Ir. J. Med. Sc.
May, 1964, pp. 191-201
Illustrated
Printed in the Republic of Ireland

THE POSSIBLE ROLE OF 5 HYDROXY TRYPTAMINE IN THE CONTROL OF GASTRIC ACID SECRETION: A NEW CONCEPT

By JEREMY H. THOMPSON, M.B., M.R.C.P.I.

THE digestive system has been shown to contain up to 60 per cent of the total body 5 Hydroxytryptamine (5 HT) in the rat[1] and dog.[2 3] In man the duodenum is richly supplied with argentaffin cells[4 5] and contains high concentrations of 5 HT.[6] Similar findings occur in other animals.[7 8]

These anatomical and chemical findings suggest that 5 HT might play a rôle in gastroduodenal physiology and various authors through the years have suggested that secretin[13] enterogastrone,[5] or the pernicious anaemia intrinsic factor,[4 5] might have their origin from argentaffin cells. It was shown that reduction of duodenal 5 HT in the rat plus degranulation of argentaffin cells occurred after perfusion of the duodenum with 0.1 N HCl in physiological amounts.[9 10] Resnick and Gray also showed that physiological HCl perfusion of the rat duodenum led to a diminution of gastric secretory volume and a rise in pH.[11] Further experiments with rats treated with reserpine and 5 HT antagonists led Resnick and Gray to believe that release of intestinal 5 HT played no role in control of gastric secretion.[11]

This paper presents further evidence in favour of the possible control of gastric acid secretion by the hydrochloric acid release of duodenal 5 HT.

Materials and Methods: All animals used were male Sprague Dawley rats weighing between 150–200 gms. Diet consisted of ordinary laboratory chow with water ad lib. Animals were fasted 24 hours prior to surgery/perfusion, or 5 HT assay, but water was not stopped. Anaesthesia consisted of open ether only.

Surgery/perfusion: The peritoneal cavity was opened with a mid-line incision, and the duodenum cannulated just distal to the pylorus. A gastrostomy was made in the rumen of the stomach. Minimal cleansing of the stomach was needed, with warm normal saline and then left resting fifteen minutes before the experiment began. After the duodenal cannula had been placed the abdomen was closed leaving free access to the wide gastrostomy. Gastric secretory volume was measured by adsorbing the gastric juice on to cotton wool plugs inserted via the gastrostomy. The plugs were small enough to avoid distention of the stomach. The dry weight of the plug being subtracted from the weight of the plug plus adsorbed gastric juice to give the volume of gastric secretion in each 5 minute period in fractions of a millilitre. Duodenal perfusion was carried out at a constant rate using an infusion pump. Three mls. O.1N HCl or 0·9% saline were solutions used. Perfusion time was 15 minutes after an initial 15 minute control period. Animals were sacrificed after each experiment.

UML 491 (a potent 5 HT antagonist: Sandoz Pharmaceutical Ltd.) was used in doses of 10 mgms./kg. intraperitoneally eighteen hours and one hour prior to perfusion.

Cocaine hydrochloride (10%) and oxethazine hydrochloride (1%) (Wyeth Pharmaceuticals Ltd.) were the local anaesthetics used (see individual experiments *infra*).

Reserpine (Serpasil: Ciba Pharmaceuticals Ltd.) was used in doses of 2·5 mgm./kg. intraperitoneally twenty-four hours and two hours prior to perfusion. (Higher doses of reserpine were used in 5 HT assay experiments *infra*.)

Each five minute sample of gastric secretion was diluted with 3·0 mls. of double distilled water and with phenolphthaline as indicator the sample titrated using 0·01N NaOH. Titration results were expressed as fractions of a millilitre of 0·01N NaOH.

Duodenal 5 HT Assays : Animals were fasted twenty-four hours prior to assay. Water was allowed. Twenty-four animals were used, with six in each group. Group (*a*) controls, (*b*) UML 491 medication and (*c*) and (*d*) reserpine medication. Open ether was used as anaesthetic. The first stage of the duodenum was rapidly excised, and carefully cleaned of blood. The tissue was then frozen, and 5 HT assays were performed using a modification of Udenfriends method.[26]

Group (*b*) rats were given UML 491. 10 mgms./kg. intraperitoneally eighteen hours and one hour prior to assay.

Group (*c*) rats were given reserpine 2·5 mgms./kg. intraperitoneally twenty-four hours and two hours prior to assay.

