

Mutations in the Ca²⁺-Sensing Receptor Gene Cause Autosomal Dominant and Sporadic Hypoparathyroidism

The 7-transmembrane, G-protein-associated, Ca²⁺-sensing receptor gene is present on chromosome 3q. Abnormalities in this gene have been associated with familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia of varying severity. Baron et al have identified 3 mutations in this receptor: Gln681His (first extracellular loop) and Ala116Thr (amino terminal, extracellular domain) in 2 different families with autosomal dominant hypocalcemia and Phe806Ser (sixth transmembrane domain) in a third patient but with sporadic hypocalcemia. Symptoms varied from muscle cramping to neonatal seizures. All had hypercalciuria despite hypocalcemia, reflecting the role of the Ca²⁺-sensing receptor in the modulation of renal calcium excretion. The authors point out that conventional treatment of this disorder with calcitriol with or without supplemental calcium may increase urinary calcium excretion. Thus, for optimal treatment of this disorder it may also be neces-

sary to administer an agent that lowers urine calcium excretion (a thiazide).

Baron J, et al. *Hum Mol Genet* 1996;5:601-606.

Editor's comment: The reader is referred to Dr. Shenker's article, Activating Mutations in G Protein-Coupled Signaling Pathways As a Cause of Endocrine Disease (GGH 1996;12[3]:33-38). These subjects are closely related. The reader also may wish to read a comprehensive review by Pearce and Brown concerning defects of the Ca²⁺-sensing receptor (J Clin Endocrinol Metab 1996;81[6]:2030-2035).

The current report is of interest because of the severity of the hypocalcemic symptoms in some of these patients. In previous subjects, hypocalcemia has been modest and the patients often mildly symptomatic or asymptomatic.

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Protein Turnover During Puberty in Normal Children

Arslanian and Kalhan performed leucine turnover studies in 20 prepubertal Tanner I and 21 pubertal Tanner II through IV nondiabetic children and adolescents. The aim of their study was to determine whether the insulin resistance of puberty involves protein metabolism. Leucine flux, oxidation, and nonoxidative disposal were measured during a primed constant infusion of [1-¹³C] leucine at baseline and during a stepwise hyperinsulinemic (10 and 40 mU/m²/min) euglycemic clamp. Indirect calorimetry was performed as well. Breath samples were collected every 5 minutes for the analysis of C13 enrichment in the expired CO₂, and continuous indirect calorimetry by ventilated hood system was used to measure CO₂ production and energy expenditure. During the hyperinsulinemic-euglycemic periods, the glucose was clamped at approximately 100 mg/dL, and arterial blood was sampled every 10 to 15 minutes for determination of isotopic enrichment of plasma ketoisocaproate, amino acids, and insulin.

Fasting plasma glucose and insulin concentrations were similar in both groups, as were leucine and other branched-chain amino acids. Whole body leucine flux, an indicator of proteolysis, was lower in the pubertal versus prepubertal subjects. Similarly, leucine oxidation was lower in pubertal than prepubertal subjects, while nonoxidative leucine disposal (an indicator of protein synthesis) did not differ between the 2 groups. There were no gender-related differences in leucine kinetics. Resting energy expenditure correlated positively with leucine turnover, oxidation, and nonoxidative disposal.

IGF-1 correlated negatively with whole body leucine flux and nonoxidative disposal. Fasting insulin correlated negatively with leucine oxidation but not with leucine flux and nonoxidative leucine disposal.

During the hyperinsulinemic-euglycemic clamp, leucine flux was suppressed from baseline and the suppression was significantly lower in pubertal than in nonpubertal subjects.

The authors conclude that whole body proteolysis is approximately 12% lower in pubertal adolescents compared with prepubertal children, and protein oxidation is 24% lower; however, protein synthesis is similar. They state that this is the first study to demonstrate changes in protein turnover during puberty compared with prepuberty. Protein turnover explained 24% of the variability in resting metabolic rate in these children. They note that the positive correlations between resting energy expenditure and leucine kinetics support the notion that protein turnover is a significant regulator of resting metabolic rate. They also note the inverse relationship between IGF-1 levels and leucine turnover, ie, the higher the IGF-1 level the lower the rate of proteolysis. In addition, studies with the hyperinsulinemic clamp show that pubertal adolescents demonstrate lower levels of proteolysis suppression.

Arslanian SA, Kalhan SC. *Am J Physiol* 1996;270:E79-E84.

Editor's comment: This is an important and carefully conducted study that significantly advances the understanding of some factors associated with growth during adolescence. The data suggest that (1) puberty is characterized by reduced protein breakdown; (2) pubertal elevations in IGF-1 may play a role in suppressing postabsorptive proteolysis; (3) approximately 20% of resting energy expenditure can be attributed to protein turnover; and (4) during puberty, whole body proteolysis is resistant to suppression by insulin. They carefully point out how their data differ from those collected by others.