

Proton pump inhibitors and gastric cancer

Randomised controlled clinical trials may fail to reveal late side-effects that occur years after study termination. It has long been known that proton pump inhibitors induce gastric cancer in rodents. There is no obvious biological reason why this should be any different in man.

Inhibition of the proton pump reduces gastric acidity, which in turn results in increased gastrin release. Gastrin is the most important regulator of gastric acidity. It stimulates acid secretion indirectly by releasing histamine from ECL (enterochromaffin-like) cells (1). Gastrin also stimulates ECL cell proliferation (2). This is the biological mechanism by which sustained hypergastrinemia can induce ECL cell tumours.

In the mid 1980s it was reported that the proton pump inhibitor (PPI) «omeprazole» induced tumours in the acid-producing part of the stomach in rats (3). All clinical trials with this highly effective PPI were therefore stopped. The tumours were localised to the acid-producing mucosa. However, Nilo Havu of the pharmaceutical company «Astra» showed that these tumours were not adenocarcinomas, which are the predominant type of gastric cancer in man, but neuroendocrine and of ECL cell origin (3). Hypergastrinemia secondary to profound inhibition of gastric acid secretion was incriminated in the tumourigenesis of omeprazole (3). It was suggested that the rat was a special case and that the ECL was of no or very little importance in gastric carcinogenesis in man. In contrast to the rat, hypergastrinemia alone was not considered sufficient to induce ECL

cell tumours. Thus, it was claimed that ECL cell carcinoids in patients with atrophic gastritis (4) were caused by a combination of the inflammatory process and hypergastrinemia, whereas the ECL-omas occurring in patients

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with gastrinoma as part of multiple endocrine neoplasia type I, were due to a combination of hypergastrinemia and the inherent genetic defect (5).

Approved despite carcinogenesis

PPIs were therefore approved for clinical use, which broke a taboo about not using a compound that had induced a malignant tumour in its target organ in animals, as a drug. Initially, PPIs were approved for use only on very strict indications. Over the years, however, this has been relaxed and

PPIs can now be prescribed for a range of diseases, including dyspepsia. They can also be given to adolescents and children as young as infants.

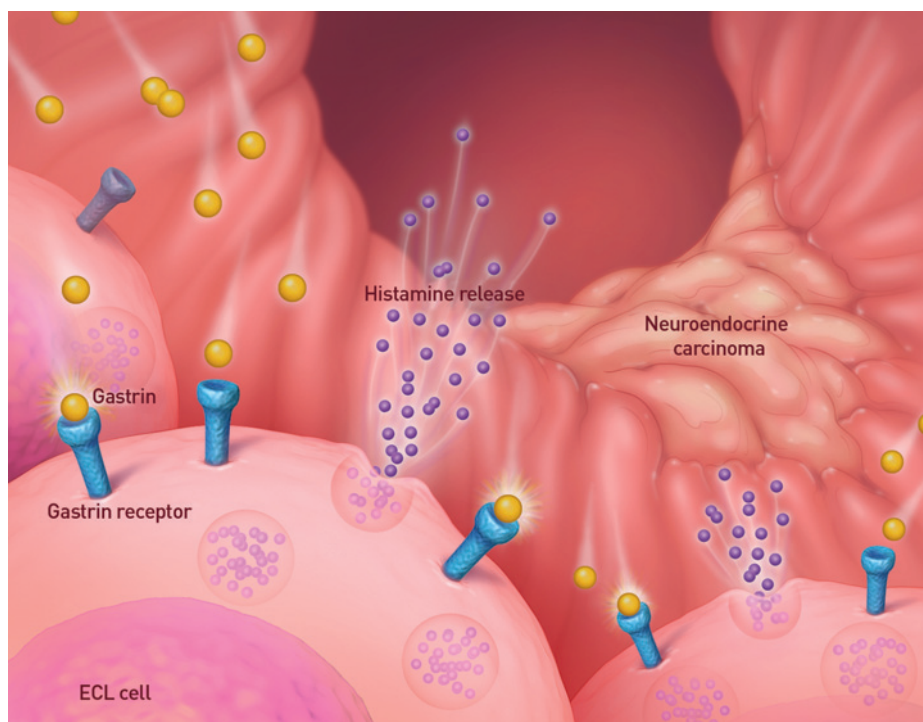
In the beginning there was uncertainty regarding classification of the gastric tumours occurring in rats after PPI exposure (3). Tumours initially thought to be adenocarcinomas turned out to be neuroendocrine carcinomas. Thus, our research group became interested in the classification of gastric carcinomas also in man. Could it be that tumours classified as adenocarcinomas were in fact neuroendocrine carcinomas originating from the ECL cell?

