REVIEW ARTICLE

The Link between Pyloric Stenosis of Infancy and Duodenal Ulcer in Adults

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ABSTRACT

The similarities and differences between pyloric stenosis of infancy and duodenal ulcer are discussed in terms of pathogenesis. In both conditions, hyperacidity plays a key role by causing repeated pyloric sphincter contraction. In the neonate, an immature negative feedback between acid and gastrin creates a temporary developmental peak acidity at the time when symptoms begin. In both the conditions, gastric holdup provokes further hyperacidity. Prostaglandins, locally secreted in response to hyperacidity, may also act to cause sphincter contraction. It is argued that both the conditions are different presentations of an inherited enlarged parietal cell mass.

Key words: duodenal ulcer, etiology, neonatal hyperacidity, pyloric stenosis of infancy

INTRODUCTION

Our sophisticated technical world uses controlling negative feedback mechanism. An engine becomes overheated, and cooling mechanisms - the negative feedback response - are triggered.

Biological systems naturally have always been ahead of the game. With too much thyroxine, for example, the secretion of thyrotropic-stimulating hormone is depressed and rising thyroxine levels are brought under control. Most hormonal syndromes are similarly controlled.

The control of gastric acid secretion is another case in point. If there is hyperacidity, the level of gastrin secretion falls, and thus, the acid secretion falls. Gastrin then rises, acidity increases and so on. By such means, acid secretion is controlled.[1] Claude Bernard, the architect of the constancy of the internal milieu (homeostasis), knew what he was talking about!

The first part of the duodenum is vulnerable to acid damage. It is here where negative feedback begins.

There are three main negative feedback mechanisms when duodenal hyperacidity occurs:

- The pyloric sphincter contracts when the duodenum is dangerously acid. Further acid entry to the duodenum is prevented.[2]
- Gastrin, the hormone responsible for acid secretion, falls and somatostatin, the hormone responsible for lowering acid secretion, rises.[1]
- Prostaglandins (PGs) are locally secreted from the stomach and reduce acid secretion and also probably cause sphincter contraction.[3,4]

The duodenal acid sensing systems which trigger this protection reside at the mucosal and submucosal level. They function through neural and hormonal mechanisms.[5]

Acid secretion uses up energy intensely and requires regulation. Direct sensing and indirect sensing using mediators are involved.[1] A luminal pH <3 inhibits acid secretion, and at pH 1.0, further acid output is completely abolished.[1]

The major indirect mediator of inhibition is the hormone somatostatin from D cells which, through paracrine (local diffusion) and endocrine pathways, inhibits parietal cell function both directly and indirectly through reduction of gastrin secretion.[6]

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The stimulus which releases somatostatin may be calciotonin gene-related peptide (CGRP) secreted from nerve terminals in response to acid exposure.[5]

PYLORIC SPHINCTER CONTRACTION

The strategy of acid-induced intermittent pyloric contraction[2,7] restricts hyperacidity to the more resistant stomach mucosa. The repeatedly contracting sphincter is particularly prone to develop hypertrophy due to the gastrointestinal growth effect of neonatal hypergastrinemia[8] coupled with the appetite-fuelled frequency of feeding in the first few weeks of life.

Pyloric stenosis (PS) babies, like their adult duodenal ulcer (DU) counterparts, have hyperacidity which, by continuing after successful pyloromyotomy,[5a,6a,7] reveals that it is not due to retained acid secretion. Since PS may be created in normal puppy dogs when hyperacidity is stimulated,[8a] it is accepted that an inherited hyperacidity - an increased parietal cell mass (PCM) as with DU patients - is the prime mover.[8b]

Neural reflexes involving acid-sensitive neurons adjust the tone of the pyloric sphincter.[6] In adults with hyperacid disease, the early symptom of post-prandial bloating (pyloric delay) is quickly abolished by antacid therapy. The first consequence of giving intravenous gastrin to adults is pyloric delay from presumed sphincter contraction.[9a]

If too much gastric acid enters the duodenum, a duodeno-pyloro-gastric reflex is elicited, which not only contracts the pylorus but also inhibits gastric motor activity - both combining to halt further gastric emptying. These coordinated motor reactions are controlled by acid-sensitive neurons which, in turn, activate multiple neural circuits involving enteric, sympathetic, and vagal nerve pathways.[10] The interstitial cells of Cajal may also be involved.

Neural acid sensors are the first responders and produce acid-induced currents evoked by specific H^+ receptors.[11] Homeostasis is so important that multiple mechanisms of acid sensing have evolved.

Capsaicin - a chemical derived from chilli - has the peculiar property of being toxic to small primary afferent (sensory) nerve fibers in the stomach. The proxy for activity in these nerves is the chemical CGRP, and capsaicin treatment abolishes the presence of this chemical in the rat gastric mucosa.[11,12,13] The normal slowing effect on gastric emptying of intragastric hydrochloric acid is partially reduced on capsaicin-treated rats.[11]

Thus, stomach relaxation and delayed gastric emptying after acid exposure have a neurological reflex basis. The process by which pyloric contraction occurs immediately after acid enters the duodenum requires a neural reflex mechanisms. Cannon's cycle while important relies on the slower hormonally mediated processes.[14]

PS OF INFANCY - WHY DO SYMPTOMS BEGIN AT 4 WEEKS? THE CONSEQUENCE OF AN IMMATURE NEGATIVE FEED-BACK

Repeated sphincter contraction attracts growth factors to the sphincter and hypertrophy follows.

