EFFECTS OF PINDOLOL AND PROPRANOLOL ON β -ADRENERGIC RECEPTORS ON HUMAN LYMPHOCYTES

P.B. MOLINOFF, R.D. AARONS, A.S. NIES, J.G. GERBER, B.B. WOLFE & M.B. GOENS

Department of Pharmacology, University of Colorado Medical Center, Denver, Colorado, USA

Experiments were carried out on lymphocytes isolated from heparinized whole blood (Aarons *et al.*, 1980). The blood is diluted with isotonic saline and layered over Isolymp. Following centrifugation the lymphocytes are collected from above the saline/Isolymp interface. This preparation contains over 90% lymphocytes. The cells are lysed by exposure to hypotonic media and membranes are collected by centrifugation. The density of β -adrenergic receptors is determined by Scatchard analysis of results obtained in studies of the binding of 125 I-iodohydroxybenzylpindolol or 125 I-iodopindolol (I-PIN).

A group of twelve normal subjects was treated with propranolol for 8 days (40 mg at 06.00 h, 12.00 h, 18.00 h and 24.00 h). Samples of blood were obtained in the late morning. This treatment protocol resulted in an increase in the density of β -adrenergic receptors, an increase that became statistically significant after 5 days of drug administration. The density of receptors returned to control levels when drug administration was discontinued. A statistically significant increase in the density of β -adrenergic receptors was still observed 48 h following discontinuation of propranolol administration. The standing and supine values of the systolic blood pressure/heart rate double product were determined as indices of myocardial oxygen consumption. The value of the orthostatic change in the double product was increased on the first two days following withdrawal of propranolol.

The relevance of changes in receptors on circulating leucocytes to changes occurring in solid tissues was assessed by determining the effect of propranolol on the densities of β -adrenergic receptors in various rat tissues. Propranolol, administered by continuous infusion from an Alzet mini pump, led to increases in the densities of β_1 and/or β_2 -adrenoceptors in rat heart, lung, cerebellum, cerebral cortex and lymphocytes. Measurement of β -adrenergic receptors on lymphocytes thus provides a useful measure of drug effects on receptors on tissues that are relatively inaccessible in humans. The change in β -adrenergic receptors associated with the administration of propranolol may explain the untoward effects observed when the administration of propranolol is abruptly discontinued.

A second study was carried out with 36 subjects

using a protocol similar to that described above except that the samples were taken 1 to 2 h following drug administration. Effects of pindolol (10 mg every 6 h) were compared with those of placebo or propranolol (administered as above). In this experiment no significant effects on the density of receptors were observed in subjects given propranolol or the placebo. Administration of propranolol resulted, however, in very large decreases in the apparent affinity of the receptor for the radioligand, I-PIN. This was probably due to the presence of propranolol adsorbed to the lymphocyte membranes and it decreased the reliability of the determination of receptor density in samples prepared from subjects being treated with propranolol.

The relatively less lipophilic nature of pindolol meant that only a small amount of pindolol was adsorbed to the membranes of the lymphocytes. Thus, there was only a small change on the apparent affinity of the receptor for I-PIN. There was, however, a very marked decrease in the density of receptors. This decrease was apparent in all twelve of the subjects treated with pindolol. The decrease was statistically significant after pindolol had been administered for only 1 day. A maximal decrease in the density of receptors of 30–50% was seen within 3 days in all twelve of the subjects treated with pindolol. This effect persisted after drug administration had been discontinued. The density of receptors in samples from subjects that had not received pindolol for 10 days was decreased compared to that observed prior to administration of pindolol. It is likely that the ability of pindolol to stimulate β -adrenergic receptors is responsible for the observed down regulation of receptors. The decrease in receptors may contribute to the beneficial therapeutic effects of pindolol. Furthermore, the fact that pindolol administration does not result in an increase in the density of receptors suggests that the delayed side effects observed following abrupt withdrawal of propranolol will not be observed following abrupt discontinuation of pindolol administration.

Reference

- AARONS, R.D., NIES, A.S., GAL, J., NEGSTRAND, L.R. & MOLINOFF, P.B. (1980). Evaluation of β -adrenergic receptor density in human lymphocytes after propranolol administration. *J. clin. Invest.*, **65**, 949–957.