The relationship between adrenaline and β_2 -adrenoceptors on human lymphocytes

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To study the relation between plasma adrenaline (AD) and noradrenaline (NA) and the β_2 -adrenoceptor number ($B_{\max}$) on lymphocytes these variables were measured in the following three groups: a) In 67 normotensive volunteers after a rest period of at least 15 min. b) In 10 essential hypertensive (HT) and 10 age and sex matched normotensive (NT) subjects before and after a standardized bicycle exercise test (BE). c) In 10 bilaterally adrenalectomized females (AF) and 10 healthy age matched females (NF) before and after a mental arithmetic test (MA). Significant correlations were found between AD and $B_{\max}$ in NT ($r = 0.30$, $P = 0.015$) and between the proportional increase in AD and the proportional increase in $B_{\max}$ after BE ($r = 0.60$, $P < 0.005$). The MA induced elevation of $B_{\max}$ was blunted after adrenalectomy. All these findings point to a relation between AD and β_2 -adrenoceptor regulation.

Keywords β_2 -adrenoceptors up-regulation adrenaline

Introduction

The regulation of adrenoceptors is far more dynamic than previously believed. β_2 -Adrenoceptor number on lymphocytes increases after a number of short-term manoeuvres, such as bicycle exercise and mental stress (Brodde *et al.*, 1984; Graafsma *et al.*, 1987). To study the relation between plasma catecholamines and β_2 -adrenoceptor density on lymphocytes these variables were measured in the following three groups (all values $\pm$ s.d.): 1) In 67 normotensive volunteers after a rest period of at least 15 min (33 males, 34 females, age 45 ± 13 , range 22–75 years). 2) In 10 essential hypertensive (HT, age 40 ± 8 years, blood pressure (BP) $146 \pm 16/101 \pm 9$ mm Hg) and 10 normotensive subjects (NT, age 38 ± 11 years, BP $117 \pm 15/71 \pm 9$ mm Hg) before and after a bicycle exercise test (BE). 3) In 10 bilaterally adrenalectomized females (AF, age 38 ± 10 years, BP $115 \pm 21/80 \pm 15$ mm Hg) and 10 healthy females (NF, age 37 ± 12 years,

BP $104 \pm 9/71 \pm 6$ mm Hg) before and after a mental arithmetic test (MA). AF had undergone bilateral adrenalectomy because of Cushing's disease 1–18 years before the study.

Methods

The majority of NT was recruited by means of a newspaper announcement. HT were selected from the outpatient clinic and were without medication for at least 4 weeks. During BE the subjects exercised continuously for three successive periods of 6 min at work loads of 25, 50 and 75% of their previously calculated maximal individual work load. MA was performed according to a standard procedure (Houben *et al.*, 1983). Plasma catecholamines were determined by a radioenzymatic assay (Hoffmann *et al.*, 1986). β_2 -Adrenoceptor characteristics on intact

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lymphocytes were measured as described earlier (Graafsma *et al.*, 1988). $(-)^{125}$ I-iodocyanopindolol binding to intact lymphocytes was measured in the presence or absence of 10^{-6} mol l $^{-1}$ CGP-12177 after an incubation of 1 h at 37° C. Statistical comparisons between paired observations were made with Student's *t*-test or Wilcoxon's rank sum test. Correlation coefficients were calculated according to the Pearson correlation or the non-parametric Spearman's rank correlation test. A *P* value < 0.05 (two-sided) was considered to be statistically significant.

Results

The results are summarized in Table 1. In the first study, a significant correlation was found between baseline $B_{\max}$ and baseline AD ($r = 0.30$, $P = 0.015$), but not between $B_{\max}$ and NA ($r = 0.23$, $P = 0.06$).

In the second study changes in heart rate and blood pressure during BE did not differ between HT and NT. Baseline receptor number was similar in HT and NT. During BE a proportional increase ($\pm$ s.e. mean) in $B_{\max}$ of $48 \pm 9\%$ in NT and of $44 \pm 8\%$ in HT was observed (difference not significant). When both NT and HT were taken together, a significant correlation between the proportional increase in $B_{\max}$ and the proportional increase in AD ($r = 0.60$, $P < 0.005$) during BE was seen. When the proportional increase of $B_{\max}$ was compared with NA, no significant correlation was observed ($r = 0.35$, $P = 0.13$).

