THE ENDOCRINE SYSTEM OF THE GUT DURING GROWTH AND REPRODUCTION, ROLE OF EFFERENT AND EFFERENT VAGAL MECHANISMS

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Summary

The endocrine system of the gut consists of at least 20 well defined peptides. The activity of this neuroendocrine system is increased during periods of growth and reproduction. Thereby digestion and anabolic processes are optimized as a means of saving energy during such extra calorie-demanding processes. This enhanced activity seems to involve central oxytocinergic transmission and also efferent vagal nerve activation. In addition, vagal afferents transfer information from the gut to the brain e.g., as to the presence or absence of calories in this region. It is well known that satiety and sedation following a meal is in part caused by a activation of vagal afferents in part caused by gastrointestinal hormones. Also, interactive behaviours such as milk ejection and maternal behaviour can be induced by such stimulation. In contrast, when no food reaches the gut the behaviour of animals as well as the hormone profile is turned into a hunger pattern - and in addition milk production and ejection is blocked. Parts of these effects are vagally mediated, since they can be observed in vagotomized rate receiving full amount of calories. Thus, afferent vagal nerve activity is one of the factors deciding whether the metabolism becomes catabolic or anabolic but also the position in a behavioural axis ranging from hunger via satiety to altruistic behaviours, such as milk ejection and other 'giving' interactions.

At no stage of life is nutrition more critical than during growth and reproduction. Any organism needs more nutrient when it is growing than when it is not. The young of many species eat (relatively) more than adults do; the calorie intake of human infants per kilogram of body weight is more than four times that of adults. The demand for food is also high in organisms undergoing reproduction, which is often preceded by a period of increased uptake and storage of energy. So important is nutrition to reproduction that reproduction simply does not take place in the absence of adequate food.

In mammals, including human beings, most reproductive work is done by the female. Women therefore differ from men in that rather having only one major period of growth, from infancy through adolescence, they may grow one or more times as adults during pregnancy. Beginning early in pregnancy a women gain weight, storing energy as fat against the demands of the foetus and in preparation for the heavy demands that will come with lactation and breast feeding. And in human beings, too, energy intake and storage are related to the ability to reproduce. If a woman is too thin, whether because of famine, self starvation or too much physical exercise, she fails to ovulate and is rendered infertile (Frisch 1988; Uvnas-Moberg 1989a, 1989b).

Since increased nutrition is a prerequisite for growth and since food is digested in the gastrointestinal tract, the stomach and intestines need to function optimally during periods of reproduction and intense growth. One way to obtain this is by an enhanced activity of the endocrine system of the gut. Some properties of the gastrointestinal endocrine system will be described below.

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I. THE ENDOCRINE SYSTEM OF THE GATROINTESTINAL TRACT

To this point at least 20 well-defined polypeptide, hormones have been demonstrated in the gatrointestinal tract, the largest 'endocrine gland' of the body. The polypeptides are produced in endocrine cells which are located in the gastrointestinal mucosa. The apex of the cells projects into the gastrointestinal lumen, which enables the gut content to influence the release of the peptides, which occurs both into the circulation and into the gastrointestinal lumen. The release of peptides from the proximal part of the gastrointestinal tract is under nervous control as well. In principle, parasympathetic (vagal) nerve activity stimulates, whereas sympathetic nerve activity inhibits the secretion of these peptides.

Gastrin and cholecystokinin (CCK), two chemically related polypeptides (the five C-terminal amino acids, containing the biological activity are identical), are produced in the gastric antrum and in the small intestine, respectively. Gastrin is related in response to protein intake and CCK mainly in response to fat. Gastrin stimulates acid secretion in the stomach and also the growth of the gastric mucosa. CCK stimulates gallbladder contraction, the secretion of enzyme-rich pancreatic juice as well as the growth of the pancreas. The release of both gastrin and CCK is stimulated by vagal nerve activation.

Somatostatin, which was originally isolated from the hypothalamus and shown to inhibit the secretion of growth hormone from the pituitary, is present in large amounts in the gastrointestinal tract, in particular in the pancreas and in the stomach. The stomach contains two types of somatostatin-producing cells, the cells in the antrum are in open contact with the gastric lumen and are sensitive to the intragastric pH, whereas the fundic cells are without such direct contact with the gastric lumen. In fact, 90 per cent of the circulating somatostatin derives from the stomach. Somatostatin inhibits gastrointestinal secretion and motility and the release of most gastrointestinal hormones. Since gut peptides such as gastrin and CCK exert trophic effects in the gastrointestinal tract, somatostatin indirectly inhibits cellular growth and proliferation in the gut. Vagal nerve activity inhibits somatostatin release and, in contrast, sympathetic nerve stimulation and circulating catecholamines increase somatostatin levels via activation of ß-receptors on the somatostatin cells (for a more detailed review see Unvas-Moberg 1987).

