arachnoid injections in a dose of 300 μg, but in a dose of 600 μg GABA had a powerful and prolonged analgesic action (Fig. 2). Sodium hydroxybutyrate, a structural analog of GABA in the same dose caused weaker analgesia, comparable with the effect of morphine in a dose of 100 μg (Fig. 2).

LITERATURE CITED

1. I. I. Abramets, N. A. Kozlova, and I. V. Komissarov, Fiziol. Zh. SSSR, 67, 1160 (1981).
2. B. V. Andreev, Yu. N. Vasil'ev, V. P. Kosinskii, et al., in: Neuropharmacological Aspects of Emotional Stress and Drug Dependence [in Russian], Leningrad (1978), p. 45.
3. A. V. Val'dman and Yu. D. Ignatov, Central Mechanisms of Pain [in Russian], Leningrad (1976).
4. Yu. D. Ignatov, Farmakol. Toksikol., No. 3, 407 (1973).
5. A. S. Kucheruk, Farmakol. Toksikol., No. 2, 190 (1965).
6. J. Davies and A. Dray, Br. J. Pharmacol., 58, 458 (1976).
7. B. T. Griersmith and A. W. Duggan, Brain Res., 187, 231 (1980).
8. W. Krivoy, D. Kroeger, and E. Zimmermann, Br. J. Pharmacol., 47, 457 (1973).
9. Y. Kuraishi, Y. Harada, and H. Takagi, Brain Res., 174, 333 (1979).
10. K. Samii, M. Chanvin, and P. Viars, Br. J. Anaesth., 53, 817 (1981).
11. P. Wood, A. Rackham, and J. Richard, Life Sci., 28, 2119 (1981).
12. P. D. Wall, J. Physiol. (London), 180, 116 (1964).

EFFECT OF RAUSEDIL AND PYRROXAN ON AUTOMATIC CONTROL OF THE CEREBRAL BLOOD FLOW

M. D. Gaevyi and V. E. Pogorelyi

UDC 615.225.2.015.4:612.824

KEY WORDS: cerebral blood flow; automatic control; rausedil; pyrroxan.

In essential hypertension the limits of automatic control reactions of the cerebral vessels are known to be shifted toward higher arterial pressure (AP) levels [12, 13]. Under these conditions a rapid fall of AP to the normal level may lead to disturbances of the cerebral circulation.

It was accordingly decided to study the effect of reserpine and pyrroxan on automatic control of the cerebral blood flow. No corresponding information about these hypotensive agents could be found in the literature.

EXPERIMENTAL METHOD

Acute experiments were carried out on 20 dogs of both sexes weighing 8-12 kg. The use of general anesthetics was avoided because they may change the character of automatic control reactions (ACR) of the cerebral vessels [1, 8], and for that reason morphine (1 mg/kg subcutaneously) was used for general analgesia and a 0.25% solution of procaine was used for local anesthesia, and listhenon for immobilization; artificial ventilation of the lungs was carried out with monitoring of pH and blood gas composition on the AZIV-2 instrument. The oxygen saturation of the arterial blood was maintained at 96-98% and pH between 7.36 and 7.42.

The cerebral blood flow (CBF) was recorded continuously with an RKÉ-01 electromagnetic flowmeter, the transducer of which was located on the vertebral artery. The general AP was recorded in the common carotid artery by a mercury manometer, the venous pressure (VP) by a water manometer in the cranial segment of the jugular vein. The perfusion pressure (PP) in the main arteries of the brain was determined as the difference between AP and VP.

Department of Pharmacology, Pyatigorsk Pharmaceutic Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 7, pp. 56-59, July, 1983. Original article submitted October 16, 1982.

