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The Developmental Physiology of the Stomach: Possible Contributions to the Regulatory Disturbances of Duodenal Ulcer Disease (41777)

SIGURD H. ACKERMAN

Department of Psychiatry, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York 10467

Abstract. Several different disturbances in the regulation of acid secretion have been found in persons with duodenal ulcer disease (DU). This paper examines the possibility that some of these regulatory disturbances might arise during postnatal development. The regulation of acid secretion is not fixed in adult form at birth, in either animals or humans. Instead, these regulatory processes continue to change during postnatal development. Examples are developmental changes in the responsiveness of the stomach to parietal cell stimulants and developmental increases and decreases in basal and maximal acid output. The unfolding of these developmental changes requires complex regulatory adjustments. It is possible that untoward environmental circumstances could induce "errors" in these regulated changes or adjustments. Some errors might persist as disturbances in the regulation of acid secretion seen in patients with DU.

Human duodenal ulcer disease is probably a heterogenous group of disorders in the sense that, presumably, many different sets of pathophysiologic processes can contribute to the occurrence of the ulceration (1). There is currently no form of DU for which the pathogenesis is fully understood. However, the occurrence of DU implies some disturbance in the normal regulation of gastric and/or duodenal physiologic functions.

In recent years a number of such physiologic regulatory disturbances have been found in patients with DU (2). Many DU patients (30–40%) have a higher than normal maximal acid output and some have a high basal output. Several different disturbances in the regulation of acid secretion have been characterized in patients with DU. These include an increase in food-stimulated release of gastrin and acid, a decrease in the ability of acid to inhibit the food-stimulated release of gastrin and acid, an increase in the sensitivity of parietal cells to secretagogues and an increased parietal cell mass. Pepsin release is increased in DU, as is Pepsinogen I (in about 40% of patients). Gastric emptying also tends to be increased.

None of these disturbances occur in all patients with DU and some occur only in relatively few. Their relevance to pathogenesis is unclear and one or more of these regulatory disturbances may have no pathophysiologic significance.

However, for the purpose of this discussion I would like to make the plausible assumption that some of these gastric regulatory disturbances can contribute to the pathogenesis of DU. I would then like to ask another question, which is: how do they get there?

The discussion here will be limited to the regulation of acid secretion. It is very likely that these various disturbances in the regulation of acid secretion result from very different kinds of processes. For example, elevated serum pepsinogen I is under genetic control and is inherited as an autosomal dominant trait (3). For persons with this trait, increased pepsin release, increased parietal cell mass, and an increased rate of acid secretion would be anticipated correlates.

Under other circumstances, the increased parietal cell mass or altered regulation of acid secretion might be state-dependent responses to external stimuli mediated through the central nervous system. There is experimental evidence suggesting that such state-dependent responses are possible. For example, in cats electrical stimulation of the anterior hypothalamus produced hyperplasia of the gastric mucosa, including an increase in parietal cell populations (4). This effect is prevented by vagotomy. In rhesus monkeys, low-level electrical stimulation of the anterior hypothalamus produced an increase in the acid secretory response to submaximal doses of histamine, but

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did not change basal or maximal secretory responses (5). The increased sensitivity to histamine was reversed by stopping the hypothalamic stimulation.

In this discussion I would like to examine another possibility, which is that some of the regulatory disturbances of DU occur neither because they are genetically controlled traits nor because they are state-dependent responses to other factors. Rather, some of the regulatory disturbances found in persons with DU might arise during postnatal development. The regulation of acid secretion is not fixed in adult form at birth, in either animals or humans. Instead, these regulatory processes continue to change during postnatal development in patterns that have only recently been partially characterized.

The unfolding of these developmental changes requires many complex regulatory adjustments. It is possible that untoward environmental circumstances could induce "errors" in these regulated changes or adjustments. Some errors might persist as disturbances in the regulation of acid secretion seen in patients with DU.

This notion of a developmental error in physiologic regulation is borrowed from Sir Archibald Garrod's concept of an inborn error of metabolism (6). Garrod postulated that a heritable "defect" could be expressed at birth as a missing or relatively inactive enzyme, critical for a specific metabolic step. More recently we have become familiar with the idea that there is a postnatal development of phenotype, not fixed at birth, the normal expression of which is regulated through interaction with environmental stimuli (7).

