Thesis Approved

By

[Signature]

Major Adviser

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CENTRAL STIMULATION OF THE VAGI AND GASTRIC SECRETION

BY

CHARLES EUGENE ROSIERE

A THESIS

Submitted to the Faculty of the Graduate School of the Creighton University in Partial Fulfillment of the Requirements for the Degree of Master of Science in the Department of Physiology

OMAHA, 1952
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### Insulin 0.8u / Kg. I.V.

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### Insulin 1.5u / Kg. I.V.

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Effect of Insulin (0.8u/Kg i.v.) on Gastric Secretion and Blood Glucose

Graph I

- Pepsin Output / 30 min
- Acid Output in mM / 30 min
- Insulin 0.8u/Kg
- Time in Hours Post Insulin
- Blood Glucose mg%
EFFECT OF INSULIN (0.8 mU/Kg. I.V.) ON GASTRIC SECRETION AND BLOOD GLUCOSE

GRAPH II

PEPSIN OUTPUT / 30 MIN

ACID OUTPUT IN ml/M/30 MIN

INSULIN 1.3 mU/Kg

CONTROL

TIME IN HOURS POST INSULIN

BLOOD GLUCOSE Mg.%
EFFECT OF HYPERGLYCEMIA ON VAGAL GASTRIC SECRETION

GRAPH III

BLOOD GLUCOSE (Mg%)  

200

100

ACID OUTPUT (mM/30 MIN)  

2.0

1.0

0

GLUCOSE  

1.0 Gm/Kg I.V.

INSULIN  

0.8u/Kg I.V.
EFFECT OF HYPERGLYCEMIA ON VAGAL GASTRIC SECRETION

GRAPH IV

BLOOD GLUCOSE (MG%)

ACID OUTPUT (mM/30 MIN)

0 200 400

2.0 4.0

GLUCOSE 10 GM/KG I.V.

INSULIN 1.3 u/KG I.V.
EFFECT OF HYPERGLYCEMIA ON VAGAL GASTRIC SECRETION

GRAPH V

BLOOD GLUCOSE (Mg%)

ACID OUTPUT (mM/30MIN)

INSULIN 0.8 u/Kg I.V.

↑↑↑

GLUCOSE 0.5 G/KG I.V.  No IV
EFFECT OF THE GASTRIN MECHANISM ON VAGAL GASTRIC SECRETION

GRAPH VI

ACID OUTPUT (mM/30 MIN)

INSULIN 1.34/Kg. I.V.

Saline in Pylorus
Cocaine in Pylorus
EFFECT OF THE GASTRIN MECHANISM ON VAGAL GASTRIC SECRETION

GRAPH VII

ACID OUTPUT (mM/30 MIN)

INSULIN 1.3 u/Kg I.V.

Saline in Rumen
Cocaine in Rumen
EFFECT OF THE GASTRIN MECHANISM ON VAGAL GASTRIC SECRETION

GRAPH VIII

ACID OUTPUT (m M/30 MIN)

INSULIN 1.3 u/Kg. I. V.

Saline in Pylorus

Cocaine in Pylorus
EFFECT OF THE GASTRIN MECHANISM ON VAGAL GASTRIC SECRETION

GRAPH IX

ACID OUTPUT (mM / 30 MIN)

INSULIN 1.3 \text{uL/kg I.V.}

Saline in Pylorus
Cocaine in Pylorus
EFFECT OF HIGHER BRAIN CENTERS ON VAGAL GASTRIC SECRETION

GRAPH X

BLOOD GLUCOSE (mg%)

ACID OUTPUT (mM/30 MIN)

DECORTICATION

DECEREBRATION

INSULIN 0.8 μg/Kg. I.V.

INSULIN 0.8 μg/Kg. I.V.
That gastric secretion may be centrally stimulated was first shown by Pavlov in 1890 (1). After first conditioning his animals to the environment of the laboratory, he was able to elicit a definite secretory response, high in acid and pepsin concentration, by sham-feeding a mixture of meat and water. He also showed that this response could be abolished by section of the vagi, proving that the efferent fibers conducting the impulses were located in the vagal trunk.

After the discovery, isolation and purification of insulin by Banting and Best in 1922 (2), its physiological and pharmacological effects were studied by a multitude of workers. The gastric secretory effect of insulin hypoglycemia was shown by La Barre and de Cespedes in 1931 (3) by cross-circulation experiments in which the hypoglycemic blood of one dog was perfused into the carotid arteries of a second intact dog. Shortly afterwards, a definite increase in gastric secretion was observed in the intact animal. The effect could be shown to be by way of the vagi, since, following section of the vagal trunk the effect was abolished. La Barre and de Cespedes concluded that insulin hypoglycemia stimulated the vagal nucleus in the medulla which in turn stimulated the vagal trunk which increases the production of acid and pepsin in the fundus of the stomach. Thus an invaluable aid was discovered which has
been of great importance in the field of gastroenterology.

