SHORT REPORT

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The atypical β-blocker S-oxprenolol reduces cachexia and improves survival in a rat cancer cachexia model

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Abstract

Background Beta-blockers and selected stereoisomers of beta-blockers, like bisoprolol and S-pindolol (ACM-001), have been shown to be effective in preclinical cancer cachexia models. Here, we tested the efficacy of stereoisomers of oxprenolol in two preclinical models of cancer cachexia—the Yoshida AH-130 rat model and the Lewis lung carcinoma (LLC) mouse model.

Methods and Results In the Yoshida AH130 hepatoma rat cancer cachexia model and compared with placebo, 50 mg/kg/d S-oxprenolol (HR: 0.49, 95% CI: 0.28–0.85, $P = 0.012$) was superior to 50 mg/kg/d R-oxprenolol (HR: 0.83, 95% CI 0.38–1.45, $P = 0.51$) in reducing mortality (= reaching ethical endpoints). Combination of the three doses (12.5, 25 and 50 mg/kg/d) that had a significant effect on body weight loss in the S-oxprenolol groups vs the same combination of the R-oxprenolol groups lead to a significantly improved survival of S-oxprenolol vs R-oxprenolol (HR: 1.61, 95% CI: 1.08–2.39, $P = 0.0185$). Interestingly, there is a clear dose dependency in S-oxprenolol-treated (5, 12.5, 25 and 50 mg/kg/d) groups, which was not observed in groups treated with R-oxprenolol. A dose-dependent attenuation of weight and lean mass loss by S-oxprenolol was seen in the Yoshida rat model, whereas R-oxprenolol had only had a significant effect on fat mass. S-oxprenolol also non-significantly reduced weight loss in the LLC model and also improved muscle function (grip strength 428 ± 25 and 539 ± 37 g/100 g body weight for placebo and S-oxprenolol, respectively). However, there was only a minor effect on quality of life indicators food intake and spontaneous activity in the Yoshida model (25 mg/kg/S-oxprenolol: 11.9 ± 2.5 g vs placebo: 4.9 ± 0.8 g, $P = 0.013$ and also vs 25 mg/kg/d R-oxprenolol: 7.5 ± 2.6 g, $P = 0.025$). Both enantiomers had no effects on cardiac dimensions and function at the doses used in this study. Western blotting of proteins involved in the anabolic/catabolic homoeostasis suggest that anabolic signalling is persevered (IGF-1 receptor, Akt) and catabolic signalling is inhibited (FXBO-10, TRAF-6) by S-pindolol, but not he R-enantiomer. Expression of glucose transporters Glut1 and Glut 4 was similar in all groups, as was AMPK.

Conclusions S-oxprenolol is superior to R-oxprenolol in cancer cachexia animal models and shows promise for a human application in cancer cachexia.

Keywords Cancer cachexia; S-oxprenolol; Intervention; Therapy; Survival; Enantiomers; Beta-blocker

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Introduction

Cancer cachexia has been widely recognized as being a common manifestation of malignant cancer in its advanced stages and causes significant morbidity and mortality.[1] A hallmark symptom of cancer cachexia is a general loss of body weight, which may be accompanied by anaemia, alterations in carbohydrate and lipid metabolism and a variety of hormonal and immune disturbances. Protein mobilization mainly resulting from increased proteolysis is the main cause for loss of skeletal muscle mass and subsequently muscle strength in cachexia.[2] As a result, cancer cachexia is associated with high morbidity and mortality rates.[3,4] Unfortunately, no approved therapeutic agents are available to treat or even prevent the onset of (cancer) cachexia.[5]

