PLASMA ERYTHROPOIETIN ACTIVITY AND INHIBITORY PROPERTIES AFTER VARIOUS ADRENERGIC INFLUENCES IN RATS

T. Ganchev, M. Georgieva

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The problem of neuro-humoral regulation of erythropoiesis is still not enough clarified. Erythropoietin (Ep) regulation (a specific factor in maintenance erythrocyte homeostasis (1, 11, 13, 15, 18) represents a particular interest. Recently, it has been accepted that another specific factor (an inhibitor of erythropoiesis (IE)) antagonizing Ep effect (10, 12, 14, 23, 24) plays also a role in erythropoiesis regulation. In our previous assays we have found out that beta-adrenoblockade and beta-adrenostimulation reduces Ep activity in rats while Reserpine (R) treatment doesn't change it significantly (5, 6). The important role of beta-adrenoreceptors in Ep activity regulation has been confirmed, recently, by Fink and Fisher (1976), too.

The purpose of the present study is to examine paralelly plasma Ep activity and IE activity after adrenergic effects by different mechanism. This would enable us to explain more accurately certain aspects of control function of adrenergic mediatory unit upon plasma. Ep activity and IE factors which erytrocyte homeostasis is dependent on.

Material and methods

The observation was carried out on 119 white rats of Wistar bred with body weight of 150—200 g. We used Isoprenaline-hydrochloride (Ip) as a stimulator of beta-adrenoreceptors (twice) in a dose of 5 mg/kg every 10—12 hours (sterile intraperitineal application) and Propranolol (pr) (Obsidan — DDR) in the same dose and way. A separate group of rats was treated with a beta-adrenoblocker and in one hour — with a beta-adrenostimulator in aforementioned doses. We applied Reserpine (R) (Rauwasedin — DDR) in a dose of 2 mg/kg s. c. as an inhibitor of neuronal link of the adrenergic mediatory unit. The controls were treated with saline (5). The treatment of rats continued 6 days long. On the 7th day their blood was sterilely collected and separated plasma was frozen until use. Plasma Ep activity was estimated on polycytaemic hypoxic mice by ^{59}Fe incorporation into new-formed erythrocytes (modification of Cotes and Bangham's method, 1961). The determination of plasma inhibitory activity has been previously described (6,25).

Results and discussion

The results from the parallel examination of plasma Ep activity are presented on fig. 1 and 2. In order to explain the mechanism of lowered Ep activity at beta-adrenostimulation and beta-adrenoblockade, we studied plasma inhibi-

tory properties in this setting. The results received are shown on fig. 3, A, B. It can be seen that plasma of rats treated with Ip shows a 7,07 % inhibition as compared to that of Ep control (fig. 3a). Plasma of rats treated with beta-adrenoblocker Pr demonstrates a more considerable inhibition of 15,86 % (fig. 3b).

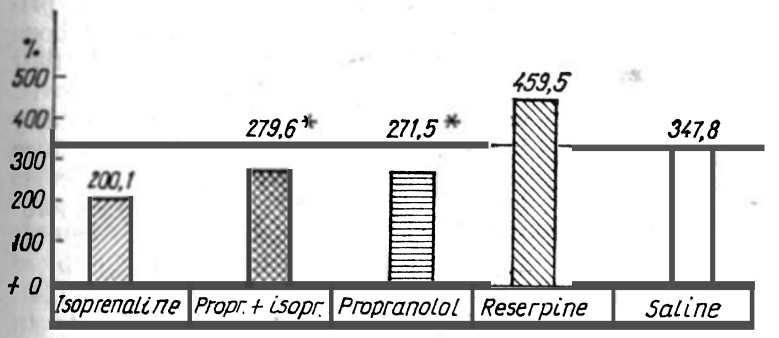

Fig. 1. Plasma Ep activity measured by the percentage of ^{59}Fe incorporated in the erythrocytes of polycytemic mice, presentel as a percentage deviation compared to the basal erythropoiesis accepted as 100 %.
*activity level of the control plasma means statistical significance at $p<0,025$

In seems that concerning any effects plasma Ep activity is increased as co m pared with basal erythropoiesis. The slightest increase is observed with beta-adrenostimulation with Ip and the biggest one after inhibition of the neurona-

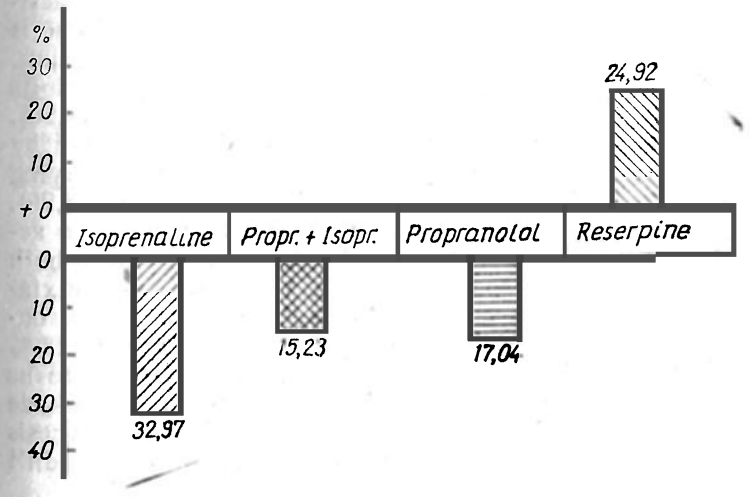

Fig. 2. Ep activity in comparison to the control plasma, accepted as 100 %.

link of the adrenergic mediatory unit with R. (fig. 1). In our opinion, the comparison of Ep activity after different adrenergic effects with that of control plasma is of a greater interest.

