# ROLE OF HYDROGEN IONS OF THE EXTRACELLULAR FLUID IN THE MECHANISM OF ACTION OF PAPAVERINE ON THE CEREBRAL CIRCULATION

S. A. Mirzoyan, É. S. Gabrielyan, and É. A. Amroyan

UDC 615.217.5:547.943].015.4:612.824

A change in pH of the CSF toward acidosis under the influence of papaverine is accompanied by an increase in the blood supply of the brain irrespective of changes in $pCO_2$ of the arterial blood. Changes of the opposite character in the cerebral circulation were discovered with a decrease in hydrogen ion concentration in the CSF. During disturbance of autoregulation (severe hypotension, hypercapnia) the blood supply to the brain is reduced, irrespective of changes in the pH of the CSF, as a result of a decrease in the systemic arterial pressure.

Papaverine has been shown to dilate the pial vessels and to increase the blood supply to the brain [10, 11, 13, 15, 16]. However, many aspects of the mechanism of action of papaverine on the cerebral circulation still remain unexplained [14]. The role of a metabolic factor in the mechanism of the effect of papaverine on the coronary circulation has been demonstrated [2].

In recent years a clear correlation has been found between changes in the hydrogen ion concentration and the resistance of the cerebral vessels under the influence of noradrenalin and barbiturates [5], and data indicating the important role of the hydrogen ion concentration of the extracellular fluid in the maintenance of homeostasis of the cerebral circulation have been obtained [4, 7, 8, 12, 17-19]. With these facts in mind it was decided to study to what extent the vasodilator action of papaverine is connected with changes in the hydrogen ion concentration in the CSF.

## EXPERIMENTAL METHOD

Experiments were carried out on 50 cats anesthetized with urethane and chloralose. Changes in the cerebral blood supply were recorded by electroplethysmography [3] and thermistrography [6]. The arterial pressure and respiration were recorded simultaneously. By means of a pH-meter (Radiometer), parallel determinations were made of pH, $pCO_2$ and $pO_2$ in anaerobically collected samples of arterial blood and of pH and $pCO_2$ in the CSF.

Papaverine (1 or 3 mg/kg) was injected intravenously as a solution warmed to body temperature. Before and 2 and 10 min after the injection the physicochemical indices were determined in the samples of CSF and arterial blood.

## EXPERIMENTAL RESULTS

Under the influence of 1 mg/kg papaverine a decrease in the hydrogen ion concentration was found in the CSF in 50% of the experiments and an increase in the other 50%. In all the experiments with a change in the pH of the CSF toward acidosis the blood supply of the brain was increased, while with a change toward alkalosis it was reduced.

Department of Pharmacology and Laboratory for Problems in Pharmacology of the Cardiovascular System, Erevan Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éskperimental'noi Biologii i Meditsiny, Vol. 74, No. 7, pp. 60-63, July, 1972. Original article submitted December 24, 1971.

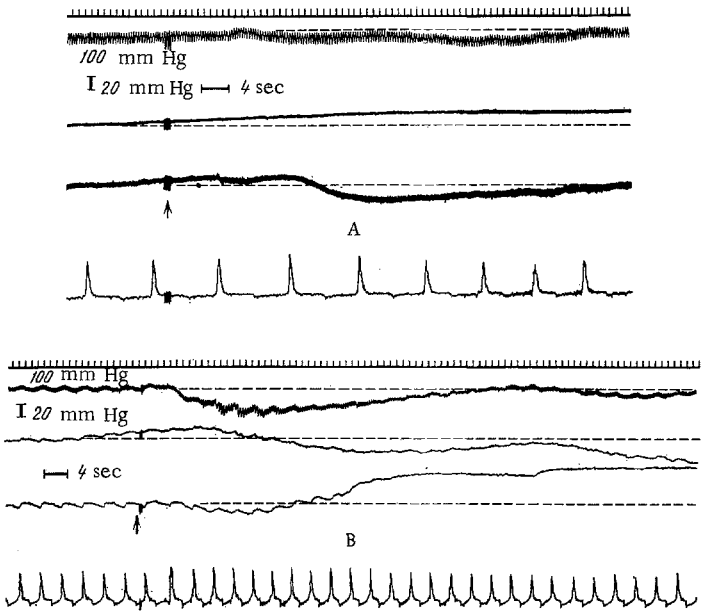


Fig. 1. Effect of papaverine (1 mg/kg) on blood supply to the brain and on some indices of acid-base balance of the CSF and arterial blood in two experiments with different changes in pH: A) CSF: pH 7.24, $pCO_2$ 34 mm. Blood: pH 7.22, $pCO_2$ 38 mm, $pO_2$ 93 mm. CSF: pH 7.17, $pCO_2$ 38 mm. Blood: pH 7.19, $pCO_2$ 40 mm, $pO_2$ 98 mm; B) CSF: pH 7.34, $pCO_2$ 17.5 mm. Blood: pH 7.31, $pCO_2$ 41 mm, $pO_2$ 120 mm. CSF: pH 7.46, $pCO_2$ 10 mm. Blood: pH 7.26, $pCO_2$ 46 mm, $pO_2$ 125 mm. Here and in Fig. 2, from top to bottom: time marker, arterial pressure of thermistrogram (upward displacement corresponds to an increase in velocity of the local cerebral blood flow), electroplethysmogram (upward displacement signifies a decrease in intracranial blood volume), respiration.

