EDITORIAL REVIEW

Gut hormones and the first meals

A. LUCAS, A. AYNSLEY-GREEN AND S. R. BLOOM
Department of Paediatrics, University of Oxford, and Department of Medicine, Hammersmith Hospital, London

Introduction

The gastro-intestinal tract is a complex endocrine organ and the development of sensitive and specific plasma radioimmunoassays for many of the regulatory peptides has now made possible investigation of its hormones. Eight peptides are released from the gut and are thought to act as true circulating hormones (Bloom, 1978) (Table 1). It is clear that there are several agonists and antagonists for the diverse physiological functions controlled by gut peptides and it will be a long time before this complex integrated control system can be defined fully.

After birth dramatic physiological changes occur in the gastro-intestinal tract. The newborn infant switches from intravenous nutrition (via the placenta) to intermittent enteral feeding. During the first days of life the gastro-intestinal tract is subjected, for the first time, to considerable volumes of milk which need to be propelled through the gut, digested and absorbed. Whereas in utero circulating levels of metabolic substrates are mostly under maternal control, after delivery the infant must achieve metabolic homeostasis unaided.

The adaptation to extra-uterine nutrition involves many changes, both in gastro-intestinal function and in intermediary metabolism. These adaptations must have an environmental trigger, since a preterm infant may make a satisfactory adjustment to enteral feeding as much as 3 months 'too soon' in biological terms. Work by Widdowson, Coloombo & Artavanis (1976) in piglets and by Lichtenberger & Johnson (1974) in rats suggests that enteral feeding itself may be an important trigger for such postnatal events. These workers showed that oral feeding after birth results in marked structural changes and in growth of the digestive tract, changes which were not seen in animals deprived of enteral feeding. In addition, oral feeding has been demonstrated to enhance gut enzyme activity (jejunal lactase and acid phosphatase) in newborn piglets (Widdowson et al., 1976) and may initiate important changes in intermediary metabolism, for example the increased responsiveness of pancreatic β-cells to glucose seen in enterally fed newborn piglets (Gentz, Persson, Kellum, Bengtsson & Thorell, 1971) and rats (Asplund, 1972).

If feeding is a key factor in inducing adaptive events which equip the newborn infant for postnatal nutrition, then what is the mechanism? Evidence is accumulating that supports the hypothesis that gut hormones may play a key role in this process. Studies in animals and adult man demonstrate that these hormones can induce some of the changes which are known to occur after birth in normally fed neonates. Thus gastrin (Johnson, 1976, 1977) and entero-glucagon (Gleeson, Bloom, Polak, Henry & Dowling, 1971; Besterman, Sarson, Blackburn, Cleary, Pilkington & Bloom, 1978a; Besterman, Bloom, Adrian, Christofides, Sarson, Mallinson, Physiolo}

<table>
<thead>
<tr>
<th>Table 1. Circulating hormones of the gut</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone</strong></td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Gastrin</td>
</tr>
<tr>
<td>Secretin</td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
</tr>
<tr>
<td>Motilin</td>
</tr>
<tr>
<td>Gastric inhibitory peptide (GIP)</td>
</tr>
<tr>
<td>Neurotensin</td>
</tr>
<tr>
<td>Enteroglucagon</td>
</tr>
<tr>
<td>Pancreatic polypeptide (PP)</td>
</tr>
</tbody>
</table>

Correspondence: Dr S. R. Bloom, Department of Medicine, Hammersmith Hospital, DuCane Road, London W12 0HS.
Pero & Modigliani, 1978b) may stimulate growth of the gastro-intestinal mucosa and cholecystokinin (Mainz, Black & Webster, 1973) and gastrin (Mayston & Barrowman, 1971) may stimulate growth of the exocrine pancreas. Moreover, it is now known that plasma concentrations of several gut hormones become elevated during the early days of life. Lichtenberger & Johnson (1974) have shown in neonatal rats that feeding produced a rise in plasma gastrin after birth, and it is of particular interest that the rise paralleled the trophic changes in the gut induced by feeding. Early feeding in the calf has been shown to stimulate a substantial elevation in enteroglucagon. Rogers, Davidson, Lawrence & Buchanan (1974) demonstrated that gastrin and enteroglucagon increased during the first 4 days of life in the human neonate. These hormones have also been shown to rise after the first feed in human infants (Aynsley-Green, Bloom, Williamson & Turner, 1977; Von Berger, Henrichs, Raptis, Heinze, Jonathan, Teller & Pfeiffer, 1976). More recently it has been possible to show that there are multiple gut-hormone surges after birth in both term and preterm neonates (Lucas, Adrian, Bloom & Aynsley-Green, 1979a; Lucas, Bloom & Aynsley-Green, 1980a; Lucas, Bloom & Aynsley-Green, 1980b; Lucas, Adrian, Bloom & Aynsley-Green, 1980c).

The data in Fig. 1 refer to basal (prefeed) plasma hormone concentrations and are compared on the graphs with the mean fasting hormone concentrations in healthy adults (broken lines). In preterm infants, by day 6, there had been a highly significant three- and four-fold rise above the level at birth (umbilical cord blood) in basal plasma concentrations of neurotensin and enteroglucagon. By day 13, basal plasma motilin had risen 13-fold and gastric inhibitory peptide (GIP) and pancreatic polypeptide (PP) threefold. Plasma concentrations of all these hormones rose significantly above adult values, in the case of enteroglucagon by a factor of 10. Plasma gastrin concentrations were elevated transiently above the fasting adult level at birth and subsequently fell to adult values before the first feed at 2–6 h of age and then rose fivefold to a peak on day 6. In addition to the rise in basal hormone values during the neonatal period, cross-sectional data analysis (where each infant contributed a single plasma sample) has shown the progressive development of a dynamic response of gut peptides to feeding (Lucas et al., 1979a, 1980c; Lucas, Adrian, Bloom & Aynsley-Green, 1980d). Thus at 6 days of age in preterm infants there were no changes in plasma gastrin, enteroglucagon, neurotensin, secretin or GIP after a feed, whereas there was a significant postprandial elevation of all these hormones by day 24.

