Neuroendocrine Diffuse System of the Respiratory Tract of *Rana temporaria*: An Immunocytochemical Study

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Abstract of:

GENERAL AND COMPARATIVE ENDOCRINOLOGY **100**, 145-161 (1995)

The neuroendocrine cell population of the respiratory system of *Rana temporaria* has been studied by means of immunocytochemical methods at the light-microscopic level. Isolatd or clustered endocrine cells have ben found in the epithelium of the buccal cavity, glottis, larynx, and lung. Nine different types on endocrine isolated cell types can be distinguished according to their immunoreactivity to several regulatory peptides [calcitonin, substance P, bombesin, peptide histidine isoleucine (PHI), cholecystokinin (CCK), and endothelin 1] and neuroendocrine markers (7B2, chromogranin, and serotonin). Neuroepithelial bodies are innervated clusters of cells simultaneously immunoreactive for serotonin and 7B2. Nerves and/or neurons have been detected in different regions of the respiratory system using antibodies against protein gene product 9.5, serotonin, calcitonin gene-related peptide (CGRP), substance P, PHI, helodermin, and CCK.

Cyclosporin A and doxorubicin-ifosfamide in resistant solid tumours: a phase I and an immunological study

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Abstract of:

British Journal of Cancer (1995) 72, 1294-1299

Summary In order to test whether circumvention of clinical resistance can be obtained in common solid tumours by targeting different drug resistance mechanism, a phase I clinical and immunological study was designed. The purpose of the study was to determine the dose of cyclosporin A (CsA), in combination with doxorubicin (DOX) and ifosfamide (IFX), needed to achieve steady-state whole-blood levels of 2000 ng ml^{-1} and the associated toxicity of this combination. Treatment consisted of CsA 5 mg kg^{-1} as a 2 h loading infusion, followed by a CsA 3 day continuous infusion (c.i.) (days 1-3) at doses that were escalated from 10 to 18 mg kg^{-1} day^{-1}. Chemotherapy consisted of DOX 55 mg m^{-2} by i.v. 24 h c.i. (day 2) and IFX 2 g m^{-2} i.v. over 1 h on days 1 and 3. Treatments were repeated every 4 weeks. Eighteen patients with previously treated resistant solid tumours received 39 cycles. Mean steady-state CsA levels $\geqslant$2000 ng ml^{-1} were reached at 5 mg kg^{-1} loading dose followed by a 3 day c.i. of 16 mg kg^{-1} day^{-1} or greater. Haematological toxicy was greater than expected for the same chemotherapy alone. One patient died of intracranial haemorrhage due to severe thrombopenia. Other observed toxicities were: asymptomatic hyperbilirubinaemia (46% cycles), mild nephrotoxicity (20% cycles), hipomagnesaemia (72% cycles), mild increase in body weight (100% cycles), hypertension (15% cycles) and headache (15% cycles). Overall the toxicity was acepta-

ble and manageable. No alterations in absolute lymphocyte number, the lymphocyte subsets studied (CD3, CD4, CD8, CD19) or CD4/CD8 ratio were observed in patients receiving more than one treatment cycle, although there were significant and non-uniform variations in the values of the different lymphocyte subsets studied when pre- and post-treatment values were compared. There was also a significant increase in the CD4/CD8 ratio. Tumour regressions were observed in two patients (epidermoid carcinoma of the cervix and Ewing's sarcoma). The CsA dose recommended for phase II trials is a 55 mg kg^{-1} loading dose followed by a 3-day c.i. of 16 mg kg^{-1} day^{-1} simultaneously with DOX and IFX at the doses administered in this study.

Key words

Resistance; doxorubicin; ifosfamide; cyclosporin A

Characterization of *Brucella abortus* and *Brucella melitensis* Native Haptens as Outer Membrane O-Type Polysaccharides Independent from the Smooth Lipopolysaccharide

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Abstract of:

Journal of Bacteriology, Feb. 1996, p. 1070-1079
Vol. 178, Nº. 4

Brucella native haptens (NHs) extracted with hot water from smooth (S)-type *B. abortus* and *B. melitensi*> were purified to high levels of serological activity and compared with the polysaccharide obtained by acid hydrolysis (PS) of the S lipopolysaccharide (S-LPS). By ^{13}C nuclear magnetic resonance analysis, NHs showed the spectrum of a homopolymer of α4-1,2- or α4-1,2- plus α4-1,3-linked 4-formamido-4,6-dideoxy-D-mannose (*N*-formylperosamine) previously reported for the LPS O chain. However, while PS contained up to 0.6% 3-deoxy-D-manno-2-octulosonate, this LPS-core markker was absent from NH. High perforrmance liquid chromatography and thin-layer chromatography showed heterogeneity in NH purified from whole cells but not in PS. By immunoprecipitation, polysaccharides indistinguishable from NH were demonstrated in extracts obtained with phenol-water, saline at 60° C, and ether-water treatments, and none of these treatments caused S-LPS hydrolysis detectable with antibodies to the O chain and lipid A. Two lines of evidence showed that NH was in the cell surface. First, NH became biotinylated when *B. abortus* live cells were labelled with biotin-hydrazide, and the examination of cell fractions and electron microscopy sections with streptavidin-peroxidase and streptavidin-coloidal gold, respectively, showed that labelling was extrinsic. Moreover, whereas only traces of NH were found in cytosols, the amount of NH was enriched in cell envelopes and in the outer membrane blebs spontaneously released by brucellae during growth. Interactions between HN and S-LPS were observed in crude cell extracts, and such interactions could be reconstituted by using purified NH and LPS. The results demonstrate that NH is not a hydrolytic product of S-LPS and suggest a model in which LPS-independent O-type polysaccharides (NH) are intertwined with the O chain in the outer membrane of S-type brucellae.