The results of one of the experiments are given in Fig. 1A. Intravenous injection of papaverine in a dose of 1 mg/kg, under close to normocapnic conditions ($p_aCO_2$ = 38 mm Hg) led to a definite increase in the velocity of the blood flow in the cerebral cortex and in the intracranial blood volume. No significant changes occurred in respiration. Meanwhile a marked increase in the hydrogen ion concentration and in $pCO_2$ was found in the CSF. Changes of similar character also were observed in the arterial blood. Considering that the brain vessels are highly sensitive to changes in $pCO_2$ it can be assumed that the parallel changes in the acid-base balance of the CSF and arterial blood are jointly responsible for the hemodynamic changes observed in the brain under the influence of papaverine.

However, as these experiments show, parallel changes were not always found in $pCO_2$ and pH of the CSF and arterial blood. It is clear from Fig. 1B that injection of papaverine in the same dose was accompanied by a sharp increase in pH of the CSF (i.e., by a change toward alkalosis) and by a decrease in $pCO_2$. By contrast, the values of $pCO_2$ and the hydrogen ion concentration in the arterial blood rose. After a brief increase in the velocity of the local cerebral blood flow and in the intracranial blood volume both showed a definite decrease. Clearly the effects of papaverine on the cerebral circulation are inseparably linked with the changes in $pCO_2$ and pH of the cerebrospinal fluid, for as Fig. 1B shows, even if $pCO_2$ of the arterial blood is increased the blood supply to the brain is reduced.

Under the influence of large doses of papaverine (3 mg/kg) there is a marked decrease in arterial pressure and, despite an increase in the velocity of the local cerebral blood flow, the intracranial blood volume showed a marked decrease. The experiments revealed changes in some indices of the acid-base balance under these conditions.

The results of an experiment in which papaverine was injected in a dose of 3 mg/kg are given in Fig. 2A. Immediately after intravenous injection of the drug there was a sharp decrease (60%) in the arterial

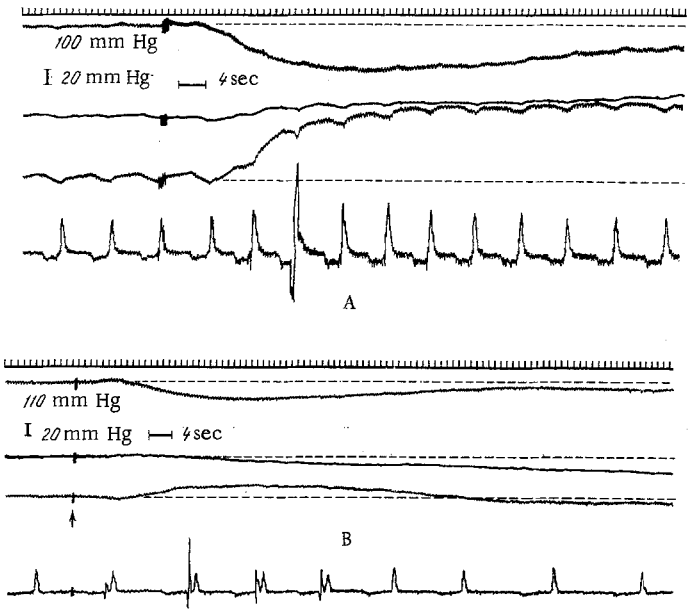


Fig. 2. Effect of papaverine on blood supply to the brain and on some indices of the acid-base balance of the CSF and arterial blood. A) Effects of 3 mg/kg papaverine: CSF: pH 7.25, $pCO_2$ 19 mm. Blood: pH 7.22, $pCO_2$ 42 mm, $pO_2$ 103 mm. CSF: pH 7.32, $pCO_2$ 24 mm. Blood: pH 7.22, $pCO_2$ 44 mm, $pO_2$ 103 mm; B) effects of 1 mg/kg papaverine during hypercapnia. CSF: pH 7.37, $pCO_2$ 25 mm. Blood: pH 7.02, $pCO_2$ 78 mm, $pO_2$ 73 mm. CSF: pH 7.20, $pCO_2$ 39 mm. Blood: pH 7.05, $pCO_2$ 7.8 mm, $pO_2$ 76 mm.