TABLE 1. Changes in CBF, CVR (in % of initial values), and C during a Rise and Fall of AP in Control Experiments (M ± m)

AP, mm Hg		CBF, ml/100 g/min	CVR, mm Hg/ 100 g/min/ml	C
200	7	+54,9±15,9 $P<0,01$	−12,0±5,6 $P>0,05$	−0,15±0,10
180	16	+16,4±3,9 $P<0,001$	+15,9±4,5 $P<0,01$	+0,49±0,15
160	8	+8,8±4,3 $P=0,05$	+20,1±4,4 $P<0,001$	+0,83±0,07
140	8	+8,3±3,0 $P<0,05$	+24,8±6,6 $P<0,01$	+0,86±0,05
120	10	−3,2±1,2 $P<0,05$	−17,0±2,8 $P<0,001$	+0,92±0,03
100	18	−4,1±1,7 $P<0,05$	−22,7±2,2 $P<0,001$	+0,91±0,05
80	15	−7,3±2,6 $P<0,05$	−25,7±2,1 $P<0,001$	+0,88±0,04
60	11	−8,0±3,5 $P<0,05$	−29,2±3,0 $P<0,001$	+0,86±0,07
40	21	−22,8±3,0 $P<0,001$	−20,1±4,2 $P<0,001$	+0,35±0,07
30	7	−47,0±9,1 $P<0,001$	+9,1±16,4 $P>0,05$	−0,08±0,24

Legend. Here and in Table 2, broken line indicates initial state. Results of tests to rise of AP shown above this line, to fall of AP below it; +) increase, −) decrease.

Changes in AP were produced by acute bleeding, by orthostatic procedures [3, 7], or by the method of decomposition (or compression) of the posterior half of the trunk in a special pressure chamber. No drugs were used for this purpose, for they have a direct effect on cerebral vascular tone [1, 2, 6, 11].

The most convenient method of producing different levels of AP was found to be by means of the special pressure chamber. For this purpose half of the animal's trunk (up to the level of the thoracic cage) was placed in a rigid cylindrical chamber. The chamber was hermetically sealed by means of a rubber cuff, firmly secured around the edge of the cylinder and the animal's trunk. The hair on the animal's body in the region of contact with the cuff was removed and the skin smeared with petrolatum. In this way the airtight closing of the chamber was reliable and did not interfere with artificial ventilation of the lungs. The chamber was connected by rubber tubes to a compressor and mercury manometer, so that the pressure inside the chamber could be monitored.

By regulating the negative pressure in the chamber a gradual fall of AP was produced to very low levels (30-20 mm Hg), so that the lower limits of ACR of the cerebral blood flow could be determined. After creation of a negative pressure in the chamber (10-30 mm Hg) AP rose by 20-30 mm Hg above its initial level. A further increase of pressure in the chamber was rarely accompanied by an increase in AP. If the pressure in the chamber was 50 mm Hg or above, disturbances of respiration were observed, AP fell, but VP rose considerably. By using a moderate increase of pressure in the chamber combined with orthostatic procedures, in some experiments a rise of AP by 40-60 mm Hg could be achieved.

The character of ACR was judged from changes in CBF and in the cerebral vascular resistance (CVR). The controllability of the intracranial circulatory system was estimated by means of a control coefficient (C) [8]. In each experiment from 5 to 10 tests were carried out with raising or lowering of AP. At the beginning of the experiment control tests were undertaken (before administration of the drug).

EXPERIMENTAL RESULTS

The experimental results are summarized in Tables 1 and 2 and Figs. 1 and 2. In the control experiments the original AP level was 135.0 ± 4.8 mm Hg, VP was 147.7 ± 9.9 mm water, CBF was 80.0 ± 4.5 ml/100 g/min, and CVR was 1.76 ± 0.09 mm Hg/100 g/min/ml. A fall of AP to 60 mm Hg was accompanied by a very slight fall in CBF and a substantial fall in CVR. A further fall in AP from 60 to 30 mm Hg was accompanied by a considerable decrease in CBF, i.e., failure of ACR took place (the value of C came close to zero). With an in-

TABLE 2. Changes in CBF, CVR (in % of initial value), and C during a Rise and Fall of BP after Administration of Rausedil and Pyrroxan (M ± m)

