

THE GASTROINTESTINAL HORMONES OR AUTACOIDS

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INTRODUCTION

It is an evident fact that bodily processes are subject to excitation and inhibition. The chief agencies through which the bodily processes are augmented and retarded, or controlled, are: (a) the nervous system and (b) the hormone or autacoid secreting cells or organs. Nerves may effect muscle tissue so that it contracts or relaxes, or secretory cells, such as the salivary glands, so that their rate of secretion increases or decreases. Hormones or autacoids also act to augment or to retard bodily processes.

The hormones have been called autacoids, meaning self-remedial substances, because they act much like drugs or remedial agents. It is believed that two sorts of autacoids exist functionally, the hormones (to excite), which augment bodily processes, and the chalones (to inhibit), which retard bodily processes.

The autacoids are secreted into the blood and/or lymph by glands without ducts, in contrast to such glands as the salivary glands, whose secretion is drained externally into the mouth by ducts. Hence, the terms "Ductless Glands" and "Glands of Internal Secretion" are applied to the autacoid producing glands. The expression "Endocrine Glands" is also used, the word "endocrine" meaning to separate within.

Since, in the gastrointestinal tract certain food substances excite the secretion of gastric and pancreatic juice, we refer to these substances as "secretagogues." Secretagogues are substances which are present in food or which arise from the digestion of food. They stimulate gastric and pancreatic secretion. As will be noted later secretagogues may excite secretion by acting locally on the lining or mucosa of the stomach and intestine or possibly by being absorbed into the blood stream. Secretagogues are not hormones, since they are not formed by the living cells of the body, but are present in or result from the digestion of food. Any blood borne or circulating agent stimulating or depressing bodily activities is called a "humoral

agent" whether it is a hormone or secretagogue, or substances of unknown nature.

SALIVARY GLANDS

All the evidence shows that the secretion of saliva is increased or decreased through a nervous mechanism. When food is placed in the mouth saliva flows because sensory nerve impulses pass to the brain and excite a salivary center (medulla), from which secretory nerve impulses pass to the salivary glands causing them to secrete. The contact of food with the oral mucosa does not cause the cells of the mucosa to secrete a hormone into the blood. For example, if lemon juice is placed in the mouth of a dog, saliva flows copiously. If the nerves to the salivary glands are cut one day and then lemon juice is applied to the mouth the next day, saliva is not formed. When extracts of the oral and pharyngeal mucosa are made and then injected intravenously or subcutaneously, the salivary glands are not stimulated.

The situation is different, however, in the case of the stomach, pancreas and liver. It is interesting that, whereas, the salivary glands appear to be controlled solely by nerves, the stomach is controlled by nerves and autacoids. Secretion of pancreatic juice and bile are controlled chiefly by autacoids and humoral (blood borne) agents. Nerves play a minor role in the formation of the latter two secretions.

GASTRIC SECRETION

The secretion of the acid gastric juice may be divided into three phases when one considers the point at which the stimuli are acting. These phases are (a) the cephalic phase, (b) the gastric phase, and (c) the intestinal phase. When food is seen, smelled or tasted in the presence of appetite, nerve impulses pass to the brain and then to the stomach by way of the vagus nerves causing the so-called "psychic" secretion of gastric juice. This phase is entirely nervous. The gastric phase is initiated by distension of the stomach and by the secretagogues in the food or the secretagogues produced by the gastric digestion of food. Whether distension of the stomach or the contact of secretagogues with the lining of the stomach excite secretion by stimulating the local enteric nervous system in the stomach wall or by causing a hormone to be produced is not known. Both may be concerned. It is known that secretagogues probably do not

act in the stomach by being absorbed (3). The intestinal phase of gastric secretion is initiated by secretagogues acting on the mucosa of the intestine. Whether they act by causing a hormone to be produced or by being absorbed into the blood is not certain. It is possible that they may act by being absorbed into the blood (3).