II. METABOLIC EFFECTS OF GASTROINTESTINAL HORMONES

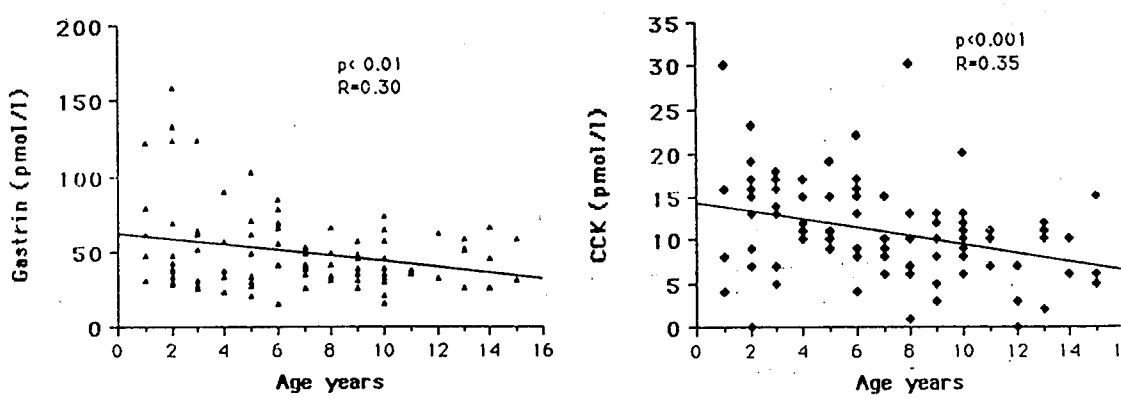
Both gastrin and CCK promote the glucose -induced insulin release. This property is shared by many other gastrointestinal hormones, such as secretin and gastric inhibitory peptide (GIP), and is called the incretin effect (Dupre 1980). The physiological role of CCK in meal-induced insulin secretion has been demonstrated in conscious rats, in which administration of specific antagonist of CCK blunted the insulin response to a meal (Rosetti et al. 1987). The incretin effect of gastrointestinal hormones at least partly explains why glucose given orally gives rise to higher insulin levels than do isocaloric i.v. glucose infusions.

Somatostatin also seems to be involved in nutrient uptake and deposition. Thus, active immunization with somatostatin or administration of somatostatin antiserum has been shown to increase growth rate in newborn rats, lambs and chicken. This effect is not mediated by growth hormone but an intact gastrointestinal tract is of importance for the effect which occurs without an increased intake of calories (Spencer et al. 1985; Spencer 1986; Spencer et al. 1986; Dubreuil et al. 1986; Bass et al. 1987). Furthermore, it has been suggested that nutrient deposition may be promoted when somatostatin levels are low (Schusdziarra et al. 1986). Thus, the gastrointestinal hormones not only take part in the digestion, but are also involved in the regulation of the postprandial metabolism of ingested food.

III. THE LEVELS OF GASTRIN, CCK AND SOMATOSTATIN ARE ELEVATED IN CHILDHOOD AS WELL AS DURING PREGNANCY AND LACTATION

The levels of gastrin, somatostatin and CCK are extremely high in newborn babies, even before the infants have had their first meal, suggesting that other mechanisms than the presence of food are responsible for the high hormone levels (Marchini et al. 1992; Uvnas-Moberg et al. 1993). In fact, basal gastrin, somatostatin and CCK levels decline up to the age of twelve at which age hormone levels equal those of grown ups. During this period, there is a strong correlation between basal levels of these hormones and age and in fact also with the rate of growth and average calorie intake (Uvnas-Moberg et al. in press) (Fig. 1). Since food by itself does not seem to be responsible for the high hormone levels at young age, a central mechanism which perhaps increases the vagal nerve tone and therapy the hormonal secretion rate may lie behind.

