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α -ADRENOCEPTOR MEDIATED INHIBITION OF HUMAN FAT CELL ADENYLATE CYCLASE

In human adipose tissue α -adrenergic receptor stimulation inhibits the formation of cAMP and lipolysis whereas β -adrenergic receptor agonists stimulate the synthesis of cAMP and lipolysis (Burns, Langley & Robison, 1972; Rosenquist, 1972). The relationship between α - and β -adrenergic responsiveness of human adipose tissue has been shown to be profoundly influenced by dietary conditions (Arner, Engfeldt & Ostman, 1979) or disease such as hypothyroidism (Rosenquist, 1972) or untreated juvenile onset diabetes mellitus (Arner *et al.*, 1979). β -adrenoceptor sites appear to be linked to the membrane-bound adenylate cyclase in most tissues including human fat tissue (Kather & Geiger 1977; Kather & Simon, 1977). As opposed to β -adrenoceptors, α -adrenergic excitation is probably mediated via distinct effector systems depending on the cellular origin of the preparation (Kunos, 1978).

The apparent effect of the naturally occurring catecholamines adrenaline and noradrenaline on the human fat cell adenylate cyclase is a stimulatory one displaying the characteristics of β -adrenoceptor mediated excitation (Kather & Simon, 1977). When added alone these agonists caused a dose-dependent increase of enzymic activity with a maximum of 50%–300% at 5×10^{-4} mol/l (Kather & Simon, 1977). Upon complete β -adrenergic receptor blockade using 0.05 mmol/l propranolol, however, an inhibitory

component of the naturally occurring mixed agonists adrenaline and noradrenaline became apparent which was not shared by the almost pure β -adrenergic receptor agonist isoprenaline (Figure 1). Under these conditions the mixed agonist noradrenaline caused a dose-dependent inhibition of basal enzymic activity with a maximum of 30%–40% at 10^{-4} mol/l. The noradrenaline-induced inhibition could be reversed by simultaneous α -adrenergic receptor blockade with 10^{-5} mol/l phentolamine. These results show that the inhibitory α -adrenergic component, like β -adrenergic stimulation, is mediated via the membrane-bound adenylate cyclase in human adipose tissue. The results of the present study thus confirm the concept of antagonistic α - and β -adrenergic receptor sites coexisting as regulatory subunits of the human fat cell adenylate cyclase as suggested by Rosenquist (1972) and by Burns *et al.* (1972).

The mutual interrelationship of α - and β -adrenergic responsiveness is poorly understood in biochemical terms. It is of special interest, however, to clarify the mechanisms and interrelationship of α - β -adrenergic responsiveness. This aspect involves questions as to the modulation of the response to drugs by diet, age or disease and is pertinent to the actual discussion about the use of β -adrenoceptor blocking agents in diabetics. Studies utilizing the human fat cell adenylate cyclase, therefore, may be

Figure 1 Inhibition of the human fat cell adenylate cyclase by the α -adrenergic component of noradrenaline.

Subcutaneous adipose tissue was from six surgical patients. Fat cells and fat cell ghosts were prepared according to Rodbell (1972). The adenylate cyclase activity was assayed according to Salomon *et al.* (1974) at 30°C, pH 8.0 and in the presence of 10 μ mol/l GTP. The concentrations of propranolol and phentolamine were 5×10^{-5} and 10^{-5} mol/l respectively. ● Propranolol alone, ▲ propranolol plus phentolamine.

useful for screening the metabolic effects of adrenergic drugs as influenced by diet, age or disease.

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DOSE-TITRATION COMPARISON OF INHALED SALBUTAMOL AND ORAL THEOPHYLLINE IN ASTHMA

β -adrenoceptor agonists by inhalation and oral theophylline, both widely used in the treatment of chronic asthma, have been compared with respect to potency and duration of action in single dose studies (Hartnett & Marlin, 1976; Marlin, Hartnett, Berend & Hackett, 1978). However, for an accurate assessment of relative potency, the relationship of the dose of the drugs to their dose-response curves must be known. The value of establishing dose-response curves when comparing the bronchodilator potencies of drugs is well established (Shenfield & Paterson, 1973; Marlin, Hartnett & Berend, 1977; Marlin,

Bush & Berend, 1978). The object of this study was to compare by dose-response curves the bronchodilator potency of salbutamol by pressurized aerosol and oral theophylline.

Eight patients, aged 32 to 78 years, with chronic, partially reversible airways obstruction due to chronic asthma, were selected for this study after their informed, written consent. Their baseline forced expiratory volume in one second (FEV₁) ranged between 29 and 56% of predicted normal and their % FEV₁ increase after 200 μ g salbutamol by pressurized aerosol was between 20 and 65%. The