In the third study AD increased significantly in NF after MA, but remained undetectable throughout the test in AF. NA levels before and after MA amounted to 1.06 ± 0.11 and 1.28 ± 0.17 nmol l $^{-1}$ in NF and to 1.48 ± 0.17 and 1.49 ± 0.21 nmol l $^{-1}$ in AF respectively. There were no statistically significant differences in NA between both groups before as well as after MA.

Table 1 Baseline plasma adrenaline (AD), noradrenaline (NA), β_2 -adrenoceptor density ($B_{\max}$) and affinity (K_D) in normotensives (NT) (values $\pm$ s.d.) and the effect of bicycle exercise (BE) in hypertensives (HT) vs normotensives (NT) and the effect of mental arithmetic (MA) in adrenalectomized (AF) vs healthy females (NF) (values $\pm$ s.e. mean)

Baseline values (n = 67)				
AD (nM)		0.16 ± 0.10		
NA (nM)		1.53 ± 1.09		
β ₂ -adrenoceptors	K _D (pM)	7.7 ± 1.9		
	B _{max} (sites/cell)	1052 ± 295		
	NT (n = 10)		HT (n = 10)	
	Before BE	After BE	Before BE	After BE
AD (nM)	0.23 ± 0.05**	0.87 ± 0.15	0.22 ± 0.03*	0.76 ± 0.16
NA (nM)	2.89 ± 0.39*	13.61 ± 3.39	2.18 ± 0.15*	9.35 ± 1.86
β ₂ -adrenoceptors				
K _D (pM)	9.2 ± 0.7	9.0 ± 1.0	7.4 ± 0.8	8.9 ± 0.7
B _{max} (sites/cell)	1137 ± 136**	1594 ± 103	1207 ± 146**	1718 ± 201
	NF (n = 10)		AF (n = 10)	
	Before MA	After MA	Before MA	After MA
AD (nM)	0.08 ± 0.01*	0.14 ± 0.02	—	—
NA (nM)	1.06 ± 0.11*	1.28 ± 0.17	1.48 ± 0.17	1.49 ± 0.21
β ₂ -adrenoceptors				
K _D (pM)	7.3 ± 0.4	7.4 ± 0.6	7.0 ± 0.4	6.6 ± 0.4
B _{max} (sites/cell)	805 ± 57*	1016 ± 88	910 ± 69	965 ± 85

* $P < 0.01$, ** $P < 0.001$

Whereas in NF a 26% increase in $B_{\max}$ during the test was found, no change was seen in AF.

Discussion

The correlation between AD and $B_{\max}$ in 67 healthy normotensives, the correlation between the proportional increase in AD and the proportional increase in $B_{\max}$ in the second study and the absence of elevation of $B_{\max}$ during MA in AF, point to a role for adrenaline in the β_2 -adrenoceptor regulation.

Whereas much is known about the mechanisms of down-regulation or internalization of β_2 -adrenoceptors, less knowledge is available about the up-regulation after short-term physical

or mental exercise. It is unlikely that the increase in the receptor number measured already after 5 min stress represents new receptor synthesis. Strittmatter *et al.* (1979) hypothesized an acute uncovering of receptor sites that may not have been accessible before. On the other hand, more recently, data became available that $B_{\max}$ differs between subpopulations of lymphocytes (Khan *et al.*, 1986). Moreover, Landmann *et al.* (1988) demonstrated that exercise induces an increase in the number of β_2 -adrenoceptors per cell in lymphocytes and a simultaneous alteration in the distribution of lymphocyte subsets in the blood. In conclusion, whatever may be the cause of the up-regulation of $B_{\max}$ on lymphocytes, our results suggest that AD seems to play a predominant role in the regulation of the β_2 -adrenoceptor density, in contrast to NA.

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