Plasma shows a tendency to lower levels after beta-adrenostimulation, beta-adrenoblockade and combination of stimulation followed by blockade. Ep acti-

vity is greater than that of the control only in animals treated with R. (fig. 2). We tend to explain its lower activity in those treated with Ip as compared to the other adrenergic effects by the lower Ep production and the presence of IE (fig 3a).

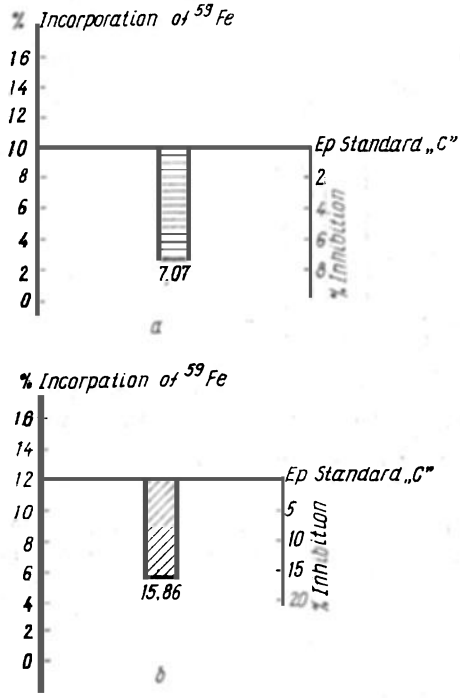

Fig. 3a, Plasma inhibitory properties of Isoprenaline-treated rats. By the ordinate to the left — % of the incorporated ^{59}Fe in polycytemic rats under the influence of 0,5E Ep standard «C» to the right — % of inhibition compared to the Ep standard «C» under the influence of the investigated plasma. Fig. 3b. Plasma inhibitory properties of Propranolol-treated rats. The same indications.

In previous studies we have established that Ip stimulated erythropoiesis primarily by its direct influence on the bone marrow (6). It is a noteworthy fact that along with Ep reduction there is also IE which probably contributes to the totally lower plasma Ep activity. IE appearance can be explained with the higher levels of erythrocytes and haemoglobin established (6) which could as well inhibit Ep production, as stimulate an inhibitor appearance by a feedback mechanism (24).

The comparison of Ep activity in animals treated with Pr and of that in control shows a tendency to levels lower by 17,04 %. This is considered to be due to the presence of IE (fig. 3b) which takes part in determination of total plasma activity. According to our opinion, one of the factors which could stimulate IE production by a feed-back mechanism is the increased reticulocyte count. It is possibly that the lower plasma Ep activity as compared with the control one is due also to the inhibited Ep production, as far as it is known that Pr inhibits a number of metabolic processes (8,20). This Pr effect is probably mediated by cAMP which is considered to be playing an important role in Ep biogenesis (18,26).

The data concerning plasma Ep activity in rats treated with Pr and Ip both represent a certain interest. The juxtaposition of this activity with that of control plasma shows a diminution of 15,23 % while in Ip treated animals this reduction is 32,97 % (fig. 2). According to us this considerable inhibition of Ip effect after a preliminary beta-adrenoblockade also points to the fact that the beta-adrenoreceptors participate in Ep biogenesis in these conditions. At present, the precise mechanism of this action couldn't be easily explained. cAMP may also take part here.

However, according to us it is more likely that Pr could reduce the renal blood flow (7, 9, 27) and it can increase renal Ep production by the way of relative renal hypoxia (17).

The tendency to increased Ep activity in rats treated with R (fig. 1, 2) is due, according to us, to its increased production on the one hand, and to its inhibited utilization, on the other one. Catecholamines depletion (17) which oc-

curs in the initial phase of adrenergic post-reserpine blockade could reduce renal blood flow (22) and hence increase Ep production.

The markedly low ^{59}Fe incorporation into erythrocytes, the reduction of both reticulocytes and myelocaryocytes (6) speaks for a low functional activity of bone marrow erythroblasts, respectively, for inhibited Ep realization.

According to opinion all this can cause the higher Ep activity in R treated rats. Our data are in concordance with the results of Gubina et al. (1974) who have found an Ep increase after renal denervation.

Our results confirm the important role of the adrenergic system in Ep activity and IE regulation, i. e. in the maintenance of erythrocyte homeostasis. Of course, this regulation is complex and is closely related to total metabolism (6). The feed-back mechanism may play an important role in this regulation. It is bound up not only with stimulation or suppression of Ep production but also with the presence of IE.

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ЭРИТРОПОЭТИНОВАЯ АКТИВНОСТЬ И ИНГИБИТОРНЫЕ СВОЙСТВА ПЛАЗМЫ КРЫС ПОСЛЕ РАЗЛИЧНЫХ АДРЕНЕРГИЧЕСКИХ ВОЗДЕЙСТВИЙ

Т. Ганчев, М. Георгиева

РЕЗЮМЕ

Изучается эритропоэтиновая активность и ингибиторные свойства плазмы после различных своим механизмом водействий на адренергическую систему крыс.

Бета-адреностимуляция изопреналином понижает эритропоэтиновую активность по отношению к контролю на 32,97 % и показывает ингибицию на 7,07 %. Частичное снятие изопреналинового эффекта после предварительной бета-адреноблокады пропранололом (от 32,97 % до 15,32 %) свидетельствует об участии бета-адренорецепторов в биогенезе эритропоэтина. Бета-адреноблокада пропранололом понижает активность эритропоэтина на 17,04 % и выявляет ингибирующие свойства плазмы — 15,86 %. Подавление невронального звена адренергической медиаторной единицы резерпином вызывает увеличение плазменного эритропоэтина на 24,92 %. Подчеркивается важная роль адренергической системы в регуляции плазменного эритропоэтина и ингибитора эритропоэза.