I will show that the postnatal development of phenotype applies also to the regulation of acid secretion. I will indicate how certain external circumstances, if powerful enough and if directed at specific developmental branch points, might permanently alter the final phenotypic expression of the regulation of acid secretion.

There is beginning to be evidence in humans to support this speculation; but most of the data come from animal studies. In our laboratory we have studied the developmental physiology of the rat stomach. We have been interested in characterizing the normal ontogeny of the regulation of acid secretion, and the patterns of proliferation of the mucosal cells during development. Our objective is to produce, experimentally, regulatory disturbances in the adult rat which are analogous to those seen in DU patients. We have not yet produced the animal models of these putative developmental disturbances of regulation. But we have indications that such models are feasible. In what follows I will describe some of the relevant observations.

(i) There are developmental changes in the responsiveness of the stomach to parietal cell stimulants and H-2 receptor blockers.

(ii) There are regularly occurring large increases and decreases in basal and maximal acid output during development.

(iii) A specific intervention during development, premature weaning, can produce long-lasting disturbances in the relationships among systems which regulate acid secretion.

The Ontogeny of Gastric Acid Secretion. *1. Responsiveness to stimuli.* In studying the ontogeny of acid secretion in the rat we first tried to determine the basal acid output (BAO) and maximal output (MAO) in young rats at various ages, beginning with postnatal Day 15. We arbitrarily chose to use histamine diphosphate as the secretory stimulant. In this and the other experiments described in this section we studied Wistar-derived rats under pentobarbitol anesthesia (5 mg/kg, Day 15) or urethane anesthesia (5 mg/kg, older rats). H^+ secretion was determined by continuous saline perfusion of the innervated gastric lumen; samples of the perfusate were collected every 10 min and each sample was automatically titrated to pH 7.0 with 0.01 *N* NaOH. Histamine (and later, other drugs) was infused through a jugular cannula. Rectal temperature was maintained at 35.5 ± 0.5°C by external regulation.

We found that, in 15-day-old rats, an intravenous infusion of histamine (2–12 mg/kg/hr) did not produce a statistically significant increase in acid output beyond the basal output. By Day 21, histamine produced a four to five fold, highly significant increase in H^+ secretion (8). In contrast to histamine, both pentagastrin and the cholinergic stimulant bethanechol produced marked increases in acid secretion in 14- to 16-day-old rats (Table I).

These findings seemed to indicate that pentagastrin and a cholinergic agonist can stim-

TABLE I. EFFECTS OF THREE SECRETAGOGUES ON ACID OUTPUT IN 2-WEEK-OLD RAT PUPS

Substance	Dose	N	Acid output	
			Basal	Stimulated
Histamine	8 mg/kg/h	10	7.62 ± 1.94	10.06 ± 0.61[a]
Pentagastrin	120 μg/kg/h	14	6.78 ± 0.81	23.0 ± 0.3[b]
Bethanechol	1 mg/kg/h	8	5.14 ± 0.7	27.1 ± 4.58[b]

Note. Values (microequivalents per hour) are means ± standard erorrs.
[a] $P > 0.10$, analysis of variance (8).
[b] $P < 0.01$.

ulate acid secretion at a time during development when histamine does not stimulate acid and, perhaps, that the nonhistamine agonists stimulate independently of the actions of histamine. We therefore attempted to verify this initial set of observations.

Histamine affects both H-1 and H-2 receptors, although only H-2 receptors are found on parietal cells. In order to eliminate possible confounding effects of histamine on H-1 receptors (e.g., affecting blood flow) we tested the response to impromidine, which selectively stimulates H-2 receptors.

In 13- to 14-day-old pups (24 to 29 g), impromidine (0.9 μmole/kg/hr) did not differ from saline in stimulating H^+ secretion. However, in the same rats, infusion of pentagastrin (120 μg/kg/hr) produced a fourfold increase in acid secretion (Fig. 1). In 16 additional rats of this age, impromidine infused through a dose range of 0.09 to 9.0 μmole/kg/hr produced no consistent differences in H^+ secretion, indicating that the lack of responsiveness is independent of the dose. Infusion of impromidine and pentagastrin in 6 rats did not potentiate the response to pentagastrin.