Several studies suggest ß-adrenergic agonists as therapeutic targets to treat muscle wasting and muscle weakness through hypertrophic (controlling protein synthesis) and anti-atrophic effects (controlling protein degradation) on skeletal muscle.[6–8] Continuous administration of ß2-adrenergic agonists such as clenbuterol or formoterol has been shown to reverse muscle atrophy processes through activation of muscle protein synthesis and/or inhibition of proteolysis, resulting in increased myofibrillar protein content.[9,10] In line with this, the ß2-adrenergic agonist formoterol was observed to decrease the mRNA expression of ubiquitin and proteasome subunits in gastrocnemius muscle, thus contributing to the observed anti-wasting effects.[7,11] We have recently reported the efficacy of the small molecule anabolic catabolic transforming agent (ACTA) S-pindolol (ACM-001) in preclinical cancer cachexia.[12] Moreover, ACM-001 showed efficacy in a cancer cachexia phase IIa trial where lean mass and handgrip strength were significantly improved[13] as well as in a rat model of sarcopenia.[14] S-oxprenolol has similar properties to ACM-001 and also combines an anabolic and anti-catabolic pharmacological profile though a non-specific ß1-adrenergic and ß2-adrenergic antagonism and an intrinsic sympathomimetic activity (ISA) on ß2-adrenergic receptors. An antagonistic effect on 5-HT1A-receptor in the brain reduces fatigue, a major symptom of cancer-associated cachexia.[5]

The aim of the present study was to explore the effects of S-oxprenolol vs R-oxprenolol in the Yoshida hepatoma AH-130 rat model of severe cancer cachexia[15,16] in order to analyse survival, quality of life and impact on skeletal muscle atrophy. Additionally, the effects of S-oxprenolol were assessed in the Lewis lung carcinoma (LLC) mouse model.[17] To our knowledge, no study has assessed the effects of R-oxprenolol vs S-oxprenolol in a disease model thus far.

Methods

For details, please see *Supporting Information*. Briefly, intra-peritoneal injection of Yoshida hepatoma AH-130 cells to male Wistar Han rats to induce cancer cachexia. Animals were treated with R-oxprenolol and S-oxprenolol daily and compared with placebo. Body composition was assessed by nuclear magnetic resonance and cardiac function by echocardiography. At necropsy, organs and tissues were weight and snap-frozen.

For the LLC model, C57BL/6 mice received an intramuscular (hind leg) inoculum and were randomized to treatment: placebo 10 mg/kg/d S-oxprenolol (n = 9). Skeletal muscular strength in mice was quantified by the grip-strength test.

Western blotting was used to analyse key proteins in muscle anabolic catabolic signalling.

Results

As expected, there were no significant differences in tumour volume and total viable tumour cells between the tumour-bearing groups in the Yoshida rat model (*Table* S1). Survival was significantly improved by 25 or 50 mg/kg/d S-oxprenolol, but not by lower doses of S-oxprenolol or any dose of R-oxprenolol (*Figure* 1 and *Table* 1). Combining the three doses (12.5, 25 and 50 mg/kg/d) that had a significant effect on body weight loss (*Figure* 2) in the S-oxprenolol groups and analysing them compared with 12.5, 25 and 50 mg/kg/d of R-oxprenolol combined showed a significant improved survival of S-oxprenolol vs R-oxprenolol (HR: 0.62, 95% CI: 0.42–0.92, P = 0.0185).

Body weight and body composition

Body weight and body composition (lean and fat mass) were similar in all groups at baseline. Weight loss was dose-dependently attenuated in groups treated with 12.5, 25 or 50 mg/kg/d S-oxprenolol, whereas 5 mg/kg/d was ineffective and no treatment dose of R-oxprenolol reduced loss of body weight (*Figure* 2). Lean mass was only protected by 25 or 50 mg/kg/d S-oxprenolol; all other groups showed no significant changes (*Figure* 2). R-oxprenolol therapy leads to a significantly reduced loss of fat mass in the 25 and 50 mg/kg/d doses. S-oxprenolol was more effective at these doses and 12.5 mg/kg/d also reduced loss of fat mass (*Figure* 2). In the LLC mouse model, tumour weight was similar at the end of the study (4.6 ± 0.2 g vs 4.8 ± 0.2 g for placebo and 10 mg/kg/d S-oxprenolol, respectively), whereas loss of body weight was non-significantly attenuated by the treatment

