Significance of Polyamine Measurements in Urine in Carcinogenesis of Endocrine Glands

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ABSTRACT

Polyamines, polycationic compounds found in urine and sera of mammals, are elevated in patients with malignancies. Like carcinoembryonic antigen, these organic structures have been investigated as potential diagnostic tools in screening at-risk individuals for cancer and for predicting prognosis. In many instances, the ubiquity of these compounds and the lack of specificity for each malignancy have negated their usefulness. Recently, investigations have included some of the endocrine carcinomas and the relationships of urine or serum polyamine measurements. This article indicates the preliminary work that has been done and future directions for the significance of polyamine measurements in urine in carcinogenesis of the endocrine glands.

Introduction

In 1971 Russell showed that polyamines are elevated in acid-hydrolysed urine from patients with cancer. This work stimulated a flurry of investigational efforts to determine the relationship of polyamines in body fluids to etiology, diagnosis and therapy of malignant diseases. Unfortunately, the early promise of polyamine measurements have been tempered by the difficulties in measuring levels accurately in body fluids and by the apparent ubiquity of these compounds in many normal or disease states. Recent advances in technology now allow picamole measurement of polyamines with automated equipment and accurate separation of the different polyamine fractions with a high degree of reproducibility. With the advent of the new technology, the interest in polyamines has been renewed, and many new applications of polyamine physiology are being investigated.

The use of polyamine measurements for determination and evaluation of endocrine malignancies is one of the newest areas of research. Although the present data are very limited, there are avenues of usage in diagnosis and evaluation of therapeutic success that may offer great potential. In order to understand the directions of future research, it is necessary to summarize briefly the present concepts of polyamine metabolism.

General

The naturally occurring polyamines are spermine, spermidine and putrescine. These polybasic amines are produced in man by the biosynthetic enzymes ornithine decarboxylase, S-adenosylmethionine decarboxylase, spermine synthetase and spermidine synthetase. The key control point of polyamine biosynthesis is ornithine decarboxylase (ODC). Ornithine decarboxylase produc-
tion is regulated through messenger ribonucleic acid (RNA),\(^1\) being continually produced and degraded during the rapid cell growth phase of normal or neoplastic cells. The turnover rate of ODC is 11 minutes, which is the shortest half-life of any known mammalian enzyme.\(^7\) The appearance of measurable ODC activity and its product, putrescine, precede morphologic evidence of cell transformation or rapid cell growth.\(^1\) Whether or not polyamine biosynthesis is a direct cause or effect of cell growth remains to be ascertained; however, the temporal relationship of polyamine production to rapid tissue proliferation makes these compounds useful in following neoplastic growth in man.

Studies by Rennert,\(^6\) Marton,\(^4\) and other investigators have shown significant elevation of polyamines in patients with leukemia and patients with cancer of the colon. Although the concentration of each polyamine varies widely between patients, the levels of polyamines definitely reflect response of malignancies to therapy. Rennert\(^6\) has shown that rising polyamine levels in bone marrow aspirates from leukemic patients reflecting impending relapse during therapy before morphological criteria were apparent. Therapy for cancer of the colon can also be monitored by serum or urine polyamine measurements; elevations in polyamine levels during therapy appear indicative of impending therapeutic failure. Unfortunately, in a general population of patients at risk for cancer of the colon, the absolute levels of total polyamines or specific fractions do not correlate with size, evidence of metastases or location of the malignancy.\(^3\)

Many variables exist which influence the serum and urinary concentrations of polyamines,—such as the age of the patient, drug effects and renal status. Rennert\(^5\) has measured the fractions of polyamines contained on the red blood cell (RBC), polymorphonuclear cell and monocyte. The majority of polyamines are bound to the cell membrane of the RBC, and measurement requires digestion of the cellular components to ascertain "serum" levels of the polyamines. The amount of polyamines bound by cellular components of blood determines the concentration of polyamines in cerebral spinal fluid (CSF) and urine, since these fluids only reflect the concentrations of free polyamines in the body.

Menstrual cycle in the female also effects polyamine levels, with a rise in concentration just prior to ovulation.\(^5\) Finally, there is a marked difference in polyamine levels between pre- and post-pubertal patients.

**Endocrine Tumors**

No large studies of endocrine tumors have yet been completed, but preliminary data on breast and pancreatic neoplasias reflect the same interpretive difficulties encountered in other malignancies.

Statistically, pancreatic cancers show an elevation of mean putrescine levels in sera and urine, but individual cases often fall in the normal range in spite of the presence of a fulminant neoplasm.\(^8\) Measurements of the other polyamine levels, spermine and spermidine, are too variable in pancreatic tumors to be considered valuable. In a specific patient, it is probable that an elevated urinary putrescine level could be used to evaluate therapeutic success, but these studies have not yet been completed.

Extensive data have been obtained on pituitary, hypothalamic and other brain tumors. Utilizing CSF polyamine determinations to screen large populations, a false positive elevation of polyamines would occur approximately one in 10. The true incidence of tumor would be 4 per 10,000. Thus, there would be 1,000 false tests for every four patients with a brain tumor,\(^2\) a figure which is unacceptable for large population screens. In patients with known tumors, CSF polyamine levels are useful in following therapeutic response. Putrescine levels in CSF have a correlation of less than 0.001 with presence of
tumor after therapy when compared to a group of patients who have responded to therapy. The normal level for putrescine in CSF is 182 ± 79 nanograms per dl as compared to 546 ± 89 nanograms per dl for patients who do not respond.

Breast cancer polyamine levels have been studied extensively by Woo et al.9 and compared to other serum markers of breast carcinoma in 73 patients. Their data indicate that plasma carcinoembryonic antigen (CEA) is positive in 76 percent of patients with proven breast cancer as compared to the urinary nucleoside levels (N₉) N₂ - dimethyl - guanosine/pseudouridine, 1 - methylinosine/pseudouridine and 1 - methylinosine/N², N² - dimethylguanosine), which were positive in only 36 percent of the patients. Urinary spermine and spermidine were elevated in 24 percent and 27 percent of patients, respectively, of patients with breast cancer, while putrescine was elevated in only 7 percent of the patients.

If pre- and post-treatment levels of CEA, the three polyamines and the three nucleosides are measured and compared to the pre- and post-treatment levels of each set of markers alone, there is a significant increase in accuracy of predicting successful therapy. The combination of polyamines and nucleosides is just slightly less predictive than all three markers, but it is better than the combination of polyamines and CEA or nucleosides and CEA.10 Therefore, it appears that urinary polyamine measurements alone are not an acceptable diagnostic or therapeutic monitor for breast cancer.

Although the present studies have not clearly defined a role for polyamine measurements and carcinogenesis of the endocrine glands, basic research efforts with endocrine systems and polyamines are very provocative. Ornithine decarboxylase activity of the ovary increases markedly in the presence of lutropin. As the ovary and testes grow and differentiate in response to gonadotropins, ornithine decarboxylase and S-adenosylmethionine decarboxylase activity increases; this is also true in uterine tissue exposed to estrogen and in testicular tissue exposed to androgens. Spermidine induces lactation in mouse mammary gland explants. Finally, the addition of progesterone to endometrial explants is accompanied by an increase in S-adenosylmethionine decarboxylase activity.9 These observations demonstrate the intimate relationships between polyamine biosynthesis and endocrine gland hormones. Exploration of these pathways in normal and neoplastic endocrine glands may elucidate the role of polyamine measurements in etiology, diagnosis and evaluation of endocrine tumors.

References