If pentagastrin-stimulated acid secretion is truely independent of H-2 receptor activation at this age then it should not be changed by the presence of an H-2 receptor antagonist. To test this possibility eight pairs of 13- to 14-day-old littermates (24–29 g) were infused with pentagastrin (120 μg/kg/hr).

At the time of maximum acid secretory response, cimetidine (6 μmole/kg) or saline was injected by intravenous bolus. Cimetidine, an H-2 receptor antagonist, did not inhibit pentagastrin-stimulated acid secretion under these conditions. In an additional four pairs of littermates, 12 μmole/kg of cimetidine also did not differ from saline in its affect on pentagastrin stimulation.

If one studies rats younger than 12 days then neither pentagastrin nor bethanechol are stimulants to acid secretion. By the fourth postnatal week, the parietal cell is responsive to pentagastrin, bethanechol, and histamine and to the potentiating effects of their interactions. Thus, in the rat, there appears to be an orderly developmental progression in the responsiveness of the parietal cell to gastrinergic, cholinergic, and histaminergic agonists (8).

We do not know whether environmental or behavioral factors can intrude upon this orderly progression to produce enduring disturbances in the regulation of acid secretion. We do know that antral gastrin (9) and gastrin receptor binding (10) in the fundus both rise rapidly to adult levels in the rat at the time of weaning (i.e., during the gradual shift from a milk to a solid food diet). This rapid rise can be delayed or attenuated if the onset of weaning is delayed (9, 10).

The long term consequences of such a delay, if any, are not known. One can speculate that it might produce a compensatory increase in the availability of, or parietal cell sensitivity to, other agonists or antagonists. Such shifts in processes regulating acid secretion if persistent could look, in the adult, like some of the regulatory disturbances found in patients with DU.

In humans, too, there appears to be a postnatal ontogeny in the regulation of acid secretion, and if there is a normal course it has the potential for becoming disturbed.

During the neonatal period and early in-

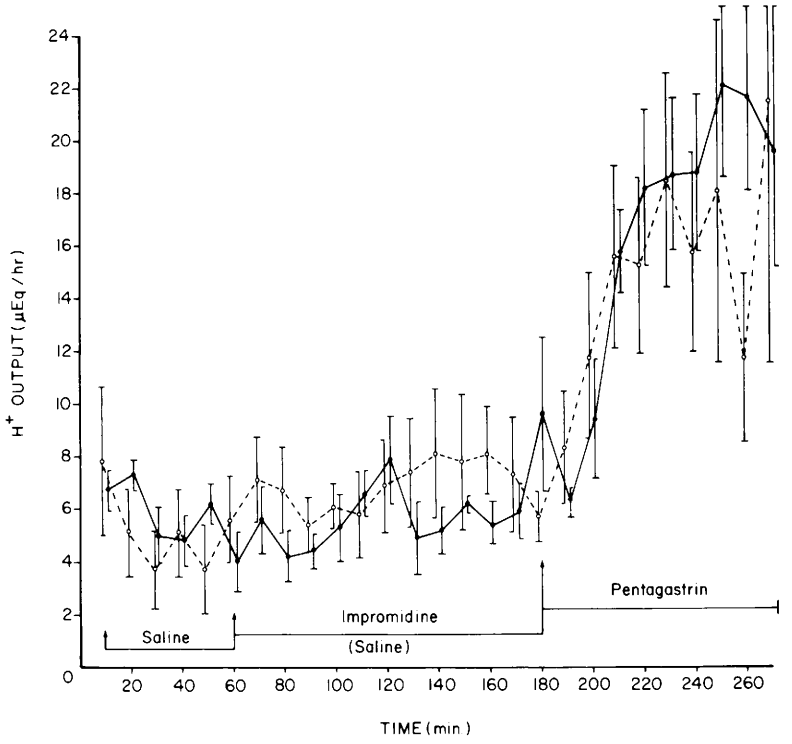

FIG. 1. Effects of impromidine (0.9 μmole/kg/hr) and pentagastrin (120 μg/kg/hr) on H^+ secretion in 13- to 14-day-old rat pups. Rats received saline (solid line; $N = 8$) or impromidine (dashed line; $N = 8$) during the second and third hours of gastric perfusion. Thereafter, all rats received pentagastrin. The effect of pentagastrin is significantly different from that of saline ($P < 0.0001$, analysis of variance), but the effect of impromidine is not.

