Comments on the Study by Bono et al

In a recent issue of the Journal, Bono et al.1 present a study on the beta2-adrenoceptor density of lymphocytes obtained from primary hypertensive and normotensive subjects. The main conclusions by the authors were that the beta2-adrenoceptor density was elevated in hypertensives as compared to normotensives. The negative correlation between receptor number and plasma epinephrine concentration, present in normotensives, was lost in hypertensives but could be restored after 1 month of treatment with the beta1-selective antagonist bisoprolol. Treatment with verapamil or enalapril did not induce such a recovery. Although the study seems carefully conducted, we think that some of the conclusions are not fully covered by the presented data.

In their paper, the authors present the increased lymphocyte beta2-adrenoceptor number in hypertensives as a well acknowledged fact. In a recent review,2 however, we presented data from 14 studies in which this issue was addressed. In eight of the 14 studies (204 hypertensives vs 161 normotensive subjects; variable numbers per study from 10 to 45) a significantly higher receptor number was found in the hypertensive group. In five out the 14 studies (146 hypertensive vs 124 normotensive subjects; again variable participation per study from 8 to 72 vs 67) no significant difference was found. In one single study only a positive correlation between blood pressure and beta2-adrenoceptor density was reported. This illustrates that still no definite consensus is reached on this subject.

By using the hydrophilic radioligand [3H]-CGP12177, the authors claim to measure the cell surface receptors that are able to activate adenylly cyclase. This statement is, in our opinion, not valid. Not the amount of beta2-adrenoceptors present on the cell surface but the fraction of receptors able to interact with G-proteins is a determinant of receptor activity. According to the model of Lefkowitz,3 only receptors that show a high affinity agonist binding profile are able to participate in signal transduction. We have determined the fraction of beta2-adrenoceptors on lymphocytes with high affinity for isoprenaline, and found that this was less than 40% in both hypertensives and normotensives. In another report it was shown that this fraction was decreased in hypertensives; together with an increased total receptor number this may render a relatively constant amount of active membrane beta2-adrenoceptors in hypertensives and normotensives.

The most intriguing finding of the study, however, is the decrease in beta2-adrenoceptor number after treatment with the beta1-selective antagonist bisoprolol. It is generally accepted that treatment with an agonist, either full or partial, can induce a decrease in the beta2-adrenoceptor number, whereas antagonists either induce no change or a small increase in beta2-adrenoceptor number.6 In the present study, the authors show that a beta1-selective antagonist devoid of partial agonistic activity can induce a significant decrease in this parameter. Moreover, the affinity of bisoprolol for beta2-adrenoceptors is relatively low, which implies that at the peak plasma concentration indicated in the paper (44.5 ng/mL) only a small part of the receptors will be occupied by the antagonist, making a competitive interaction unlikely. Because these findings can not be explained by the principles of normal receptor pharmacology, they call for further study in order to elucidate the apparently unusual action of bisoprolol on lymphocyte beta2-adrenoceptors.

REFERENCES


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Reply to Blankesteijn et al

Despite the fact that most of the studies reported an increased β2-adrenoceptor density in essential hypertensive patients, especially those that measured lymphocyte β2-adrenoceptors in intact cells, this is not an universal finding, as Blankesteijn et al stated in their extensive review. However, in most of the studies that failed to find differences between hypertensive and normotensive subjects, β2-adrenoceptor density tended to be higher in hypertensive patients. Furthermore, some studies (borderline hypertensives) showed huge differences in body mass index between patients and controls (in fact Blankensteijn et al reported in their paper that body mass index accounted for 9.2% of the variance of these receptors). The radioligand and temperature of incubation selected (all the studies made with CGP12177 as radioligand found increased β2-adrenoceptor density in essential hypertensive patients) can also explain the lack of differences in these studies.

We partially agree with Blankensteijn et al that the active receptors are those that are coupled to a G-protein and that this is only a fraction of β2-adrenoceptors. However, the use of a hydrophilic ligand allows us to selectively measure surface receptors, while lipophilic ligands also bind to internalized receptors, which are inactive. Thus, we used the expression "active" meaning "able to couple to a G protein." It is well known that not all surface receptors are coupled to adenylyl cyclase, but in our study the incubation was carried out at 4°C. Under these conditions most β2-adrenoceptors are in a high affinity state. On the other hand, a decreased β2-adrenoceptor response in vitro has been reported in hypertensive patients. Thus it can be speculated that the increased surface β2-adrenoceptor number in essential hypertension is a secondary phenomenon trying to compensate the decreased β2-adrenoceptor intracellular response.

Finally, we agree that it is difficult to explain the normalization of β2-adrenoceptor density in our patients during treatment with the highly β1-selective blocker bisoprolol. However, as we demonstrated no receptor occupancy in vitro by bisoprolol, no upregulation of β2-adrenoceptor number should be expected with bisoprolol, as Blankensteijn et al stated in their letter. Our study suggests that this decrease is associated with a normalization of β2-adrenoceptor regulation and preliminary data from our group indicate that bisoprolol treatment also restores the decreased β2-response observed in these patients. Therefore, bisoprolol treatment seems to normalize the impaired β2-adrenoceptor function in essential hypertension.

REFERENCES


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