Group (*d*) rats were given reserpine 5·0 mgms./kg. intraperitoneally twenty-four hours and two hours prior to assay.

Results

Rats with HCl perfusion of the duodenum demonstrated a fall in gastric secretory volume and a fall in the titratable acidity (Fig. I).

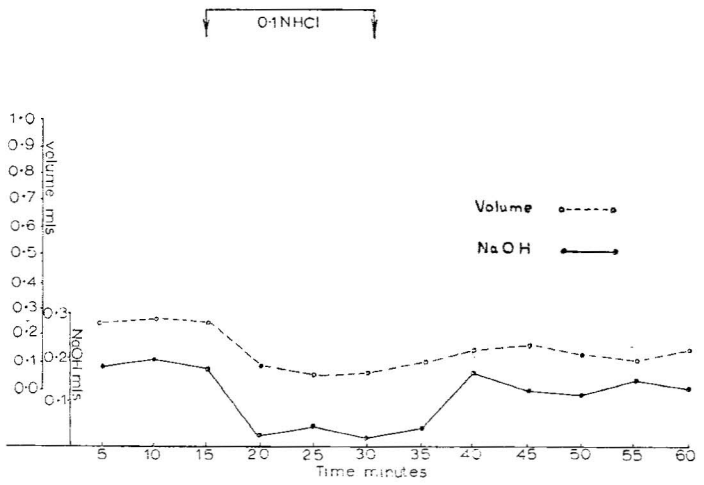

FIG. I.—Measurements of gastric secretory volume, and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 ml. 0·1 N HCl indicated by arrows.

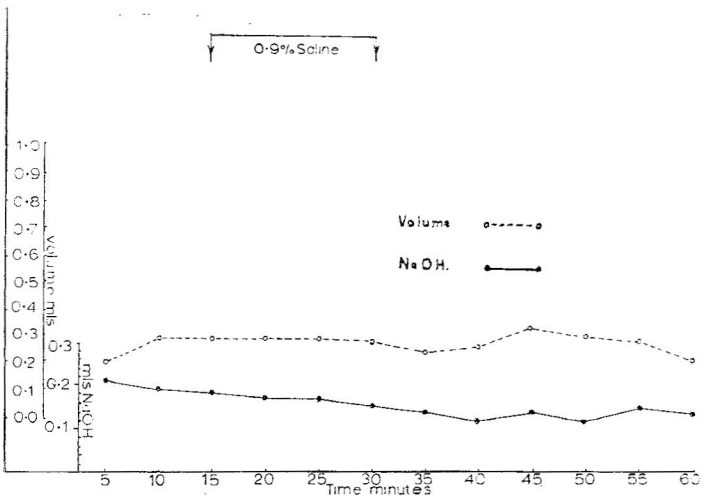

FIG. II.—Measurements of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 ml. 0·9% saline indicated by arrows.

Control rats following saline perfusion showed no alteration in either (Fig. II).

Effect of Anaesthesia of First Stage of Duodenum

Rats with a 10 per cent solution of cocaine painted on to the duodenal mucosa in a narrow band completely encircling the bowel via a

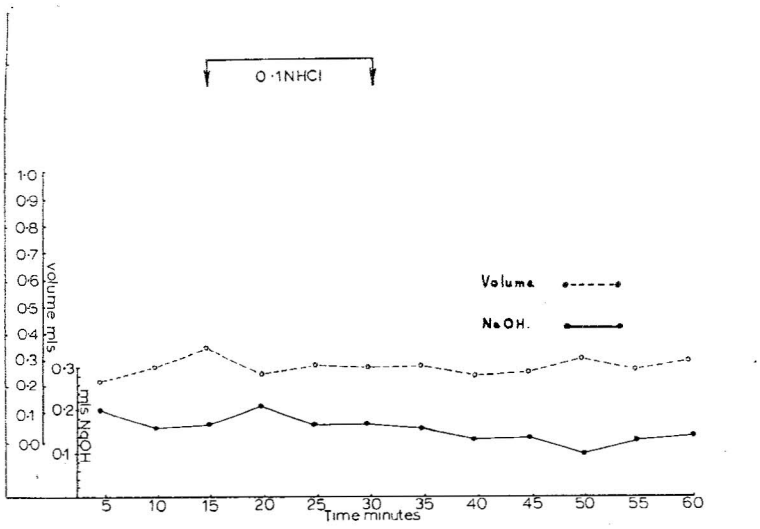

FIG. III.—Measurements of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 ml. 0·1 N HCl indicated by arrows. Prior to insertion of perfusion cannula duodenal mucosa cocainised.