fancy acid secretion probably occurs first in response to vagal stimulation, then to gastrin, and last to histamine. Neonates can increase acid secretion significantly over basal in response to food, a response which is probably vagally mediated (11). However, for the first 48 hr of life there is a low basal rate of acid secretion despite a high serum gastrin (12), and the low basal rate does not increase in response to exogenous pentagastrin (13). A secretory response to betazole does not occur until after the fourth week of life (14). These data are less rigorous than the animal data, but they are consistent with them; the same principles of normal and abnormal development could apply to both.

2. The ontogeny of basal and maximal acid output. One is familiar with linear, curvilinear or sigmoid-shaped curves representing age related changes in various measures. In the rat the increase in body mass and stomach mass is linear from about Day 15 to 200 (approximately 30–400 g). The increase in rat gastric histidine decarboxylase activity or antral gastrin is approximately sigmoid-shaped.

Thus, it is typical for serial measures obtained during postnatal development to go from low to high, from less to more, as the animal grows from infancy to adulthood. However, measures of some functions do not follow this pattern. An example is the change in the rate of acid secretion. We determined basal acid output (BAO) and maximally stimulated acid output (MAO) at three different ages: Days 15 (1 week preweaning), 30, and 100.

We obtained MAO separately from six different acid secretory stimulants. These included pentagastrin (120 μg/kg/hr), bethanechol (1 mg/kg/hr), histamine diphosphate (8 mg/kg/hr), impromidine (0.9 μmole/kg/hr), pyloric ligation (4 hr), and low ambient tem-

perature (core temperature reduced to 29°C). All of the data were collected from anesthetized, lumen-perfused rats as described in the previous section (except that, following pyloric ligation, the rats were conscious and gastric secretion was collected after 4 hr).

We found that both BAO and MAO increase through the first 4 weeks of life. Then, between postnatal Days 30 and 100 there is a 50% *decrease* in BAO and a two- to eightfold *decrease* in MAO/unit stomach weight (the effect size depending on the secretory stimulant used). We found that this pattern of age-related changes in MAO occurred regardless of which of six secretory stimulants we used (15). Table II shows the pattern of response to the six secretory stimulants.

We do not yet know the mechanisms which regulate these developmental changes in acid secretion. We do know, from other studies in our laboratory (with D. M. Jacobs) (16), that these developmental changes in BAO and MAO do not correspond to changes in parietal cell size, number or density, i.e., to parietal cell mass. Other possibilities are that:

(i) The availability of any of the three endogenous secretagogues (histamine, acetylcholine, and gastrin), or secretory inhibitors (such as somatostatin), may have a corresponding increase and decrease over developmental time. However, neither gastric mucosal histamine (17) nor whole stomach histidine decarboxylase (18) show this relative increase in 30-day-old rats; nor does antral gastrin or gastrin binding (10). The developmental course of gastric cholinergic activity is not known.

(ii) Parietal cells in 30-day-old rats may have relatively greater sensitivity to secretagogues or insensitivity to inhibitors of parietal cell activity.

(iii) A higher percentage of histologically identifiable parietal cells may actually be secreting H^+ in 30-day-old rats than in 100-day-old rats.

(iv) There may be relatively greater tonic vagal activity in 30-day-old rats, accounting for both the higher BAO (directly) and the higher MAO (indirectly, by potentiating the effects of noncholinergic secretagogues).

(v) The H^+ secretory capacity of individual parietal cells may not be the same at all ages.

