DAIRY RESEARCH HIGHLIGHTS

Growth Hormone

2. Milk Safety

The debate continues over the use of growth hormone (GH) to enhance milk production. Although a number of scientific reviews have concluded that consumption of meat and milk from treated animals does not present a health risk to consumers, the scientific basis for such conclusions has been challenged.

Recombinant bovine Growth Hormone (rbGH) is not biologically active in humans. And although other species (e.g., the rat) may be reponsive to rbGH administered through the bloodstream, oral administration produces no effect. In the cow, GH treatment results in increased availability of nutrients for milk synthesis, accompanied by altered metabolism in various tissues. Some of these changes are mediated by insulin-like growth factors (IGFs), directly regulated by GH. Since the safety of rbGH itself has been generally accepted, concern has shifted to the potential hazards of increased milk concentrations of IGFs. The purpose of this review is to gather scientific facts regarding IGF concentrations in milk and their potential biological effects on humans.

Insulin-like Growth Factors (IGFs)

Like GH itself (see page **1G1:1**), IGFs are small proteins - short chains of amino acids referred to as polypeptides (article **1P1** figure 1). Two main types of IGFs have been defined: IGF-I, a 70-amino acid polypeptide, and IGF-II, a 67-amino acid polypeptide. A family of minor forms also exists. A truncated form of IGF-I, lacking 3 of its N-terminal amino acids, has been isolated from bovine colostrum and human brain. Bovine IGF-I (bIGF-I) and its truncated form (-3N:bIGF-I) are the only known growth factors which are structurally identical with their human counterparts - hIGF-I and -3N:hIGF-I. The relative potency of -3N:IGF-I was found to be 10-fold greater than the potency of IGF-I.

IGFs are known to be bound to binding proteins which are presumed to reduce the rate of IGF breakdown. However, it is the free, unbound form which is thought to be the active form of IGF-I. At calving, up to 83% of the IGF-I in colostrum may be in the free form. By 4 days post partum this fraction may represent only 15 % of the total. A similar proportion (19%) of free IGF-I is found in milk from mid-lactation, rbGH-treated cows.

IGFs in cows' milk

In the studies surveyed, IGF concentrations measured in milk from untreated cows varied from 0.7 to 1350 nanograms/ml for IGF-I and from 1 to 117 ng/ml for IGF-II (a nanogram is one billionth of a gram = 10^{-9} grams). IGF concentrations varied with farm, stage of lactation, parity and method of analysis.

In a large survey of pooled bulk tank samples, IGF-I varied from 0.7 to 30.5 ng/ml, with an overall mean of 8.6 ng/ml. Other studies that included fewer pooled samples reported IGF-I values from less than 3 to 38.2 ng/ml. IGF-I in colostrum was consistently higher than in milk, ranging from 26 to 1450 ng/ml depending on the time of sampling after calving. Concentrations over 1000 ng/ml can be found in mammary secretions during the dry period.

Treatment with rbGH generally provokes increased IGF-I concentrations in milk, although the increase is small and in some instances, only temporary. Across the studies surveyed, IGF-I in milk from treated cows ranged from 2.2 to 35.5 ng/ml, while control cows had values from 1.6 to 33 ng/ml. No significant responses of IGF-II to rbGH treatment were recorded. The level of -3N:bIGF-I in milk from treated cows was found in one study to be less than 3% of the total IGF-I concentration.

IGFs in human milk

As in cow's milk, IGF-I concentrations in human milk vary with stage of lactation. IGF-I was found to be highest in milk several hours after birth, and lowest at 3 to 16 months of lactation. The overall range of values were from 1.1 to 49 ng/ml. IGF-II was reported to be between 1.4 to 3.8 ng/ml in milk at 3 to 16 months of lactation.

IGFs in human body fluids

In one study, the mean plasma IGF-I in 14 normal adults was 185 ± 37 ng/ml, while in 14 obese subjects the values tend to be lower: 169 ± 49 ng/ml. Similar values were reported in a second study where the mean from 31 adults was 193 ± 58 ng/ml. In the same study, the highest level of IGF-I was in 12-year old girls and 14-year old boys (range 400-600 ng/ml). IGF-I in 1 month old newborns was the lowest at 51 ± 20 ng/ml. IGF-II in adults was 641 ± 58 ng/ml.