Figure 1. Plasma levels of gastrin and CCK in relation to age of children



In infants, the release of gastrointestinal hormones is also stimulated by the suckling stimulus. In the breastfed infant, the two components of hormone release can be clearly distinguished. Thus, a rapid peak-shaped release of gastrin and CCK ensures at the onset of breast feeding, later followed by a more protracted release of these hormones, occurring when food has reached the intestine and is being absorbed (Marchini et al. 1992; Uvnas-Moberg et al 1993). Furthermore, sucking of a pacifier alone causes increased insulin levels and when combined with tube feeding significantly reduces somatostatin release into the gastric lumen caused by the meal (Marchini et al. 1987; Widstrom et al 1988). The sucking-related endocrine affects are likely to be due to vagal nerve activation occurring in response to the sucking stimulus.

The neurogenic activation of the gut and of its endocrine system caused by sucking ought according to the discussion above contribute to growth and development of the gastrointestinal tract of the infant and consequently to an optimal digestion and to an anabolic metabolism and growth. In fact, non-nutritive sucking has been shown to induce several beneficial effects in infants. It enhances the growth rate in tube-fed premature infants without an increase in calorie intake and shortens the hospital stay. Gastrointestinal transit time is shortened and the transition from gavage to oral feeding is accelerated (Kessen et al. 1963; Kessen et al.

1967; Burroughs et al. 1978; Porter et al. 1979; Bernbaum et al. 1983; Fiels et al. 1984; Paludetto et al 1984).

It is also possible to cause vagal efferent nerve activity by somatosensory stimulation. Thus, brushing, stroking, warm temperature, vibration and other non-noxious kinds of somatosensory stimulation cause an enhanced activity in the vagal nerve and a release of gastrointestinal hormones (Fig. 2 & 3) (Uvnas-Moberg et al. 1992, in press). Also in infants massage has been shown to promote growth and maturation, in spite of an unchanged calorie intake, suggesting a better use of ingested calories. Obviously, the inborn high vagal nerve activity of infants can be reinforced by various kinds of non-noxious sensory stimulation (Uvnas-Moberg et al. 1987).

Figure 2. Plasma levels of gastrin and CCK, 0 and 60 minutes after exposure to vibration at 100 Hz for 30 minutes in anaesthetised rats.

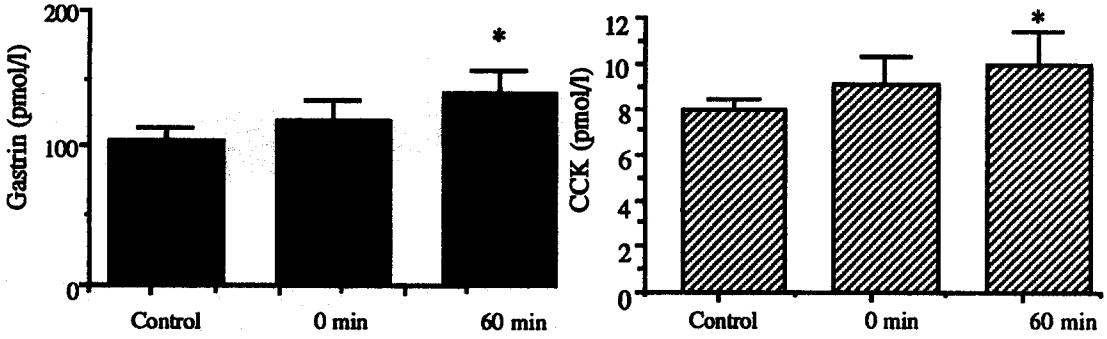
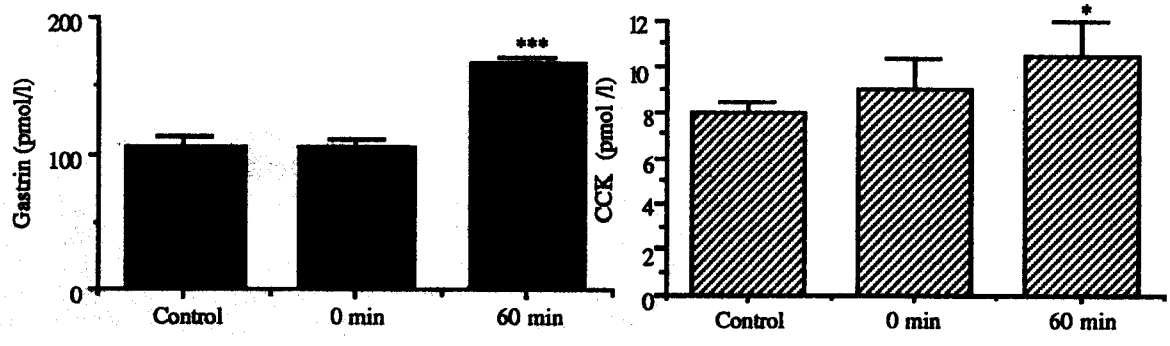


Figure 3. Plasma levels of gastrin and CCK, 0 and 60 minutes after exposure to warm temperature 40°C in anaesthetised rats.