pressures with a definite decrease in the intracranial blood volume. The small increase in $pCO_2$ was accompanied by a marked decrease in the hydrogen ion concentration in the CSF, i.e., by a shift toward alkalosis. These changes were observed against the background of relative stability of the indices for the acid-base balance of the arterial blood. It could be postulated that a decrease in hydrogen ion concentration counteracts the effects of papaverine on the smooth muscle of the cerebral vessels. However, a decrease in the blood supply under the influence of large doses of papaverine also was observed in acidosis, i.e., with a decrease in pH of the CSF. Consequently, the effects of comparatively large doses of papaverine on the cerebral circulation are most likely due to a disturbance of autoregulation, with the appearance of a passive dependence of the blood flow on pressure as the result of the sharp fall of arterial pressure [1]. This hypothesis is supported by experiments performed during hypercapnia, when, as data in the literature show, the mechanism responsible for autoregulation of the cerebral vessels also are disturbed [9]. As Fig. 2B shows, in the control series $pCO_2$ of the arterial blood was 78 mm Hg and pH was 7.02.

Intravenous injection of papaverine in a dose of 1 mg/kg was accompanied by a marked increase in the hydrogen ion concentration and by an increase in $pCO_2$ in the extracellular fluid. Contrary to expectation, even with a moderate fall of arterial pressure (by 30%) there was an accompanying decrease in the linear velocity of the cerebral blood flow and in the intracranial blood volume, which was not observed in the experiments on animals in a state close to normocapnia. Consequently, hypercapnia disturbs the correlation between the hydrogen ion concentration of the extracellular fluid and the cerebral blood flow found under the influence of small doses of papaverine.

Changes in the hydrogen ion concentration of the extracellular fluid thus play an important role in the effects of papaverine on the cerebral circulation.

When the mechanisms of autoregulation of the brain vessels are disturbed (in severe hypotension or hypercapnia), correlation between the pH of the extracellular fluid and the cerebral blood flow is disturbed and a passive dependence of the blood flow on the arterial pressure is found; these effects are reflected in

a decrease in the intracranial blood volume and in the rate of the cerebral blood flow, even in the presence of a moderate decrease in the systemic arterial pressure.

The results described in this paper suggest an active role of the hydrogen ions of the extracellular fluid in the mechanism of the relaxant action of papaverine on the smooth-muscle structures of the walls of the cerebral vessels.

## LITERATURE CITED


1. É. S. Gabrielyan and A. M. Garner, Byull. Éksperim. Biol. i Med., No. 6, 9 (1970).
2. I. Kisin, Effect of Coronary Dilators on the Circulation and Energy Metabolism of the Heart [in Russian], Leningrad (1966).
3. Yu. E. Moskalenko, Dynamics of the Blood Volume of the Brain under Normal Conditions and during Gravitational Overloads [in Russian], Leningrad (1967).
4. E. Betz, Y. Pickerodt, and A. Weidner, The Cerebro-spinal Fluid, New York (1968).
5. H. Bienmuller and E. Betz, in: Arztliche Forschung, Munich (1970), p. 97.
6. R. Cooper, Med. Electron. Biol. Eng., 1, 529 (1963).
7. S. Cotev, J. Lee, and J. W. Severinghaus, Anesthesiology, 29, 741 (1968).
8. V. Fencl, I. R. Gale, and J. R. Broch, Scand. J. Clin. Lab. Invest., Suppl. 102, 8B (1968).
9. A. M. Harper and H. I. Glass, Neurol., Neurosurg., 28, 449 (1965).
10. H. W. Jayne, P. Scheinberg, M. Rich, et al., J. Clin. Invest., 31, 111 (1952).
11. N. Lubsen, Acta Brev. Neerl., 10, 183 (1940).
12. J. S. Meyer and F. Gotoh, A. M. A. Arch. Neurol. (Chicago), 3, 539 (1960).
13. J. S. Meyer and F. Gotoh, Neurology (Minneapolis), Part 2 (1961).
14. P. Scheinberg, in: Cerebrovascular Disease, New York (1966), p. 216.
15. M. Schneider and D. Schneider, Arch. Exp. Path. Pharmak., 175, 640 (1934).
16. S. de Seze, Sem. Hop. Paris, 14, 307 (1938).
17. J. W. Severinghaus, in: Regional Cerebral Blood Flow, Copenhagen (1965), p. 116.
18. J. W. Severinghaus and S. Cotev, Scand. J. Clin. Lab. Invest., Suppl. 102, IE (1968).
19. J. E. Skinhoj, Scand. J. Clin. Lab. Invest., Suppl. 102, 16D (1968).