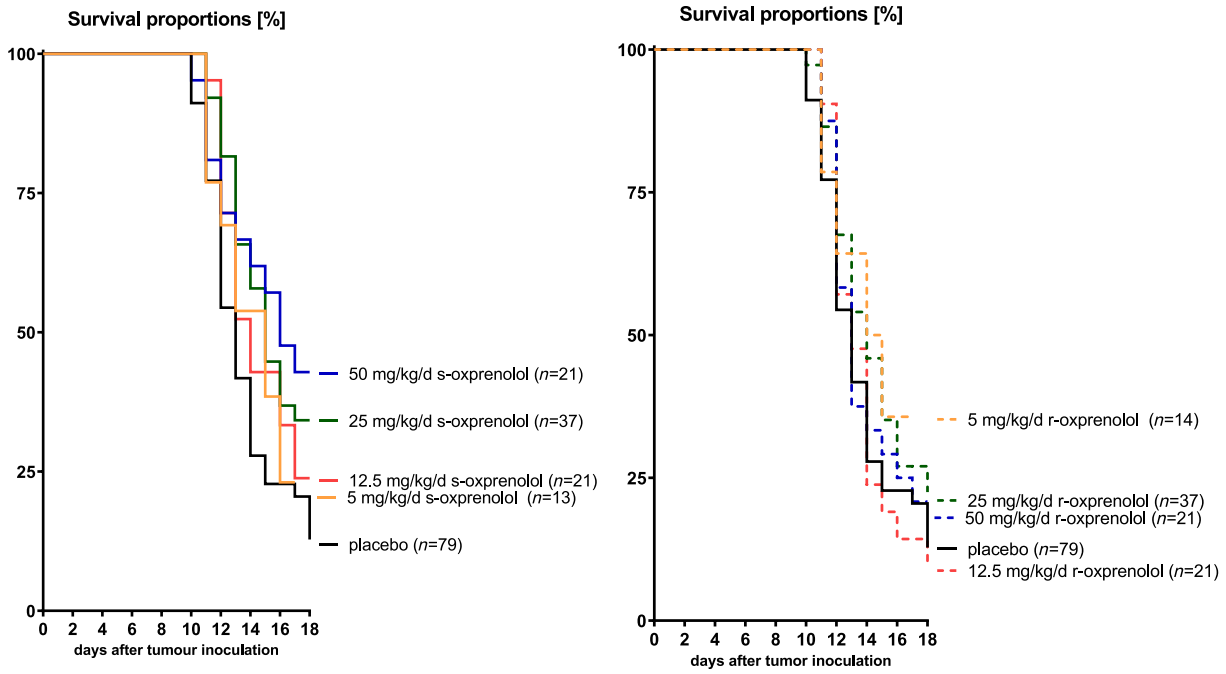

Figure 1 Kaplan–Meier plots of survival (= reaching ethical endpoints) after tumour inoculation in group treated with S-oxprenolol (left) or R-oxprenolol (right). *$P < 0.05$, **$P < 0.01$ vs placebo.

Table 1 Hazard ratios for treated groups vs placebo

	HR	95% CI	*P* value
5 mg R-oxprenolol vs placebo	0.64	0.32–1.27	0.20
12.5 mg R-oxprenolol vs placebo	0.99	0.55–1.78	0.97
25 mg R-oxprenolol vs placebo	0.71	0.44–1.14	0.15
50 mg R-oxprenolol vs placebo	0.83	0.38–1.45	0.51
5 mg S-oxprenolol vs placebo	0.79	0.39–157	0.50
12.5 mg S-oxprenolol vs placebo	0.67	0.38–1.17	0.16
25 mg S-oxprenolol vs placebo	0.52	0.33–0.84	0.007
50 mg S-oxprenolol vs placebo	0.49	0.28–0.85	0.012

95% CI, 95% confidence interval; HR, hazard ratio.
All groups in mg/kg/d.

(−1.2 ± 0.3 vs −0.4 ± 0.7 for placebo and 10 mg/kg/d S-oxprenolol, respectively).