AP, mm Hg	Number of tests	CBF, ml/100 g/min	CVR, mm Hg/100 g/min/ml	C
		After rausedil		
180	3	+30,3±3,2	+12,3±2,0	+0,34±0,03
160	4	+1,0±1,2*	+30,3±12,8	+0,92±0,08
140	7	+1,3±4,7*	+36,9±10,3	+0,94±0,05
120	8	+1,1±4,6*	+18,0±6,6	+0,94±0,27
100	12	−1,1±1,5*	−15,3±2,5	+1,00±0,06
80	12	−20,3±6,6	+1,9±9,0*	+0,25±0,23*
60	10	−26,7±5,4	−2,8±6,4*	+0,12±0,15*
40	14	−38,3±3,5	+2,4±5,6*	−0,06±0,10*
30	8	−28,6±6,8	−23,1±7,8	+0,44±0,13
		After pyrroxan		
120	7	+12,3±2,5	+17,7±5,0	+0,57±0,08
100	13	+6,2±3,6*	+32,1±5,8	+0,92±0,06
80	6	−3,5±3,5*	−15,3±1,7	+0,91±0,13
60	8	−16,0±4,3	−26,6±3,7	+0,62±0,11
40	7	−16,0±4,9	−35,7±7,7	+0,67±0,08
30	5	−15,8±3,6	−42,0±6,5	+0,74±0,04

*Difference not significant (P > 0.05).

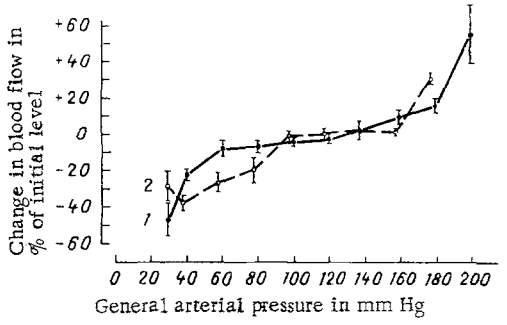

Fig. 1. Time course of changes in CBF for different levels of PP. 1) Control, 2) preliminary reserpinization in a dose of 1 mg/kg, subcutaneously.

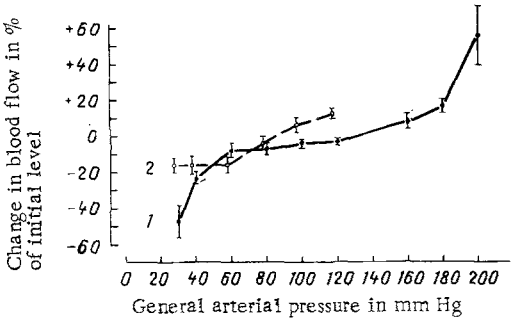

Fig. 2. Time course of changes in CBF for different levels of BP. 1) Control, 2) intravenous injection of pyrroxan in a dose of 0.5 mg/kg.

crease in AP to 160 mm Hg from its initial level CBF in most tests was unchanged but in three cases it increased a little. A further rise of AP to 180 mm Hg or above was accompanied by a considerable increase in CBF. Under our experimental conditions, the automatic control mechanisms of the cerebral vessels thus remained capable of maintaining a comparatively stable blood flow during changes in AP within 60 and 70 mm Hg. A fall of AP below 60 mm Hg or a rise above 170 mm Hg was accompanied by passive changes in CBF, or in other words, by failure of ACR.

Considering the definite time course of development of the sympatholytic effect of reserpine [10], ACR was investigated 12 h after injection of rausedil (1 mg/kg, subcutaneously). By this time the AP level was 108.0 ± 6.0 mm Hg, VP was 156.0 ± 17 mm water, CBF was 84 ± 7.0 ml/100 g/min, and CVR was 1.31 ± 0.88 mm Hg/100 g/min/ml. These values were taken as the initial values for investigation of ACR in this series of experiments.

It will be clear from Table 2 and Fig. 1 that a fall of AP in reserpinized animals from its initial level to 90 mm Hg was accompanied by definite ACR (C = 1). With a further decline in AP, passive dependence of CBF on AP was observed, i.e., failure of ACR (C close to 0). With a rise of AP from its initial level to 160 mm Hg, a good ACR was observed (C close to 1). A further rise in AP to 180 mm Hg was accompanied by considerable weakening of ACR.

