ACTION OF THE β_2-BLOCKER PROPRANOLOL ON LYMPHOCYTE ADRENERGIC RECEPTORS IN ESSENTIAL HYPERTENSION

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The use of analysis of the receptor characteristics of human blood cells (platelets, lymphocytes) for the diagnosis and effective choice of therapeutic agents for the treatment of certain diseases (bronchial asthma, essential hypertension — EH) is becoming more widespread in recent times. The study of receptor characteristics of cells during treatment with various antihypertensive drugs, and in particular, the widely used β-blockers, is particularly interesting [3, 12]. Investigations on normal subjects have shown that therapeutic doses of propranolol increase the density of lymphocyte β_2-adrenoreceptors, and thus lead to the development of hypersensitivity [3]. The character of the changes in lyphocyte β_2-receptors caused by β-blockers in patients with EH is unknown.

In the investigation described below the characteristics of lymphocyte β_2-adrenoreceptors in patients with EH were studied after a short course of propranolol monotherapy.

EXPERIMENTAL METHOD

The investigation was conducted on 15 men with stage IIB of EH, and aged from 26 to 56 years. Treatment was withheld for not less than 2 weeks before the investigation began (patients previously receiving long-term treatment with β-blockers were not included in the group). Before the investigation began, the patients' blood pressure (BP) was measured during the control period (7-10 days): the initial BP, when the severity of EH and degree of the hypotensive effect were assessed, was taken as the average BP during the last 3 days of the control period. At 9 a.m. on the day of investigation venous blood was taken from the patients for isolation of mononuclear lymphocytes [1] and determination of the plasma renin activity (PRA) by kits from CIS (France) at rest and after strenuous walking for 1 h. The daily urinary excretion of adrenalin, noradrenalin (NA), and vanilylmandelic acid (VMA) was determined fluorometrically [2]. The patients received propranolol monotherapy. Its dose was increased during the first 3 days to 160-240 mg daily, with monitoring of the heart rate (HR). The duration of monotherapy was 10-12 days, after which a further sample of venous blood was taken from the patients for analysis. The hypotensive effect was estimated as the difference between averaged BP before and after propranolol treatment. The density of β_2-adrenoreceptors on intact lymphocytes was determined by the method described previously [1]: in three patients with the use of ^{3}H-dihydroalprenolol (^{3}H-DHA, 52 Ci/mmole; Amersham Corporation, England), in the rest with ^{125}I-cyanopindolol (^{125}I-CIP; from Sandoz, Switzerland). Iodination of the cyanopindolol was carried out by the method in [7] and the original specific activity of the ^{125}I-CIP was 2037 Ci/mole. To reduce nonspecific binding of ^{125}I-CIP with the cells, receptor binding was carried out by a modified method [10]. Activity due to ^{3}H on the filters was analyzed in Bray's mixture on a RackBeta counter (LKB, Sweden), and activity due to ^{125}I was measured in a 50% mixture of ethanol and water in a RackGamma counter (LKB). Specific binding was determined as the difference between total and nonspecific binding; the density of the receptors (B_{max}) and the dissociation constant (K_d) were calculated by Scatchard linearization of the values obtained.

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TABLE 1. B_{max} (in fmoles/10^6 cells), K_d (in pM), PRA (in mg/ml/h), BP_{syst}, BP_{diast}, BP_{mean} (in mm Hg), and HR (beats/min) for Patients with EH before (A) and after (B) a Short Course of Propranolol Monotherapy ($X \pm S_m$, $P \leq 0.05$)

Parameter	Group of patients			
	1-		2-	
	A	B	A	B
B_{max}	1,93±0,73 n=6	5,37±2,01 n=6	4,09±0,36 n=6	1,96±1,09 n=6
K_d	66,2±20,3 n=5	230,2±171,9 n=5	119,5±55,8 n=4	55,1±33,7 n=4
PRA (at rest)	0,51±0,16 n=5	0,72±0,60 n=4	3,58±2,90 n=7	0,67±0,42 n=5
PRA (after exercise)	1,65±0,68 n=5	1,83±0,37 n=4	4,88±3,25 n=5	0,76±0,53 n=5
BP_{syst}	164±7,7 n=7	−15,6±7,2* n=7	166±7,2 n=8	−26,3±3,2* n=8
BP_{diast}	108±3,6	−12,1±2,3*	109±3,1	−15,7±1,5*
BP_{mean}	126,9±4,0	−11,9±2,4*	126,7±4,0	−19,2±1,9*
HR	72±3 n=7	−14±3* n=8	87±3 n=8	−30±3* n=8

