Meanwhile the charge on the membrane is known to correlate with its viscosity, its phospholipid composition, and the level of its free-radical processes [12]. These last factors, in turn, determine the functional state of BDRC [6] and are essential for the formation of the effects of the benzodiazepine anxiolytics and anticonvulsants [2]. It can therefore be tentatively suggested that genetic control of regulation of BDRC, dependent on the Cl^--ionophore, discovered in the present investigation, is based in unequal, charge-determined membrane structural changes that are responsible for different conformational changes in BDRC and, as a result of this, a specific pattern of physiological effects linked with it.

The existance of these mechanisms, consolidated during evolution, suggests that they can be regarded as the target for psychopharmacological action and it explains the presence of psychotropic properties, similar to those of BD, in a series of membrane-active compounds that do not bind directly with the benzodiazepine receptor [4].

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EFFECT OF PYRROLIDONE-2 ON THE CEREBRAL CIRCULATION

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Our ideas on the role of the principal inhibitory neurotransmitter of the brain, namely GABA, are continually being widened and deepened through the discovery of additional facts [5, 9, 14]. Many studies of its role in the regulation of blood pressure (BP) have now been published [15]. However, as long ago as in 1964, it was discovered that GABA can stimulate the cerebral circulation and, at the same time, raise the partial pressure of oxygen in brain tissues [2]. GABA promotes the formation of several active substances in the brain, many of which give rise to physiological and pharmacological effects [4].

The discovery of pyrrolidone-2 [10], a cyclic derivative of GABA, and that linear and cyclic GABA derivatives differ in their action [6, 7] prompted the authors to undertake further investigations.

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TABLE 1. Effect of Intracarotid Injection of Pyrrolidone-2 in a Dose of 10 mg/kg of LCBF in Parietal Cortex of Cats (M ± m, n = 12)

Experimental conditions	Parameter		
	LCBF, ml/100 g/min	RCA, mm Hg/ml/min/100 g	SBP, mm Hg
Control	45,2±3,6	2,32±0,30	105±3,0
End of infusion	68,4±4,8*	1,53±0,10*	108±4,1
Time after infusion, min:			
5	73,71±4,2*	1,42±0,10*	106±3,5
10	56,6±4,7*	1,87±0,13*	105±3,9
15	49,5±3,8	2,12±0,16	106±4,3
20	48,3±4,3	2,17±0,10	105±3,4

TABLE 2. Effect of Intravenous Injection of Pyrrolidone-2 in a Dose of 20 mg/kg of LCBF in Parietal Cortex of Cats (M ± m, n = 8)

Experimental conditions	Parameter		
	LCBF, ml/100 g/min	RCA, mm Hg/ml/min/100 g	SBP, mm Hg
Control	47,61±5,8	2,63±0,37	128,7±2,5
End of infusion	47,02±12,7	2,55±0,61	112,5±2,5
Time after infusion, min:			
5	58,61±5,54*	1,85±0,46*	108,3±2,9
10	61,56±4,20*	1,74±0,17	107,5±2,5
15	76,85±3,29*	1,42±0,05*	108,3±2,9
20	74,25±2,95*	1,85±0,39*	110,0±1,1
25	71,77±2,47*	1,5±0,09*	107,5±2,5

Legend. Here and in Tables 2 and 3, *P < 0.05 compared with control.

EXPERIMENTAL METHOD

Experiments were carried out on 12 cats anesthetized with urethane and chloralose and on 24 cats and eight dogs receiving an intraperitoneal injection of pentobartital sodium.

Quantitative change in the volume velocity of the local cerebral blood flow (LCBF) were recorded by means of the hydrogen clearance method [8]. After the control curves had been recorded pyrrolidone-2 was injected during the period of peak saturation with hydrogen, soon after which the inhalation of hydrogen ceased, and the clearance process was recorded. Changes in resistance of the cerebral arteries (RCA) were determined in accordance with the results [11]. Blood vessels of dogs (middle cerebral and basilar arteries, arteries of the circle of Willis), 300-600 μ in diameter, were investigated.