TABLE II. MAXIMAL ACID OUTPUT AT THREE DIFFERENT AGES[a,b]

	Day		
	15	30	100
Pentagastrin	76.4 ± 6.0 (47)[c]	174.6 ± 23.1 (14)	29.8 ± 5.2 (16)
Bethanechol	93.7 ± 11.6 (10)	156.5 ± 19.3 (8)	19.5 ± 2.7 (6)
Histamine	31.2 ± 4.8 (10)	158.8 ± 23.0 (10)	74.4 ± 10.4 (15)
Impromidine	53.5 ± 7.6 (9)	277.4 ± 46.3 (6)	21.4 ± 3.8 (5)
Cold	9.5 ± 2.0 (10)	163.1 ± 13.8 (15)	38.6 ± 11.6 (10)
Pyloric ligation	23.6 ± 4.5 (11)	125.3 ± 12.0 (31)	37.0 ± 9.7 (18)

[a] H^+ output in μeq/hr/100 g body weight (means ± SEM). Body weight is used for convenience since body weight and fundic weight are highly correlated across ages ($r = 0.948$, $P < 0.001$) (24).

[b] For each stimulus, all differences between ages are significant at $P \leq 0.05$ (analysis of variance with post hoc comparisons).

[c] (N) = number of animals.

The relevant point here is that there is a presumably regulated increase and then decrease in BAO and MAO during postnatal development. One could speculate that an "error" or disturbance in the process of down-regulation after Day 30 could produce rats with a persistently elevated BAO and MAO—analogous to the secretory status of some patients with DU.

There are indications that increases and decreases in the rate of acid secretion also occur during postnatal development in humans (12, 14, 19, 20), although the data from several studies are not sufficiently systematic or consistent with each other to allow one to characterize these changes with any confidence. What is likely is that there *are* developmental changes in the rate of acid secretion in humans.

In the context of this discussion, a further question is whether specific environmental factors can influence these normal developmental changes. Parenteral nutrition for example, transiently decreases basal and pentagastrin-stimulated acid secretion in infants and children; normal acid output returns when the children resume enteral feeding (21). It is

possible that such interventions at a critical juncture or over a critical interval of development could produce permanent effects on basal or maximal acid secretion.

To put it yet another way, I am describing a developmental *strategy* for trying to understand certain pathophysiologic phenomena observed in adult patients with DU (and other disorders). Obviously, not all abnormal physiologic processes seen in DU patients result from warps and biases arising during postnatal development. Perhaps none do, but some may.

If this argument is tenable one ought to be able to show in the animal laboratory that developmental errors of physiologic regulation can be induced. One such disturbance is illustrated next.

3. The timing of developmental interactions. In the preceding sections the emphasis has been on quantitative changes and linear relationships in normal development—an increase in vagal tone over the first 4 postnatal weeks might produce an increase in the rate of acid secretion. It is possible that pathologic states could result from disturbances of these quantitative changes. But there are other kinds of developmental disturbances which could also produce pathologic states. There could be disturbances in the *timing* of changes among several interacting sets of processes—changes which normally are coordinated.

An example comes from the study of experimental gastric erosions. A rat's susceptibility to restraint-induced gastric erosions (RGEs) normally changes with age so that, under specifiable conditions, about 10–20% of 30-day-old rats develop RGEs as compared to about 60% of 200-day-old rats. (In our laboratory the conditions are 24 hr of food deprivation followed by 24 hr of restraint at 22°C.) If rats are weaned from their mothers 1 week early, on postnatal Day 15 instead of Day 21, then by Day 30 about 90% of the rats subjected to restraint will develop RGEs. This effect of early weaning persists beyond 100 days of age (22).

Early weaning also produces a "latent" disturbance in temperature regulation. Rats are poikilothermic through the first two weeks of life, but in the third and fourth weeks they develop stable mechanisms for homeothermic temperature control. Under ordinary laboratory conditions early weaned rats also appear to regulate body temperature normally in the third and fourth weeks. But during food deprivation and restraint these regulatory mechanisms fail; the rats become markedly hypothermic, with core temperature often falling below 30°C. The available evidence is that this latent disturbance in temperature regulation probably reflects a delay in normal maturation of the relevant control systems, a delay which is induced by early weaning (23).

We found that this disturbance (or delay) in temperature regulation is closely connected with the increased vulnerability to RGEs of early weaned, 30-day-old rats. The extent of the fall in core temperature is highly correlated with the severity of the erosions (estimated as total lesion length/rat) and accounts for 62.4% of the variance in severity. If 30-day-old, early weaned rats are restrained at a high ambient temperature (30°C), so that the restraint-induced hypothermia is prevented, the excess occurrence of RGEs is prevented also. Conversely, if normally weaned, 30-day-old rats are restrained at an ambient temperature of 17°C, which is just low enough to elicit hypothermia during restraint, then these rats develop RGEs at the rate of early weaned rats (23).