Organ and tissue weights

Compared with non-tumour-bearing animals, all tumour-bearing groups in the Yoshida rat model treated with the oxprenolol enantiomers or placebo showed lower weight in tissue and organs (*Table* 2). Similar to overall fat mass, R-oxprenolol treatment led to increased white (WAT) and brown adipose tissue (BAT) weights at the 25 and 50 mg/kg/d doses, although there was no effect on cardiac and skeletal muscle weights (*Table* 2). S-oxprenolol-treated rats had higher weights of gastrocnemius, tibialis and extensor digitalis longus, but not the mainly slow muscle soleus and the heart; however, S-oxprenolol also protected WAT and BAT (*Table* 2). In the LLC model, treatment with 10 mg/kg/d S-oxprenolol was also muscle protective, as the weight of the heart, gastrocnemius, tibialis, extensor digitalis longus, soleus and diaphragm were increased compared with placebo, although there were no significant effects on WAT and BAT mass (*Table* 3). As a result, grip strength corrected for initial body weight was significantly higher in the S-oxprenolol group compared with placebo (428 ± 25 and 539 ± 37 g/100 g body weight for placebo and S-oxprenolol, respectively). Moreover, the change in grip strength (baseline to day 14) corrected for initial body weight was −59 ± 50 g/100 g body weight in the placebo group vs 45 ± 15 g/100 g body weight in the S-oxprenolol group.

Food intake and spontaneous activity

Food intake and locomotor activity were only assessed in sham or placebo 5 or 25 mg/kg/d R-oxprenolol and S-oxprenolol (*Figure* 3). Food intake was improved in the 25 mg/kg/d S-oxprenolol dose at day 11, but no treatment had any significant effects on activity (*Figure* 3).

Cardiac function

Cardiac function was assessed at baseline and on day 11 after tumour inoculation. Baseline values for left ventricular (LV)

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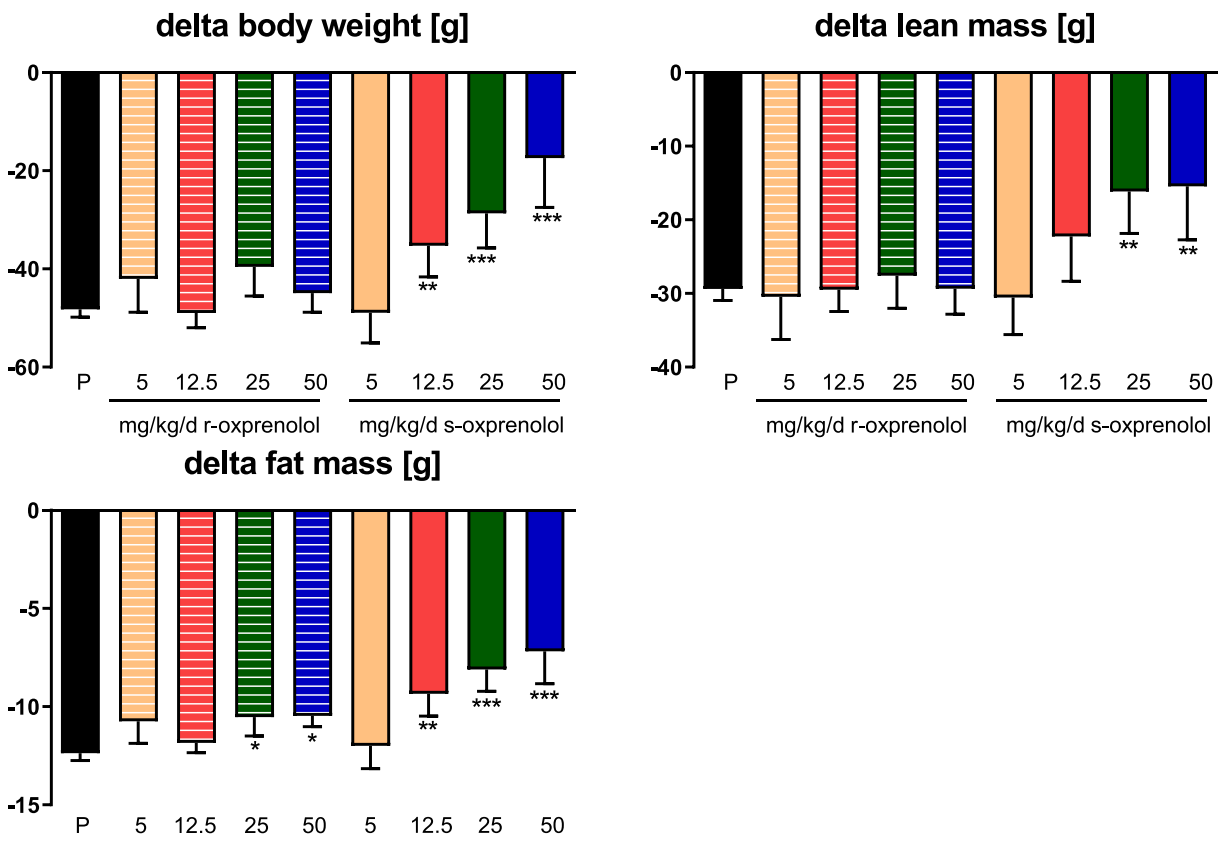

