for a role of HDLP in the transport of excess CS from the tissues into the liver has been postulated [7]. A diet with CS increases the outflow of CM into lymph of ILT, and this undoubtedly promotes lipoidosis of the blood vessel walls and, in particular, the walls of the vessels of the heart [4].

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INVESTIGATION OF THE ROLE OF CYCLIC AMP AND PROSTAGLANDIN E_2 IN THE MECHANISM OF THE INHIBITORY ACTION OF NICOTINIC ACID ON PLATELET AGGREGATION

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UDC 612.111.7.015.2:577.175.859].014.46:615.356:577.164.15

KEY WORDS: cyclic AMP; prostaglandin E_2; nicotinic acid; platelet aggregation.

Nicotinic acid inhibits platelet aggregation in man and animals *in vivo* [1].

The object of this investigation was to study the mechanism of the antiaggregating action of nicotinic acid on platelets and, in particular, to determine the character of its immediate effect on platelet function *in vitro* and also on the concentration of cyclic adenosine-3,5-monophosphate (cAMP) and of prostaglandin E_2 (PGE_2), which are endogenous regulators of platelet aggregation [2-4, 6, 8], in the platelets.

EXPERIMENTAL METHOD

Nicotinic acid was added in a concentration of 16.2 mM to whole donors' blood, kept in TsOLIPK 7b preservative. The aggregating power of the platelets was studied and their content of cAMP and PGE_2 determined 1.5-2 h after the blood was taken and also after keeping for 1, 3, 5, and 7 days at 4°C.

Platelet aggregation induced by ADP (1 μM), adrenalin (5 μM), and thrombin (0.5 i.u./ml), was studied by Born's method [5]. The degree of aggregation was determined by the method of Wu and Hoak [11]. The intracellular platelet concentration of cAMP was determined radioimmunologically with the aid of a diagnostic kit from the Radiochemical Centre, Amersham, England. The PGE_2 concentration in the platelets was investigated radioimmunologically by means of the diagnostic kit from Clinical Assays, USA. In control experiments donors' blood not containing nicotinic acid was used. Each index was studied in 15-30 series of experiments. The experimental results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

During storage of preserved blood there was a constant rise in the cAMP level (Table 1), which became statistically significant on the first day ($P < 0.05$). The PGE_2 level also was statistically significantly increased on the 3rd day of keeping ($P < 0.05$), but later it fell,

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(Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 93, No. 4, pp. 17-19, April, 1982. Original article submitted May 28, 1981.

TABLE 1. Effect of Nicotinic Acid on Content of cAMP and PGE_2 in Platelets from Donors' Blood (in pg/10^9 platelets)

Time of investigation after addition of nicotinic acid to blood	Parameter studied	Blood samples tested	
		whole blood (control)	whole blood with nicotinic acid (expt.)
1½—2 h	cAMP	6,4±1,2	22,6±1,4*
	PGE_2	1138±233	1556±323
1 day	cAMP	8,5±1,5	17,0±3,0*
	PGE_2	1618±354	2387±408*
3 days	cAMP	11,5±3,4	37,4±2,3*
	PGE_2	2234±250†	2606±460
5 days	cAMP	13,1±1,9†	38,2±5,4*
	PGE_2	2070±355†	2394±320
7 days	cAMP	18,1±3,4†	41,0±3,1*
	PGE_2	1229±289	1430±266

*Differences between groups statistically significant ($P < 0.05$).
†Differences statistically significant compared with values obtained after keeping for 1.5-2 h ($P < 0.05$).

