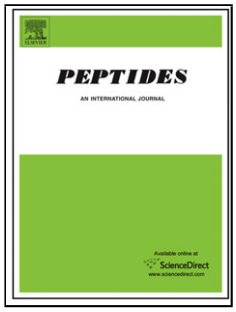

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Oxyntomodulin Analogue Increases Energy Expenditure via the Glucagon Receptor

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Highlights

- The sustained-release oxyntomodulin analogue OX-SR increases energy expenditure in rats, measured by indirect calorimetry.
- Blocking the GLP-1 receptor with Ex9-39 does not affect this increase in energy expenditure.
- If activity at the glucagon receptor is blocked, OX-SR no longer increases energy expenditure.
- This shows that OXM increases energy expenditure via the glucagon and not GLP-1 receptors.

Abstract

The gut hormone oxyntomodulin (OXM) causes weight loss by reducing appetite and increasing energy expenditure. Several analogues are being developed to treat obesity. Exactly how oxyntomodulin works, however, remains controversial. OXM can activate both glucagon and GLP-1 receptors but no specific receptor has been identified. It is thought that the anorectic effect occurs predominantly through GLP-1 receptor activation but, to date, it has not been formally confirmed which receptor is responsible for the increased energy expenditure.

We developed OX-SR, a sustained-release OXM analogue. It produces a significant and sustained increase in energy expenditure in rats as measured by indirect calorimetry. We now show that this increase in energy expenditure occurs via activation of the glucagon receptor. Blockade of the GLP-1 receptor with Exendin 9-39 does not block the increase in oxygen consumption caused by OX-SR. However, when activity at the glucagon receptor is lost, there is no increase in energy expenditure. Glucagon receptor activity therefore appears to be essential for OX-SR's effects on energy