulation, the circulation in the midbrain artery was recorded simultaneously with the circulation in the ipsilateral common carotid artery. ND was shown to induce biphasic changes in the midbrain artery circulation. Immediately after injection of the preparation we observed a slight (8-11%) and transient (1-3 min) reduction of the circulation in the artery system. Starting from the 5th min postinjection, a gradual increase of the circulation was noted, which attained the maximum (53±8.1%) 45 min postinjection (Figs. 2, 3). We did not observe the restoration of the initial circulation in the midbrain artery at the end of the majority of experiments (90-180 min). It should be emphasized that ND started to gradually lower the vascular resistance in the midbrain artery immediately after the injection (Fig. 2). The most pronounced drop of the vascular tonus (41±3.9%) was attained at the 45th min and lasted to the end of the experiment. As is seen from the experimental data, ND substantially increased the circulation in the common and internal carotid arteries and in the midbrain artery. We did not reveal any significant difference between these values, and this suggests that the preparation almost equally improves the blood supply of the brain and extracranial parts of the head.

An interesting feature emerged from the study of the dynamics and duration of changes in the circulation and the resistance of the vascular bed in the common and internal carotid and midbrain arteries: the circulation in the carotid arteries changed most 3-5 min postinjection and returned to the initial values after 45-60 min, while in the midbrain artery the circulation started to increase from the 5th min (after an initial slight transiant decrease), attained the maximum after 45-60 min, and retuned to the initial values at the end of the experiment (90-120 min). Thus, ND induced successive changes in the tonus of the common and internal carotid and midbrain arteries. It should be noted that the changes in the midbrain artery were similar in magnitude but considerably surpassed in duration those observed in the carotid arteries. This also follows from a study of the redistribution of

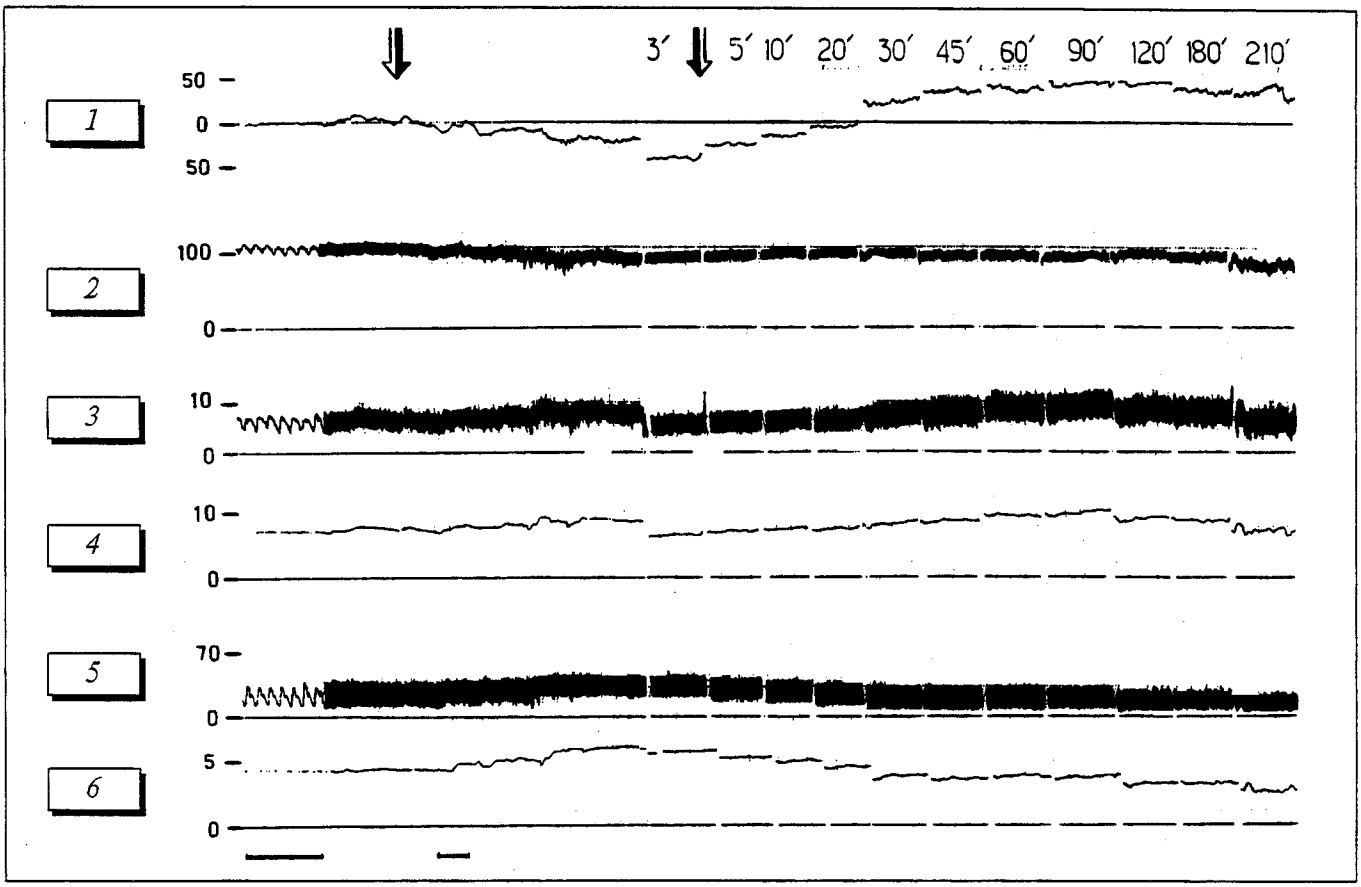

Fig. 3. Dynamics of ND-induced redistribution of circu-lation between the right common carotid and midbrain arteries of rats. *1*) balance between circulation in the right common carotid and midbrain arteries (upward-directed curve corresponds to increase of circulation in the midbrain artery vis-a-vis circulation in the common carotid artery), %; *2*) arterial pressure; mm Hg; *3*) pulse blood flow in the right midbrain artery, cm/sec; *4*) averaged blood flow in the right midbrain artery, cm/sec; *5*) pulse blood flow in the right carotid artery, cm/sec; *6*) volume blood flow in the right common carotid artery, ml/min.

the circulation in the midbrain and common carotid arteries (Fig. 3). During the first 3-10 min after injection of ND the increase in the circulation in the common carotid artery surpassed that in the midbrain artery, but then the balance shifted in favor of the midbrain rtery. The initial slight reduction of the circulation in the midbrain artery is apparently due to a marked dilation of the extracranial vessels and increased blood flow to this part of the head. These findings are consistent with published data [1,5-9], which point to the ability of ND to improve the cerebral circulation. However, we cannot agree with the popular view on the selectivity of the cerebrovascular effect of ND.

Thus, ND induces biphasic changes in the circulation in the midbrain artery: an initial slight and short-term reduction followed by a considerable and long-term increase. The circulation in the common and internal carotid arteries also increases considerably and to the same extent, but the increase is of shorter duration and outstrips ahead of the hemadynamic shifts in the midbrain artery.

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