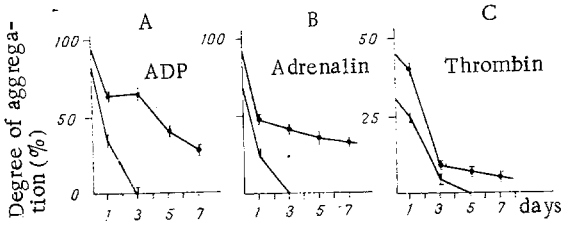

Fig. 1. Effect of nicotinic acid on platelet aggregation induced by ADP (A), adrenalin (B), and thrombin (C). Line with dots represent platelet aggregation in whole blood, line without dots denotes platelet aggregation in blood containing nicotinic acid.

and by the 7th day of keeping differences from the initial PGE_2 level were not significant ($P > 0.05$). The addition of nicotinic acid to the donors' blood caused a decrease in the ability of the platelets to be aggregated by ADP, adrenalin, and thrombin during the next 1.5-2 h (Fig. 1). During keeping of the blood the inhibitory action of nicotinic acid of platelet aggregation was manifested more clearly. For instance, whereas 1.5-2 h after the beginning of incubation of the blood with nicotinic acid the degree of ADP-induced platelet aggregation was reduced by approximately 10%, after 1 day the decrease reached 44%, and starting with the 3rd day, platelets from blood treated with nicotinic acid had completely lost their ability to aggregate under the influence of ADP. A similar pattern also was found in the experiments in which adrenalin and thrombin were used as inducers of platelet aggregation.

Addition of nicotinic acid to the blood caused an increase in the cAMP and PGE_2 content in the platelets. The cAMP level in platelets from blood incubated with nicotinic acid was almost 3 times higher than initially after 1.5-2 h. Throughout the period of observation the ratio between the concentration of cAMP in platelets from the control and experimental blood samples remained almost the same, although after 1 day this ratio was 1:2. The PGE_2 content in the platelets was increased after 1.5-2 h on average by 36% under the influence of nicotinic acid. At subsequent times of observation its concentration in platelets from blood incubated with nicotinic acid continued to exceed the control level, but these differences gradually increased, and on the 3rd-7th day they amounted to approximately 15%.

The investigations thus showed that nicotinic acid inhibits the aggregating activity of platelets *in vitro* and increases their content of cAMP and PGE_2. It has recently been shown that intensification of cAMP synthesis in platelets is accompanied by depression of their aggregating power [9]. PGE_2 in small doses induces platelet aggregation, but in high concentrations inhibits this process [7].

The results show that the cAMP level in platelets of blood incubated with nicotinic acid is increased more on average (almost threefold) than their PGE_2 content (by 36-15%) relative to the initial concentration of the same parameter in control blood samples.

The results of these experiments suggest that the mechanism of the inhibitory action of nicotinic acid on platelet aggregation is due to its ability to act directly on these blood cells and to disturb their homeostatic balance of regulators of platelet aggregation, chiefly in the direction of an increase in the synthesis of its inhibitor, cAMP. This conclusion is also supported by the ability of nicotinic acid to inhibit the formation of thromboxane A_2, a highly active inhibitor of platelet aggregation, in the platelets.

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SEASONAL DIFFERENCES IN THE ACTION OF MORPHINE AND NALOXONE ON THE RESPONSE OF *Helix* NEURONS TO DOPAMINE

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UDC 615.212.7:547.943+615.214.31].015.4:612.822.3-019:594]:613.13

KEY WORDS: morphine; naloxone; responses to dopamine; mollusk neurons.

Investigations of the membrane mechanisms of effects of agonists (morphine and enkephalins) and antagonists (naloxone) of opiate receptors have shown that opiates can not only act on the membrane potential of *Helix* neurons [3, 4], but can also weaken the response of these neurons in a naloxone-dependent manner to serotonin [1] and dopamine [2], by a noncompetitive mechanism.

Considering the abundant data in the literature on seasonal differences in intracellular metabolism and the state of neuronal reception in mollusks [6, 10, 11] and also data [13] on seasonal differences in the effect of opiates on the content of cyclic nucleotides in the brain of these animals, it appeared interesting to study seasonal differences in the action of morphine and naloxone on functional activity of molluscan neurons and, in particular, on their response to dopamine.

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Snezhnevskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 93, No. 4, pp. 19-21, April, 1972. Original article submitted June 8, 1981.