THE EFFECT OF SHORT TERM FASTING ON GROWTH PLATE DEVELOPMENT: AN ANALYSIS OF CATCH-UP GROWTH IN YOUNG MALE RATS

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Introduction: For at least 100 years it has been recognized that children with retarded growth due to undernutrition will respond with a growth rate higher than normal if the food restriction is removed. Additionally, height velocities that are supranormal are seen in children recovering from either starvation or illnesses such as acute renal failure. This phenomenon has been called ‘catch-up growth’, defined as “height velocity above the statistical limits of normality for age and/or maturity during a defined period of time, following a transient period of growth inhibition.”(1) There is experimental evidence that the GH/IGF-1 axis is responsive to changing nutritional status (2), and growth responses to food deprivation also have been shown to involve the hormone leptin which is secreted from adipocytes (3). In previous studies of catch-up growth, weights and final bone lengths have been the only parameters examined to determine the extent of the response. We have developed a post-weaning model of a brief period of food withdrawal to follow long bone growth in the catch-up period as a way to determine the time course of the actual growth rate response in both growth plates of the rat tibia.

Materials and methods: Rats born to and raised in litter sizes of 10-12 animals were weaned at 3 weeks and fed ad lib until four weeks. Male littermates were assigned to groups as pairs, one to continue to be fed ad lib, the other to be fasted for 3 days, with water provided. Collections of proximal and distal tibial growth plates were made at 0, 1, 2, 3, 7, 14, 21, 28, 30 days. Animals were injected with oxytetracycline (OTC) 24 hours before sacrifice, and BrdU 30 minutes before. All procedures were approved by the Institutional Animal Care Committee. Fixation was by 2% glutaraldehyde/2% paraformaldehyde with 0.7% ruthenium hexamine trichloride followed by embedment in Epon Araldite. 24-hour growth was measured from the fluorescent OTC band to the chondroosseous junction, using ten measurements averaged over two blocks. Animals were weighed at least 5X/week, and food consumption also was monitored. There were six animals per time period in control and experimental groups, 96 animals in all. Differences between groups were analyzed by two-way ANOVA, at p<05.

Figure 1

Results: Rates of elongation of the proximal tibia in the control and fasted groups are shown in Figure 1. With the exception of the first three days, the data for the proximal tibial growth plate of the control animals show a steady rate of decline in rate of growth over the experimental period. In contrast, rates in the fasted group, although starting at a level which is only 30% of control, accelerate rapidly in the first ten days and plateau at a level that exceeds that of the control animals for the next three weeks. This is shown dramatically in Figure 2 where the ratio of the rates (fasted/control) is shown. The accelerated rate of growth in the proximal tibia of the fasted animals continues at 110% of control after day 14. In contrast, in the distal tibia where growth rates immediately after the fast also are only 30% of control, growth accelerates to ~160% of control before plateauing to the control level at 21 days. In both groups of animals growth of the distal tibia was less than 30um/day by 21 days, effectively minimizing further addition to total bone growth from this growth plate. Figure 3 demonstrates that this short fasting period resulted in a dramatic weight differential in the two groups (fasted only 60% of control). Four weeks later the fasted animals essentially had caught up, reaching 95% of the weight of their non-fasted littermates.

Discussion and conclusions: In both the prenatal and the postnatal animal, there is a complex interplay between overall nutritional status and growth. Nutritional effects on growth are particularly important when considering syndromes such as Intrauterine Growth Retardation or the stunting of nutritionally deprived children in poverty. In previous models of catch-up growth only body weights and final bone length have been measured. This is the first time that an experimental model of catch-up growth has been analyzed following growth rate data in specific growth plates. This study documents both the time course and the extent of the dramatic rate response in the proximal and distal growth plates in this model. The difference in rates of growth are more dramatic than the differences in weight. This study will be continued by analyzing multiple chondrocytic kinetic parameters to test the hypothesis that the reduced rate of elongation following food deprivation as well as increased rates following return to normal nutrition are regulated by altering the rate chondrocytes proceed through their differentiation cascade, amplified by volume changes at the level of the hypertrophic chondrocyte. This would be consistent with a response mediated by changes in the GH/IGF1 axis.

References:
1. Boersma and Wit, Endocrine Reviews, 18:646-661,1997

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