Figure 2 Change in body weight, lean and fat mass at the time of euthanasia. S-oxprenolol attenuated loss of body weight lean and fat mass, whereas R-oxprenolol only had an effect on fat mass. $*P < 0.05$, $**P < 0.01$, $**P < 0.001$ vs placebo.

Table 2 Organ and tissue weights in the Yoshida rat model

	Heart	GAS	Tibialis	Soleus	EDL	WAT	BAT
Sham	875 ± 24***	919 ± 12***	309 ± 6***	74 ± 1***	78 ± 2***	1753 ± 163***	280 ± 32***
Placebo	561 ± 10	525 ± 13	183 ± 4	50 ± 1	45 ± 1	87 ± 19	91 ± 4
5 R-oxp	576 ± 26	552 ± 29	193 ± 11	52 ± 2	45 ± 2	176 ± 86	128 ± 13**
12.5 R-oxp	578 ± 17	523 ± 15	171 ± 6	47 ± 1	45 ± 1	181 ± 37*	86 ± 5
25 R-oxp	590 ± 17	561 ± 24	190 ± 8	53 ± 2	48 ± 2	427 ± 125**	111 ± 8**
50 R-oxp	579 ± 21	523 ± 19	172 ± 8	52 ± 1	43 ± 2	208 ± 49*	84 ± 6
5 S-oxp	545 ± 29	490 ± 43	188 ± 10	57 ± 3*	49 ± 3	152 ± 87	115 ± 10*
12.5 S-oxp	572 ± 20	561 ± 28	192 ± 10	53 ± 3	48 ± 29	317 ± 81**	107 ± 10
25 S-oxp	589 ± 18	590 ± 29*	195 ± 10*	54 ± 3	52 ± 3**	676 ± 182***	119 ± 9**
50 S-oxp	584 ± 29	601 ± 37*	199 ± 14	54 ± 3	50 ± 3*	660 ± 182***	107 ± 15

BAT, brown adipose tissue; EDL, extensor digitalis longus; GAS, gastrocnemius; R-oxp, R-oxprenolol; S-oxp, S-oxprenolol; WAT, white adipose tissue (epididymal fat).
All groups in mg/kg/d, all weights in mg.
$^{*}P < 0.05$.
$^{**}P < 0.01$.
$^{***}P < 0.001$.

mass, ejection fraction (EF), fractional shortening (FS), end-diastolic diameter (EDD), end-systolic diameter (ESD), thickness of the interventricular septum (IVS) and posterior wall (PWT) in systole and diastole, stroke volume (SV) and heart rate (HR) showed no differences. As expected, tumour-bearing rats showed a loss of cardiac mass and function. Treatment with either R-oxprenolol or S-oxprenolol at 5 or 25 mg/kg/d did not have any significant effects on cardiac function with the exception of preserving LVEDD, LVESD and LVSV in the 25 mg/kg/d S-oxprenolol group (*Table* S2).

Signalling

The protein synthesis-inducing Akt was significantly lower expressed in animals treated with R-oxprenolol compared

Table 3 Organ weight in the mouse LLC model

	Heart	GAS	Tibialis	Soleus	EDL	Diaphragm	WAT	BAT
Placebo	107 ± 5	75 ± 2	25 ± 1	6.1 ± 0.2	5.6 ± 0.2	67 ± 2	52 ± 14	63 ± 4
10 mg-S-oxp	121 ± 3*	87 ± 2**	27 ± 1*	6.9 ± 0.3*	6.4 ± 0.2*	75 ± 3*	67 ± 8	78 ± 11

BAT, brown adipose tissue; EDL, extensor digitalis longus; GAS, gastrocnemius; S-oxp, S-oxprenolol in mg/kg/d, all weights in mg; WAT, white adipose tissue (epididymal fat).
*$P < 0.05$.
**$P < 0.01$.