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IGF-I has been measured in a number of exocrine secretions of the human gastrointestinal tract including saliva (6.88 ng/ml), gastric juice (26.74 ng/ml), jejunal chyme (187.94 ng/ml), pancreatic juice (27.5 ng/ml), and bile (6.88 ng/ml). Unlike IGF-I in serum, IGF-I in the gastrointestinal lumen is not bound to binding proteins, thus may be high enough to exert biological activity.

Food safety

Given the possibility that dairy products contain elevated levels of IGF, can IGF enter the bloodstream from the digestive tract? It is generally believed that, in adults, the products of protein and polypeptide digestion enter the blood stream almost entirely as free amino acids. The transport of intact proteins across the intestinal wall in mature animals has not been extensively studied. However, the presence of circulating antibodies to food proteins in human blood suggests that proteins may be absorbed intact.

In newborn animals, orally administered growth factors are biologically active. In the newborn, the time of closure of gut permeability to proteins may occur before birth or as long as 3 months after. However, it has been shown that another small polypeptide, epidermal growth factor, may continue to appear in the portal blood after closure, suggesting an alternate means of entry. IGF-I may be similarly absorbed intact from the small intestine.

In response to these findings, Elanco and Monsanto have conducted toxicity studies on rats to determine whether IGF-I is active when administered orally. Results of the Elanco study indicated no effects of orally administered IGF-I. In the Monsanto trial, the effects of IGF on growth were inconclusive.

One area of the biology of IGF-I that may not have been sufficiently investigated is the direct role of milk-borne IGF-I in the developing gastrointestinal tract. In one study, 78 % of the IGF-I administered orally to rat pups was retained, predominantly in the stomach and intestinal lining. These results suggest that oral IGF may be able to survive digestion and interact with the gastrointestinal tract.

Assuming an average milk intake of 750 ml/day for breastfed infants, an IGF-I concentration of 49 ng/ml would result in the ingestion of 37 micrograms of growth factor. It may be speculated that an increase of IGF-I in the milk of rbGH-treated cows may result in higher, and potentially hazardous levels of IGF-I in commercially prepared formula. However, the heat applied during formula preparation results in the irreversibly denaturation of most of the IGF-I.

Conclusion

From the data above, it can be concluded that IGF-II is biologically inactive in humans and its level in cows' milk does not increase in response to rbGH treatment. Reported IGF-I concentrations in cows' milk vary widely, reflecting individual differences, stage of lactation, age, management and differences in methodology. Treatment with rbGH may result in a slight, but significant increase in milk concentrations that are still within the physiological range. The rbGH treatment has no effect on the proportions of free and bound forms of IGF-I in milk.

The size of the IGF-I molecule makes its absorption across the gut wall of adults unlikely. However, even assuming 100% absorption, ingestion of 1 litre of milk from treated cows would result in an increase of 0.06-0.25% in blood IGF-I compared with the ingestion of 1 litre of normal milk. The increased contribution of milk IGF-I to gastrointestinal IGF-I would also be low (0.15-0.54%), given the average amount of gastrointestinal fluids secreted in 24 hours (7 litres containing 390,000 ng IGF-I). Over 80% of this would be in the inactive form, bound to carrier proteins. The amount of -3N:bIGF-I in treated milk is minimal - equivalent to 0.7-10.65 ng/ml of the regular form. It must be remembered that truncated forms occur naturally not only in milk, but in other body tissues as well, although the proportions have not always been reported.

Nursing infants may be the the most (and perhaps only ones) sensitive to increased levels of growth factors in food. IGF concentrations in human milk are in the same range as those found in the milk of cows, whether treated or untreated with rbGH. Since infant formula contains only denatured residues of IGF-I, it can therefore be regarded as safe.

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Key references

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