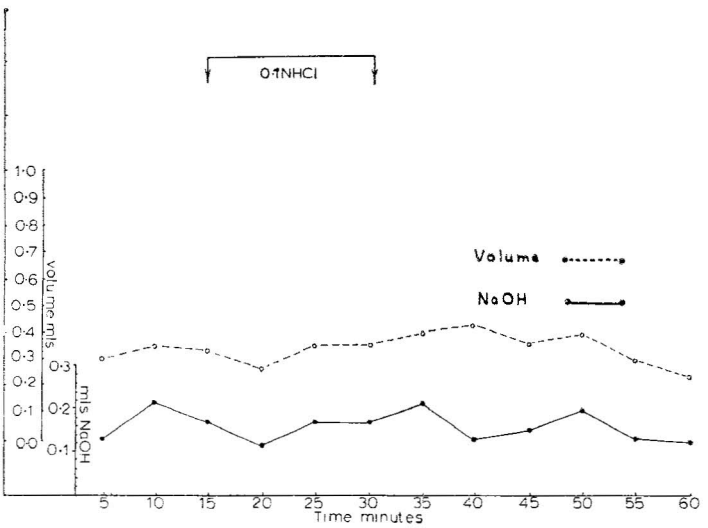

FIG. IV.—Measurements of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 ml. of 0·1 N HCl indicated by arrows. Fifteen minutes prior to perfusion complete separation of the bowel at the pylorus between sutures.

duodenostomy prior to the insertion of the cannula showed no alteration in gastric secretory volume, or titratable acidity following HCl perfusion of the duodenum (Fig. III). Rats with a 1 per cent solution of oxethezine hydrochloride applied in a similar manner gave like results (Fig. VI).

Effect of Discontinuity of the Pyloro-Duodenal Canal

Rats with the intestine separated between sutures at the pylorus, so that no serosal, muscular, nervous or mucosal continuity remained between the stomach and the duodenum showed no alteration in gastric secretory volume or titratable acidity (Fig. V).

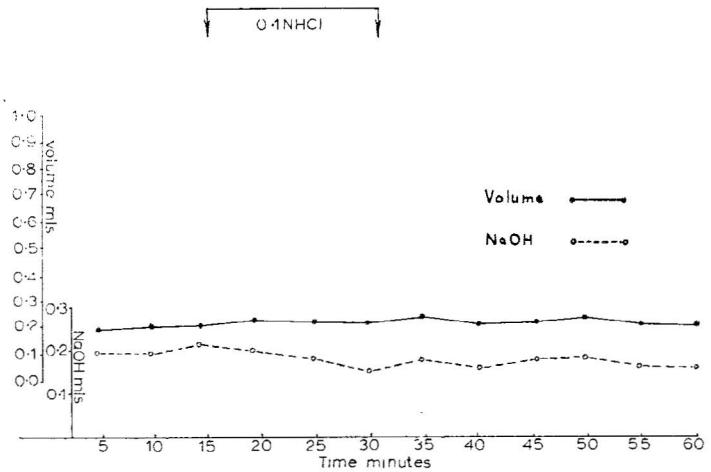

FIG. V.—Measurements of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 mls. 0·1 N HCl indicated by arrows. UML 491 (10 mgms./kg.) 18 hours, and 1 hour prior to perfusion, intraperitoneally.

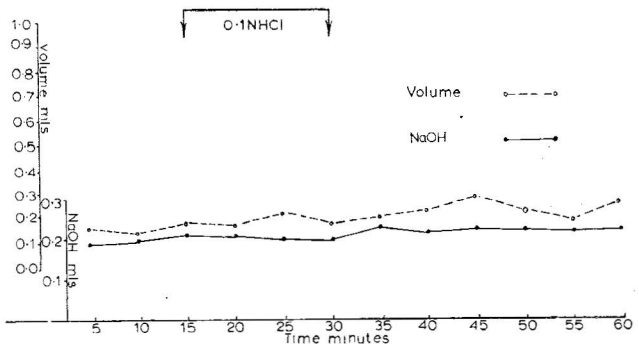

FIG. VI.—Measurement of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 mls. 0·1 N HCl indicated by arrows. Prior to insertion of perfusion cannula duodenal mucosa painted with 1% oxethazine hydrochloride.