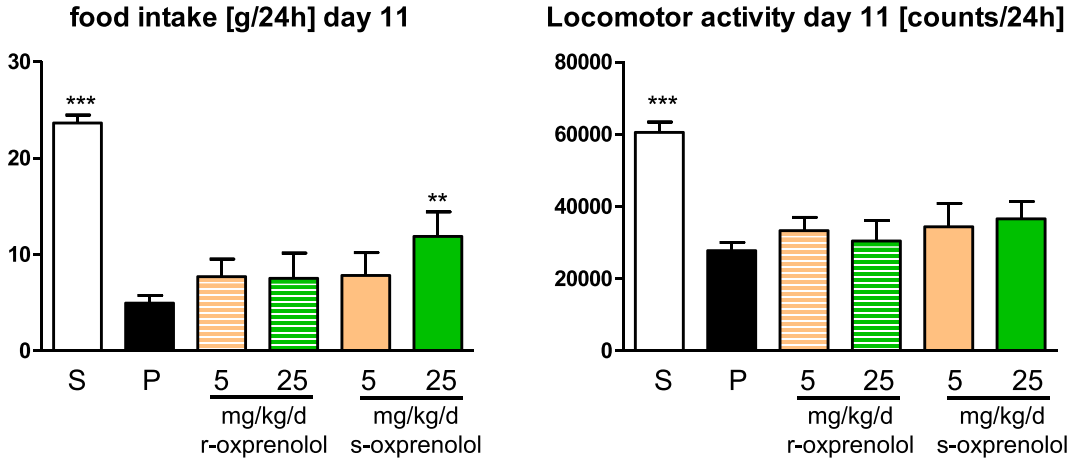

Figure 3 Food intake and spontaneous activity on day 10/11 assessed over 24 h. S-oxprenolol had a beneficial effect on food intake. **$P < 0.01$ vs placebo.

with S-oxprenolol, its phosphorylation (= activation) was significant higher in S-oxprenolol vs placebo, whereas R-oxprenolol had no effect vs placebo (*Figure* 4). Moreover, the ratio of p-Akt/Akt was significantly increased by S-oxprenolol. The expression of the IGF-1 receptor was significantly increased by S-oxprenolol vs placebo, but the phosphorylation of the receptor was similar in all groups. The expression of the glucose transporters Glut1 and Glut4 was similar in all groups, as was one of their regulators AMPK and its phosphorylation (*Figure* 4). The E3 ubiquitin-ligase FBXO-40 has been show to specifically target the substrate of the IGF-1 and insulin-receptors IRS-1 and mark it for degradation.[18] Its expression is induced under atrophic conditions in skeletal muscle.[18] S-oxprenolol reduced the expression of FBXO-40 significantly compared with placebo and R-oxprenolol (*Figure* 4). TRAF-6 is associated with TNF-α signalling and increased catabolic signalling; again, S-oxprenolol inhibited the expression of TRAF-6 vs placebo. The myokine musculin, shown to be cardio-protective,[19] was not regulated by S-oxprenolol, but induced by R-oxprenolol significantly compared with placebo and S-oxprenolol (*Figure* 4). BMP-1 protein levels were similar in all groups.

Discussion

In the Yoshida hepatoma rat cancer cachexia model, S-oxprenolol had superior effects on survival and weight loss compared with R-oxprenolol. This could be expected as the eutomer of oxprenolol (S-oxprenolol) is the active form, whereas R-oxprenolol is the distomer, which is not necessarily inactive, but usually majorly contributes to the side effects of a racemic drug.[20] For oxprenolol, this was shown for the first time in an animal disease model. It had been known that the enantiomers of oxprenolol show different plasma levels with R-oxprenolol levels being higher. When looking at the main metabolites of oxprenolol, oxprenolol-glucuronides, the enantiomer-glucuronides of S-oxprenolol showed higher levels in plasma than R-oxprenolol.[21,22] Oxprenolol enantiomers also show different tissue levels, for example, higher S-oxprenolol levels in brain and higher R-oxprenolol levels in heart and muscle, 8 h after dosing.[23]

