PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE SUPERACTIVITY: DETECTION, CHARACTERIZATION OF UNDERLYING DEFECTS, AND TREATMENT

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Phosphoribosylpyrophosphate (PRPP) synthetase catalyzes the synthesis of PRPP, a critical substrate common to the de novo and salvage pathways of purine nucleotide synthesis. The PRPP synthetase reaction involves the transfer of the terminal pyrophosphate group of ATP (as a MgATP complex) to the C-1 carbon of ribose-5-P and is dependent on inorganic phosphate (Pi) and Mg\(^{2+}\) which serve as enzyme activators as well as cofactors. Activity of PRPP synthetase is inhibited by a number of phosphorylated compounds including the reaction products (PRPP) and AMP), purine, pyrimidine, and pyridine nucleotides and 2,3-DPG. Human PRPP synthetase is composed of a single polypeptide subunit\(^2\) the structural gene for which maps to the long arm of the X-chromosome.\(^3\) Under appropriate conditions of enzyme and effector concentration in vitro, PRPP synthetase subunits are capable of reversible self-association to aggregates containing 2,4,8,16 and 32 subunits, with only the largest two of these containing significant enzyme activity.\(^4\)

Since the initial report by Drs. Sperling and de Vries and their colleagues,\(^5\) inherited superactivity of PRPP synthetase has become established as an unusual cause of purine overproduction, hyperuricemia, and gout in man. To date, detailed investigations of 7 families with superactive PRPP synthetase have been published,\(^5\) and I am aware of 4 additional families currently under study. In each family, the index cases have been males, and where studied, the patterns of inheritance of the enzyme aberrations have been consistent with X-linked transmission,\(^5\) reflecting the apparent structural basis of superactivity in each defective enzyme.

Most affected male patients have shown the onset of acute gouty arthritis and/or uric acid urolithiasis in early adulthood. In these
individuals, the clinical course has been dominated by the usual consequences of excessive uric acid production and excretion, and no readily apparent associated disease has been identified in these adult patients, the oldest of whom was 63 years of age at the time of detection of enzyme superactivity. Although excessive daily urinary uric acid excretion has been found in several heterozygous female carrier relatives of the adult patients, these women have not shown clinical abnormalities.\textsuperscript{5,6,11}

Evidence of purine overproduction in childhood has led to detection of superactive PRPP synthetases in 2 families which are of special interest for several reasons.\textsuperscript{9,14} First, the hemizygous affected males in these families show severe sensorineural deafness in addition to uric acid overproduction. Second, the mothers of these boys share both the metabolic and hearing abnormalities with their sons, and one of these women\textsuperscript{9} has had both acute gouty arthritis and uric acid urolithiasis. Finally, as discussed below, the functional derangement in the enzyme of one of the families\textsuperscript{9} is unusually marked with more severe metabolic consequences of PRPP synthetase superactivity which might explain the childhood clinical onset, the development of gout in the mother, and even the associated deafness.

Structural alteration in PRPP synthetase appears to underlie enzyme superactivity in each family studied in detail.\textsuperscript{6-11} Evidence to support this contention is indirect, since no precise alteration in enzyme primary structure has been demonstrated. Nevertheless, each superactive enzyme studied in partially purified or homogenous preparation has shown at least one variant property in either electrophoretic mobility,\textsuperscript{8,11,15} thermal stability,\textsuperscript{9,11,15} substrate affinity,\textsuperscript{8} inhibitor responsiveness,\textsuperscript{7,9} or immunochemical inactivation\textsuperscript{9,11,15} when compared to normal enzyme of comparable purity. Moreover, the pattern of variant properties of each aberrant enzyme has been distinct indicating that enzyme superactivity can result from a diverse array of inherited structural changes in PRPP synthetase.

Despite structural diversity in the superactive enzymes of individual families, studies of PRPP and purine metabolism carried out both \textit{in vivo} and in cells cultured from affected hemizygous males support the idea that a common mechanism accounts for the association of PRPP synthetase superactivity with uric acid overproduction.\textsuperscript{6-11} Increased intracellular PRPP concentrations and rates of PRPP generation as well as increased rates of all PRPP-dependent purine nucleotide synthetic processes are constant accompaniments of enzyme superactivity. These findings suggest a scheme to explain the association of the enzyme defect with uric acid overproduction: PRPP synthetase superactivity $\rightarrow$ increased intracellular PRPP generation and concentration $\rightarrow$ increased rate of purine nucleotide synthesis $\rightarrow$ excessive uric acid synthesis.

In addition to heterogeneity in the structural defects leading to