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Milk-Derived Growth Factors as Neutraceuticals

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ABSTRACT

Colostrum has lots of bioactive components and many growth factors including insulin-like growth factors, transforming growth factors and epidermal growth factor. Colostrum and milk derived growth factors widely mediate the growth of overall development and could be used as treatment of gastrointestinal disorders, wound repair process, bioactivity in the neonatal GI tract and induction of oral tolerance. It is possible that milk derived growth factors as potential neutraceuticals for the specific consumers may have a great role in future food industry.

(**Key words** : growth factors, colostrum, neutraceuticals)

INTRODUCTION

Growth factors are composed of a heterogeneous group of proteins and peptides that initiate cellular growth and expression of differentiated function. The efficacy of growth factors has been attracted a great deal of interest as a potential source of functional ingredients. Milk has a number of complex and biologically active growth factors. Most of colostral milk exhibit relatively high concentration of growth factors and as lactation begins the contents are sharply diminished to a normal level. These are thought to be an effective nutritional transportation condition between female and new born mammals right after parturition(Uruakpa *et al.*, 2002). Colostrum- and milk-derived growth factors may also mediate the growth of tissues not directly associated with the GI tract and therefore may have greater implications for overall growth and development of the neonate(Donovan and Odle, 1994 ; Murphy, 1998). In particular, little is known about the mechanisms of responses observed following oral administration of growth factors, but the potentially therapeutic role of oral or systemic administration of growth factors during compromised states may lead to their future application in the human nutrition. The purpose of this review is to suggest the possibility of use milk or colostrum-derived growth factors as dietary supplements or neutraceuticals.

1. Colostrum as a Reservoir of Growth Factors

Table 1. Concentration of major milk growth factors in human and bovine milk

	Colostrum	Normal milk	References
EGF			
Human	200㎍/L	-	Read *et al.*(1985)
Bovine	30~50㎍/L	2~324㎍/L	Iacopetta *et al.*(1992)
IGF-Ⅰ			
Human	18㎍/L	7.1~19.1㎍/L	Baxter *et al.*(1984)
Bovine	500㎍/L	5.0±2.0	Vega *et al.*(1991)
IGF-Ⅱ			
Human	NR	2.7±0.7	Donovan *et al.*(1991)
Bovine	187㎍/L	32㎍/L	Lee *et al.*(1991)
NGF			
Human	Identified	Identified	Wright *et al.*(1983)
Bovine			

Colostrum is secreted into the mother's milk for approximately from one to three days after birth. Most pharmaceutical treatments have toxic side effects or long-lasting residues, whereas colostrum promotes homeostatic balance in the body (Ley, 1997). Peptide growth factors content of milk have interested recently with discovery of the high content of growth factors in mammalian colostrum.

2. Insulin like Growth Factors(IGF-Ⅰ and IGF-Ⅱ)

IGF-Ⅰ and IGF-Ⅱ are secreted by liver, but not stored within the liver. These polypeptides in the human and cow's milk consist of 70 and 67 amino acid residues, respectively (Hadley, 1996). Both IGF-Ⅰ and IGF-Ⅱ are heat- and acid-stable and are widely distributed mediators of cellular growth (Pakkanen and Aalto. 1997). IGF-Ⅰ has a proinsulinlike struc-

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ture with a shorter connecting peptide of 12 amino acids and has a similarity to insulin actions. Nutritional status is very important regulator of IGF-1 production and release, so malnutrition and fasting markedly lowers IGF-Ⅰ levels(Simon *et al.*, 2002). It was reported that supplement of milk-borne IGF-Ⅰ apparently enhanced growth in newborn rats and supplement of IGF-Ⅰ by injection or oral administration (Hikino *et al.*, 2001 ; Juskevich and Guyer, 1990).

Heaney *et al.*(1999) demonstrated that two hundred four healthy older adults(aged 55 to 85 years), who habitually consumed less than 1.5 servings of dairy foods were instructed to consume 3 servings a day of nonfat milk or 1% milk. The results were increase of serum IGF-Ⅰ content by 10% in the milk group, and also increase calcium intake for bone resorption in skeletal metabolism.