In a separate series of studies we unexpectedly observed that a fall ambient temperature is a potent stimulus to acid secretion (24). In conscious, lightly restrained rats, a change in ambient temperature from 22 to 10°C produces a two to threefold increase in acid secretion, (Fig. 2), which is nearly comparable to the maximal response to pentagastrin. We found that this increase in acid secretion occurs even if the gastric temperature is held constant experimentally and core temperature remains normal.

It is possible, although not yet demonstrated, that the vulnerability of 30-day-old, early weaned animals to RGEs is linked to their temperature instability through the mechanisms of a cold-stimulated increase in acid secretion during restraint.

This formulation is consistent with other developmental observations. Cold is not a stimulus to acid secretion in 15-day-old rats. Accordingly, restraint does not induce gastric erosions in rats of this age although they almost always become hypothermic during restraint.

One can speculate that the problem with

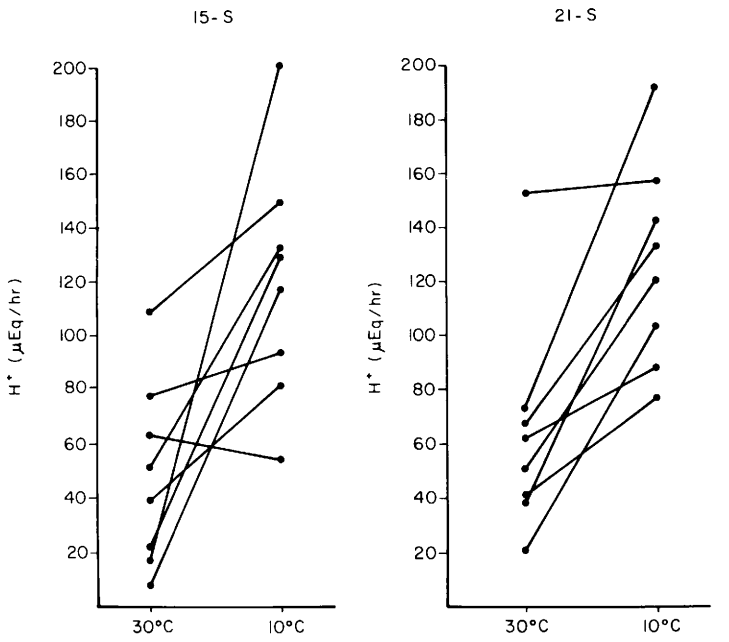

FIG. 2. Acid output for individual rats obtained initially at an ambient temperature of 30°C and then at 10°C. Temperature of the gastric lumen in each rat was maintained at 36°C. Prematurely weaned (15-S) rats show a similar magnitude of acid output and direction of change in response to the change in ambient temperature.

early weaned, 30-day-old rats is that their acid secretory response to cold has developed normally, whereas their control over body temperature regulation has not.

Thus, normal 30-day-old rats will increase acid secretion and develop RGE's if they become hypothermic, but they are very unlikely to become hypothermic. Normal 15-day-old rats are very likely to become hypothermic but the hypothermia does not stimulate acid secretion and these rats are very resistant to RGE formation. The prematurely weaned, 30-day-old rats have a normal development of acid secretory responses but a retarded ontogeny of stable body temperature regulation. When this thermoregulatory instability is elicited by food deprivation and restraint the early weaned rat is very likely to become hypothermic, have increased acid secretion and develop RGEs.

In this formulation, nothing is quantitatively abnormal. Instead, the important consideration may be that there is a disturbance in the normal developmental synchrony between interacting systems, one of which develops on time and the other of which is late. As a consequence, the regulation of acid output is affected rather than the integrity of the secretory response per se.

The main point is that a developmental circumstance—premature weaning—intrudes on normal physiologic ontogeny to produce effects both on the regulation of acid secretion and on the animals' vulnerability to RGEs. Gastric erosions in the rat are very different from human DU. Yet it is worth considering that, in human life, circumstances of development might also have an effect on the maturation of acid secretory mechanisms and other gastroduodenal processes, with potential long-term consequences for the pathogenesis of disease.

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