It has been established that a humoral mechanism (agents such as a hormone or secretagogues) for stimulating gastric secretion exists. This was first shown (1, 4) (Ivy and Farrell) by auto-transplanting a small pouch of the stomach beneath the skin. When such an animal is fed, the transplanted pouch secretes acid gastric juice. Hence, when the animal ate, some substance or substances passed into the blood which stimulated the transplanted pouch. Whether the humoral or blood borne substance is of the nature of a hormone or of the nature of secretagogues is not certain.

An acid, saline, or alcoholic extract of the mucosa of the pyloric portion of the stomach, when injected subcutaneously, stimulates gastric secretion. The active principle of such extracts is called gastrin or the gastric hormone. Histamine in crystalline form has been isolated from such extracts, and the evidence indicates that histamine is the sole secretory excitant in such extracts (5). It cannot be concluded, however, that histamine is the gastric hormone, (a) because it has not been shown clearly that the histamine content of the blood increases after eating, and (b) because it has been reported that a substance has been dialyzed from the blood of a fed animal which on subcutaneous injection stimulates gastric secretion but does not depress blood pressure on intravenous injection like histamine.

Histamine is now frequently used in man to test the ability of the stomach to secrete acid.

PANCREATIC SECRETION

It is known that nerves are present in the vagus nerve trunks which excite and inhibit the formation of pancreatic secretion. Nerve fibers are present in the splanchnic nerve trunks which when stimulated cause a decrease in blood flow to the pancreas and a decrease in the formation of pancreatic juice. A "psychic" secretion of pancreatic juice occurs, but is relatively small in volume (5-10 cc., rarely more).

The principle mechanism which has been demonstrated to exist for the stimulation of pancreatic secretion when a meal is ingested is the elaboration of the hormone secretin. This hormone is produced when dilute acids, fatty acids, soaps and peptones contact the upper intestinal mucosa.

The discovery of this hormone by Bayliss and Starling in 1902 constitutes one of the major historical events in the field of Endocrinology. To stimulating principles, such as secretin, Starling (7) applied the term, hormone. The essential observations made by Bayliss and Starling were as follows: It had been known for sometime that dilute acid applied to the duodenal mucosa would cause the pancreas to secrete. This secretion was thought to be excited by a nervous reflex, and Bayliss and Starling desired to test this theory. They found that application of acid to the duodenum after the nerves to the pancreas had been sectioned still caused the gland to secrete, and that acid injected intravenously did not. They then made acid extracts of the duodenum and found that such extracts on intravenous injection stimulated the pancreas to secrete. It was then shown that when the circulation of two dogs was connected and acid placed into the duodenum of one, the pancreas of both secreted. Later it was shown that acid applied to an autotransplanted loop of intestine caused an autotransplanted portion of the pancreas to secrete (8). The possibility that secretagogues, after being absorbed into the blood, stimulate the pancreas, has been shown to be improbable (8a).

Purified preparations of secretin have been injected into normal human subjects (9). The secretion of the pancreas was, of course, stimulated. Secretin has apparently been crystallized (10); secretin crystals have also been prepared in the author's laboratory (11). From 0.016–0.008 mg. of the secretin base, from which crystals of secretin picrolonate were made, is adequate to stimulate the pancreas of dogs.

It is of interest that crystalline secretin stimulates the liver to secrete bile (12). The crucial experiment proving this was performed on animals deprived of their pancreas and gastrointestinal tract, so that the increase in flow of bile could not be secondary to increased activity of the pancreas and intestine. The cholagogue action of secretin, however, is not as marked as that of bile salts.

GALL BLADDER

Nerves pass to the gallbladder, but when stimulated only a small and variable amount of contraction occurs. It now appears to be established that the hormone cholecystokinin is the chief cause of gallbladder contraction and evacuation. This hormone is produced when dilute acids and fatty acids contact the duodenal mucosa. The essential facts demonstrating the existence of such a hormone are as follows: Extracts of duodenal mucosa have been made and injected into human and canine subjects; the gallbladder contracted and evacuated. Further, if the circulation of two dogs is connected and acid is placed in the duodenum of one, the gallbladder of both animals will contract. The intravenous injection of acid or of finely emulsified fat or chyle does not cause the gallbladder to contract. This shows that the absorption of acid or the products of the digestion of fat do not act as humoral agents for gallbladder contraction and evacuation.