Houle *et al.*(1997) demonstrated that the effect of orally administered IGF-Ⅰ at 200μg/kg per day developed intestinal disaccharidase enzymes and villus height in pigs. This result was responsive to orally administered IGF-Ⅰ supporting a potential role for milk born IGF-Ⅰ in neonatal intestinal development. Bassett *et al.*(1998) hypothesized the increase in milk IGF-Ⅰ levels observed is likely to be derived from the circulation rather than the mammary gland itself. Another study also has shown that IGF-Ⅰ can passage from the plasma to milk in lactating goats(Prosser *et al.*, 1991), supporting the hypothesis that IGF-Ⅰ could across the mammary epithelium.

Bovine milk IGF-I has a high heat-resistance and could fairly resist the common pasteurization in the dairy industry, such as LTLT(Low temperature-Long time) pasteurization at 63~65 ℃ for 30min, and HTST(high temperature-short time) treatment at 72℃ for 15s. Recently, Kang *et al.*(2006) determined the influence of heating on IGF-I concentration in raw bulk milk using tubular-type heat exchanger. They found that heating at 75℃ and 85℃ for 15min reduced the IGF-I concentration by 45.0% and 45.2%, respectively.

IGF-Ⅱ is three times more abundant in the adult circulation or bovine milk than IGF-Ⅰ. Pygmies have decreased circulating levels of IGF-Ⅰ, but plasma levels of IGF-2 were within the range found in normal adults(Hadley, 1996). Malven *et al.* (1987) demonstrated that the overall concentration of IGF-Ⅱ in bovine milk over d 4 through 6 averaged 117±10ng/mL, which was 4.9-fold greater than the concentration of IGF-Ⅰ.

IGFs circulate in the serum as high molecular weight binding proteins(IGF-Binding Proteins; IGFBPs) complexes and very low levels of free IGFs are detected in plasma. Human milk contains IGFBP-1, -2, and -3 the functions of which remain unclear. In addition, IGFBP-4 has been identified in rat, porcine, and bovine milk. IGFBP-3 is the major binding protein of IGFs in milk formed the 150- to 200-kDa complex that is not translocated from serum into milk. It is suggested that IGFBP-3 may enter milk from circulation in the free form or complexed to IGF-Ⅰ (Fig. 1). The exact role of IGFBPs in milk is possibly to protect against the degradation of milk IGF-Ⅰ or to modulate the local mitogenic activity of the IGFs (Rajaram *et al.*, 1997).

3. Nerve Growth Factor(NGF)

Nerve Growth Factor(NGF) was first identified as a neurotropic growth factor for embryonic neurons. It consists of 121 amino acids and has three intra-chain disulfide links. NGF is critical for development of sympathetic nervous system and possibility of treatment central nervous system. NGF is present in mouse milk at concentrations of 30~1,000μg/liter(Grueters *et al.*, 1985) and has also been identified in human milk(Wright and Gaull, 1983). Appearance ^{125}I-NGF in the blood of neonatal rodents following oral(Aloe *et al.*, 1982) or ileal(Siminoski *et al.*, 1986) administration suggests that NGF may survive gastric digestion and may be absorbed intact. Neuronal hypertrophy was observed in mice fed NGF for the first week of life (Aloe *et al.*, 1982). NGF is crucial to the survival of specific neurons of the peripheral nervous system(Hadley, 1996).

4. Epidermal Growth Factor(EGF)

Epidermal growth factor consists of 53 amino acids and three intra chain disulfide bonds. Some known biological

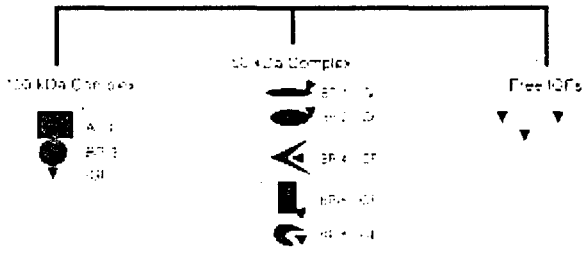

Fig. 1. Proposed model of the forms in which IGFs circulate in human serum. The 150-kDa complex consists of 7.5 kDa IGF-1 or IGF-2 plus 38~43 kDa IGFBP-3 and a 80- to 90-kDa non-IGF-binding acid labile component called ALS. The 50-kDa complex consists of IGF-Ⅰ or IGF-Ⅱ bound to one of the remaining five IGFBPs.