Why are the plasma concentrations of gut peptides attained in the neonatal period so high? The concentrations observed in the studies cited above were far in excess of the peak postprandial levels reported in healthy adults (Besterman, Bloom, Sarson, Blackburn, Johnston, Patel, Stewart, Modigliani, Guerin & Mallinson, 1978c). Deficient plasma-clearance mechanisms in the newborn may contribute. It is possible, however, that the most important factor explaining the high circulating gut peptide concentrations in the neonate is the finding that the gut endocrine cell mass of several peptide-producing cells increases rapidly in the late foetus (M. G. Bryant, S. R. Bloom, M. Gregor, M. A. Ghatei, A. M. J. Buchan & J. M. Polak, unpublished work). Gut hormones may thus play a unique role in the newborn. It is tempting to speculate that it is they that induce the adaptive changes in physiology associated with the commencement of feeding after birth. For example, motilin stimulates gastro-intestinal motility (Ruppin, Sturm, Westhoff, Domscheke, Domscheke, Wünsch & Demling, 1976) and enhances the rate of gastric emptying (Christofides, Modlin, Fitzpatrick & Bloom, 1979) in adult man. Could the postnatal elevation in plasma motilin contribute to the known increase in motor activity of the gut that occurs during the neonatal period (Smith, 1976)? Could the rise in plasma enteroglucagon and gastrin be important factors in the increase in gut growth in enterally fed neonates? GIP is thought to be an important stimulus to insulin release and to mediate the enteroinsular axis (Dupre, Ross, Watson & Brown, 1973; Creutzfeldt, 1979). Might not the postnatal surge in the basal GIP concentrations, together with the development of the ability to release GIP after a feed, result in the progressive enhancement of insulin release (Lowy & Schiff, 1968) and the improvement in glucose tolerance (Nakai, Hyaashi, Kanazawa & Sakamoto, 1976) described in the neonatal period? These questions certainly merit further investigations.

If the hypothesis is valid, that feeding after birth stimulates the postnatal changes described partly through the mediation of gut hormones, then it would be predicted that infants deprived of enteral feeding should show no hormone surges during this period. In a group of 10 preterm infants who, on account of hyaline membrane disease, had received only 5% intra-
Neonatal gut hormones

![Graphs showing plasma concentrations of gut hormones (pmol/l ± SEM) in preterm infants.](image)

**FIG. 1.** Postnatal surges in plasma concentrations of gut hormones (pmol/l ± SEM) in preterm infants (mean gestation 33.5 ± 1 weeks, birth weight 1950 ± 30 g), at birth (cord blood, n = 6) and at days 2.5 (n = 8), 6 (n = 10), 13 (n = 12) and 24 (n = 8). Cross-sectional data, each infant contributing to one datum point only, are shown. Broken lines show mean adult fasting values. Similar changes were seen in term infants fed by either breast or bottle. GIP, Gastric inhibitory peptide; PP, pancreatic polypeptide.
venous glucose solution for the first 6 days after birth, there was no postnatal rise (above the cord blood level) during this period in the plasma concentrations of motilin, gastrin, enteroglucagon, GIP or neurotensin (Lucas et al., 1979a, 1980b). In contrast levels of all these hormones rose dramatically by day 6 in preterm infants who had been fed orally (Fig. 1). Although the presence of hyaline membrane disease in the unfed group complicates the interpretation of the results, the study provides some evidence that enteral feeding is likely to be the triggering mechanism for the gut hormone surges seen after birth.

Thus it is possible that the dietary experience of a newborn infant may affect several aspects of postnatal maturation and is reflected in, and may be mediated by, gut hormone release. It is of interest that 6-day-old breast-fed and bottle-fed infants differ markedly not only in their basal circulating concentrations of several gut peptides (VIP, GIP, motilin and neurotensin), but also in their dynamic hormonal responses to feeding, notably with respect to the release of insulin, motilin, neurotensin, enteroglucagon and pancreatic polypeptide (Lucas, Adrian, Bloom & Aynsley-Green, 1979b). Further studies are needed to assess the possible influence of the mode of nutrition on physiological development.

Conclusions and clinical application

There is now increasing, though not conclusive, evidence that enteral feeding after birth, which stimulates surges in circulating gut hormones, may in turn induce the adaptive events that equip the newborn infant for the profound change in its mode of feeding that occurs postnatally.

The results of the studies discussed above may have implications for the nutritional management of newborn infants. For example, the low birth-weight high-risk neonate may be deprived of enteral feeding for a period of time as part of the routine management of conditions such as hyaline membrane disease. Yet it is possible that the consequent attenuation of postnatal surges in gut hormones could retard some adaptations to postnatal life. If so, could prolonged deprivation of enteral feeds result in permanent damage, such as atrophy of the gut? There is some evidence that short periods (up to 10 days) without intraluminal food in the gut, are followed by delay in obtaining gut hormone surges of normal amplitude when food is reintroduced. But what of the newborn infant who has undergone gastro-intestinal surgery for a congenital gut anomaly and who is fed solely by the parenteral route for more prolonged periods? If further study demonstrates that there is indeed a deleterious effect of withholding enteral feeding in certain sick newborn infants, then investigation is needed into the therapeutic possibility of prescribing oral feeds in tiny 'subnutritional' quantities in order to maintain the stimulus to gut peptide release. Eventually gut hormones themselves might be used to manipulate postnatal adaptive processes of sick or immature infants.

References


