BLOOD CATECHOLAMINE-PROSTAGLANDIN RATIO IN RATS EXPOSED AND ADAPTED TO ACUTE STRESS

M. G. Pshennikova, B. A. Kuznetsova, M. V. Shimkovitch, D. B. Saprygin, and F. Z. Meerson

UDC 613.863-036.11-092.9-07:[616.154:577.175.52+577.175.859]

KEY WORDS: catecholamines; prostaglandins; rat blood; stress; adaptation

The important role of activation of the stress-limiting systems of the body in the mechanism of the protective action of adaptation to stress in injuries due to stress, ischemia, or other factors, is now no longer in dispute [1, 3]. An important place among these systems is occupied by the prostaglandin (PG) system. This group of eikosanoids is able to limit the activity of the adrenergic stage of regulation [6, 13] and, consequently, the harmful action of catecholamines, and it also has a direct cytoprotective action at the level of effector organs [8, 12]. Meanwhile, changes in the PG system during stress and adaptation to stress situations and other environmental factors have still received only little study. Accordingly the aim of the present investigation was to study the effect of a single acute exposure to stress and adaptation to repeated stress on the ratio of activity of the adrenergic system and activity of the PG system in rats by determining plasma concentrations of catecholamines, PG-E, PG-$F_{2\alpha}$, prostacycline (PG-I_2), and thromboxane (TxA_2).

EXPERIMENTAL METHOD

Experiments were carried out on four groups of male Wistar rats weighing 360 ± 30 g. Group 1 consisted of intact rats (control); group 2 of rats subjected to a single acute exposure to stress (stress group); group 3) rats adapted to repeated exposure to stress (adaptation group); group 4) rats subjected to acute stress after preliminary adaptation (adaptation plus stress group). Adaptation was created by repeated sessions of immobilization of the animals in the supine position. The duration of the session was 15 min on the 1st day of adaptation, 30 min on the 2nd, 45 min on the 3rd, 1 h on the 4th day, and thereafter 1 h on alternate days, 12 immobilization sessions altogether. Acute exposure to stress consisted of fixing the animals in the supine position for 1 h. The rats were killed by decapitation: in group 2 immediately after exposure to stress, in group 3 on the 2nd day after the last adaptation session, in group 4 after acute exposure to stress, taking place 2 days after the last adaptation session. After decapitation, blood was quickly collected in a test tube with 0.2 ml heparin (on ice), the contents were then poured into two test tubes, to one of which were added EGTA and glutathione (for determination of catecholamines), whereas to the other were added EGTA and indomethacin (for determination of PG and TxA_2); the contents of the tubes were centrifuged in the cold for 15 min at 1000*g* and the supernatant was kept at −20°C until the determinations. Adrenalin (A), noradrenalin (NA), and dopamine (DA) were determined by radioenzyme assay using standard "Catechol" kits (Czechoslovakia). PG-E and PG-$F_{2\alpha}$ were determined by radioimmunoassay using a kit from "Clinical Assays" (USA) for PG-E, and from the Hungarian Institute of Isotopes for PG-$F_{2\alpha}$; a Mark 3 scintillation counter was used. PG-I_2 and TxA_2 were determined by the same method, based on the level of stable metabolites 6-keto-PG-$F_{1\alpha}$ and TxB_2 respectively, using kits from the Hungarian Institute of Isotopes and a "Tracor-Analytic" gamma-counter. The results were subjected to statistical analysis by Student's method.

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR. A. N. Bakulev Research Institute of Cardiovascular Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 6, pp. 534-535, June, 1990. Original article submitted November 30, 1989.

TABLE 1. Plasma Concentrations of Catecholamines, PG, and TxA_2 in Rats Following Exposure to Acute Stress and Adaptation to Stress ($M \pm m$)

Parameter	Control (n = 8)	Stress (n = 7)	Adaptation	Adaptation plus stress (n = 6)
A, pmoles/ml	4,06±0,73	51,5±11,4	20,87±2,0	28,91±4,25
NA, pmoles/ml	3,86±0,75	31,6±10,3	13,33±1,53	14,52±2,26
DA, pmoles/ml	0,45±0,28	10,6±4,2	2,30±0,33	3,03±1,18**
PG-E, pg/ml	506,0±58,3	553,3±144,0	868,4±73,6	961,5±62,5
$PG-F_{2\alpha}$, pg/ml	178,3±18,3	651,4±73,6	357,5±18,3	480,0±86,6
$PG-E/PG-F_{2\alpha}$	2,8±0,6	1,00±0,29	2,45±0,33	2,66±0,80
$PG-I_2$, mg/ml	358,8±25,0	962,7±82,0	549,5±65,0*	655,6±55,0
TXA_2, mg/ml	449,0±18,0	1780,3±98,0	988,5±25,0	1216,0±55,0
$PG-I_2/TXA_2$	0,80±0,08	0,54±0,05*	0,56±0,09	0,54±0,04*

Legend. $*p < 0.05$ compared with control; $**p < 0.05$ compared with stress.

