

**EXPRESSION AND BIOLOGICAL ACTIVITY OF THE NATURAL GROWTH HORMONE-RELEASING PEPTIDE GHRELIN AND OF ITS RECEPTORS IN HUMAN PANCREAS CARCINOMA CELL LINES**

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Durata del Dottorato in anni: 3. Sede di servizio: Dipartimento di Anatomia, Farmacologia e Medicina Legale, Sezione di Farmacologia Medica, Università di Torino, via P. Giuria 13, 10125 Torino.

Ghrelin, a 28-amino acid octanoylated peptide predominantly produced by the stomach, displays strong growth hormone (GH)-releasing activity mediated by the hypothalamus-pituitary GH secretagogue type 1a receptor (GHS-R1a), which is specific for synthetic peptidyl and non-peptidyl GHS (1). Ghrelin acts also on other central and peripheral receptors (GHS-R1a and GHS-R1b isoforms) and shows other actions including orexia and fat deposition coupled with control of endocrine and non-endocrine gastro-entero-pancreatic functions (2). Based on the foregoing, this study has examined the expression of GHS-R and ghrelin in pancreas cancer cells. GHS-R1a, GHS-R1b and ghrelin mRNA expression were detected by RT-PCR in oestrogen-independent (CAPAN-1) and oestrogen-dependent (CAPAN-2) human pancreas carcinoma cell lines. Ghrelin and GHS-R1b mRNAs were present in both cell lines, whereas mRNA for GHS-R1a was only detected in CAPAN-1 cells. The presence of specific GHS binding sites in the above cell lines was confirmed by radioreceptor binding assay using <sup>125</sup>I-labelled ghrelin as the radioligand. In addition, human pancreas adenocarcinomas (n=3), collected from surgical specimens, also expressed ghrelin mRNA and were all positive for GHS-R (case 1 and 2: positive for both receptor isoforms; case 3: positive for GHS-R1b only). Incubation of CAPAN-1 cells in serum-free conditions with physiological ghrelin concentrations (from 1 to 100 nM) over a 24 h period resulted in decreased cell growth as compared with untreated controls (P<0.05). This effect was dose-related and maximal at 100 nM ghrelin, when viable cell numbers showed a 35% decrease, compared to the corresponding controls. In CAPAN-1 cells, ghrelin was also able to inhibit <sup>3</sup>H-thymidine incorporation secondary to stimulation by insulin-like growth factor-I (IGF-I) and exhibited synergistical antiproliferative effect with the antitumoural drug, doxorubicin. Similar results were also found in the CAPAN-2 cells. In conclusion, this study is the first to demonstrate that ghrelin and GHS-R are co-expressed in human pancreas carcinomas and cell lines. It also provides evidence that a previously unrecognised autocrine/paracrine ghrelin circuit, capable of inhibiting growth, exists in neoplastic pancreas.

References

1. Kojima M. et al. (1999) *Nature* 402: 656-660.
2. Muccioli G. et al. (2002) *Eur J. Pharmacol.* 440: 235-254.