Ghrelin Induces Growth Hormone (GH) Secretion via Nitric Oxide (NO)/cGMP Signaling

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ABSTRACT: Ghrelin, a recently discovered 28-aa peptide, stimulates GH release through a mechanism involving PLC- and cAMP-related signaling pathways. Recently, nitric oxide (NO) and its mediator, cGMP, have been shown to be required for the response of somatotropes to various regulators (GHRH, somatostatin, leptin). Here, we explore the possible role of the NO synthase (NOS)/NO/guanylate cyclase (GC)/cGMP signaling pathway in ghrelin-induced GH release from cultured pig somatotropes using blockers or activators of this route.

KEYWORDS: ghrelin; GH secretion; NO; cGMP

In addition to the two classic factors that are well known to regulate GH secretion (GHRH and somatostatin), a novel GH secretagogue was recently isolated from rat stomach extracts, the so-called ghrelin, which appears to play a relevant role in somatotrope regulation. As shown for GHRH and somatostatin, ghrelin stimulates GH release from pig somatotropes by activation of the AC/cAMP and PLC/PKC intracellular signaling pathways. However, recent studies have reported that the NOS/NO and the GC/cGMP intracellular routes also participate in the control of GH secretion. In the present study, we have evaluated their involvement in the ghrelin-induced GH release from cultured porcine somatotropes by using specific activators and inhibitors for different components of these pathways.

RESULTS AND DISCUSSION

Previous studies indicate that NO induces porcine GH secretion by functioning as a mediator of somatotrope response to several factors, including GHRH and somatostatin. Here, we have evaluated the effects of NOS/NO activators in basal as well as ghrelin-induced GH release. In vitro treatment with both an NO donor
(SNAP) or an NOS activator (L-AME) resulted in a significant increase in basal GH release, similar to that induced by ghrelin. However, only L-AME enhanced the ghrelin effect. On the other hand, NOS/NO inhibition with a specific NO scavenger (hemoglobin) or an NOS blocker (NAME) did not affect basal secretion, but abolished ghrelin-induced GH release. These results indicate that the stimulatory effect of ghrelin on GH secretion is exerted through the required activation of the NOS/NO intracellular pathway in cultured porcine somatotropes.

It has been proposed that NO can stimulate GH release by itself or by activation of GC with the subsequent production of cGMP. To test whether the somatotrope response to ghrelin is mediated by activation of the latter pathway, we have investigated the effects of a cGMP analogue (8-Br-cGMP) and a GC blocker (LY-83,583) on basal and ghrelin-stimulated GH secretion. Our results show that treatment with 8-Br-cGMP promotes GH release without affecting the ghrelin stimulatory effect. Furthermore, ghrelin-induced GH release was completely suppressed after blockage of GC by LY-83,583.

Taken together, our results demonstrate that the NOS/NO/GC/cGMP signaling pathway is essential in the stimulatory action of ghrelin on porcine somatotropes. Furthermore, NO appears to exert its action indirectly via cGMP production.

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