DISCOVERY OF AN ATYPICAL ß-ADRENORECEPTOR IN RAT SKELETAL MUSCLE

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Pharmacological investigations suggest that clenbuterol and other ß-adrenoreceptor (ß-AR) agonists regulate protein turnover in skeletal muscle through interaction with an atypical ß-AR (Sillence et al. 1990). The present study was designed to characterise the ß-ARs in skeletal muscle of the rat.

Sarcolemmal membranes were prepared from gastrocnemius, soleus, and plantaris muscles from the hind limbs of female rats. Binding studies were performed using the non-selective ($ß_1/ß_2$) radioligand [^{125}I]iodocyanopindolol (ICYP). Competition studies were performed using ß-AR agonists and antagonists, and ligands selective for α-AR and serotonergic binding sites. Kinetic studies of the association and dissociation of ICYP were also executed. All data were analysed using the LIGAND computer program.

Competition experiments yielded a rank order of affinity for adrenergic agonists ((-)isoprenaline>(-)adrenaline>(-)noradrenaline) expected in a preparation of predominantly $ß_2$-ARs. The receptors showed stereoselectivity, preferentially binding the laevorotatory isomers of isoprenaline and propranolol. Ligands selective for $ß_1$-ARs (RO363), α-ARs (phentolamine), and 5-HT receptors (methysergide) were poor competitors of ICYP, binding with low affinity to a single site. In contrast, a $ß_2$-AR selective antagonist (ICI 118551) produced a bi-phasic displacement curve, suggesting the presence of two receptors, one a high affinity $ß_2$-AR, and the second a relatively high affinity, but atypical ß-AR.

In kinetic experiments, [^{125}I]ICYP binding was explained significantly better by a model of two receptor sites than by a model of one site ($P<0.05$). Association and dissociation rates were used to calculate the equilibrium dissociation rate constants (K_D) of [^{125}I]ICYP for the two sites.

Ligand	K_{DHIGH} pM	K_{DLOW} pM	K_{DLOW}/K_{DHIGH}
ICYP	0.246	14.6	59.30
ICI 118551	855	1330	1.56

These results illustrate that rat skeletal muscle is host to a population of $ß_2$-ARs, and a significant proportion of atypical ß-ARs. Further investigations will elucidate the role of the atypical ß-AR in mediating the anabolic effects of $ß_2$-AR agonists in skeletal muscle.

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