This hormone is closely related to secretin chemically; but the two may be separated by an appropriate chemical procedure (12a).

ENTEROGASTRONE

Neutral fat inhibits gastric secretion and motility. This has been known for many years. It was formerly believed, however, that when fat contacted the stomach and duodenum the gastric activities were reduced by a nervous reflex. We now know that this inhibitory action of fat is due to the chalone enterogastrone, although the possibility that nerves are also concerned has not been entirely ruled out.

The essential facts showing that enterogastrone exists are as follows: When a small pouch of the stomach is transplanted beneath the skin and a balloon is inserted into the pouch so as to record its movement, it is found that the movements are markedly diminished a few minutes after fat is placed into the duodenum (13). The same is true for the acid secretion of the transplanted pouch (14). A concentrated solution of glucose or cane sugar acts similarly to fat. Gastric secretion and motility are not inhibited when finely emulsified fat or chyle is injected intravenously. This shows that it is not the absorbed food fat circulating in the blood that causes the inhibition of the movements and secretion of the pouch. Hence, the inhibition must

be due to some specific substance or chalone secreted by the duodenal mucosa into the blood. Further, extracts of duodenal mucosa have been made which, when injected intravenously or subcutaneously, inhibit gastric secretion and motility (21).

The enterogastrone preparations made to date are not toxic, but they are not sufficiently "pure" to use in man. When the chalone has been prepared in a sufficiently "pure" or concentrated form, it may prove to be of value in the management of patients with "peptic" ulcer.

OTHER GASTRO-INTESTINAL HORMONES

Incretin: Rather strong presumptive evidence indicates that the duodenal mucosa produces a hormone which stimulates the islet cells of the pancreas to secrete insulin (1). It also appears to have a direct hypoglycemic property, since it lowers the blood sugar level in depancreatized animals (15, 16).

Enterocrinin, the hormone for the stimulation of intestinal secretion: When one observes the secretion of a loop of intestine which has been transplanted beneath the skin, it is noted that a copious flow of intestinal juice from this loop does not occur after feeding the animal (17). Closer study, however, indicates that some increase in the volume of secretion and output of enzymes occurs (18). A preparation of the intestinal mucosa has now been made free of blood pressure depressing substances which on injection increases the formation of intestinal juice. This hormone is called enterocrinin (Nasset).

Enterocin, the gastro-intestinal motor hormone: The possible existence of a hormone produced by the intestinal mucosa which augments gastro-intestinal tone and motility during digestion has been suggested by a number of observers (1). Although the motility of a transplanted loop of intestine is not definitely increased after the ingestion of a meal, closer analysis may show that it is. Preparations (1) of intestinal mucosa have been made which on injection augment intestinal motility (19). The active principle (the author calls this principle enterocin) has certain chemical properties related to secretin, but is not identical with it (20). It is not related to acetyl choline because its motore effect is not antagonized by atropine.

Concerning an erythropoietic hormone, it has been suggested that the gastrointestinal mucosa produces a hormone which is related to erythropoiesis. Little or no evidence exists to substantiate such a suggestion. The *desiccated* stomach, duodenum

and colon of the pig is active in the management of pernicious anemia. But, this is probably due to the presence of an enzyme (intrinsic factor of Castle) which reacts with substances in the cells of the gut wall to produce the active erythropoietic substance. During life it is believed that the enzyme is secreted into the gastric and intestinal juice, and acts on certain foods, such as meat, to produce a substance which is absorbed into the blood and is used by the bone marrow to produce erythrocytes.

SUMMARY

From this brief review it is clear that the mucosa of the gastrointestinal tract is a veritable storehouse of autacoids. Seven or more hormones may be produced. The existence of three, namely, secretin cholecystokinin and enterogastrone, may be considered as established. The evidence is strongly presumptive for the existence of three others, namely, gastrin, incretin, and enterocrinin. Good physiological evidence for the existence of enterocin has not been produced.

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