PLATELET AGGREGATION IN PLASMA AND WHOLE BLOOD DURING HYPERVENTILATION (HYPOCAPNIA) IN CATS

E. A. Amroyan

UDC 611-018.5+616-001.8

KEY WORDS: hypocapnia; platelet aggregation; ADP; collagen; arachidonic acid.

Carbon dioxide plays an important role in the mechanisms of metabolic control of the cerebral circulation [5]. Platelets, which are a rich source of formation of vasoactive compounds, under conditions favoring release and aggregation, can lead to intravascular thrombosis and to disturbance of the regional, including cerebral, circulation. The writer showed previously that as well as producing marked dilatation of the cerebral vessels, hypercapnia can also induce marked inhibition of platelet aggregability [1]. Data on the character of the change in aggregation mechanisms under conditions of hypocapnia could not be found in the accessible literature, which makes it much more difficult to assess the role of platelets in the vasoconstrictor effect of hypocapnia relative to the cerebral vessels.

The aim of this investigation was to compare platelet aggregability in platelet-enriched plasma (PEP) and in whole blood under conditions of hyperventilation (normoxic hypocapnia) in cats.

EXPERIMENTAL METHOD

Acute experiments were carried out on 22 cats of both sexes weighing 2.5-4 kg, anesthetized with pentobarbital (30 mg/kg, intraperitoneally), with artificial ventilation of the lungs with a mixture of nitrogen and oxygen (4:1). Hypocapnia was induced by hyperventilation, monitored by recording parameters of the acid-base balance (ABB) of the arterial blood by means of a BMS 3, Mark 2 (Radiometer, Denmark) microsystem. The partial pressure of CO_2 (pCO_2) was maintained at 15-20 mm Hg and pO_2 between physiological limits. Platelet aggregation was investigated before (control) and after hyperventilation for 30 min. Platelet-rich and platelet-deprived plasma were prepared by differential centrifugation of citrated blood (9:1). Synchronized studies were made of: optical aggregation in PEP by the method [2] on an aggregometer (Payton, USA), impedance aggregation in whole blood by the method in [3] on a whole-blood aggregometer (Chrono-Log, USA). Aggregation was induced by ADP (in concentrations of $2 \cdot 10^{-4}$ M for PEP and $5 \cdot 10^{-6}$ M for blood), collagen ($2 \cdot 10^{-4}$ and $2 \cdot 10^{-6}$ g/ml, respectively), and arachidonic acid (AA, 10^{-3} and $2 \cdot 10^{-3}$ M, respectively). The data were subjected to statistical analysis by Élektronika computer.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that under conditions of hypocapnia platelet aggregation in PEP was increased by ADP by 13.5%, by collagen by 8.2%, and by AA by 41.2% compared with the control (during normocapnia). In whole blood under similar conditions, platelet aggregability was considerably increased (by 59.6%) in response to ADP, whereas under the influence of collagen and AA the change was diametrically opposite in direction: platelet aggregation induced by collagen was reduced by 41.8%, and that induced by AA was reduced by 16.7% compared with the control.

Hyperventilation led to a fall in pCO_2 in the arterial blood, i.e., to acute respiratory alkalosis, with the corresponding hemodynamic changes.

In particular, it was found that during hyperventilation myocardial contractility [9] and vascular tone in nearly all regions of the vascular bed of the animal are increased. The

Laboratory of Pharmacology of the Cerebral Circulation, Erevan Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 6, pp. 648-649, June, 1987. Original article submitted June 26, 1986.

 0007-4888/87/0006-0730$12.50

TABLE 1. Changes in Parameters of ABB, Impedance Aggregation of Platelets in Whole Blood, and Optical Aggregation in Platelet-Enriched Plasma during Hypocapnia in Cats (n = 22)

Parameter of ABB and inducer of aggregation	Control	Hypocapnia	p
ABB			
pH	7,29±0,05	7,62±0,03	<0,001
pCO_2, mm Hg	30,15±1,80	16,60±1,63	<0,001
pO_2, mm Hg	98,62±3,76	104,30±4,81	>0,05
Aggregation in PEP			
ADP	66,52±2,41	75,55±2,77	<0,05
Collagen	67,90±1,65	73,52±4,89	>0,05
AA	27,31±1,43	38,56±1,75	<0,001
Aggregation in whole blood			
ADP	14,25±1,70	22,75±1,44	<0,001
Collagen	47,25±3,68	27,50±3,80	<0,001
AA	24,20±2,27	20,17±2,43	>0,05

blood vessels of the brain respond particularly strongly to hypocapnia, and as a result a marked decrease in the cerebral blood flow takes place [10]. In acute respiratory alkalosis, moreover, a marked shift of the oxyhemoglobin dissociation curve to the left is observed, evidence of the development of a deficiency in the oxygen supply to tissues and cells [6]. Taken in conjunction with the changes mentioned above, those in platelet aggregability are of great interest.