During lactation an activation of the material gastrointestinal endocrine system occurs in response to a particular form of non-noxious somatosensory stimulation, i. e. suckling. Thus, material somatostatin levels are lowered and gastrin and CCK levels are increased in connection with each suckling period in rats, pigs, cows and dogs (Uvnas-Moberg et al. 1984; Erickson et al. 1987; Linden et al. 1987). The suckling-induced effect is mediated via an activation of the vagal nerves (effects are abolished by vagotomy) (Linden et al. 1990). In women, the levels of gastrin rise following breast-feeding, whereas somatostatin levels fall or rise (Widstrom et al. 1988a). Low somatostatin levels during breast-feeding are correlated to a

high milk yield and a long period of breast-feeding (Widstrom et al. 1988). In pigs, the fall of somatostatin levels is directly proportional to the amount of udder massage given by the piglets and as a consequence also to milk production, and prolactin, the hormone that promote milk production, is also released in proportion to the amount of udder massage (Algers et al. 1991). Thus, the capacity for energy intake and uptake is adapted to the 'losses' of energy occurring during lactation and both are related to the amount of sensory stimulation given by the piglets.

The endocrine system of the gut is changed into a 'vagal pattern' also during pregnancy. Thus, the levels of CCK are elevated during pregnancy in dogs and in women and the somatostatin levels are decreased (Linden et al. 1987; Frick et al. 1990). This hormonal pattern is induced already within a few weeks of pregnancy and is probably related to the changed levels of sex steroids, since a similar effect on the levels of these hormones is found in women taking low dose oral contraceptives (Stilber et al. 1991).

In conclusion, the levels of gastrointestinal hormones are related during periods of growth in children and also during pregnancy and lactation. It is important to state that the changes in hormone levels per se are of functional importance because they do contribute to stimulation of growth. In addition, they are reflections of a major change of endocrine balance and of autonomic nervous tone aimed at promotion of nutrient assimilation and storage.

IV. MECHANISM BEHIND ELEVATION OF GATROINTESTINAL HORMONES DURING PERIODS OF INTENSE GROWTH OR REPRODUCTION

As mentioned before, it is likely that ingested food is not alone responsible for the high levels of gatrointestinal hormones in the 'growth situations' and we have postulated that an increased vagal tone may be involved. But through which mechanisms in CNS is this accomplished? Several hypothalamic peptidergic projections such as CRF (corticotropin-releasing factor), TRF (thyroid hormone-releasing factor) and also oxytocin reach the vagal motor nucleus from which the vagal nerve activity is controlled. CRF and TRF have been shown to influence vagal nerve activity in stressful situations (Tache et al. 1991). Since oxytocin is of major importance during reproductive behaviours and oxytocin levels rise in response to suckling and are elevated during pregnancy we have concentrated our studies around this peptide (for a review on oxytocin see Richard et al. 1991).

Oxytocin is a nonapeptide in the supraoptic and paraventricular nuclei. In addition to being released from the neurohypophysis into the circulation, oxytocin-containing neurons emanating from the paraventricular nucleus project to many areas of the brain including the vagal motor nuclei in the brain stem (Sawchenko and Schmid 1985). We have studied the influence of oxytocin on the release of gastrointestinal hormones and found that depending on the dose level entirely different effects can be obtained. When small amounts (2-20 ng) of oxytocin are given intracerebroventricularly (i.c.v.) to conscious rats, blood levels of CCK and gastrin decrease. In contrast, in response to similar doses of the oxytocin antagonist 1-deamino-2-D-Tyr-(OET)-4-Thr-8-Orn-Oxytocin, specific for the uterine oxytocin-receptor, the levels of gastrin and CCK rise. If instead 1000 - fold higher doses of oxytocin are administered or even given intraperitoneally (i.p.), CCK levels rise. This effect is not blocked by the oxytocin antagonist shown to inhibit the effect exerted by oxytocin in low amounts.