EXPERIMENTAL RESULTS

The data in Table 1 show that exposure of unadapted animals to acute stress for 1 h caused an increase in the plasma concentrations of A, NA, and DA by 12, 6, 8.1, and 23.5 times respectively compared with the control, reflecting marked stress-induced activation of the adrenergic system. Meanwhile stress induced an increase in the plasma concentration of $PG-F_{2\alpha}$ in these animals by 3.5 times, and if the almost unchanged PG-E concentration was taken into account, this led to a decrease in the $PG-E/PG-F_{2\alpha}$ ratio by 2.8 times; stress also caused the $PG-I_2$ concentration to rise by 2.4 times and the TxA_2 4.4 times, leading to a decrease in the $PG-I_2/TxA_2$ ratio by 1.5 times compared with the control. Thus acute stress in unadapted rats not only caused an excess of catecholamines in the blood, which is a damaging situation [2], but also shifted the $PG-I_2/TxA_2$ ratio toward predominance of TxA_2 and the $PG-E/PG-F_{2\alpha}$ ratio toward predominance of $PG-F_{2\alpha}$; taken as a whole, these changes created the conditions for vasoconstriction and, what is particularly important, for spasm and thrombosis of the coronary arteries [10, 11].

Adaptation to repeated stress caused different changes. As Table 1 shows, during adaptation the blood catecholamine level fell, and after completion of the adaptation sessions the catecholamine level was only 1/3-1/2 as high as in the unadapted animals after a single exposure to stress. Lowering of the plasma catecholamine level in the adapted animals was combined with an increase in activity of the PG system. The blood level of PG-E in these animals was increased by 70%, of $PG-F_{2\alpha}$ by 100%, and $PG-I_2$ by 53%. As a result, as will be clear from data in Table 1, the ratio $PG-E/PG-F_{2\alpha}$ was restored to the control level during adaptation despite the continued action of the stress sessions. Under these circumstances the TxA_2 concentration fell by almost half compared with that in unadapted rats after acute stress, whereas the $PG-I_2/TxA_2$ ratio showed a tendency to recover. Thus in adapted animals, the intensity of the risk factors of stress-induced vasoconstriction and thrombosis was reduced. In fact, in the adapted animals (Table 1) acute stress, first, caused no significant increase in the blood catecholamine concentration compared with the initial level (adaptation), and second, it did not lead to any decrease in the $PG-E/PG-F_{2\alpha}$ ratio, which is characteristic of unadapted animals, so that the efficacy of PG-E was enhanced in the adapted animals during exposure to stress. Third, the TxA_2 concentration in these animals was increased under the influence of acute stress by only 23% of the initial level, i.e., significantly less than in the unadapted rats, in which the blood TxA_2 level rose by 4.4 times. As a result, in the adapted rats the TxA_2 concentration in the blood was 33% lower after exposure to acute stress ($p < 0.01$) than in unadapted animals exposed to the same stress.

When the data are analyzed it must be recalled that synthesis and release of PG of the E group and of $PG-I_2$ in the heart and many other organs are activated during the stress reaction under the influence of catecholamines, vasopressin, and other hormones [4, 7, 9]. These PG can effectively limit activation of the adrenergic system and, consequently, the damaging action of the stress response due to inhibition of NA release from adrenergic terminals [6, 13], cytoprotective action [8, 12], and also on account of prevention of vasoconstriction and thrombosis [10, 11]. In agreement with this, the observed increase in the plasma PG-E and $PG-I_2$ concentrations in the adapted animals, evidence of activation of their PG system, is evidently one factor which limits catecholamine secretion and the damaging effects of the stress response in these animals during stress. This point of view is confirmed by data [12] to the effect that during adaptation to stress activity of the PG system in the stomach is increased, and this limits the development of stress-induced ulcerative lesions of this organ, adrenergic in their nature, and also protects it against the direct harmful action of chemical factors.

The mechanism of adaptive activation of the PG system requires further study. We know, however, that synthesis of eikosanoids is coupled with activation of free-radical oxidation, and it has been shown that antioxidants increase PG-E and PG-I_2 synthesis but inhibit TxA_2 synthesis [5]. It can be tentatively suggested that adaptive changes in the PG system are connected with activation of the antioxidant system, which has been demonstrated in this kind of adaptation [2].

Thus the results reflecting the ratio between total activities of the stress-realizing adrenergic and the stress-limiting PG system, suggest that enhanced PG activity in the adapted animal can play a definite role in the limitation of the damaging action of catecholamines and, in this way, in the protective effects of adaptation.

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