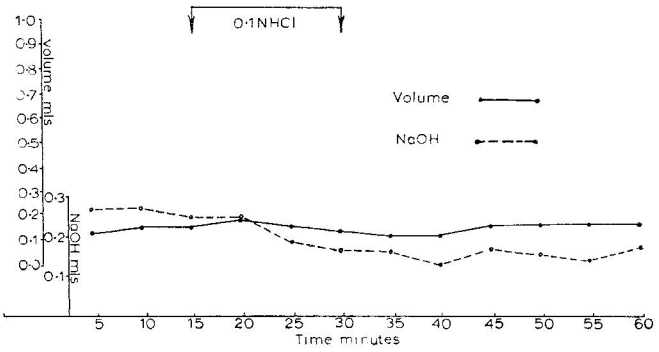

FIG. VII.—Measurement of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 mls. 0·1 N HCl indicated by arrows. Reserpine (2·5 mgms./kg.) twenty-four and two hours prior to perfusion, intraperitoneally.

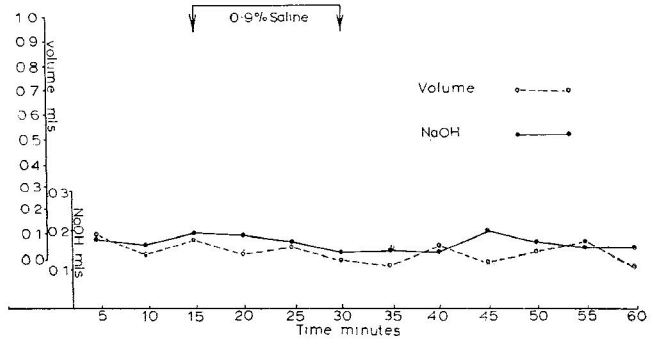

FIG. VIII.—Measurement of gastric secretory volume and titratable acidity at 5 minute intervals over a period of 1 hour. Each score is the mean for six rats. Duodenal perfusion with 3·0 mls. 0·9% saline indicated by arrows. Reserpine (2·5 mgms./kg.) twenty-four and two hours prior to perfusion, intraperitoneally.

Effect of Reserpine

Rats treated with reserpine (2.5 mgms/kg 24 hours and two hours) pre-duodenal HCl perfusion (Fig. VII) demonstrated no fall of gastric secretory volume, but showed a fall of titratable acidity. Control rats treated with reserpine, and then perfused with saline showed no fall in gastric secretory volume, or titratable acidity (Fig. VIII).

Rats given higher doses of reserpine were difficult to keep alive under ether anaesthesia and no reliable experimental results could be obtained with higher reserpine dosage.

Methods of Statistical Analysis

The data are presented in the form of graphs, each point being the mean for six animals.

Reliability of between-group differences

Wilcoxon's unpaired replicates test was used as modified by White.[12]

No differences were seen at 5 per cent level of significance between the pre-perfusion and post-perfusion scores, except in the HCl perfused animals with no duodenal anaesthesia, or bowel separation (Fig. I), where the scores showed significant difference, and in the reserpine treated animals perfused with HCl where a significant fall in titratable acidity occurred, with no secretory volume change (Fig. VII).

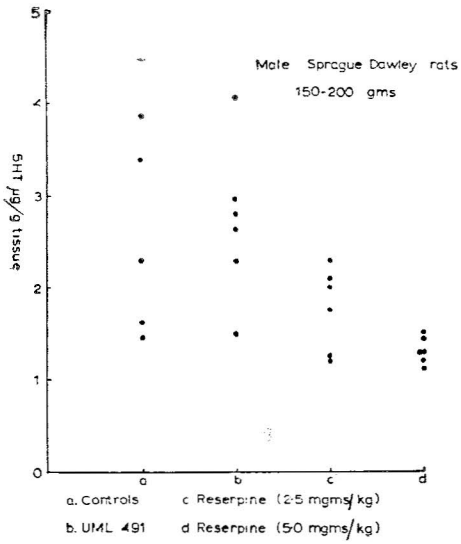

FIG. IX.—5 HT levels of first stage duodenum. Each score is one result. UML 491 and reserpine dosage explained in text.

Duodenal 5 HT Assays

The results of 5 HT assays are set out graphically (Fig. IX).