Indirect support of a role for oxytocin in suckling-induced rises of maternal gastrointestinal hormone levels are our findings showing that lesions of afferent projection to the oxytocinergic neuron in the midbrain is accompanied not only by a loss of milk ejection but also of the rise of gastrin and CCK levels (Linden et al. 1990). The suckling-related release of maternal CCK is not blocked by the oxytocin antagonist mentioned above, suggesting that this effect corresponds to the high dose effect of oxytocin.

During pregnancy oestrogen may increase the oxytocin release and consequently induce an enhanced vagal activity. This latter hypothesis is supported by the finding that low

dose oral contraceptives give rise to increase oxytocin levels in humans and also to lowered somatostatin levels (Silber et al. 1987; Silber et al. 1991). By what mechanism gastrointestinal hormone levels are kept high in infants and children is not known but could hypothetically be caused by an oxytocinergic activation of vagal centres, since oxytocin levels are elevated in childhood (Alfven et al. submitted).

V. ROLE OF VAGAL AFFERENT NERVE ACTIVITY

As discussed above, an organism needs nutrient when it is growing and several physiologic adaptations help the organism to ascertain that ingested calories are used in an optimal way. However, since growth requires calories, growth cannot simply occur if the supply of nutrients is too small. Since there is a limit to when growth and its extension reproduction can occur, the controlling systems in the brain that regulates these functions must be continuously informed about the nutritional status. The endocrine system of the gut plays an important role in this respect too, since it signals to the brain via afferent vagal nerves whether calories have been ingested or not.

(a) Effects on metabolism

We have recently performed experiments to show how afferent vagal nerve activity influences the levels of metabolically active hormones. When CRF, a stress related peptide, is given i.c.v. to anaesthetized rats, somatostatin levels increases if the animals have been fed recently but not if the animals have been food-deprived for 24 hours (Smedh et al. submitted). No somatostatin increase is observed in fed, vagotomized animals. We can therefore conclude that the response caused by CRF is modified by impulses from the gut mediated by afferent vagal nerve activity.

In another series of experiments performed on lactating rats, we found that the suckling-induced release of gastrointestinal hormones is dependent on the state of feeding. Normally a release of somatostatin is seen in response to suckling but if the rats have been food deprived for 24 hours, a decrease is seen, suggesting that when afferent impulses from the stomach signalling the presences of calories are lacking, the peripheral stimulus is differently handled and is transformed into a metabolic pattern which is suitable for food deprivation (Ericsson et al. submitted). From a functional point of view this means that by lowering somatostatin levels an extremely economical handling of calories is induced, since when somatostatin levels are low, nutrient assimilation is favoured.

(b) Effects on behaviour

It is well known that during feeding vagovagal reflexes are elicited which contributes to the control of the digestive process. However, vagal mechanisms also transfer information to higher centres of the brain. Since i.p. administration of CCK causes satiety in rats, an effect which is blocked by vagotomy (Smith et al. 1984), it has been suggested that ingested food causes a release of CCK, which then binds to receptors in the stomach or on the vagal nerves and thereby causes activation of vagal afferent fibres. Consequently, hypothalamic centres are 'informed' and food intake is reduced. Oxytocinergic mechanisms seem to be involved in the satiety effect, since the satiety effect caused by i.p. administration of CCK is abolished by administration of oxytocin antagonist (Olson et al. 1991). In support of this, it has recently been shown by C-fos technique that oxytocinergic and CRF neurons in the paraventricular nucleus

(PVN) are activated in response to feeding (Verbalis et al, 1991). The same type of activation of the PVN can be mimicked by CCK given i.p. to conscious rats.

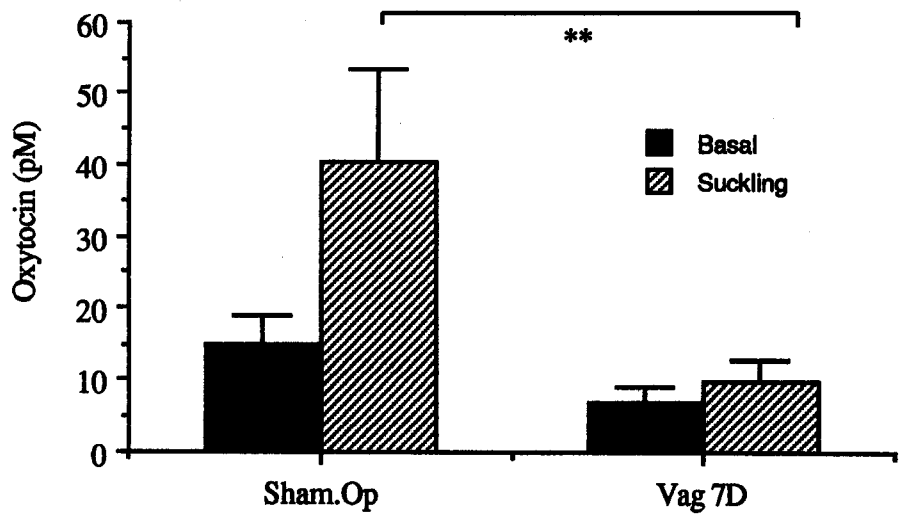
It is, of course, very logical that the presence of calorie in the gut should have an influence on satiety. But in addition to satiety both food intake and i.p. injections of CCK cause sedation (Mansbach et al. 1983). Again this could be an oxytocin-mediated behaviour, since i.p. injections of high amounts of oxytocin cause sedation (Uvnas-Moberg et al. 1992).

