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ARTICLE

# WNT/β-catenin increases the production of incretins by entero-endocrine cells

**J. M. García-Martínez · A. Chocarro-Calvo · C. M. Moya · C. García-Jiménez**

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**Abstract**
*Aims/hypothesis* Glucose-dependent insulinotropic peptide (GIP) plays a pivotal role in the regulation of glucose homeostasis. Rates of diet-induced obesity, insulin resistance and type 2 diabetes are decreased when GIP signalling is disturbed in mice, suggesting that GIP plays a role in the onset of type 2 diabetes. WNT signalling is linked to type 2 diabetes and induces synthesis of the other incretin, glucagon-like peptide 1 (GLP-1). GLP-1 analogues improve treatment of type 2 diabetes patients in whom GLP-1 signalling is intact and have captured clinical attention. GIP levels are altered at the onset of type 2 diabetes and later on, while GIP signalling is impaired. Thus, GIP is not a candidate for treatment but might be an important target from a prevention perspective. Hypothesising that hypersecretion of GIP links altered WNT signalling to the onset of type 2 diabetes, we sought to determine whether WNT signalling induces GIP production by entero-endocrine cells.
*Methods* RT-PCR and chromatin immunoprecipitation (ChIP) were used to study *Gip* gene induction. *Gip* promoter elements mediating WNT/lithium induction were identified (electrophoretic mobility shift assay, co-transfection of deletion mutants, ChIP).
*Results* Lithium or WNT/β-catenin signalling enhanced GIP production by entero-endocrine cells through a conserved site in the proximal *Gip* promoter. Lithium favours lymphoid enhancer factor-1/β-catenin binding to *Gip* promoter and diminishes ChIP through T cell factor-4 and histone deacetylase 1.
*Conclusions/interpretation* Lithium and WNT are incretin inducers in general. This work provides a novel link between WNT signalling, obesity and diabetes.

**Keywords** β-Catenin · Chromatin · Diabetes · Glucose-dependent insulinotropic peptide · Incretin · Lithium · Obesity · WNT

**Abbreviations**

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|---|---|
| ChIP | Chromatin immunoprecipitation |
| EMSA | Electrophoretic mobility shift assay |
| GIP | Glucose-dependent insulinotropic peptide |
| GLP-1 | Glucagon-like peptide 1 |
| GSK3β | Glycogen synthase kinase 3β |
| HDAC1 | Histone deacetylase 1 |
| LEF | Lymphoid enhancer factor |
| TCF | T cell factor |

J. M. García-Martínez and A. Chocarro-Calvo contributed equally to this work.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00125-009-1429-1) contains supplementary material, which is available to authorised users.

J. M. García-Martínez · A. Chocarro-Calvo · C. García-Jiménez (✉)
Dptal I. Despacho 020, Facultad de Ciencias de la Salud,
Universidad Rey Juan Carlos,
28922 Alcorcon, Madrid, Spain
e-mail: custodia.garcia@urjc.es

C. M. Moya
Instituto de Investigaciones Biomédicas,
Consejo Superior de Investigaciones Científicas (CSIC),
Madrid, Spain

## Introduction

Incretins are hormones that enhance insulin secretion in response to an oral glucose load. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), produced along the small intestinal epithelium,