The effects of inflammatory cytokines on the expression of ghrelin

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Abstract. In the current study, we examined the effects of LPS and inflammatory cytokines including IL-1 β , TNF- α , and IL-6 on the expression of ghrelin in MGN3-1 cells. We found that IL-1 β , and TNF- α with lesser extent, significantly suppressed ghrelin mRNA expression in the cells. MGN3-1 cells expressed IL-1 β receptor and IL-1 β significantly stimulated NF- κ B, p38, JNK, and ERK pathways. Knockdown of IKK2 by siRNA significantly attenuated the suppression of ghrelin mRNA by IL-1 β . These results indicate that IL-1 β directly suppressed ghrelin mRNA *via* NF- κ B pathway at least partially, which may have a role in the regulation of appetite during inflammation.

Key words: Ghrelin, IL-1, TNF- α , NF- κ B

IT IS WELL KNOWN that infection induces anorexia in the host, which is considered to be mediated by microbial products and cytokines [1]. Ghrelin is an orexigenic hormone, mainly produced by the stomach [2], playing major roles in the regulation of food intake [3]. It has been reported that systemic administration of LPS suppresses plasma ghrelin levels in rats [4, 5]. It remains unclear the molecular mechanisms involved in the LPS-induced ghrelin regulation. Previously, we established a ghrelin-producing cell line MGN3-1 [6], originated from a gastric ghrelinoma developed in ghrelin-promoter SV40 Tag transgenic mice [7], in order to explore the mechanism of ghrelin production and secretion in molecular basis [1, 8, 9]. In the current study, we examined the effects of LPS and inflammatory cytokines including IL-1 β , TNF- α , and IL-6 on the expression of ghrelin in MGN3-1 cells [10].

Materials and Methods

Detailed materials and methods were described previously [10].

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Results and Discussion

LPS is recognized by Toll-like receptor 4 on the various kinds of the cells, activating intracellular signaling pathways such as NF- κ B, p38, JNK, and ERK, triggering the release of cytokines including IL-1 β , TNF- α and IL-6 [11]. We first examined the effects of these cytokines and LPS on the ghrelin mRNA levels in MGN3-1 cells to reveal if the reported suppressive effects of LPS on ghrelin mRNA levels in animal models were direct or indirect. We found that IL-1 β , and TNF- α with lesser extent, significantly suppressed ghrelin mRNA expression levels in the cells, while neither IL-6 nor LPS showed any effect on ghrelin mRNA levels, suggesting that the suppressive effects of LPS on the ghrelin mRNA levels were indirect, primarily mediated by IL-1 β . Reflecting the suppression of ghrelin production, ghrelin secretion from MGN3-1 cells was also significantly suppressed after IL-1 β treatment.

MGN3-1 cells and at least part of the ghrelin-producing cells in the mouse stomach expressed IL-1 β receptor. IL-1 β significantly stimulated NF- κ B, p38, JNK, and ERK pathways in MGN3-1 cells. Knockdown of IKK2, one of the key molecules in NF- κ B pathway, with siRNA significantly attenuated the suppression of ghrelin mRNA by IL-1 β , while inhibitors of JNK

p38 MAPK and ERK pathways had no effects on the suppression of ghrelin mRNA levels by IL-1 β . These results indicate that IL-1 β directly suppressed ghrelin mRNA *via* NF- κ B pathway at least partially.

Asakawa *et al.* reported that administration of IL-1 β to mice suppressed ghrelin mRNA in the stomach [12]. Our results were consistent with their findings. IL-1 β has roles not only in the inflammatory processes but also in the regulation of food intake, by suppressing it

[13, 14]. Considering the potent orexigenic activity of ghrelin, it seems reasonable that ghrelin production is suppressed by IL-1 β .

In conclusion, IL-1 β , but not LPS, directly suppressed ghrelin mRNA expression in the ghrelin-producing cells, suggesting the role of ghrelin in the IL-1 β -mediated anorexia during inflammation. The details of the current study have been published previously [10].

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