If normal conscious rats are vagotomized, their behaviour is changed. Thus, in spite of eating normally the animals tend to show a higher degree of explorative behaviour than do unoperated rats, suggesting that the lack of satiety signals from the gut somehow influence the behaviour in a chronic way (Uvnas-Moberg et al., in preparation).These results support the view that the vagal nerves continuously transfer information from the gut to the brain, which influences behavioural activity.

(c) Effect on lactation performance

In order to study the role of the vagal nerve activity for lactation performance, lactating rats were vagotomized. These vagotomized rats did not loose more weight than sham-operated controls and continued to suckle their offspring. However, after seven days the vagotomized animals in spite of eating normally failed to give milk to their offspring which stopped growing (Ericksson et al. submitted). The basal oxytocin and prolactin levels were found to be lowered in comparison to controls and reduced amounts of oxytocin and prolactin were released in response to suckling (Fig. 4).

Figure 4. Plasma levels of oxytocin before and after suckling in sham operated and vagotomised (7 days after) lactating rats.



In this situation it seems that a tonic influence from the gut which sustains the activity in the oxytocin neurons has been lost. Consequently, oxytocin secretion diminished and a loss of the milk ejection reflex occurred. Again, these data can be interpreted in a functional way. There should, of course, be a continuous information from the gut, telling the oxytocin system that food is available. If so, it is possible to give calories to the litter as milk but if not, the calories had better stay within the mother. Obviously, vagotomy mimics starvation in the sense that no reports on intake of calories reach the brain. Following vagotomy, the mother actually

gives up her litter in favour of creating a new one later on when presumably food supply is richer.

The presence of this close connection between vagal nerve function and lactation performance has also been confirmed in experiments performed on pigs. In this species, both the oxytocin and the prolactin secretion in response to suckling is dependent on the state of feeding. Prolactin levels, for example, completely fail to respond to suckling after 24 hours of food deprivation. If then food is given, not only do basal prolactin levels rise within minutes. the suckling-related release of prolactin is also restored (Rojkittikhun et al., submitted). Thus, it seems to be a general mechanism in mammals to link food intake with milk production not only as a direct consequence of the presence of calorie or nutrients in the circulation but in addition by means of neutral information from the gut.

Lactating rats not only give milk to their offspring, they also take care of their young, i.e. they exhibit a maternal behaviour. Administration of oxytocin has been shown to induce maternal behaviour in oestrogen-primed rats (Argiolas et al. 1991). We have recently been able to show that also i.p. injections of CCK can induce maternal behaviour in oestrogen-primed rats (Linden et al. 1990b). Thus, not only milk production, but also a 'giving' interactive behaviour is promoted by the presence of calories in the gut - a situation mimicked in the present study by an injection of CCK.

VI. CONCLUSION

In conclusion, we have shown that afferent vagal mechanisms not only influence gastrointestinal motility and secretion as well as appetite as shown before, they also influence behaviour, endocrine patterns and reproductive behaviour. Obviously, the presence of calories in the gut has an enormous impact on brain function. It is not surprising that these effects are most easily demonstrated in lactating animals when the calorie intake is so crucial. However, similar but less apparent effects are likely to operate also during other circumstances.

That the presence or absences of food has an enormous impact on human behaviour is well known or as elegantly expressed by Brecht 'Erst kommt das Fressen dann die Moral' -or as Shakespeare puts into Julius Caesar's mouth 'Let me have men about me that are fat; /Sleek-headed men and such as sleep o'nights; /Yond Cassius has a lean and hungry look; /He thinks too much: such men are dangerous'.

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