Just imagine what would happen in normal development if the adult negative feedback between gastrin and acidity took some weeks to mature. We would expect that:

- Neonatal gastrin levels and neonatal acid secretion would progressively rise to a peak before gradually falling. Neither gastrin nor acid secretion would be restrained by the other. This is indeed what happens.[8,15] It is in essence like a mini Zollinger-Ellison syndrome.
- The stimulated and unrestrained gastrin would not be further increased by a feed. This is also what happens. It is only when negative feedback has matured that fasting gastrin falls and a post-feed increase occurs.[16,17,17a]
- A progressive rise in acidity would occur which will only fall when feedback has matured. This has been documented with a temporary peak acidity at around 17 days of life.[13] Indeed, in the first few days of life, there is little difference between maximally stimulated acid secretion and the fasting value.[16] The basal secretion is already maximally stimulated.
- Babies destined to develop PS due to an inherited hyperacidity would develop symptoms soon after the time of peak acidity.

The mean time for symptom development is around 4 weeks of age. The classical symptoms and signs of pyloric sphincter hypertrophy and acid loss - the vomiting and the alkalosis - occur within 2 weeks of the time of peak acidity.

The hyperacidity of PS of infancy may be due to an inherited large PCM or by a failure of some of the acid-sensing negative feedback mechanisms outlined above.

The male preponderance in PS of 5/1 parallels the male preponderance in adult DU. The preponderance of blood Group O and hyperacidity is similarly shared.[13,18] Male adults are also known to have a greater PCM than females.[19]

Hence, it is logical to assume that a greater PCM in the PS babies is the cause of hyperacidity rather than a failure of acid-sensing mechanisms. The inherited PCM is not static and may be increased by hypergastrinemia. Emerging gastric

outlet stenosis or obstruction by creating hypergastrinemia is also a stimulus to further PCM increase.[20-22]

PROSTAGLANDINS (PG) AND THEIR LINK TO SPHINCTER HYPERTROPHY

These chemicals were first isolated by Von Euler fom the semen and thought to come from the prostate, hence the name. They were actually produced in the seminal vesicles. They consist of 20 carbon atoms and 5 carbon rings. They are present in very many tissues and originate from nucleated cells from chemical manipulation of lipid-arachnodoic acid. They have many functions and possible therapeutic actions. The synthesis was achieved by by Bergstrom, Samuelson, and Vane in 1982 who were jointly awarded the Nobel prize for physiology.

They come in a variety of chemical configurations and have different names. The letter used relates to the type of carbon ring and the number used is related to the number of double bonds between carbon atoms. For example, PG - stands for PGs and PG E1 (alprostadil) means 1 double bond with the E configuration of the ring. They are known as local hormones because their short half-life means that they only act on the cell that produces them (autocrine action) or on nearby cells (paracrine action). They are also secreted from many different sources.

Their function is usually determined by the receptor which they engage. Hence, dependent on the receptor, the same PG can have opposing and different actions. Two common uses are for inducing labor (PG pessaries sensitize the cervix and uterine muscle to the effects of oxytocin) and for keeping the ductus arteriosus patent in cases of cyanotic congenital heart disease, due to the vasodilatory effects of alprostadil (PG E receptor 1 [PGE1]).

PGs, HYPERACIDITY, AND PYLORIC SPHINCTER CONTRACTION

Several observations suggest that PGs released locally into the gastric juice act to connect hyperacid states with sphincter work hypertrophy (PS). Such a mechanism would be common to both neonatal and adult conditions.

In PS babies both before and after pyloromyotomy, an inverse relationship exists between PGs in gastric juice and gastric pH. In other words, the greater the acidity, the greater release of PG into the gastric lumen.[3]

Lubiprostone, a chemical compound derived from PG, is a medication for constipation. With up to 54% PGEP2 activity, lubiprostone also exerts an EP1-mediated contractile effect on intestinal smooth circular muscles. A dose-related increase in contractile tone can be demonstrated in isolated murine pyloric sphincter muscle strips when tested in a muscle bath. This effect is inhibited by antagonists of PG EP1. These receptors exist in the smooth muscle layers of the gastric body and antrum. The existence of EP1 or other PGE2 receptors in the pyloric sphincter is implied by these findings. These pharmacological effects need confirmation on human tissue.[4]

There have been repeated reports that babies with cyanotic heart disease who receive continuous infusions of PGE1 (alprostadil) develop antral mucosal hyperplasia with gastric outlet obstruction (GOO).[23] The GOO disappears when the infusion stops. Sometimes, after a significant total PGE1 load, classical PS develops which requires pyloromyotomy.[24]

There is no suggestion that there is anything abnormal in the PG mechanism which occurs in normal PS babies. It is simply responding to antral hyperacidity in PS babies.