As mentioned in the Introduction, oxprenolol is a non-selective β1-adrenoceptor blocker with ISA effects on the β2-adrenoceptor and central 5HT1α effects that stimulate food intake, so essentially its effects are similar to pindolol and acebutolol. However, the best S-oxprenolol dose

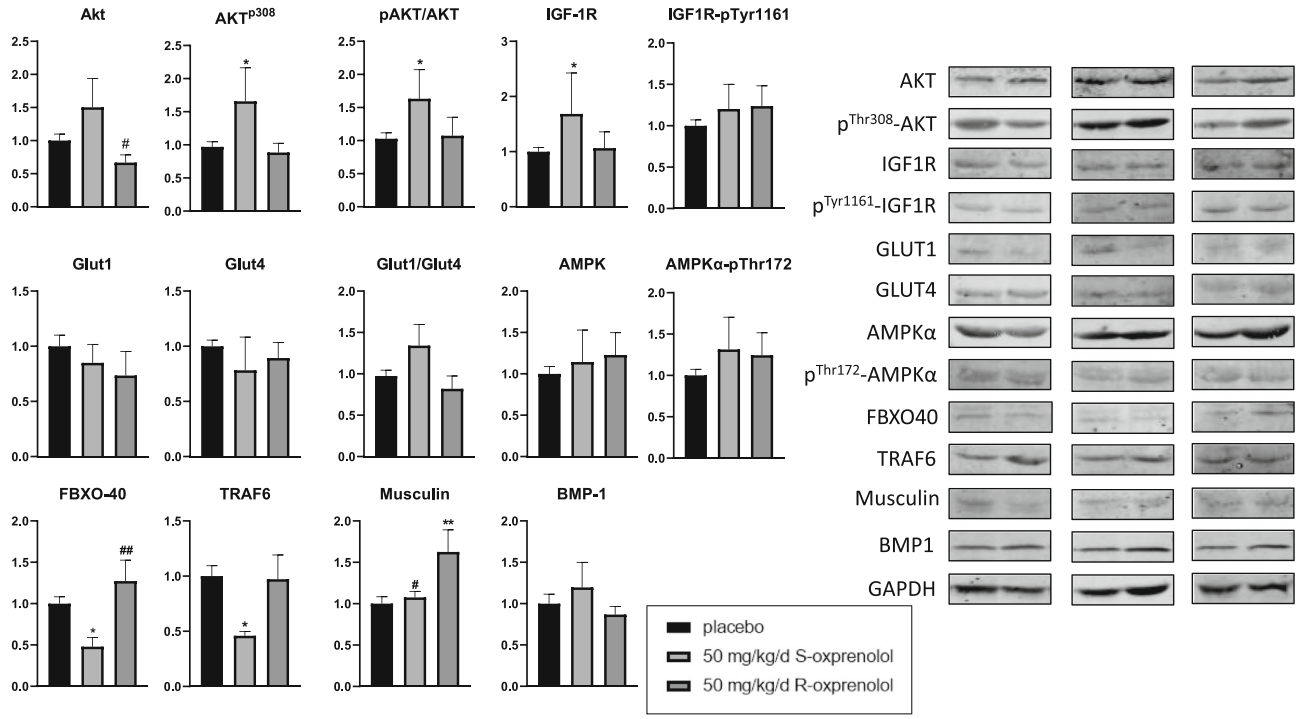

Figure 4 Expression of key proteins in anabolic/catabolic signalling. S-oxprenolol shows positive effects on signalling that are not seen with R-oxprenolol. *$P < 0.05$, **$P < 0.01$ vs placebo, #$P < 0.05$, ##$P < 0.01$ S-oxprenolol vs R-oxprenolol.

