Treatment with the β_2-agonists formoterol or salmeterol produce greater muscle hypertrophy in rats than fenoterol

J.G. Ryall, D.R. Plant and G.S. Lynch, Muscle Mechanics Laboratory, Department of Physiology, The University of Melbourne, Victoria 3010, Australia.

Although traditionally administered at low doses for treating asthma, at higher doses, β_2-adrenoceptor agonists (β_2-agonists) have potent muscle anabolic effects. As such, β_2-agonists may have therapeutic potential for pathologies where muscle wasting is indicated, such as cancer cachexia, muscular dystrophy and age-related muscle wasting (sarcopenia). Before these drugs can be considered as legitimate therapies, some safety concerns, especially their effects on the heart, need to be considered. The β_2-agonists, formoterol and salmeterol were originally developed to increase the duration of bronchodilation. Previous studies have shown formoterol and salmeterol to have a duration of action of four and eight times greater, respectively, than the most widely used asthma drugs (Anderson, 1993). We have previously shown that the (short-acting) β_2-agonist fenoterol has greater anabolic effects on skeletal muscle than the most widely described, in relation to skeletal muscle, β_2-agonist, clenbuterol (Ryall *et al.*, 2002). In the present study, we tested the hypothesis that due to their long duration of action, chronic administration of salmeterol and formoterol would produce greater skeletal muscle hypertrophy than fenoterol. One of our research goals is to optimise the safe and effective use of β_2-agonists to ameliorate muscle wasting in a number of pathologies.

Fenoterol, formoterol and salmeterol (kindly supplied by Astra-Zeneca) were administered to male Fischer 344 rats (12 weeks/age, body mass, 265g) at one of five different doses (0.025 - 2 mg/kg/day) for four weeks. Fenoterol and formoterol were administered by daily i.p. injection in saline, and compared to a control group receiving an equivolume of saline. Due to its highly lipophillic nature, salmeterol was administered via a daily i.p. injection in a lipid vehicle, and compared to a control group receiving an equivolume of lipid vehicle. The rats were deeply anaesthetised (sodium brietal, 60 mg/kg), and the heart, and the EDL and soleus hindlimb muscles were surgically excised, weighed, and then stored for histological analyses.

The rank order of efficacy (E_{max}), based on skeletal muscle hypertrophy (β_2-agonist induced increase in mass above control), was salmeterol = formoterol >> fenoterol. Salmeterol had an E_{max} at a dose of 1 mg/kg/day, increasing EDL, soleus and heart mass, 39, 28 and 25% above values for lipid vehicle control. Formoterol had an E_{max} at a dose of 0.5 mg/kg/day, increasing EDL, soleus and heart mass, 36, 26 and 26% above values for saline control. Fenoterol had an E_{max} at a dose of 2 mg/kg/day, increasing EDL, soleus and heart mass, 25, 14 and 23% above values for saline control. At the lowest dose examined (0.025 mg/kg/day) formoterol exhibited the greatest hypertrophy of both skeletal and cardiac muscle compared to values for saline control, (19, 13 and 12% greater for EDL, soleus and heart, respectively).

Our findings indicate that the β_2-agonists, formoterol and salmeterol, have anabolic effects on muscle and produce greater muscle hypertrophy than fenoterol. Further research is needed to examine the effect of these drugs on skeletal and cardiac muscle function before their full therapeutic potential can be realised.

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