effects of EGF in the mammal include the following: 1) Enhanced proliferation and differentiation of the epidermis, 2) increased growth and maturation of the fetal pulmonary ephithelium, 3) acceleration of the healing of the wounds of the corneal epithelium, and phosphorylation of membrane and nuclear proteins(Hadley, 1996). EGF is a major growth-promoting agent in breast milk, because EGF is not entirely destroyed in the digestive tract, it might act directly on tissues of the digestive tract. Studies have shown that oral administration of EGF can stimulate gastric and duodenal mucosal growth in adult rats, and in neonatal animals increased growth of the stomach, small intestine, colon have been reported. Another study has shown that bovine milk may contain specific inhibitors that protect EGF from proteolytic degradation in human gastric lumen (Rao, 1991; Rao, 1998).

The EGF content of mouse(Beardmore and Richards, 1983) and porcine milk(Jaeger *et al.*, 1987) is higher than that of human milk, whereas levels in rat milk are lower(Raaberg *et al.*, 1990). Concentrations ranging from 2~324μg/liter have been repotted in fresh cow milk(Iacopetta *et al.*, 1992).

EGF is resistant to degradation within the gastric milieu of the suckling(Britton *et al.*, 1988) and preterm infant(Britton *et al.*, 1989), which suggests that milk-borne EGF retain bioactivity in the neonatal GI tract. EGF breakdown may also be reduced if it is ingested with other dietary proteins because these may competitively inhibit the digestive enzymes(Murphy, 1998).

5. Transforming Growth Factor(TGF-α and TGF-β)

TGF-α is consisting 50 amino acids per chain and bears 30~40% amino acids sequence homology to EGF. It is secreted from neurons, salivary glands, hepatocytes and plays roles for hepatocyte regeneration and wound healing such as burns treatment. TGF-α can stimulate mitotic events through the EGF receptor(Hadley 1996). TGF-α levels in human milk (0~8.4μg per liter) are low compared with EGF and relatively constant during the first week postpartum(Connolly and Rose, 1988; Okada *et al.*, 1991).

TGF-β is a homodimer consisting of 112 amino acids. Two different types of TGF-β (β1, β2) were found in bovine milk. TGF-β acts as multifunctional depending on the cell type, growth conditions, the state of differentiation, and the presence of other growth factors. Recent studies have greatly increased our knowledge of the potential role of TGF-α and TGF-β in intestinal development. TGF-α and -β are present in milk(Connolly and Rose, 1988; Okada *et al.*, 1991) and appear to be important in mammary gland development(Daniel and Robinson, 1992; Plaut, 1993). TGF-β growth factors are thought to modulate development and differentiated function(Robinson *et al.*, 1993) of the mammary gland and may play a role in development of the suckling neonate TGF-β also stimulates IgA production by intestinal lymphodal cells (Chen and Li, 1990) and may thus play a role in the immunological protection of the GI mucosal surface.

CONCLUSION

Milk and colostrum contain valuable biologically active substances, in addition to their essential nutrients. Milk proteins are one of the richest sources of functional substances present in milk and colostrum. It is natural that biotechnological food companies are producing large quantities of colostrum derived growth factors that have high nutritive qualities. Several studies have pointed to the prospective biological activities of milk peptides(Clare and Swaisgood, 2000; Gobbetti *et al.*, 2002). The biological activities exhibited by milk-derived growth factors may not be wholly analogous to their human counterparts, some efficacy should be expected, as a great deal of structural homology is shared between cow and human growth factors.