Normal control levels were 2.8 $\pm$ 1-2 µg/g tissue. Similar levels of 2.7 $\pm$ 0.08 µg/g tissue were seen after UML 491 medication. It is not known how UML 491 acts as an antiserotonin. It is not by depleting stores as in reserpine medication (probably by blocking an active transport system[18]), but more likely as a competitive inhibitor at effector sites, or a blockade of release from stores. Either of these latter two mechanisms would explain the similar 5 HT levels between the normal control group, and the animals treated with UML 491.

Levels of duodenal 5 HT after reserpine (2.5 mgm/kg) were 1.76 $\pm$ 0.46 µg/g tissue and after double dosage of reserpine levels of 1.31 $\pm$ 0.15 µg/g tissue were found. There being no difference between these latter two groups it seems unlikely that complete duodenal depletion of 5 HT by reserpine is possible. This latter point will be discussed later in more detail.

Discussion

These results lend support to the idea that the release of duodenal 5 HT by physiological HCl perfusion helps (via a feed-back mechanism) to control gastric secretion.

Wermel and Kacharova[13] in 1948 described depletion of argentaffin cell granules by HCl contact. Resnick and Gray[9] showed that a maximal 5 HT tissue fall occurred within one hour following HCI perfusion and in subsequent experiments that preferential release occurred in the first fifteen minutes,[10] with complete restoration to normal after 3-6 hours (presumably on the basis of 5 HT resynthesis). This fall in 5 HT content was not caused by tissue injury, was seen with relatively low quantities of HCl and was similar to the reduction seen after reserpine administration.[9] In man the duodenal pH often falls to levels that could liberate duodenal 5 HT,[27] but acid induced serotonin release has yet to be shown in man. Resnick and Gray also noted that HCl perfusion of the duodenum led to a reduction of gastric acidity (as measured by pH), and a fall in secretory volume, they attempted to prove a possible feed-back mechanism, involving duodenal 5 HT release using rats treated with reserpine, and serotonin antagonists, UML 491 (methyl-D-lysergic acid butanolamide) and BOL 148 (2 Bromo-D-lysergic acid diethylamide).[11]

In their reserpinised animals the 5 HT content of the duodenal argentaffin cells had fallen to 1.6 μg/g tissue from 2.8 μg/g tissue and in these animals, as well as those treated with the 5 HT antagonists BOL 148 and UML 491 perfusion of the duodenum led to diminution of gastric secretory volume and a rise in pH, viz. no change from their original observations. Resnick and Gray therefore concluded that intestinal 5 HT release probably played no role in the control of gastric secretion.[11]

Their conclusion can be questioned. It is known that even with massive doses of reserpine complete reduction of bowel 5 HT is unlikely,[15] while in the rabbit the 5 HT content in the stomach fundus may increase with non-depletory doses of reserpine and with doses that deplete pyloric serotonin there is no effect seen on fundal 5 HT.[14]

Resnick and Gray found on assay that the 5 HT content of the duodenal argentaffin cells had fallen to 1.6 μg/g tissue from 2.8 μg/g tissue after reserpine dosage of 2.5 mgms/kg. Similar levels of 5 HT depletion have been found and no greater depletion can be seen with increased reserpine dosage in the rat (Fig. IX).[15] In guinea-pig and rabbit bowel reserpine causes 5 HT reduction, and not depletion.[16 17] Therefore it can be postulated that the reduction of duodenal 5 HT by reserpine in Resnick and Gray's experiments to 1.6 μg/g tissue still left ample serotonin and this latter quantity might be sufficient for physiological activity. It can be seen from Fig. VII that with similar doses of reserpine to those given by Resnick and Gray no inhibition of gastric secretory volume has been produced, but a fall in the titratable acidity is shown. This, however, is not as great as the fall seen in the perfused rat without reserpine pre-treatment (Fig. I). Even though reserpine reduces argentaffin cell granules complete depletion seems impossible. This can be seen from Fig. IX, where even reserpine in doses of 5.0 mgms/kg yielded duodenal 5 HT levels similar to those seen with lesser reserpine dosage. So even with maximum reserpine dosage some physiological activity presumably remains.

Secondly, Resnick and Gray found that rats treated with UML 491 in

doses of 10 mgms/kg 1 hour prior to perfusion showed no depression of gastric secretory volume and titratable acidity after duodenal HCl perfusion.

As has been said previously it is not certain how UML 491 acts as an antiserotonin. Resnick and Gray in their experiments used UML 491 one hour prior to perfusion, and demonstrated no change in the reflex response. In experiments with increased UML 491 dosage complete blockade of the reflex depression is seen. Thus it is tempting to postulate that the " loading " dose of UML 491 eighteen hours prior to perfusion was the vital factor in possible 5 HT blockade as seen in Fig. V.