EXPERIMENTAL RESULTS

Pyrrolidone-2 caused a marked increase in the cerebral blood flow. For instance, immediately after intracarotid injection of the compound in a dose of 10 mg/kg the blood flow in the cortex was increased by 51.3%. Later an even greater increase in the blood flow was observed, to reach a maximum (an increase of 63.2% compared with the control) at the 5th minute after injection. After 10 min a tendency was observed for LCBF to return to normal, and the initial value was reached at the 20th minute of recording the clearance. Incidentally, the increase in the cortical blood flow under the influence of pyrrolidone-2 was accompanied by a fall of 38.8% of RCA without any statistically significant changes affecting the systemic BP (SBP; Table 1).

Pyrrolidone-2, a cyclic derivative of GABA, passes readily through the blood-brain barrier [13]. The effect of pyrrolidone-2 on the cerebral circulation is observed after both intracarotid and intravenous injection. The greatest increase (by 60.5%) in blood flow was observed 15 min after injection, and it still remained higher than initially after 20-25 min. RCA under these circumstances was reduced by 51.5%, and it still remained lower than in the control after 25 min (Table 2).

The study of the effect of the cyclic GABA derivative on the cerebral blood flow when the blood supply to the brain was disturbed showed that, in the presence of unilateral occlusion of the common carotid artery, the ability of pyrrolidone-2 to potentiate the cerebral blood flow was much greater than normally. The blood flow in the parietal cortex was reduced by 45.9% 20 min after compression of the artery (from 63.1 ± 3.5 to 34.1 ± 4.1 ml/100 g/min, P < 0.05). After intravenous injection of the compound in a dose of 20 mg/kg the cerebral blood flow increased after ligation by 87.8% (to 65.0 ± 4.9 ml/100 g/min, P < 0.05), and regained the control value after 20 min.

To study the role of GABA receptors in the realization of the action of pyrrolidone-2 on the blood supply to the brain a series of experiments was carried out to study the effect of pyrrolidone-2 on the LCBF during infusion of bicuculline. Intravenous infusion of bicu-

TABLE 3. Effect of Intravenous Injection of Pyrrolidone-2 in a Dose of 20 mg/kg on LCBF of Cats Receiving Infusion of Bicuculline in a Dose of 0.1 mg/kg (M ± m, n = 7)

Experimental conditions	Parameter		
	LCBF, ml/100 g/min	RCA, mm Hg/ml/min/100 g	SBP, mm Hg
Control	42,01±5,27	2,79±0,49	113,7±4,7
Bicuculline			
end of infusion	36,31±5,23	2,99±0,25	112,5±9,0
5 min	36,83±4,50	3,23±0,4	118,3±2,9
10 min	32,67±4,41*	3,71±0,23*	120,0±1,2
Bicuculline + pyrrolidone-2			
10 min	36,56±3,98	3,35±0,46	121,7±2,9
20 min	33,74±3,85	3,72±1,02	125,0±1,1

culline in a dose as low as 0.1 mg/kg (duration 3 min) reduced LCBF (this was shown previously also [1]) by 22.5%. Intravenous injection of pyrrolidone-2 in a dose of 20 mg/kg against this background caused no significant changes in the cortical blood flow (Table 3).

In view of evidence that pyrrolidone-2 can increase the cerebral blood flow and the ability of bicuculline to block this effect, it was decided to study the effect of pyrrolidone-2 on the contractile properties of isolated vascular segments of the brain, for the presence of GABA-receptors has been established in the walls of the cerebral arteries also [12]. The results showed that when the tone of the cerebral vessels was increased by injection of a 10^{-6} M solution of serotonin injection of a 10^{-2} M solution of pyrrolidone-2 caused total relaxation of isolated segments of the cerebral arteries, and an equimolar solution of bicuculline perceptively weakened this property of pyrrolidone-2.

It can thus be concluded from comparison of the data on the effect of pyrrolidone-2 on the cerebral blood supply with the corresponding action of GABA [3] that pyrrolidone-2 gives a stronger and more prolonged effect, and that it can be recommended as a vasoactive agent in disturbances of the cerebral circulation.

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