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Role of growth hormone and insulin-like growth factor-1 in the protective effect of ghrelin in ischemia/reperfusion-induced acute pancreatitis

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Abstract

Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, has been shown to exhibit gastroprotective properties. The aim of present study was to determine whether ghrelin administration protects the pancreas against ischemia/reperfusion-induced pancreatitis and, if so, what is the role of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in this effect. In sham-operated or hypophysectomized rats, acute pancreatitis was induced by pancreatic ischemia followed by reperfusion. Ghrelin (4, 8 or 16 nmol/kg/dose) or IGF-1 (20 nmol/kg/dose) were administered intraperitoneally twice before and during induction of acute pancreatitis. In pituitary-intact rats, treatment with ghrelin attenuated the development of ischemia/reperfusion-induced pancreatitis and this effect was associated with partial reversion of the pancreatitis-evoked decrease in serum concentration of GH and IGF-1. Hypophysectomy eliminated GH from the serum, reduced serum IGF-1 concentration by 90% and increased in the severity of ischemia/reperfusion-induced pancreatitis. Administration of ghrelin was without any beneficial effect in this group of rats. In contrast, administration of IGF-1 in hypophysectomized rats reduced the severity of ischemia/reperfusion-induced pancreatitis in hypophysectomized rats. We conclude that administration of ghrelin inhibits the development of ischemia/reperfusion-induced pancreatitis and this effect is mediated by its influence on the release of GH and IGF-1.

Keywords: Hypophysectomy; Interleukin-1β; Lipase; Poly-C ribonuclease; Pancreatic DNA synthesis

1. Introduction

Ghrelin, an acylated 28-amino acid peptide, was originally discovered in the rat and human stomach [1,2]. The stomach is a main source of ghrelin [1,2], but this peptide has been also detected in other organs such as the bowel, pancreas, kidney, pituitary and hypothalamus [1,3]. Ghrelin is a natural ligand for growth hormone secretagogue receptor (GHS-R) [1]. GHS-Rs are predominantly expressed in the pituitary and hypothalamus; however their presence has also been shown in

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other central and peripheral tissues, but at much lower levels [3]. Acting on GHS-R, ghrelin strongly and dose dependently stimulates release of growth hormone (GH) from the anterior pituitary [1]. Beside a release of GH, ghrelin has also been found to stimulate a release of adrenocorticotropic hormone, corticosterone, and prolactin [3,4]. Ghrelin increases food intake and fat deposition in adult rats [5] and humans [6]. The orexigenic effect of ghrelin is mediated by activating of hypothalamic neurons expressing neuropeptide Y, agouti-related protein and orexin [3,7]. Plasma level of ghrelin is increased under negative energy balance conditions, such as fasting, anorexia nervosa or cachexia [2,3,8,9]; whereas obesity and food intake decrease plasma ghrelin concentration [2,3,8].

Presence of ghrelin in the pancreas is age-dependent. In fetal period of life, pancreatic ghrelin cells are relatively numerous [10]. Later, the number of ghrelin-immunoreactive cells is reduced and these cells are localized at the periphery of human and rat pancreatic islets [10,11]. The influence of ghrelin on insulin secretion is unclear. Some studies have reported that ghrelin inhibits insulin secretion in the perfused rat pancreas [12], in anesthetized mice and in isolated mouse islets [13] and in humans [4]. Other studies have shown that ghrelin stimulates insulin secretion in isolated rat pancreatic islets [11] and in anesthetized rats [14]. Effect of ghrelin on pancreatic exocrine secretion seems to be more established. Experiments performed by Zhang et al. [15] have shown that intravenous administration of ghrelin inhibits the cholecystokinin- and 2-deoxy-D-glucose-stimulated pancreatic exocrine secretion in anesthetized rats, as well as ghrelin inhibits the potassium-stimulated amylase secretion from pancreatic lobules in in vitro study. On the other hand, Sato et al. have reported that intracerebroventricular administration of ghrelin increases pancreatic exocrine secretion and vagal nerve is involved in this effect [16].

In young rats, the influence of exogenous ghrelin on pancreatic growth and content of digestive enzymes is age-dependent. Ghrelin reduces pancreatic growth in suckling rats; whereas in weaned and young seven week old animals, treatment with ghrelin increases pancreatic growth and pancreatic activity of amylase. This effect seems to be related to low release of insulin-like growth factor-1 (IGF-1) in response to ghrelin administration in neonatal rats [17].

Administration of ghrelin stimulates GH release [1]. GH is the first step in GH-IGF-1-hepatocyte growth factor (HGF) hormonal axis [18–20]. Treatment with GH [21], IGF-1 [22] or HGF [23,24] has been reported to reduce pancreatic damage in experimental acute pancreatitis. Previous study has also shown that pretreatment with ghrelin inhibits the development of edematous pancreatitis evoked by cerulein [25].

Present study was undertaken to examine whether ghrelin administration protects the pancreas against ischemia/reperfusion-induced pancreatitis and, if so, what is the role of endogenous growth hormone and IGF-1 in this effect.

2. Materials and methods

2.1. Animals and treatment

Studies were performed on male eight week old Wistar rats weighing 180–200 g and were conducted following the experimental protocol approved by the Committee for Research and Animal Ethics of Jagiellonian University.

Rats were anesthetized with ketamine (50 mg/kg i.p., Bioketan, Vetoquinol Biowet, Gorzów Wielkopolski, Poland) and sham-operated or hypophysectomized via the transauricular approach according to a method described previously [26]. Two weeks later, rats were reanesthetized and acute hemorrhagic pancreatitis was induced by clamping of inferior splenic artery for 30 min followed by 6-h reperfusion as described earlier [27].

Experiments were performed in two series. In the first series of studies we used pituitary-intact animals. Experiments were carried out in the following experimental groups: (1) sham-operated saline treated control rats; (2) saline-treated rats with acute pancreatitis; (3–5) sham-operated rats treated with ghrelin at the dose of 4, 8 or 16 nmol/kg/dose, respectively (ghrelin was administered intraperitoneally twice, 30 min prior to sham-operation and after next 3 h); (6–8) rats with acute pancreatitis and treated with ghrelin at the dose of 4, 8 or 16 nmol/kg/dose, respectively (ghrelin was administered intraperitoneally twice, 30 min prior to the start of ischemia and after next 3 h).

In the second series of study with hypophysectomized rats, we used following experimental groups: (1) sham-operated hypophysectomized saline-treated control rats; (2) sham-operated hypophysectomized rats treated with ghrelin at the dose of 8 nmol/kg/dose (ghrelin was administered intraperitoneally twice, 30 min prior to sham-operation and after next 3 h); (3) hypophysectomized saline-treated rats with acute pancreatitis; (4) hypophysectomized rats with acute pancreatitis and treated with ghrelin at the dose of 8 nmol/kg/dose (ghrelin was administered intraperitoneally twice, 30 min prior to the start of ischemia and after next 3 h); (5) hypophysectomized rats with acute pancreatitis and treated with rat IGF-1 (Pro-Spec-Tany TechnoGene Ltd., Rehovot, Israel) the dose of 20 nmol/kg/dose (IGF-1 was administered intraperitoneally twice, 30 min prior to the start of ischemia and after next 3 h).