Rocha e Silva *et al.* and Robertson[19 20] agreed, on excellent experimental evidence, that the action of 5 HT on guinea-pig ileum was due to stimulation of post-ganglionic cholinergic nerve fibres. Argentaffin cells are derived from the neural ectoderm and are seen on histological examination of the bowel to be richly supplied with nerve endings.[21] This suggests that the function of the nerve is closely related to the function of the argentaffin cell, or vice versa.

Attempts to demonstrate an increase in serotonin concentration in portal vein blood of rats after acid perfusion of the duodenum have been a failure.[10] However, Smith[22] employing a bioassay technique, demonstrated an increase in portal vein serotonin concentration in dogs after feeding them a meal. This may be due to duodenal 5 HT release as during the cephalic phase of gastric secretion the duodenal pH in dogs may fall to levels of 2-3.[23] Due to the large quantities of monoamine oxidase in the liver presumably no free amine reaches the peripheral circulation. Repeated doses of serotonin creatinine sulphate into the portal vein produce no effect on gastric secretion.[11]

There is another possible mechanism responsible for the gastric secretory changes noted. Can it be that the fall in gastric secretory volume and pH rise following HCl perfusion of the duodenum is due to 5 HT release from argentaffin cells acting as a cholinergic stimulus (directly or indirectly) and setting up a nerve reflex passing up the bowel in a retrograde manner to the stomach? Evidence for the presence of this reflex is seen in Figs. III, IV, V and VI. In Figs. I and II the results of previous workers have been reproduced by a different method. In Figs. III, IV, V and VI, evidence for a possible nervous pathway is immediately obvious. In Fig. III where cocaine has been painted onto the duodenal mucosa physiological HCl perfusion of the duodenum has no effect on gastric secretory volume or acid output. In this case presumably the cocaine has blocked either the release of 5 HT and/or nerve conduction. Secondly, the cocaine was painted on the duodenal mucosa in a band just distal to the pylorus and as near a few millimetres in width as possible. Humeral agents would hardly be affected by such a small area of local anaesthesia. Oxethezine gave similar results (Fig. VI), and as well as being a local anaesthetic, has some antiserotonin properties on rat bowel.[29]

In Fig. IV where the continuity of the bowel has been interrupted between sutures, physiological HCl perfusion again has no effect on gastric secretory volume or acid output. This experiment gives further support for the presence of a nerve reflex, as if some humeral agent

was responsible for these gastric changes, under discussion, release of the hormone would probably not be effected by bowel section.

In Fig. V where no effect is seen on gastric secretion after UML 491 the discrepancy between Resnick and Gray's results and those reported here can possibly be explained by the increased UML 491 dosage as UML 491 is a potent inhibitor of 5 HT in the rat duodenum.[24]

Thus it has been shown that acid perfusion of the duodenum leads to depression of gastric secretion, as measured by volume and acidity. No such changes occur when the duodenal mucosa has been anaesthetised with cocaine, or oxethazine (possible inhibition of 5 HT release and/or intramural nerve block), or after pyloric section where any intramural duodenogastric nerve reflex would be severed, leaving duodenal humeral agents unaffected. Furthermore, no reflex depression of gastric acidity is seen with HCl perfusion after use of UML 491, a potent serotonin antagonist in rat duodenum.[24]

However, the conflicting results seen after reserpine medication invite remark.

Resnick and Gray in their initial experiments showed that the gastric secretory volume and acidity depression seen after duodenal acid perfusion, occurred also in animals treated with reserpine. Thus they argued that as reserpine is known to deplete bowel 5 HT stones, and the reflex is not altered by reserpine, 5 HT release probably plays no part in the depression of gastric secretory volume and acidity after HCl perfusion of the duodenum. This conclusion was strengthened by experimental results with UML 491 and BOL 148. Again with these serotonin antagonists Resnick and Gray were unable to abolish the reflex depression of gastric secretion (however, as was pointed out supra, probably the loading dose of UML 491 eighteen hours prior to perfusion—which Resnick and Gray did not use—was the vital factor as complete inhibition of the reflex is possible with this higher UML 491 dosage (Fig. V)).

