PHYSIOLOGY

Effect of Neurotropin on Regional Cerebral Blood Flow and Systemic Blood Pressure

G. I. Kvrivishvili and N. P. Mitagvariya

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 6, pp. 612-614, June, 1998
Original article submitted May 15, 1997

Experiments on rabbits show that neurotropin has no effect on regional cerebral flow and systemic blood pressure under normal conditions, but reduces regional cerebral flow in partial circulatory hypoxia (ischemia) and recirculation.

Key Words: *regional cerebral circulation; ischemia; neurotropin; bradykinin*

High prevalence of cerebrovascular diseases, in particular, acute impairment of cerebral circulation dictates the necessity of effective means for prevention and/or pharmacological correction of cerebrovascular disorders. Using a model of partial transient circulatory hypoxia [2], we studied in acute experiments the effect of neurotropin (NT, a nonprotein extract from the skin of rabbit infected with *Vaccinia virus*, Nippon Zoki Pharmaceuticals Co.) [1] on regional cerebral blood flow (RCBF) and systemic blood pressure (SBP). NT exerts a broad spectrum of clinical effects and is extensively used in various pathologies of the central and peripheral nervous systems [6].

MATERIALS AND METHODS

Experiments were performed on 19 rabbits weighing 2-3 kg anesthetized with urethane (1.0-1.2 g/kg). After tracheotomy and institution of artificial ventilation, both common carotid arteries were separated with ligatures and both femoral arteries were catheterized: one for SBP monitoring and the other for bloodletting into a reservoir of SBP compensation system. Myorelaxants and NT were injected via a catheter inserted into the femoral vein. The animal head was fixed in a stereotactic apparatus, and left-sided craniotomy above the sensorimotor cortex was performed.

Regional cerebral blood flow was assessed by the hydrogen clearance method [4] and recorded using an OH-105 universal polarograph (Radelkis). In the first series (n=11), RCBF and SBP were measured before and for 30-40 min after intravenous injection of NT in a dose of 20 mg/kg (0.1 ml/kg). After that both common carotid arteries were occluded and systemic arterial hypotension (SBP=50-60 mm Hg) was modeled by bloodletting. Twenty minutes later the common carotid arteries were opened and reperfusion was performed for 60 min. RCBF was measured at each stage of experiments. In the second series (control, n=8) NT was omitted.

The data were processed statistically using the Student t test.

RESULTS

Thirty-forty minutes after intravenous injection of NT, SBP slightly decreased to 99.89% of the initial level, while RCBF increased to 102.3%. Unfortunately, we found no publications on the effect of NT on cerebral vessels. According to Nippon Zoki information (Osaka, 1984), oral administration of NT induced no cardiovascular effects in healthy volunteers during both rest and physical strain. A negligible

Laboratory of Regulatory Mechanisms of Metabolic Support of Brain Functions, I. S. Beritashvili Institute of Physiology, Georgian Academy of Sciences, Tbilisi

0007-4888/98/0006-0540$20.00

TABLE 1. Effect of NT on SBP and RCBF under Normal Conditions

No.	SBP, mm Hg		RCBF, ml/100 g/min	
	baseline	NT	baseline	NT
1	107.5	98.0	63.5	66.2
2	102.5	110.0	86.3	97.9
3	100.0	90.0	116.5	98.3
4	106.7	108.6	—	—
5	75.0	78.3	90.6	45.5
6	73.3	80.0	31.7	38.0
7	75.0	76.2	111.8	139.2
8	105.0	112.2	70.15	123.7
9	85.3	64.0	80.2	84.8
10	100.7	106.0	56.3	29.9
11	74.0	80.5	—	—
M±m	91.4±4.4	91.2±4.98	78.6±8.9	80.4±12.8

increase in RCBF after injection of NT against the background of unchanged SBP observed in our experiments (Table 1) agreed with these clinical data. However, NT considerably changed the dynamics of RCBF under conditions of ischemia and reperfusion.

During ischemia and reperfusion in NT-treated animals RCBF constituted 47.1 and 57.9% of the control level, respectively, while in controls (without NT) the corresponding values were 67 and 80%. The lower RCBF during ischemia in NT-treated animals compared with the control can be attributed to the release of bradykinin, which was shown to induce concentration-dependent relaxation of isolated human, cat, and rabbit cerebral vessels [9,11,12] and vasodilation of cat pial vessels *in situ* [8]. Potential vasodilatory effect of bradykinin in perivascular application and cortical perfusion was previously reported [10]. Bradykinin among other polypeptides is released during ischemia and increases permeability of vascular wall [10]. In 1967, V. A. Levtov showed that bradykinin induces vasodilation in some pathological states, in particular, in ischemia [3]. Nippon Zoki also reported inhibition of kinin release (specific inhibition of bradykinin during painful stimulation). It can be hypothesized that under our experimental conditions inhibition of bradykinin re-leased during ischemia aggravates the RCBF decrease during ischemia and reperfusion. Moreover, it has been previously found that transitory ischemia is accompanied by a massive norepinephrine release [5]. There is evidence that damage to the blood-brain barrier induced by some pathological states, in particular cerebral ischemia [10], considerably modulates typical vasoconstrictory effect of norepinephrine, so that it improves RCBF and cerebral metabolism. According to Nippon Zoki information, NT prevents the rise of norepinephrine concentration in the circulation, which probably contributes to the decrease in RCBF in our experiments.

Thus, despite the broad spectrum of clinical effects of NT our experimental data argue against its use in cerebral circulatory disturbances of various origin.

REFERENCES

1. M. M. Gogoberidze, V. O. Nikuradze, D. Konishi, M. M. Khananashvili, *Izv. Akad. Nauk. Gruzii, Ser. Biol.*, **19**, No. 2, 77-81 (1993).
2. G. I. Kvrivishvili, E. I. Dzamoeva, A. Sh. TsiTsishvili, *et al., Ross. Fiziol. Zh.*, **80**, No. 5, 31-40 (1994).
3. V. A. Levtov, *Chemical Regulation of Cerebral Circulation* [in Russian], Leningad (1967).
4. K. Aukland, *Acta Neurol. Scand. Suppl.*, **41**, No. 14, 42-45 (1965).
5. M. Y. Globus, R. Busto, W. D. Deitrich, and E. Marinez, *J. Cereb. Blood Flow Metab*, **9**, 892-896 (1989).
6. T. Hata and T. Kita, *Folia Pharmacol.*, **79**, 335-340 (1982).
7. T. Kita and T. Hata, *Jpn. J. Pharmacol.*, **29**, 29-32 (1979).
8. H. A. Kontos, E. P. Wei, J. T. Povlishock, C. W. Christman, *Circ. Res.*, **55**, 295-303 (1984).
9. N. Toda, *Am. J. Physiol.*, **232**, H267-H274 (1977).
10. M. Wahl, L. Schilling, A. Uterberg, *et al., Acta. Neurochir. Suppl (Wien)*, **57**, 64-72 (1993).
11. E. T. Whalley and M. Wahl, *Pflugers Arch*, **398**, 175-177 (1983).
12. E. T. Whalley, H. Fritz, and R. Geiger, *Naunyn Schmiedebergs Arch. Pharmacol.*, **324**, 296-301 (1983).