REFERENCES

1. Aloe, L., Calissano, P. and Levi-Montalcini, R. 1982. Effects of oral administration of nerve growth factor and its antiserum on sympathetic ganglia of neonatal mice. Dev. Brain Res. 4:31-34.
2. Bassett, N. S., Currie, M. J., Breier, B. H., Klempt, M., Min, S. H., McCutcheon, S. N., MacKenzie, D. D. S. and Gluckman, P. D. 1998. The effects of ovine placental lactogen and bovine growth hormone on hepatic and mammary gene expression in lactating sheep. Growth Hormone and IGF Research 8:439-446.
3. Baxter, R. C., Zaltsman, Z. and Turtle, J. R. 1984. Immunoreactive somatomedin-C/insulin-like growth factor I and its binding protein in human milk. J. Clin. Endocrinol. Metab. 58:955-959.
4. Beardmore, J. M. and Richards, R. E. 1983. Concentrations of epidermal growth factor in mouse milk throughout lactation. J. Endocrinol. 96:287-292.
5. Britton, J. R., George-Nascimento, C. and Koldovsky, O.

1988. Luminal hydrolysis of recombinant human epidermal growth factor in the rat gastrointestinal tract: segmental and developmental differences. Life Sci. 43:1339-1347.

6. Britton, J. R., George-Nascimento, C., Udall, J. N. and Koldovsky, O. 1989. Minimal hydrolysis of epidermal growth factor by gastric fluid of preterm infants. Gut 30:327-332.
7. Chen, S-S and Li, Q. 1990. Transforming growth factor-β1 (TGF-β1) is a bifunctional immune regulator for mucosal IgA responses. Cell. Immunol. 128:353-361.
8. Clare, D. A. and Swaisgood, H. E. 2000. Bioactive milk proteins: A prospectus. J. Dairy Sci. 83:1187-1195.
9. Connolly, J. M. and Rose, D. P. 1988. Epidermal growth factor-like proteins in breast fluid and human milk. Life Sci. 42:1751-1756.
10. Daniel, C. W. and Robinson, S. D. 1992. Regulation of mammary growth and function by TGF-β. Mol. Reprod. Develop. 32:145-151.
11. Donovan, S. M., Hintz, R. L. and Rosenfeld, R. G. 1991. Insulin-like growth factors Ⅰ and Ⅱ and their binding proteins in human milk : Effect of heat treatment on IGF and IGF binding protein stability. J. Pediatr. Gastroenterol. Nutr. 13:242-253.
12. Donovan, S. M. and Odle, J. 1994. Growth factors in milk as mediators of infant development. Annu. Rev. Nutr. 14: 147-167.
13. Gobbetti, M., Stepaniak, L., De Angelis, M., Corsetti, A. and Di, R. 2002. Latent bioactive peptides in milk proteins: Proteolytic activation and significance in dairy processing. Crit. Rev. Food Sci. Nutr. 42:223-239.
14. Groeters, A., Lakshmanan, J., Tarris, R., Aim, J. and Fisher, D. A. 1985. Nerve growth factor in mouse milk during early lactation: lack of dependency on submandibular salivary glands. Pediatr. Res. 19:934-937.
15. Hadley, Mac. E. 1996. Growth hormones in endocrinology. 4th ed. Univ of Arizona Tucson, Arizona. US. p 257-289.
16. Heaney, R. P., McCarron, D. A, Dawson-Hughes, B., Oparil, S., Berga, S. L., Stern, J. S., Barr, S. I. and Rosen, C. J. 1999. Dietary changes faborably affect bone remodeling in older adults. J. American Dietetic Association. 99: 1228-1233.
17. Hikino, S., Ihara, K., Yamamoto, J., Takahata, Y., Nakayama, H., Kinukawa, N., Narazaki, Y. and Hara, T. 2001. Physical growth and retinopathy in preterm infants: Involvement of IGF-I and GH. Pediatr. Res. 50:732-736.
18. Houle, V. M., Schroeder, E. A., Odle, J. and Donovan, S. M. 1997. Small intestinal disaccharidase activity and ileal villus height are increased in piglets consuming formula containing recombinant human insulin-like growth factor-Ⅰ. Pediatric Research 42:78-86.
19. Iacopetta, B. J., Grieu, F., Horisberger, M. and Sunahara, G. I. 1992. Epidermal growth factor in human and bovine milk. Acta Paediatr. 81:287-291.
20. Jaeger, L. A., Lamar, C. H., Bottoms, G. D. and Cline, T. R. 1987. Growth-stimulating substances in porcine milk. Am. J. Vet. Res. 48:1531-1533.
21. Juskevich, J. C. and Guyer, C. G. 1990. Bovine growth hormone: human food safety evaluation. Science 249:875-884.
22. Kang, S. H., Kim, J. U., Imm, J. Y., Oh, S. and Kim, S. H. 2006. The effects of dairy processes and storage on insulin-like growth factor-I(IGF-I) content in milk and in model IGF-I-fortified dairy products, J. Dairy Science 89:402-409.
23. Ley, B. M. 1997. Colostrum : Nature's gift to the immune system. BL publications, Aliso Viejo, CA, US.
24. Malven, P. V., Head, H. H., Collier, R. J. and Buonomo, F. C. 1987. Periparturient changes in secretion and mammary uptake of insulin and in concentrations of insulin and insulin-like growth factors in milk of dairy cows. J. Dairy Sci. 70:2254-2265.
25. Murphy, M. S. 1998. Growth factors and the gastrointestinal tract. Nutrition 14:771-774.
26. Okada, M., Ohmura, E., Kamiya, Y., Murakami, H. and Onoda, N., et al. 1991. Transforming growth factor(TGF)-β in human milk. Life Sci. 48:1151-1156.
27. Pakkanen, R. and Aalto, J. 1997. Growth factors and antimicrobial factors of bovine colostrum. Int. Dairy Journal. 7 :285-297.
28. Plaut, K. 1993. Role of epidermal growth factor and transforming growth factors in mammary development and lactation. J. Dairy Sci. 76:1526-1538.
29. Prosser, C. G., Royle, C., Fleet, I. R. and Mepham, T. B. 1991. The galactopoietic effect of bovine growth hormone in goats is associated with increased concentrations of insulin-like growth factor-Ⅰ in milk and mammary tissue. J. Endocrinol. 128:457-463.
30. Raaberg, L., Nexø, E., Tollund, L., Pouisen, S. S, Christensen, S. B. and Christensen, M. S. 1990. Epidermal growth factor reactivity in rat milk. Regul. Pept. 30:149-157.
31. Rajaram, S., Baylink, D. J. and Mohan, S. 1997. Insulin-