As can be seen from Fig. IX the levels of duodenal 5 HT after reserpine dosage of 2.5 mgms/kg, or 5.0 mgms/kg are similar. In Fig. VII with rats treated with reserpine 2.5 mgms/kg prior to perfusion inhibition of the gastric secretory volume has not been produced, but the titratable acidity fell. This latter finding is in agreement with Resnick and Gray's results,[11] but it is interesting to note that these workers also showed a gastric secretory volume fall. No reliable data could be collected on animals perfused after higher doses of reserpine as the ether anaesthena used was difficult to control in these animals. Finally, it is known that serotonin acts on post-ganglionic cholinergic nerve fibres[19 20] and that on histological examination of the bowel mucosa argentaffin cells are closely associated with nerve fibres.[21]

Thus an intramural duodeno-gastric reflex has been postulated, which is possibly dependent on duodenal acidity liberating 5 HT which either directly or indirectly leads to an inhibition of gastric secretion mediated via a nerve reflex as measured by volume and total acidity. In these experiments no enzyme studies were undertaken.

Other experimentors in this field have measured the gastric secretory changes over periods of hours, rather than minutes, so direct comparison

between this present study and those of Resnick and Gray[9 10 11] Code and Watkinson[28] and Andersson[30 31] could be questioned. That these authors demonstrated duodenal acid " control " of gastric secretion over periods of hours, rather than minutes (as in this paper) does not detract from the validity of this present study, but suggests that possibly there are several mechanisms interrelated and both leading to gastric secretory depression. Andersson put forward evidence that one of the duodenal depressive mechanisms operating on Heidenhain pouches in dogs, was a humeral one acting at the parietal cell level.[31]

However, this present study favours a duodeno-gastric nerve reflex mediated by duodenal 5 HT release. It is of interest that Code and Watkinson showed in 1955[28] that the depressive action of duodenal acid perfusion on gastric secretion in vagally innervated pouches in dogs, was lost after vagal section. However, as was mentioned above this vagal dependant depressive reflex was shown only with secretory studies over hours, rather than minutes.

Further experiments on this possible duodeno-gastric feed back reflex, in animals treated with atropine, hexamethonium, a high 5 HT, or 5 Hydroxytryptophane diet, or after prolonged fasting should be of interest.

If these results have any counterpart in human gastrointestinal physiology is another question altogether.

Summary

Changes in gastric secretory volume and acidity associated with duodenal infusion of HCl have been produced with evidence of a possible feed back control mechanism via intramural nerve impulses travelling in a retrograde fashion from the duodenum to the stomach. The evidence that 5 HT is involved has been discussed.

Acknowledgment

The author would like to thank Dr. John Field (Office of the Dean, UCLA Medical School) for the funds with which this work was carried out, and Mr. Harry Althouse of Sandoz Pharmaceuticals Ltd., San Francisco for the supply of UML 491. Mr. Robert C. Fulcher (Wyeth Pharmaceuticals Ltd., Philadelphia, Pa.) supplied the oxethazine hydrochloride, and the 5 HT duodenal assays were kindly performed by Prof. S. Eiduson (NPI, UCLA Medical School).

References

1. Erspamer, V. (1954). " Observations of the metabolism of endogenous 5 Hydroxytryptamine (enteramine) in the rat." *Experientia*, 10, 471.
2. Feldbergh, W. and Toh, C. C. (1953). " Distribution of 5 hydroxytryptamine (serotonin, enteramine) in the wall of the digestive tract." *J. Physiol.*, 119, 352.
3. Dalgeish, C. E. *et al.* (1953). " Fractination of the smooth muscle stimulants present in extracts of gastrointestinal tract. Identification of 5 Hydroxytryptamine and its distinction from substance P." *J. Physiol.*, 120, 298.
4. Jacobson, W. (1939). " The argentaffin cells and pernicious anaemia." *J. Path. and Bact.*, 49, 1.
5. Maximow, A. A. and Bloom, W. *Textbook of Histology.* W. B. Saunders and Co., Philadelphia.
6. Resnick, R. H. and Gray, S. J. (1961). " Distribution of Serotonin (5 Hydroxytryptamine) in the human gastrointestinal tract." *Gastroenterology*, 41, 119.
7. Gillman, J. " The structure of the basal granular cell (argentaffin) in the human (Bantu) alimentary canal with special reference to the anti anaemic factor." *S. Af. J. Med. Sci.*, 7, 144.