As the results showed, the direction of the changes in platelet aggregation during hypocapnia in experiments with PEP was the same for all aggregation indueers (ADP, collagen, and AA), and this was reflected in enhancement of aggregability. This change fits well into the general picture of the hemodynamic changes mentioned above, due to hypocapnia. In whole blood, however, increased platelet aggregability in hypocapnia was observed only in response to ADP. This effect may be due either to increased sensitivity of the platelet ADP receptors or to an increase in rigidity of the erythrocyte membranes (reduced deformability of the erythrocytes) under conditions of alkalosis, leading to an increase in viscosity of the blood, which brings with it the risk of development of hyperaggregation, intravascular thrombosis, and other serious consequences.

During the study of platelet aggregation in whole blood, the proaggregating effect of collagen and AA under hypocapnic conditions was inhibited and aggregability was reduced, especially when collagen was used. The reason for this is most probably the presence of leukocytes. Investigations in recent years have demonstrated their important role in the development of intravascular thrombosis. It must be recalled that the influence of leukocytes on platelet aggregation is by no means uniform in direction but may be manifested as either increased or reduced aggregability [4]. Leukocytes, for example, can prevent platelet aggregation by destroying ADP [8] by adhesion to a layer of adherent platelets, with their subsequent destruction, and by production of prostacycline and superoxide or hydroxyl radicals, which sharply depress platelet aggregability [7]. At the same time, leukocytes can induce platelet aggregation on account of the thromboxanes, platelet aggregation factor, and other factors synthesized in them.

The metabolic cascade of AA, which proceeds along cyclo-oxygenase and lipoxygenase pathways has been shown to play an important role in the functional activity of leukocytes, as well as of erythrocytes and platelets. The ability of leukocytes to generate all the main types of prostaglandins and leukotrienes has been demonstrated [4]. The data given above suggest that leukocytes play an active part in the mechanisms of platelet aggregability under the influence of collagen and AA, with a shift toward the formation of antiaggregants, capable of counteracting the direct aggregating action of collagen and AA in hypocapnia. As regards the role of leukocytes in the mechanisms of ADP-induced aggregation this is unlikely on account of their ability to destroy ADP, which was mentioned above.

The increase in platelet aggregability in whole blood in hypocapnia under the influence of ADP, a powerful natural inducer of platelet aggregation, may thus become a risk factor for intravascular thrombosis. It must also be taken into account that during the investigation of any factors influencing the vessel — blood system, in which homeostasis is maintained by a combination of the effect of many factors of varied importance, belonging to different morphological and functional systems, the study of this process is more appropriate and informative when carried out in whole blood.

LITERATURE CITED

1. É. S. Gabrielyan and É. A. Amroyan, Byull. Éksp. Biol. Med., No. 4, 391 (1984).
2. G. V. Born, Nature, 194, No. 9, 927 (1962).
3. D. C. Cardinal and R. J. Flower, J. Pharmacol. Methods, 3, 135 (1980).
4. J. Harlan, Blood, 65, No. 3, 513 (1985).
5. M. Reivich, Am. J. Physiol., 206, 25 (1964).
6. J. W. Severinghaus, J. Appl. Physiol., 12, 485 (1958).
7. D. G. Sladdin, P. H. Levine, and N. J. Krinsky, Circulation, 62, No. 4, 192 (1980).
8. G. M. Smith, G. D. Smith, and T.J. Peters, Clin. Chim. Acta, 101, No. 2, 287 (1980).
9. E. M. Vaughan Williams, J. Physiol. (London), 129, 90 (1955).
10. A. J. Wasserman and J. L. Patterson, J. Clin. Invest., 40, 1297 (1961).

PARKINSON'S SYNDROME SIMULATED BY INJECTION OF KAINIC ACID INTO THE CAUDATE NUCLEI

G. N. Kryzhanovskii,* R. F. Makul'kin, A. A. Shandra, L. S. Godlevskii, and V. S. Rozhkov

UDC 616.858-008.-092.9-02:[615.31:547.466.64].032.813.2

KEY WORDS: Parkinson's syndrome; kainic acid; caudate nuclei; rat brain.

The creation of generators of pathologically enhanced excitation (GPEE) in certain parts of the CNS, which convert these formations into pathological determinants, inducing the formation of pathological systems, provides a method of modeling various neuropathological syndromes. It has been shown that the creation of a GPEE in the rostral portions of the caudate nuclei (CN) by microinjection of tetanus toxin (TT) induces the development of Parkinson's syndrome [3, 4]. Under these conditions GPEE formation was connected with blockade of dopamine secretion by TT, as a result of which the cholinergic neurons of CN, which form the GPEE, were disinhibited. The question arose, can Parkinson's syndrome be induced by forming a GPEE in CN through activation of the main cholinergic neurons without primary blockade of dopamine secretion.

The aim of this investigation was to study this problem. To create a GPEE we used kainic acid (KA), an analog of glutamic acid, the natural mediator of certain afferent connections of CN [9]. The mechanism of the epileptogenic action of KA is connected with its direct excitatory action and blockade of GABA-ergic neurons, with the result that cholinergic neurons are disinhibited [8].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats of both sexes weighing 250-350 g. The animals were anesthetized with hexobarbital (100 mg/kg) after which metal cannulas (exter-

*Academician of the Academy of Medical Sciences of the USSR.

Department of Pathological Physiology, N. I. Pirogov Odessa Medical Institute. Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow.

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 6, pp. 650-653, June, 1987. Original article submitted June 17, 1986.

0007-4888/87/0006-0732$12.50