Legend. B_{max}) only for 12 patients, because B_{max} for three patients was significantly higher before β-blockade: 10.5, 11, and 15.7, whereas after β-blockade it was 11.9, 6.9, and 4.8, respectively; according to changes in B_{max}, PRA, BP, and HR the first patient belongs to group 1, the other two to group 2 (the reason for the high initial B_{max} is unknown). Values of K_d and PRA given as x ± s. Asterisk indicates that data were analyzed by the statistical difference method.

The mean BP was determined by the equation

$$BP_{mean} = \frac{BP_{syst} - BP_{diast}}{} + BP_{diast}.$$

The results of all analyses were subjected to statistical analysis ($P \leq 0.05$).

EXPERIMENTAL RESULTS

Specific binding of ^{125}I-CIP with intact cells, like that of ^{3}H-DHA [1], was characterized by high affinity and saturation. The linear nature of the Scatchard plot (r between −0.95 and −0.99) is evidence of the homogeneity of the receptor population.

On the basis of changes in the density of lymphocyte β_2-adrenoreceptors of patients with EH after treatment with propranolol, the subjects as a whole could be divided into two groups (Table 1). Group 1 included patients responding to the β-blocker by an increase (on average, about threefold) in B_{max} and K_d. In subjects of group 2 the density of the β_2-receptors was reduced (on average by about half), whereas K_d was either unchanged or reduced. The patients in the groups did not differ in age (42.6 ± 3.7 years in group 1; 44.1 ± 3.0 years in group 2), the duration of the disease (9.9 ± 2.7 and 11.8 ± 3.7 years), or the initial BP level. The hypotensive effect of propranolol was stronger in the patients of group 2 and was characterized by a significantly greater decrease in HR and a definite tendency toward a more marked fall of the systolic and mean BP.

No significant differences were found between the groups with respect to the levels of adrenalin and NA excretion, whereas in the subjects of group 2 there was greater VMA excretion before β-blockade (10.70 ± 3.74 mg/day in group 2; 2.50 ± 1.23 mg/day in group 1).

The results of determination of PRA (Table 1) showed that a subnormal PRA was characteristic of the patients of group 1 (below 1 ng/ml/h), whereas a normal or increased PRA was characteristic of the patients of group 2. Before β-blockade, stimulation by walking caused an increase in PRA in the patients of both groups, but after β-blockade PRA was unchanged in the subjects of group 1, and significantly reduced in the patients of group 2.

Thus changes in the density of lymphocyte β_2-adrenoreceptors were opposite in direction in patients with EH after a short course of monotherapy with the nonspecific β-blocker, unlike the response of normal human lymphocytes. Virtually all the subjects of group 2, who responded to the β-blocker with a decrease in the number of β_2-receptors, had signs of sympathetic hyperactivity and they were patients with normal or raised plasma renin levels. Propranolol monotherapy in this group led to a marked fall in PRA, HR, and the systolic BP. The hypotensive effect of β-blockers, as recent investigations have shown [12], is linked with blockade of β_2-presynaptic adrenoreceptors of nerve endings. Strong correlation exists between the increased density of β_2-receptors of lymphocytes in patients with EH and the BP level, and it is considered that the density of lymphocyte β-receptors corresponds to the density of β_2-presynaptic receptors [4, 13]. We know that these receptors are regulated by adrenalin [11], the concentration of which is raised in the plasma of patients with EH [6]. Increased sympathetic nervous activity in EH [5, 9, 14] may perhaps be determined in the patients of group 2 by a combination of two factors: an increased density of β_2-presynaptic adrenoreceptors and a high adrenalin concentration, and administration of β-blockers to these patients as antihypertensive agents is effective.

The mechanism maintaining the high BP in patients of group 1, who responsed with an increase in the density of lymphocyte β_2-adrenoreceptors to propranolol monotherapy, is probably determined by other factors.

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