Gut physiology

Trophic control of the intestinal mucosa

from Jared M. Diamond and William H. Karasov

IT is a familiar fact that the mass of a muscle varies with use and disuse. Bodybuilders exploit this fact to develop particular muscles by exercising them, while conversely the muscles of bed-ridden patients or people with severed nerves atrophy. The mechanism of this trophic control is incompletely understood[1-4]. Concealed inside us is another, less familiar trophic variation: the growth and atrophy of the intestinal mucosa. Current research on trophic control of the intestine combines basic studies of hormones, transport mechanisms and cell growth with clinical studies of patients recovering from intestinal surgery.

Under what circumstances does our intestinal mucosa receive more 'exercise'? Two familiar situations are pregnancy and lactation, both of which are associated with increased calorie requirements and food intake. Intestines of pregnant or lactating rats and hamsters can absorb more glucose, amino acids, zinc, copper and iron than can intestines of control animals[5-7]. This is made possible by increased absorptive area (increased intestinal length, villus height and mucosal area) resulting from stimulation of cell division[6,8,9]. The intestine responds in a similar way to diabetes, which results in increased calorie requirements because of renal loss of glucose[10,11].

A factor common to these three conditions is increased feeding rate (hyperphagia), which may be necessary and sufficient to produce the responses. Rats induced to overeat by cold or by hypothalamic lesions also exhibit increased mucosal growth[12,13]. Restricting the food intake of lactating or diabetic rats to normal levels prevents the mucosal growth that would otherwise occur[14,15].

A clinically important instance of trophic stimulation occurs after surgical resection of a diseased intestinal segment. Humans and rats with half of the small intestine excised maintain normal growth rates and absorptive capacities because an increase in mucosal mass and villus height in the remaining intestine compensates for the loss[16-19].

When does our intestine receive less 'exercise'? Starvation is one such situation; the intestinal mucosa atrophies and absorption rates decrease. These effects are directly due to disuse of the intestine: rats nourished parenterally (that is, by intravenous infusion) for 7 days show no loss of body weight but do exhibit mucosal atrophy and reduced glucose absorption rates[20,21].

The various trophic responses of the intestine to use or disuse beg the question of the proximate signals. An intestinal cell has no direct experience of the fact that its owner is pregnant, nursing, starving, diabetic, or endowed with a surgically shortened gut.

The rat with total parenteral nutrition is a particularly convenient preparation for identifying the signals[20,22-25]. Instilling nutrients into the intestinal lumen of parenterally nourished rats reverses the atrophy. The efficacies of different sugars and amino acids can be compared in order to elucidate the relative roles of their osmotic activity, affinity for transport mechanisms and metabolism as signals. Such observations are relevant to interpreting the proximal-to-distal decrease in mucosal mass, villus size, and sugar and amino acid absorption exhibited by the normal intestine. These normal anatomical and physiological gradients parallel the gradient in nutrient concentrations along the gut and may represent 'standing gradients of trophic response' to the luminal nutrient gradient. For instance, the anatomical and physiological gradients virtually disappear along with the nutrient gradient during parenteral nutrition. When distal segments of intestine are shifted more proximally by surgical transplantation or by resection of a medial segment, their villus size and glucose and amino acid transport rates increase to the levels seen in the intestinal segment normally found at that distance from the pyloric sphincter[26].

While the trophic effect of luminal solutes is largely direct, there is also evidence for an additional indirect effect mediated by hormones and/or nerves. Some of this evidence has been obtained by surgically isolating a loop of intestine, complete with its nerve and blood supply, from the intestinal canal and rejoining the severed proximal and distal ends of the canal. Nutrients infused into the main canal of parenterally nourished rats stimulate cell growth not only in the main canal but also, more weakly, in the bypassed loop, which has no direct contact with the nutrients[20]. Similarly, amino acids infused into the distal intestine of parenterally nourished rats stimulate growth proximally as well as distally[27]. Lactating animals or ones with resected intestines exhibit cell growth and enhanced transport in bypassed loops as well as in the main canal[28-30]. When only one member of a parabiotic pair of rats undergoes intestinal resection, intestinal cell growth is stimulated in both rats[30,31]. Possible mediators of these indirect effects include nerves and various hormones such as gastrin, glucagon, enteroglucagon, cholecystokinin, secretin, insulin and prolactin[32,33]. The hormonal trophic effects on the main canal may in turn by partly mediated by the flows of pancreatic juice and bile that several of these hormones stimulate[18,20,34].

It is interesting to compare the obvious trophic effects of exercise on muscle with the less obvious effects of 'exercising' the intestinal mucosa. In both cases, at least part of the response depends on a system self-contained within the responding cell and not requiring other cells. Trophic responses of muscle can be obtained even after severing the motor nerve, by stretching the muscle or by producing muscle contraction through direct stimulation of the muscle membrane[35]. Similarly, much of the trophic response of the intestinal mucosa appears to result from direct effects of luminal solutes on the absorbing cells. However, there are also indirect effects in both systems, mediated by motor nerves in the case of muscle, and by hormones, pancreatic and biliary secretions, and possibly nerves in the case of the intestine. In both systems the details of the proximate signals and the effector mechanisms underlying trophic effects are poorly understood. They constitute one of the most challenging issues in developmental biology.   □

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