In the experiments with pyrroxan ACR was investigated 60-90 min after injection of the drug (0.5 mg/kg intravenously). By this time AP was 87.5 ± 4.1 mm Hg, VP 136.9 ± 7.4 mm Hg, CBF 79.0 ± 13.7 ml/100g/min,

and CVR 1.41 ± 0.32 mm Hg/100 g/min/ml. These values were taken as the initial level for the study of ACR. A fall of AP under these conditions to 40-30 mm Hg was accompanied by satisfactory ACR. A rise of AP from its initial level to 100 mm Hg was accompanied by good ACR (C close to 1). With a further rise of BP to 120 mm Hg, weakening of ACR was observed. AP could not be raised to higher levels after administration of pyrroxan, except in a few cases in which definite failure of ACR was observed when AP rose above 120 mm Hg.

Rausedil thus weakens ACR to a fall of AP considerably without causing any significant changes in this response when AP rises. Pyrroxan, on the other hand, considerably weakened ACR when AP was raised, whereas with a fall in AP, ACR improved appreciably. Analysis of the results shows a definite role of the sympathicoadrenal system in the mechanism of the ACR, confirming previous data obtained by the present writers and others [4, 5]. Differences found in the action of rausedil and pyrroxan on ACR can be explained by the time course of development of the sympatholytic effect which is characteristic of rausedil, whereas pyrroxan has a direct α-adrenoblocking action.

It will be recalled that 12 h after injection of reserpine (the end of these observations) intensive release of monoamines takes place from stable fractions, and serotonin is liberated and its storage disturbed. These substances have high vasoconstrictor activity on the cerebral vessels. These circumstances may have contributed to the disturbance of ACR of the brain vessels when AP fell in animals receiving rausedil. Meanwhile preservation (restoration in some cases) of ACR to a definite degree when AP fell to very low levels (40-30 mm Hg) against the background of rausedil and pyrroxan, which was not observed in the control experiments, must be noted. This was evidently due to the participation of other mechanisms of ACR (possibly myogenic and metabolic).

LITERATURE CITED

1. É. S. Gabrielyan, Some Aspects of the Physiology and Pharmacology of the Cerebral Cirulation [in Russian], Erevan (1977).
2. M. D. Gaevyi, Pharmacology of the Cerebral Circulation [in Russian], Moscow (1980).
3. M. D. Gaevyi, V. G. Mal'tsev, and V. E. Pogorelyi, Fiziol. Zh. SSSR, No. 2, 263 (1979).
4. V. G. Mal'tsev and M. D. Gaevyi, Byull. Éksp. Biol. Med., No. 9, 309 (1978).
5. J. S. Meyer, E. O. Ott, M. Aoyagi, et al., Fiziol. Zh. SSSR, No. 10, 1518 (1975).
6. R. S. Mirzoyan, "Pharmacology of adrenergic control of the cerebral circulation," Author's Abstract of Doctoral Dissertation, Moscow (1977).
7. Yu. E. Moskalenko, N. N. Benua, and O. V. Grunov, Fiziol. Zh. SSSR, No. 4, 405 (1963).
8. Yu. E. Moskalenko, G. B. Vainshtein, I. T. Demchenko, et al., Intracranial Hemodynamics [in Russian], Leningrad (1975).
9. G. I. Mchedlishvili, Spasm of Arteries of the Brain [in Russian], Tbilisi (1977).
10. Yu. B. Rozonov, in: Pharmacology of Monoaminergic Processes [in Russian], ed. V. V. Zakusov and N. V. Kaverina [in Russian], Moscow (1971), pp. 78-100.
11. A. S. Saratikov, V. V. Belopasov, and M. B. Plotnikov, Experimental and Clinical Pharmacology of the Cerebral Circulation [in Russian], Tomsk (1979).
12. E. V. Shmidt, D. K. Lunev, and N. V. Vereshchagin, Vascular Diseases of the Brain and Spinal Cord [in Russian], Moscow (1976).
13. S. Strandgaard, Acta Neurol. Scand., 57, Suppl. No. 66, 1 (1978).