When PGs (PGE2 and PGE1) are artificially exposed to the gastric mucosa, both basal and stimulated gastric acid secretions are reduced.[25]

Endogenous PGs alter gastric motility and sphincter contraction. They increase tone in the proximal stomach and change the rate of progressive contraction in the distal stomach (chronotropic effect).[4]

They act when applied locally as a negative feedback to reduce acidity in hyperacid conditions and help to cause sphincter contraction in acid states.

Hence, activated duodenal acid sensors cause sphincter contraction most probably through the immediate effect on sensory nerves with reflex contraction. A direct effect of PGs released in hyperacid conditions also will cause sphincter contraction and GOO.

THE POSITIVE FEEDBACK CONSEQUENCES OF PYLORIC SPHINCTER HOLDUP

What happens when GOO begins?

Artificial mechanical narrowing of the pylorus in rats stimulates the growth of the gastric mucosa, increases the PCM, and causes hypersecretion of acid through an increased gastrin level and an increased PCM.[21,22] This implies that, with GOO and high gastrins, the rate of sphincter hypertrophy in PS is further increased.

DU patients similarly develop an increased PCM and even more acid when GOO supervenes.[20] It is a self-perpetuating

phenomenon in both. With the untreated PS baby, a fatal outcome may result.

Our early theory of the cause of PS was that duodenal hyperacidity fuelled by neonatal hypergastrinaemia would cause repeated sphincter contraction. Repeateded contraction would cause sphincter work hypertrophy and GOO. Stagnating milk feeds would cause antral distension and reduce acidity sufficiently to allow a maximal secretion of gastrin. Even more, acid secretion would follow with more contraction and so on. As far as acid and its consequences were concerned, it was a form of positive feedback.

Reducing the frequency and volume of feeds or reducing acid secretion would stop this process.

Dividing the sphincter would, of course, produce a long-lasting cure. The divided sphincter will not contract, the narrow opening is widened, and the positive feedback is abolished.

Ghrelin, the recently discovered gastric hormone, which increases appetite and facilitates the release of growth hormone, is also increased in GOO. Rats with a narrowed pylorus develop high ghrelin plasma levels. Hyperplasia of the gastric muscle layers with enhanced expression of neuromuscular markers[22] was also observed. The hunger of the PS baby may be increased by high ghrelin levels.

Confirmatory evidence exists in the human condition. In 2016, an Indian baby began vomiting non-bilious milk from birth. Ultrasonic investigations, at 22 days of age, revealed a duplication cyst of the anterosuperior part of the pyloric canal and hypertrophic PS with obvious GOO. Excision of the cyst and pyloromyotomy produced a cure. The likely pathogenesis is that GOO so increased acid secretion that a secondary PS developed. The sphincter thickness was 16.7 mm.[26]

Despite the rarity of the pyloric location of the cyst - about 2–3% of all cysts - other examples of an associated pyloric stenosis exist in the literature.

Hence, the classical baby with PS on developing GOO will so further increase acid secretion that his fate is sealed. Only surgery or diminished feeding and antacid measures will break the cycle.

THE LINK BETWEEN PS OF INFANCY AND DU IN ADULTS

The Number of Similarities is Extraordinary

- Both are due to hyperacidity and a large PCM.
- They have the same 5/1 male/female ratio and the same retained appetite. The leading peculiarity of duodenal disease is that food is taken with relish."[27]
- Post-prandial bloating signifying acid induced sphincter contraction occurs in both.
- PS babies occasionally have superficial DU and frequently develop hyperacidity problems later.[28]
- They share the same blood group predominance of blood Group O.[13,18]
- Both may be cured with acid-blocking drugs.
- The inheritance is multifactorial.

Simple division of the sphincter is also effective in DU. Judd in 1930 reported a 60% success with pyloroplasty alone.[29] Abolishing a positive feedback may be the explanation.

THE DIFFERENCES BETWEEN DU AND PS

- Adults are more able to withstand acid-induced sphincter thickening without causing GOO and a positive feedback.
- Hyperacidity in adults can safely act over a long time, long enough to produce a chronic ulcer, without precipitating (as it does with neonates) a fatal outcome or urgent surgery.
- *Helicobacter pylori* infection: This is not seen in PS babies. It is detected in about 90% of DU patients and in 29–70% of non-DU patients. *H. pylori* by maximizing acid secretion releases the potential of the PCM. High constitutional acidity may give *H. pylori* a survival advantage and explain its greater frequency in DU adults. Surgical cure rates required a reduction in acid secretion. Hence, hyperacidity, as with PS babies, still appears to be the primary problem.[30]

CONCLUSION

There are two main forms of hyperacidity disease which affect human beings - A baby form (PS of infancy) and an adult form (DU).

The important differences related to age such as developmental changes, neonatal hypergastrinemia, voluntary or involuntary feeding, and relation of pyloric lumen size to viscosity of food all determine that their symptoms are different.

The essential pathogenesis remains the same - an inherited PCM at the top of the range.

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