Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 21, No. 1, pp. 33–41, 2007
doi:10.1016/j.beem.2006.12.002
available online at http://www.sciencedirect.com

3

Biochemistry of neuroendocrine tumours

Wouter W. de Herder* MD, PhD

Consultant Endocrinologist

Department of Internal Medicine, Sector of Endocrinology, Erasmus MC, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

Several circulating or urinary tumour markers can be used for the diagnosis and follow-up of functioning and clinically non-functioning neuroendocrine tumours of the pancreatic islet cells and intestinal tract. Among the specific tumour markers are serotonin and its metabolites – e.g. 5-hydroxyindoleacetic acid (5-HIAA) – in carcinoid tumours and the carcinoid syndrome, insulin and its precursors or breakdown products in insulinoma, and gastrin in gastrinoma. Plasma vasointestinal polypeptide (VIP) determinations have been used in the diagnosis of VIPoma, plasma glucagon for glucagonoma, and serum somatostatin for somatostatinoma. Among the tumour-non-specific markers are: chromogranins, neuron-specific enolase (NSE), α-subunits of the glycoprotein hormones, catecholamines, pancreatic polypeptide (PP), ghrelin and adrenomedullin.

Key words: serotonin; 5-HIAA; carcinoid; insulinoma; gastrinoma; VIPoma; glucagonoma; somatostatinoma; chromogranins; neuron-specific enolase (NSE); α-subunits of the glycoprotein hormones; catecholamines; pancreatic polypeptide (PP); ghrelin; adrenomedullin.

Neuroendocrine tumours originate from pancreatic islet cells, neuroendocrine cells distributed throughout the intestinal and respiratory epithelium, and parafollicullar cells distributed within the thyroid. These tumours may produce specific hormones and, as a result, specific hypersecretory symptoms/syndromes.[1] The diagnosis of neuroendocrine tumours is therefore based on clinical presentation, hormone assays, radiological and nuclear medicine imaging, and pathology.[1]

In patients with clinically functioning (neuroendocrine) tumours, specific biochemical tests should be requested in blood or (24-hour) urine samples obtained with or without provocative testing. Levels of circulating markers or urinary excreted products can be monitored and used for tumour follow-up.[2]

This review will only focus on tumour markers in patients with neuroendocrine tumours of the pancreatic islet cells and intestinal tract.

* Tel.: +31 10 4635950; Fax: +31 10 4633268.
E-mail address: w.w.deherder@erasmusmc.nl.

SPECIFIC TUMOUR MARKERS

Serotonin and its metabolites in carcinoid tumours and the carcinoid syndrome

Carcinoid tumours arise in the diffusely dispersed endocrine cells throughout the intestinal and respiratory epithelium. Carcinoids can synthesize and secrete, to varying extents, serotonin, tachykinins, prostaglandins, catecholamines and histamine.[3,4] The carcinoid syndrome is associated with carcinoid tumours of the midgut (small intestine, appendix, caecum, and proximal colon). This syndrome consists of a constellation of symptoms due to the secretion of large amounts of the above-mentioned factors, among which serotonin is very prominent. Carcinoid tumours of the foregut (respiratory tract, stomach, duodenum, biliary system, and pancreas) produce less serotonin as compared to midgut tumours, whereas tumours of the hindgut (distal colon and rectum) seldom produce serotonin.[3–5] Foregut tumours, however, can produce 5-hydroxytryptophan (5-HTP), which is the precursor of serotonin. The breakdown product of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), is secreted in the urine. Urinary 5-HIAA excretion is widely used as a marker for diagnosis and follow-up of patients with the carcinoid syndrome. Urinary 5-HIAA excretion correlates with the severity of carcinoid heart disease in patients with the carcinoid syndrome and with prognosis.[6,7]

Certain foods and drugs will affect the urinary excretion of 5-HIAA if they are taken just before collection of the urine sample. Banana, avocado, aubergine, pineapple, plums, walnut, paracetamol, fluorouracil, methysergide, naproxen and caffeine may cause false-positive results. Levodopa, aspirin, adrenocorticotrophic hormone (ACTH), methyldopa and phenothiazines may give a false negative result.[8,9]

Serotonin concentrations can be determined in platelet-enriched plasma. These levels vary with time of day and meals and therefore are not currently used routinely. Similarly, urinary serotonin excretion is not routinely measured.[10–13]

Insulin and its precursors or breakdown products in insulinoma

The differential diagnosis of insulinoma includes non-insulinoma pancreatogenous hypoglycaemia/nesidioblastosis.[14–19]

The diagnosis of insulinoma can be established using the following six strict criteria[14,16,20–23]:

- documented blood glucose levels $\leq$2.2 mmol/L ($\leq$40 mg/dL);
- concomitant serum insulin levels $\geq$6 μU/L ($\geq$36 pmol/L; $\geq$3 μU/L by ICMA);
- plasma/serum C-peptide levels $\geq$200 pmol/L;
- serum proinsulin levels $\geq$5 pmol/L;
- serum β-hydroxybutyrate levels $\leq$2.7 mmol/L;
- absence of sulfonylurea (metabolites) in the plasma and/or urine.

Further controlled testing includes the 72-hour fast, which is the gold standard for establishing the diagnosis of insulinoma. When the patient develops symptoms and the blood glucose levels are $\leq$2.2 mmol/L ($\leq$40 mg/dL), blood is also drawn for C-peptide, proinsulin and insulin determinations. Failure of appropriate insulin suppression in the presence of hypoglycaemia substantiates an autonomously secreting insulinoma. It is