like growth factor binding proteins in serum and other biological fluids: Regulation and functions. Endocrine Reviews. 18(6):801-831.

32. Rao, R. K. 1991. Biologically active peptides in the gastrointestinal lumen. Life Sci. 48:1685.
33. Rao, R. K., Baker, R. D. and Baker, S. S. 1998. Bovine milk inhibits proteolytic degradation of epidermal growth factor in human gastric and duodenal lumen. Peptides 19(3) :495-504.
34. Read, L. C., Francis, G. L., Wallace, J. C. and Ballard, F. J. 1985. Growth factor concentrations and growth-promoting activity in human milk following premature birth. J. Dev. Biol. 7:135-145.
35. Robinson, S. D., Roberts, A. B. and Daniel, C. W. 1993. TGF-β supresses casein synthesis in mouse mammary explants and may play a role in controlling milk levels during pregnancy. J. Cell Biol. 120:245-251.
36. Siminoski, K., Gonella, P., Bernanke, J., Owen, L., Neutra, M. and Murphy, R. A. 1986. Uptake and transepitbelial transport of nerve growth factor in suckling rat ileum. J. Cell. Biol. 103:1079-1090.
37. Simon, A. R., Perin, L., Meaume, S., Lesourd, B., Moulias, R., Postel-Vinay, M. C. and Le Bouc, Y. 2002. IGF-I, IGF-I-binding proteins and GH-binding protein in malnourished elderly patients with inflammation receiving refeeding therapy. European Journal of Endocrinology 146:657-665.
38. Uruakpa, F. O., Ismond, M. A. H. and Akobundu, E. N. T. 2002. Colostrum and its benefits: a review. Nutrition Research 22:755-767.
39. Vega, J. R., Gibson, C. A., Skaar, T. C., Hadsell, D. L. and Baumrucker, C. R. 1991. Insulin-like growth factor(IGF)- I and - II and IGF binding proteins in serum and mammary secretions during the dry period and early lactation in dairy cows. J. Anim. Sci. 69:2538-2547.
40. Wright, C. E. and Gaull, G. E. 1983. Nerve growth factor is present in human milk. Pediatr. Res. 17:144(Abstr.)