INTESTINAL SURVIVAL AND ABSORPTION OF EPIDERMAL GROWTH FACTOR IN THE SUCKLING NEONATE.

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by

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THESIS ABSTRACT

In addition to meeting the requirements for protein and calories, milk contains a wide spectrum of growth factors which stimulate growth and differentiation of various tissues both *in vitro* and *in vivo*. These growth factors include insulin, epidermal growth factor (EGF), and insulin-like growth factors. Human milk appears to be particularly rich in EGF, the concentrations exceeding adult serum levels by 1000-fold in day 1 milk and 100-fold in milk expressed at later stages of lactation. This has led to the hypothesis that milk-derived EGF may play an important role in neonatal growth and development.

The physiological role of milk-derived EGF in the suckling neonate may only be assessed after quantitative studies on both the survival and absorption of orally-administered EGF in the neonatal intestine. In this thesis, the fate of orally-administered EGF was examined both in the human infant and in an experimental animal model, the newborn lamb. Since a quantitative evaluation of EGF metabolism is not feasible in the human neonate, the intestinal survival and absorption of EGF was assessed by a study of the relationship between the level of dietary EGF intake and urinary EGF excretion in premature infants. This indirect method provided a non-invasive, yet ethically practical evaluation of EGF uptake. A quantitative examination of both the intestinal survival and the rate of intestinal absorption of EGF was examined using the newborn lamb as a model of the human infant.

The results of the human study were found to be consistent with the hypothesis that EGF crosses the gastrointestinal wall to enter the general circulation.

Premature infants receiving higher levels of EGF in their diet showed greater urinary EGF excretion after the second postnatal week. Whilst this finding could also be explained by an indirect effect of some breast milk component on rates of endogenous EGF synthesis, they are nonetheless consistent with the absorption of intact EGF across the neonatal intestine.

The lamb was used as an experimental animal model of the human infant to study both the intestinal survival and absorption of EGF. To assess intestinal survival, reentrant catheters were inserted into the mid-small intestine of suckling lambs. A minimum of 15-30% of intragastric ^{125}I-labelled EGF reached the mid-small intestine as immunologically intact EGF, providing strong evidence that a substantial proportion of milk-derived EGF would reach the small intestine intact.

Intestinal uptake of unlabelled EGF was measured in vivo using the autoperfused lamb intestine. In lambs of age 1-18 days, immunologically intact EGF was absorbed into blood but not lymph at rates that showed no correlation with the age of the lamb. The rates of absorption were low, resulting in a mean venous blood concentration of 0.02nM following infusion of 50μg EGF into a 20cm segment of gut. Given these low concentrations plus the known rapid clearance of EGF from plasma by various organs including the liver, it appears that very little luminal EGF would reach peripheral tissues intact in the neonatal lamb.

The studies in lambs therefore suggest that the direct growth-promoting actions of milk-derived EGF in the suckling infant are likely to be confined to the gastrointestinal tract and possibly the liver. Any actions in other tissues

are more likely to be mediated by secondary responses to the actions of EGF in the gut and the liver.