8. Collier, H. O. J. in G. P. Lewis, editor. 5 *Hydroxytryptamine*, London, Pergamon Press, Inc., p. 5.
9. Resnick, R. H. and Gray, S. J. (1962). "Chemical and Histological demonstration of Hydrochloric acid induced release of serotonin from intestinal mucosa." *Gastroenterology*, 42, 48.
10. Resnick, R. H. and Gray, S. J. (1962). "Serotonin release by Hydrochloric acid." I. *In vivo* and *in vitro* demonstration." *J. Lab. Clin. Med.*, 59, 462.
11. Resnick, R. H. and Gray, S. J. (1961). "Serotonin release by Hydrochloric acid. II. Is a feed back mechanism involved ?" *Am. J. Physiol.*, 201, 1017.
12. White, C. (1952). "The use of ranks in a test of significance for comparing two treatments." *Biometrics*, 8, 33.
13. Wermel, E. M. and Kacharova, E. A. (1948). "The role of the basal granular cells of mucosa of the small intestine in the production of secretin." *Anat. Rec.*, 101, 595.
14. Pletscher, A. (1958). "Topographical difference of the behaviour of 5 Hydroxytryptamine in the gastric mucosa after reserpine administration." In Lewis, G. P., editor. 5 *Hydroxytryptamine*. London, Pergamon Press, Inc., p. 84.
15. Author. To be published.
16. Benditt, E. P. and Wong, R. L. (1956). "The release of enterochromaffin cell substance by reserpine." *Am. J. Path.*, 32, 638.
17. Robson, J. M. and Stacey, R. S. *Recent advances in Pharmacology*. J. & A. Churchill Ltd., London, p. 147.
18. Brodie, B. B. (Dec. 1962). "Some current views on brain monoamines." *Psychopharmacology Service Center Bulletin*, Vol. 2, No. 5, p. 1.
19. Rocha e Silva, M., Valle, J. R. and Picarelli, Z. P. (1953). "A pharmacological analysis of the mode of action of serotonin (5 Hydroxytryptamine) upon the guinea pig ileum." *Brit. J. Pharmacol.*, 8, 378.
20. Robertson, P. A. (1953). "An antagonism of 5 Hydroxytryptamine by atropine." *J. Physiol.*, 121, p. 54.
21. Schofield, G. C. (1960). "Experimental studies on the innervation of the mucus membrane of the gut." *Brain*, 83, 490.
22. Smith, A. N. (1958). "The effect of 5 Hydroxytryptamine on acid gastric secretion." In Lewis, G. P. editor, 5 *Hydroxytryptamine*. London, Pergamon Press, Inc., p. 183.
23. Humphreys, J., Grindlay, J. H. and Bollman, J. L. (1960). "Duodenal acidity and experimental peptic ulceration." *Gastroenterology*, 38, 374.
24. Gyermek, L. (1961). "5 Hydroxytryptamine Antagonists." *Pharm. Rev.*, 13, 399.
25. Bogdanski, D. F., Bonomi, L. and Brodie, B. B. (1963). "Occurence of serotonin and catechol amines in brain and peripheral organs of various vertebrate classes." *Life Sciences*, No. 1, 80–84.
26. Weissbach, H., Waalkes, T. P. and Udenfriend, S. (1958). "A simplified method for measuring serotonin in tissues." *J. Biol. Chem.*, 230, 865.
27. Atkinson, M. and Henley, K. S. (1955). "Levels of intragastric and intraduodenal acidity." *Clin. Scien.*, 14, 1.
28. Code, C. F. and Watkinson, G. (1955). "Importance of vagal innervation in the regulatory effect of acid in the duodenum on gastric secretion of acid." *J. Physiol.*, 130, 233.
29. Fulcher, R. C. (Wyeth Pharmaceuticals Ltd.). Personal communication.
30. Andersson, S. (1960). "Inhibitory effects of hydrochloric acid in Antrum and Duodenum on gastric secretory responses to insulin hypoglycaemia in Pavlov pouch dogs." *Acta Physiol. Scan.*, 50, 23.
31. Andersson, S. (1960). "Inhibitory effects of Hydrochloric acid in the duodenum on gastrin-stimulated gastric secretion in Heidenhain pouch dogs." *Acta Physiol. Scan.*, 50, 105.

ROYAL ACADEMY OF MEDICINE IN IRELAND

Mr. Terence Edward Cawthorne, President of the Royal Society of Medicine, was admitted on 17th April, 1964, to the Honorary Fellowship of the Royal Academy of Medicine in Ireland by the President, Professor D. K. O'Donovan.