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# EFFECT OF INHIBITORS OF PROSTAGLANDIN BIOSYNTHESIS ON RESISTANCE OF MICE TO COOLING: FACT AND HYPOTHESIS

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Prostaglandins (PG) play an active role in temperature regulation [3]. At low ambient temperatures PGE induce hypothermia after intrahypothalamic, intraventricular, and also intraperitoneal injection [6]. This is basically connected with negative modulation of the function of catecholaminergic systems by PG [3, 6], whose determinative role in protection against cold is well known [1]. PG are unstable substances; they are not stored until required, but are synthesized in response to various stimuli [8]. Intense cooling is a powerful source of such stimuli (hormonal, etc.). Of course the diversity of functions of the prostanoids [8] does not rule out a preventive action of some of these classes in the pathogenesis of hypothermia. However, the usefulness of inhibiting the action of PG in poststress pathological states (postradiation esophagitis, endotoxic shock) has already been demonstrated [9, 12].

In this investigation an attempt was made to increase resistance to cold in acute experiments using inhibitors of PG biosynthesis.

## EXPERIMENTAL METHOD

Experiments were carried out on 470 (CBA × C57BL)$F_1$ hybrid male mice weighing 18-22 g.

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TABLE 1. Fffect of Inhibitors of PG Biosynthesis on Resistance of Mice to Acute Intensive Cooling at −20°C (M ± m)

| Blocker of PG synthesis and time before exposure | Number of animals | Length of time during which body temperature was kept above 10°C (min) | Effect, % |
|---|---|---|---|
| Control | 85 | 50,1±1,5 | 100±3 |
| Aspirin | | | |
| 500 mg/kg, 30 min | 36 | 74,8±3,8 | 149±8* |
| 500 mg/kg, 60 min | 5 | 77,1±4,1 | 154±9* |
| Mephenamic acid, 50 mg/kg, 30 min | 24 | 76,7±4,8 | 153±10* |
| Indomethacin, 50 mg/kg, 60 min | 10 | 68,1±3,9 | 136±8* |
| Voltaren, 25 mg/kg, 90 min | 10 | 68,7±5,4 | 137±11* |

Legend. *P < 0.01

The animals were cooled in the MKK-3 climatic chamber at −20°C. The animals were cooled until the moment of death — in mice this takes place when the body temperature falls below 10°C. The resistance of mice of the control and experimental groups to cold was compared with reference to the length of time the body temperature was maintained above 10°C on account of biological (regulatory) mechanisms. It was determined as the difference between the length of life of the animals during cooling and the time taken for the body of a dead mouse (killed by compression of the cervical division of the spinal cord) to cool from 38 to 10°C at the same ambient temperature (−20°C). This parameter is more sensitive to regulatory influences than simple determination of the duration of life, for it elimates from the calculations a substantial background factor — counteraction of body cooling by purely physical factors (the heat capacity of the body, the hair cover, etc.), which, and only which, determine the rate of cooling of a dead (physical) body, but are not subject to influences either of endogenous regulators of all types or of substances introduced from outside; the parameter studied thus takes into consideration the time of maintaining body temperature only on account of biological mechanisms peculiar to living matter, or in other words, controllable mechanisms, which include heat production, vasoconstriction, and piloerection.

Blockers of PG synthesis were injected intraperitoneally: acetylsalicylic acid (ASA), ibuprofen and diclofenac sodium in aqueous solutions, indomethacin, mephenamic acid, ibuprofen, voltaren (from Pliva, Yugoslavia), in 1% solution of Tween-80. Control animals received an injection of the corresponding volume of water or 1% Tween-80, which itself had virtually no effect on resistance to cold.

## EXPERIMENTAL RESULTS

The results are given in Table 1. Blockers of PG synthesis, if injected 30-90 min before cooling, evidently increased resistance to cold (by 36-54%). Ibuprofen, which gave no stable effect within the dose range studied (5-200 mg/kg), was the exception. The remaining blockers were almost or completely ineffective in doses smaller than those indicated in Table 1. The doses effective in the present experiments were evidently higher than those effective for rodents on models of acute inflammation *in vivo*. This difference may perhaps be connected with the shorter exposure between injection of the blockers of PG synthesis and stress stimulation in these experiments. In other investigations this time was measured in hours or days, and often a course of injections was given, just as in clinical practice. Shortening the exposure in our opinion, is important in principle, having regard to the initial aim of the investigation. Meanwhile a course of aspirin injections (500 mg/kg daily for 3 days) did not have a greater effect than a single dose given 30 min before the experiment (43 ± 20%, n = 18, $p < 0.05$).

The almost equal effect of all blockers of PG synthesis may be evidence that the doses of the drugs used were sufficient to cause marked inhibition of PG biosynthesis with a short exposure, and that their protective effect was due, not to special influences of individual blockers, but to a common mechanism shared by all.

The increase in resistance to cold of animals "deprived" of PG may be associated primarily with activation of the temperature-regulating functions of catecholamines (CA), which stimulate heat production and reduce heat loss. Blockers of PG synthesis also increase the already increased CA excretion in the cold [10]. This may be evidence both of their increased synthesis (since blockers of PG synthesis stimulate activity of tyrosine hydroxylase, the limiting enzyme of CA synthesis [2]) and secretion [3, 4, 8], and a reduction of the metabolic inactivation of CA because of inhibition of the activating effect of PGE on monoamine oxidase [5]. It can be postulated that ultimately blockers of PG synthesis can increase or maintain the CA concentration in the tissues, which is important for survival in a cold environment, for the CA concentration in intact animals progressively falls in many tissues during hypothermia [1].

Meanwhile administration of exogenous CA to intact animals does not increase their resistance to cold. Exogenous CA likewise do not help adrenalectomized animals, but they restore the ability of adrenodemedullated and sympathectomized rats to survive in a cold environment [7]. It has been suggested that the effectiveness of endogenous and exogenous CA is increased by corticosteroids (CS), adrenocortical hormones whose secretion is sharply increased during cooling. In fact, exogenous CA administered after exogenous CS restore the resistance of adrenalectomized rats to the control level [7]. The protective action of CS is associated not with their own action, but with the so-called permissive action of CS on the temperature-regulating effects of CA (stimulation of heat production, vasoconstriction, and piloerection). Neither Ingle, who specially introduced this term in 1956, nor the authors cited in [7], who demonstrated its particular importance in protection from cold, was able to explain the mechanism of this "permissive" effect. It can be tentatively suggested that blocking of the formation or action of PG plays a role in the mechanism of this "permissive" effect during cooling. This hypothesis is supported by the following facts: 1) PG are negative modulators of CA secretion [4, 8]; 2) PGE and $PGI_2$ (prostacyclin) have a direct dilator action on blood vessels and inhibit the response of smooth muscles of the vessel wall to electrical stimulation of nerves and to noradrenalin [11]; 3) CS are inhibitors of PG biosynthesis [8]; 4) exogenous CS increase the resistance of animals with intact endogenous CA to cold or if given in conjunction with exogenous CA [7]; 5) the phenomenon of increased resistance of animals with intact endogenous CA to cold under the influence of nonsteroid blockers of PG synthesis, described in the present communication.

The phenomenon discovered requires a detailed study of its mechanism. Even at this stage, however, it can be stated that the increase in resistance to cold under the influence of blockers of PG synthesis undoubtedly has practical importance.

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