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EFFECTS OF TWO ß-AGONISTS ON GROWTH AND HEART RATE IN RATS

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In a previous study, ketoclenbuterol (KETO) was shown to be more potent than clenbuterol (CLEN) in reducing urinary nitrogen output in female rats, despite the fact that the affinity of KETO for binding to ß-adrenoceptors was extremely weak (Sillence et al. 1991). From these observations we predicted that KETO may be an effective growth promoter, and that the compound may lack the undesirable effects of CLEN, which include increased heart rate and cardiac hypertrophy. In the present study we have extended these observations by comparing the effects of CLEN and KETO on isolated heart tissue and on weight gain in rats.

The chronotropic and inotropic actions of the ß-agonists were tested using rat atria and ventricular papillary muscle respectively. The tissues were suspended in organ baths containing oxygenated Tyrode's solution at 35°C, and contractions were measured using an isometric force transducer. Each muscle was used to obtain a single concentration-response curve, and six curves were obtained for each drug tested. The effects of KETO and CLEN were compared with those of the endogenous ß-agonist noradrenaline (NADR). Results are expressed as the negative log of the concentration of drug which caused a half-maximum increase in the rate or force of contraction (pD_2). For chronotropic and inotropic responses to NADR, pD_2 values were 6.51 ± 0.14 and 6.28 ± 0.07 respectively. In atria, CLEN caused only 62 % of the maximum response achieved with NADR, but produced a response at lower concentrations (pD_2 7.38 ± 0.08). KETO caused no effect in atria, and neither KETO or CLEN caused a response in papillary muscle at concentrations up to 10 µM.

To test the effect of the drugs on growth, six rats per treatment (mean body weight 183 ± 5 g) were housed in individual cages and allowed free access to standard control powdered diet, a diet containing 2.5 mg CLEN/kg feed, or a diet containing an equimolar amount of KETO (2.2 mg/kg feed). The rats were weighed daily, and on day eight were killed. Hearts were removed and weighed, along with a muscle bundle comprising the gastrocnemius, plantaris and soleus muscles.

Parameter	Control	KETO	CLEN	SEM
Average daily gain (g) 0.54*		4.40^{a}	5.71^{ab}	6.51^{b}
Average daily feed intake (g)	21.36^{a}	23.82^{b}	23.79^{b}	0.62*
Muscle bundle mass (g)	2.96^{a}	2.96^{a}	3.24^{b}	0.07†
Heart mass (g) 0.03†		0.73^{a}	0.74^{a}	0.83^{b}

^{a,b}Means with different superscripts differ (†P<0.1, *P<0.05).

The observations that KETO had no effect on isolated heart tissue, or on heart mass in vivo, confirm our hypothesis that animals treated with KETO suffer fewer cardiovascular effects than those treated with CLEN. The effect of KETO on weight gain was encouraging also, but the lack of effect of KETO on the mass of the hind-limb muscle bundle suggests that further experiments are required to determine whether that KETO is an effective anabolic agent.

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