(50 mg/kg/d) had a lesser effect on survival vs placebo compared with 3 mg/kg/d S-pindolol (= ACM-001, HR: 0.49, 95% CI: 0.28–0.85; $P = 0.012$ vs HR: 0.29, 95% CI: 0.16–0.51, $P < 0.001$ for S-oxprenolol and S-pindolol, respectively).[12] This may be due to a more variable bioavailability of oxprenolol of 20–70% (a newer paper puts it at 44%[24]), high protein binding of 80%[25] and a short half-life in plasma and serum of 1–2 h.[25] For pindolol, the bioavailability is 40–90% with a newer paper putting it at 88%,[24] the protein biding is 42%,[25] and the half-life in plasma/serum 2.2 h.[25] Hence, S-pindolol has superior pharmacokinetics to S-oxprenolol possibly explaining the observed differences in the Yoshida model. Unfortunately, we did not assess the pharmacokinetics of S-oxprenolol in our experiments. A further possibility is that both S-oxprenolol and S-pindolol may have improved survival by inducing vascular stabilization or may have had other effects on vascular function. However, we feel that the anti-cachectic effect is the main mechanism, as we know from previous experiments with other drugs such as the antidepressant tandospirone,[26] erythropoietin[27] and inhibition of the xanthine oxidase[28] that attenuating weight loss is a key to improved survival. Signalling analysis in skeletal muscle of the present study showed increased anabolic and decreased catabolic protein expression. Whereas the expression of the IGF-1 receptor was induced by S-oxprenolol, the activation (= phosphorylation) was not, the reduction of the IRS-1-specific E3 ligase FBXO-40 suggests an improved IRS-1 and possibly improved insulin = anabolic signalling. Interestingly, there were no differences in glucose transporter and AMPK expression between the groups pointing towards an adapted glucose metabolism. The expression of TRAF-6 was reduced in S-oxprenolol-treated animals, suggesting an impaired downstream signalling of the catabolic TNF-α and TWEAK.[29] The unchanged musculin expression by S-oxprenolol may partly be responsible for the lack of effects on cardiac function, as muscle atrophy reduces musculin levels in skeletal muscle, which has been shown to be cardio-protective.[19]

The muscle-sparing effect of S-oxprenolol in the Yoshida and LLC models and the effect on grip strength in the LLC model is likely due to the ISA effect on the β2-adrenoceptor that, when stimulated with clenbuterol or formoterol, shows protective effects on muscle mass and strength.[7,10,30] In contrast, R-oxprenolol had no significant effect body weight and lean mass or individual muscle weight, which is likely due to being the distomer of oxprenolol. The S-oxprenolol effects may be partially due to an increase in food intake compared with placebo and R-oxprenolol, although more food intake does not necessarily mean reduced weight loss in animal models and the clinical situation.[31,32] Attenuation of weight loss has been shown to improve survival of animals and patients suffering from cancer cachexia.[33–36]

Both oxprenolol enantiomers had no effect on heart rate compared to placebo, which is most likely due to the ISA effect on the ß2-adrenoreceptor. The presence of ISA has been described to result in less resting bradycardia and less of a decline in cardiac output than is observed with beta-blockers without ISA.[37,38]

The study has some limitations; no tissue was fixed for histology to determine muscle fibre composition of the muscle and their diameter. We did not determine grip strength in the rat model and have no information on cardiac function in the mouse model. This is due to the phenotypical equipment limitations at both sides. We did not check for a possible in vivo conversion of the purified enantiomers on blood.

In conclusion, S-oxprenolol potently and dose-dependably attenuated the progression of cancer cachexia and improved survival compared with R-oxprenolol in the Yoshida rat model and also spared muscle mass and grip strength in the LLC mouse model, making S-oxprenolol an interesting candidate for clinical studies in cancer cachexia.

Conflict of interest

AJSC, SDA, SvH and JS are shareholders of Actimed Therapeutics. SDA reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier and Vifor Pharma and grant support from Abbott and Vifor Pharma. MSA reports personal fees from Servier, outside the submitted work. JS is a paid consultant for Actimed Therapeutics and Pephexia Therapeutics and received grant support from Boehringer Ingelheim. AJSC declares having received honoraria and/or lecture fees from Astra Zeneca, Boehringer Ingelheim, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia and Viatris. JMA declares having received honoraria and/or lecture fees from Amgen, Novartis, Smartfish, Rottafarm/Madhaus, Numico, Danone, Grunenthal, Fresenius, Merck KGaA, Merk Sharp & Dohme, Serono, Procter and Gamble, Santhera Pharmaceuticals, Bristol-Myers Squibb and Nutricia.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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