Hormones and carcinogenesis

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Abstract

Hormones are important regulators of growth. By stimulating proliferation, hormones may increase the risk of mutation and at the same time stimulate the replication of the mutated cell. Thus, hormones are complete carcinogens. A direct carcinogenic effect of oestrogen in man is known from the occurrence of vaginal carcinomas in girls born of mothers who were treated with oestrogen during pregnancy. There are also experimental animal studies indicating that even peptide hormones may induce malignant tumours.

An excellent example is the so-called enterochromaffin-like cell (ECL-cell) carcinoid of the stomach, which is caused by hypergastrinaemia and where the pathogenesis is diffuse hyperplasia, linear and nodular hyperplasia, dysplasia (with micronodules), intramucosal carcinoid, and invasive carcinoid. This sequence of events can be followed not only histopathologically but also by means of image DNA cytometry of the nuclei of the ECL-cells. As soon as clear-cut neoplasia is present, the cytometric DNA distribution pattern switches from the normal diploid type to an aneuploid one. The hyperplastic lesions are all reversible, as soon as the hypergastrinaemia is eliminated.

Introduction

In general pathology, there are two classical, fundamental concepts concerning the cause of a disease: namely aetiology and pathogenesis. Aetiology refers to the agent that evokes the disease, for instance bacteria, viruses, radiation; pathogenesis refers to the mechanisms through which the causative agent evokes the histopathological lesions, the clinical symptoms and the laboratory signs of the disease. In tumour pathology, the pathogenesis of neoplastic disease is often better known than its aetiology. As a matter of fact, there are only few malignant tumours in which not only the aetiology has been revealed but also each single step in the sequence that ultimately leads to the establishment of a malignant neoplastic lesion. In recent years, it has become increasingly evident that various kinds of hormones can be both real aetiological agents in benign as well as malignant tumours, and be actively involved in the pathogenesis of the neoplastic lesion.

The role of hormones in the regulation of growth and development has been known for a long time. Similarly, it has been realised that hormones may play an important role in the genesis of benign tumours like pituitary adenomas (Furth et al. 1955). Moreover, the importance of sex hormones in the mammary and prostatic glands is well known (Henderson et al. 1982, Williams et al. 1991). However, although hormones have been thought to be important in growth regulation, they have not been regarded as the cause of carcinomas. This view may now be challenged based upon new knowledge of carcinogenesis.

Carcinogenesis

Carcinogenesis has been believed to be initiated by a factor inducing a mutation followed by other factors (promoters) stimulating the growth of the mutated cell (Berenblum & Shubik 1947). It is now, however, realised that carcinogenesis is a multi-step process (Armitage & Doll 1954) involving many mutations, preferentially in genes regulating growth control, resulting in increased stimulation (oncogenes (Weinberg 1984)) or removal of inhibition (tumour suppressor genes (Marshall 1991)). Thus, carcinogenesis is a continuous process, affecting cellular growth control. Implicated in such a view is the fact that a hyperplastic lesion or a benign tumour can predispose to a malignant neoplasm. Clinically and histopathologically the transformation from simple hyperplasia, via an adenoma to a carcinoma, is perhaps most clearly observed in the epithelium of the colorectal mucosa (Cappell & Forde 1989).
Mutations occur at cell divisions with a certain frequency. Mutagens increase the risk of mutation via a direct effect on the genes. Whether a mutation induced by a mutagen gives rise to a clinically overt tumour depends on the type of mutation and also on the replication of the mutated cell. Hormones may stimulate the growth of cells including mutated cells, and they have, therefore, been thought to be important co-carcinogens. By stimulating mitosis, hormones increase the risk of mutation solely by increasing the number of cell divisions (Ames & Gold 1990). Normally most mutations are corrected by DNA repairing mechanisms (Lindahl 1976). These repairing processes take time, and there is reason to believe that speeding up the rate of cell division may increase the risk of permanent mutations being transferred to daughter cells. Thus, hormones may not only be co-carcinogens, but in reality be among the most important carcinogens by increasing the risk of mutations in their normal target cells and at the same time stimulating the growth of the mutated cells.

**Hormones and growth control**

The lipid soluble steroid hormones affect the growth of their target cells by interaction with hormone responsive elements in the nucleus, affecting the regulation of gene expression (Reichel & Jacob 1993). Peptide hormones influence cellular growth by interacting with their cell membrane receptor, which, via a cascade reaction, affects gene expression. Among the peptide hormones a growth stimulatory effect has been attributed mainly to the hormones interacting with receptors coupled to the formation of inositol trisphosphate (Berridge & Irvine 1984), and only to a lesser extent to hormones coupled to adenylate cyclase (MacManus & Whitfield 1969). We (Brenna & Waldum 1992) and others (Petersen et al. 1978, Prinz et al. 1994) have presented data supporting the view that hormones control both the function and the growth of their target cell via the same receptor and with the same ligand concentration dependence.

