

Abstract

J Nutr Biochem. 2009 Jun 26. [Epub ahead of print]

Biotin increases glucokinase expression via soluble guanylate cyclase/protein kinase G, adenosine triphosphate production and autocrine action of insulin in pancreatic rat islets.

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OBJECTIVE: Besides its role as a carboxylase prosthetic group, biotin has important effects on gene expression. However, the molecular mechanisms through which biotin exerts these effects are largely unknown. We previously found that biotin increases pancreatic glucokinase expression. We have now explored the mechanisms underlying this effect.

METHODS: Pancreatic islets from Wistar rats were treated with biotin, in the presence or absence of different types of inhibitors. Glucokinase mRNA and 18s rRNA abundance were determined by real-time PCR. Adenosine triphosphate (ATP) content was analyzed by fluorometry.

RESULTS: Biotin treatment increased glucokinase mRNA abundance approximately onefold after 2 h; the effect was sustained up to 24 h. Inhibition of soluble guanylate cyclase or protein kinase G (PKG) signalling suppressed biotin-induced glucokinase expression. The cascade of events downstream of PKG in biotin-mediated gene transcription is not known. We found that inhibition of insulin secretion with diazoxide or nifedipine prevented biotin-stimulated glucokinase mRNA increase. Biotin treatment increased islet ATP content (control: 4.68±0.28; biotin treated: 6.62±0.26 pmol/islet) at 30 min. Inhibition of PKG activity suppressed the effects of biotin on ATP content. Insulin antibodies or inhibitors of phosphoinositol-3-kinase/Akt insulin signalling pathway prevented biotin-induced glucokinase expression. The nucleotide 8-Br-cGMP mimicked the biotin effects. We propose that the induction of pancreatic glucokinase mRNA by biotin involves guanylate cyclase and PKG activation, which leads to an increase in ATP content. This induces insulin secretion via ATP-sensitive potassium channels. Autocrine insulin, in turn, activates phosphoinositol-3-kinase/Akt signalling.

CONCLUSION: Our results offer new insights into the pathways that participate in biotin-mediated gene expression.

PMID: 19560332