# Beta-3 adrenergic receptor blockade prevents alterations in feeding behavior in lymphoma-bearing mice in a sex-dependent manner

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## Introduction

Cancer cachexia is a metabolic syndrome defined by an ongoing loss of adipose and muscular tissue and is characterized by a reduced food intake. Local β-3 adrenergic receptor activation in adipose tissue induces lipolysis, whereas β-3 signaling in tumors has been shown to be tumorigenic in some cancer models. Therefore, β-3 signaling may be a therapeutic target in cancer cachexia. The aim of this study was to assess the role of β-3 adrenergic signaling in feeding behavior, body composition, and tumor progression in the L5178Y-R murine lymphoma model.

## Methods

In our study we used BALB/c mice of both sexes, which were divided in tumor-free and tumor-bearing groups. For the tumor model, L5178Y-R lymphoma cells were subcutaneously administered into animals right flank. These groups of mice intraperitoneally received L-748,337, a beta-3 antagonist, at a 50 mg/kg/day dose, starting the day after tumor implantation. Food and water intake were monitored every other day and body mass index (BMI) was calculated at the end of the experiment. Animals were euthanized for necropsy, when endpoint criteria were achieved. Transcriptional expression of *Ucp-1,* a molecular marker of thermogenesis, was quantified in interscapular adipose tissue.

## Results

We observed a 15% and 35% reduction in food intake in tumor-bearing male and female mice, respectively. This effect was not observed in male mice treated with the β-3 adrenergic receptor antagonist L-748,337. In females, such an effect persisted despite beta-3 blocking. Reduced water intake was also observed in tumor-bearing animals, which was not altered by beta-3 antagonism. We also observed that tumor-free mice of both sexes showed reduced water intake after L-748,337 treatment. Furthermore, reduced BMI was observed in tumor-bearing animals of both sexes, which was not changed by β-3 blocking. Interscapular adipose tissue loss was observed in females (51.06%) but not in males. Additionally, 1.7-fold and 4.4-fold reduction in *Ucp-1* gene expression was shown in tumor-bearing males and females, respectively. Decreased final tumor weight was observed only in tumor-bearing females treated with L-748,337 ($p < 0.05$).

## Conclusion

In L5178Y-R tumor-bearing BALB/c mice, selective blocking of beta-3 adrenergic signaling prevents alterations in food intake in a sex-dependent manner.