**Hormonal overstimulation or removal of hormonal inhibition may lead to benign pituitary tumours (Furth et al. 1955). The recent report of hyperfunctioning thyroid adenomas secondary to mutations in the thyrotrophin receptor (Parma et al. 1993) also indirectly supports the importance of hormonal stimulation in the genesis of benign tumours.**

**Hormones and carcinomas**

The role of sex hormones in mammary and prostatic carcinoma (Henderson et al. 1982) is well established. Thus, mammary carcinomas seldom occur in males (Bhagat & Kline 1990). Furthermore, the racial differences in the incidence of prostatic carcinomas are paralleled by differences in the testosterone levels (Ross et al. 1995). Moreover, the growth of mammary carcinomas is influenced by oestrogens (Dickson & Lippman 1987), and the presence of oestrogen receptors in such tumours indicates a positive clinical effect of anti-oestrogen treatment (Rose et al. 1985). Interestingly, breast carcinomas may become independent of oestrogen during their progression (Schmitt 1995). Thus oestrogen receptor negative tumours too may have been oestrogen dependent at an initial stage of the development, which is in agreement with the well-known sex difference in the prevalence of mammary carcinomas (Bhagat & Kline 1990). These well-known clinical data do not, however, mean that these tumours are caused by sex hormone overstimulation. The vaginal carcinomas that occurred in girls born of mothers treated with oestrogen in large doses during pregnancy (Greenwald et al. 1971), on the other hand, show that sex hormones alone can induce human carcinomas. Perinatal treatment of female mice with oestrogens has also been shown to give uterine adeno-carcinomas (Newbold et al. 1990), thus demonstrating that oestrogens are complete carcinogens.

Even in adults, short periods of hormonal overstimulation may induce malignant tumours as indicated by the recent report on increased risk of ovarian carcinomas in women given gonadotrophin or the gonadotrophin releaser clomiphene to induce ovulation for in vitro fertilisation purposes (Willemsen et al. 1993, Rossing et al. 1994). The more recent description of follicle-stimulating hormone receptors in the surface epithelium of the ovaries (Zheng et al. 1996) makes it more probable that gonadotrophins really may play a role in carcinogenesis in the ovaries. Thus, not only steroid, but also peptide hormones could be of importance in carcinogenesis.

The role of gastrin in the regulation of growth (Tielemans et al. 1990) of the enterochromaffin-like cell (ECL-cell) and the development of ECL-omas in the rat have been thoroughly studied. The ECL-omas are classified as carcinoids; seldomly they can metastasise (Poynter et al. 1985) and can, therefore, be looked upon as slow-growing malignant tumours like other carcinoids. Their aetiology has been proven to be hypergastrinaemia and the stepwise pathogenesis has been experimentally established in detail. The first effect of the hypergastrinaemia, either experimentally induced via proton-pump inhibitor drugs (Havu 1986), histamine-receptor blockers (Poynter et al. 1985) or partial corpectomy (Mattsson et al. 1991), or evoked (clinically) via atrophic gastritis (Havu et al. 1991), with or without concomitant pernicious anaemia (Borch et al. 1985), is a diffuse hyperplasia of the ECL-cells. The next step is a linear hyperplasia (Solcia et al. 1988). The first sign of a developing tumour is when the linear hyperplasia...
becomes nodular (Solcia et al. 1988). These lesions are still, however, reversible and non-neoplastic. The ‘point of no return’ is reached when the nodular hyperplasia switches over to an intramucosal microcarcinoid. An invasively growing ECL-cell carcinoid is the neoplastic end stage. As mentioned above, metastatic lesions in the lymph nodes or in the liver almost never appear in the gastrin-induced carcinoids. There are, however, other, rare, gastric carcinoids that are not associated with hypergastrinaemia but from which metastases may appear (Rindi et al. 1993). Multiple primary lesions occur in the stomach mucosa and can resolve spontaneously. By means of a new, consecutive staining technique, it has been shown that in the pathogenesis of the hypergastrinaemia-induced ECL-cell carcinoids of the stomach, a switch from a euploid to an aneuploid nuclear DNA distribution pattern occurs in the ECL-cells when they pass from a state of hyperplasia to that of genuine neoplasia (Falkmer & Falkmer 1995).

Also in man, long-term hypergastrinaemia leads to ECL-cell hyperplasia and ECL-omas (Bordi et al. 1974, Borch et al. 1985). Moreover, patients with pernicious anaemia not only have an increased risk of ECL-cell carcinoids, but also of carcinomas in the oxyntic mucosa (Zamcheck et al. 1955). We have previously presented data suggesting that a proportion of the gastric carcinomas actually are malignant ECL-omas (Waldum et al. 1991). These findings have not been disproved. Thus, gastrin may play a role in carcinogenesis in the stomach. However, patients with antral resection and thus hypogastrinaemia, also have an increased risk of gastric carcinomas (Stalsberg & Taksdal 1971). In the oxyntic mucosa there are many neuroendocrine cell types (Sundler et al. 1992) which, like the ECL-cell (Tielemans et al. 1990), are probably all capable of replication. Among these cells, gastrin stimulates the growth only of the ECL-cell, and on the other hand, inhibits the growth of the somatostatin producing D-cell (Chen et al. 1992). We therefore re-examined gastric stump carcinomas for D-cell derived tumour cells. Half of the tumours were of the diffuse type according to Lauren’s criteria (Lauren 1965), and among them 40% showed neuroendocrine differentiation (Waldum et al. 1994). One of these tumours with neuroendocrine differentiation could be classified as a D-cell carcinoid, suggesting that hypogastrinaemia could play a role in the development of such tumours (Waldum et al. 1994). The median time between antrectomy and clinical gastric stump carcinoma was found to be 38 years (Waldum et al. 1994).

Conclusions
There is a certain probability of mutation and tumour development in all cells having the ability to divide. By stimulating growth, hormones increase the probability of mutation in their target cell. At the same time they stimulate the growth of the mutated cell. Thus, hormones are complete carcinogens. There is reason to believe that hormones and local paracrine substances play a fundamental role in carcinogenesis in most organs. When evaluating the risk of hormones in carcinogenesis, one has to take into account the long latency for tumours to develop. Our review underlines the importance of the fact that a classification of tumours should not be based on their organ of origin only, but mainly on their cellular origin. Based upon knowledge of the growth control of the normal cell giving rise to the tumour, a rational therapy may then be initiated.

References
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