51a Antiproteolytic Action of Low-Dose Insulin Delivered Orally Using pH-Responsive Hydrogels

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Negative nitrogen balance is a typical metabolic response to a variety of pathological conditions such as burn trauma, sepsis, or cancer cachexia. It is due to a misbalance in the intracellular kinetics of protein-amino acid balance in the skeletal muscle system. This alteration drains the muscle proteins by the loss of nitrogen from the body via urinary excretion. Previously, our group has shown that subcutaneous administration of low dose insulin to 20% total body surface area (TBSA) rats restored the body weight by regaining the intracellular protein content in the skeletal muscles. This is primarily by reducing the accelerated rate of protein degradation and insulin decreases the up-regulated enzymatic activity of ubiquitin-conjugation and lysosomal cathepsins. Also, insulin increases the rate of wound closure by increasing collagen deposition.

To improve the method of insulin treatment for a clinical setting, we investigated the effect of insulin delivered orally through pH-responsive, poly(methacrylic-g-ethylene glycol) (P(MAA-g-EG)) hydrogels in a 20% TBSA rat burn injury model. P(MAA-g-EG) were synthesized and loaded with insulin following published reports. After initial loading and unloading characterization using HPLC and EIA, 20% TBSA burned rats were treated with insulin loaded gelatin capsules daily. The dosage of insulin in each capsule was adjusted to match our previous publications [1]. In brief, after 24 hours of 20% total body surface area burn injury, animals were treated with first dose of 0.25U insulin and the subsequent doses were given at 11:00-12:00 hour intervals and was gradually increased from 0.25U (day 2), 0.5U (day 3) and 1.0U (day 4) per 100 gm body weight. To prevent hypoglycemia, the insulin treated rats received 5% sucrose in drinking water combined with 10% sucrose in rat chow. After the treatment period, all animal groups were returned to individual metabolic cages and their physical activity, body weight, food consumption, water uptake and urinary tyrposine content were monitored everyday for up to four days postburn. Results show that the oral insulin delivery to restored the body weight of the burned rats by regaining the intracellular protein content in the skeletal muscles, similar to our previous results. The measured physiological parameters showed no side effects. In addition, these results also showed significant influence on wound healing on day 6. In conclusion, this study indicates that the muscle wasting can be significantly inhibited by oral administration of insulin.

1. Solomon, V., Madihally, S.V., Mitchell, R.N., Yarmush, M., and Toner, M., Antiproteolytic Action of Insulin in Burn-Injured Rats. *J. Surg. Res.* **105**: 234-242, 2002.