Hypergastrinemia induces cancer

Over a period of more than 20 years we have shown that a significant proportion of gastric carcinomas in man are neuroendocrine carcinomas (6, 7). We have therefore claimed that hypergastrinemia secondary to profound inhibition of acid secretion would, in the long term, necessarily increase the risk of gastric cancer (8). A paper elegantly showing that hypergastrinemia alone induces malignant tumours also in man, has recently been published (9). The paper describes ten siblings, four of whom are homozygous for a mutation in one of the genes coding for the proton pump and have thus been anacidic and hypergastrinemic from birth. All four developed gastric tumours at the age of about 30 years (9). Three of these tumours were classified as ECL cell carcinoids, the fourth as an adenocarcinoma (9). However, the adenocarcinoma was positive for the somatostatin-2 receptor which suggests that it is probably a neuroendocrine carcinoma. This shows unambiguously that hypergastrinemia in man, just as in rodents, is sufficient to induce ECL cell-derived tumours of differing degrees of malignancy.

Blind faith in evidence-based medicine

When we have previously claimed that this could be the case, we have been ignored or opposed. There can be many reasons for this, but I suspect that one important factor is that biological understanding has been replaced by blind faith in evidence-based medicine. Other doubtful aspects of evidence-based medicine have been discussed previously in this journal (10). If clinical practice is based solely upon evidence-based medicine, long-term side effects will be detected only after decades have passed. Such side effects will, however, often be



A fall in acidity triggers the release of gastrin, which stimulates ECL cells to release histamine. Gastrin also stimulates ECL cell proliferation. This can lead to hyperplasia and cancer, most commonly neuroendocrine carcinoma. Illustration: Scott Leighton/Medicus Media

detected in animal studies. It has to be remembered that the rat and man are more than 90 % genetically identical. Presently, it is demanded that side effects found in experimental animals are also shown to apply to man. The opposite should be required: An explanation as to why side effects described in animals are *not* relevant for man.

Another cause of the negative response to our research may be the involvement of economic interests. In this context I will mention a conversation I had with Basil Hirschowitz, a friend of Norway and the man who invented the first flexible endoscope: «You are fighting a product sold for 10 billion dollars a year; you have no chance», he said. To which I replied: «In the long run biology will always beat economy».

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References

1. Waldum HL, Sandvik AK, Brenna E et al. Gastrin-histamine sequence in the regulation of gastric acid secretion. *Gut* 1991; 32: 698–701.
2. Brenna E, Waldum HL. Trophic effect of gastrin on the enterochromaffin like cells of the rat stomach: establishment of a dose response relationship. *Gut* 1992; 33: 1303–6.
3. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion* 1986; 35 (suppl 1): 42–55.
4. Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. *Gastroenterology* 1985; 88: 638–48.
5. Solcia E, Capella C, Fiocca R et al. Gastric argyrophil carcinoidosis in patients with Zollinger-Ellison syndrome due to type 1 multiple endocrine neoplasia. A newly recognized association. *Am J Surg Pathol* 1990; 14: 503–13.
6. Waldum HL, Haugen OA, Isaksen C et al. Are diffuse gastric carcinomas neuroendocrine tumours [ECL-omas]? *Eur J Gastroenterol Hepatol* 1991; 3: 245–9.
7. Waldum HL, Aase S, Kvetnoi I et al. Neuroendocrine differentiation in human gastric carcinoma. *Cancer* 1998; 83: 435–44.
8. Waldum HL, Brenna E, Sandvik AK. Long-term safety of proton pump inhibitors: risks of gastric neoplasia and infections. *Expert Opin Drug Saf* 2002; 1: 29–38.
9. Calvete O, Reyes J, Zuñiga S et al. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour. *Hum Mol Genet* 2015; 24: 2914–22.
10. Wyller TB. Evidensbasert medisin eller vulgær-cochranisme? *Tidsskr Nor Lægeforen* 2011; 131: 1181–2.

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