Since the effect of insulin hypoglycemia on gastric secretion was definitely shown to be mediated by the vagi, it proved to be a very useful tool in evaluating the integrity of the vagal supply to various types of pouches. It was in this way that Jemerin, Hollander, and Weinstein (4) observed that a large number of so-called Pavlov pouches of the stomach actually had very little or no vagal innervation. In a like manner insulin was used to detect the completeness of vagotomy in patients following vagotomy for peptic ulcer. Hollander in 1946 (5) did a quantitative study on the threshold level of hypoglycemia necessary for the stimulation of gastric secretion and found a blood sugar level of 50 mg.% to be necessary for the stimulation of gastric secretion.

To determine whether hyperinsulinism was a factor in the etiology of peptic ulcer, Abrahamson (6) conducted extensive experiments on patients with peptic ulcer. He found no significant difference between the blood sugar levels of the control patients and those known to have peptic ulcer. He concluded that hyperinsulinism is not a factor in the etiology of peptic ulcer.

Because of the tremendous importance of central stimulation of gastric secretion in the understanding and treatment of peptic and duodenal ulcers, much experimental work followed which concerned itself with the inhibition of
gastric acid and pepsin evoked by central stimulation. In view of the observation that hypoglycemia caused a stimulation of gastric secretion, the first obvious step was to determine the effect of hyperglycemia on central stimulation. Long before the isolation of insulin, Lecompte in 1900 (7) showed that instillation of 25% glucose into the duodenum caused a definite inhibition of gastric secretion. He believed that this inhibitory effect was due to a chalone being released from the duodenal mucosa acting much in the same manner as enterogastrone. The effects of intravenous glucose were studied in 1939 by Day and Komarov (8) who found that intravenous administration of 166 ml. of 30% glucose definitely inhibited the gastric secretory response elicited by sham feeding. They also showed that glucose in the same quantity had very little or no effect on the gastric secretory response elicited by histamine, a chemical which stimulates the parietal cells of the fundus directly. They concluded that hyperglycemia probably inhibits central stimulation of gastric secretion by diminishing the irritability of the vagal nucleus and peripheral stimulation by disrupting the osmotic balance of the parietal cell. The effect of intravenous glucose was shown in some very interesting experiments conducted by Hans Selye and MacLean in 1944 (9). Rats were given a severe stimulus which in the control experiments caused peptic ulcers. If large quantities of dextrose were given orally or intravenously before the severe alarm reaction
the ulcers were prevented.

Since it has long been known that the right vagus enervates the pyloric region of the stomach, it was suggested by Lim and Moser in 1951 (10) that central stimulation might exert an influence on the gastrin mechanism, an hypothesis they termed the adenteric reflex. They put forth this hypothesis following experiments in which the gastric secretory response following sham feeding was positively inhibited by locally anesthetizing the mucosa of an enervated pouch by perfusing it with a solution of 5% cocaine HCl.

In 1949, Jogi, Strom, and Uvnas (11) showed the effect of the higher brain centers on gastric secretion induced by insulin hypoglycemia. Their surgical preparations were conducted under nembutal or chloralose anesthesia on dogs whose control response to insulin hypoglycemia had previously been determined. In those preparations in which the cerebral cortex was removed by suction, and with environmental temperatures maintained at body temperature, it was observed that the gastric secretory response was abolished or markedly diminished during the first few post operative days. However, the response to insulin gradually increased in the course of 2 to 3 weeks post operative but never attained the control level, nor was the general nature of the response altered from that obtained in the intact animal. In the same manner they decerebrated 10 dogs and observed a marked
reduction in the gastric secretory response due to insulin hypoglycemia. In three of their preparations there was a significant amount of gastric secretion but was considerably less than the control level. They concluded that the vagal impulses are stimulated either by the removal of (cortical) inhibitory influences or by the activation of sub-cortical regions. They also assume that in the intact animal the secretory impulses for the control of gastric secretions emanate from the hypothalamic region.
STATEMENT OF THE PROBLEM

In order to study the mechanisms involved in the stimulation of gastric secretion caused by insulin hypoglycemia, it was first necessary to conduct control experiments. After the experiments were standardized, an attempt was made to analyze the data quantitatively with particular emphasis being given to: (1) the latent time, or the time between the administration of insulin and the succeeding gastric secretory response, (2) the threshold blood sugar level, or the level of hypoglycemia necessary to initiate a gastric secretory response, (3) the time between the initiation of the secretory response and the end of the response, i.e. the duration time, and (4) the presence or absence of the phenomena of "after discharge."

In view of the conclusions of Day and Komarov (8) mentioned previously an attempt was made to elaborate on the effects of intravenous glucose on the stimulatory action on insulin hypoglycemia.

Suspecting that stimulation of the vagi might possibly cause the release of gastrin, thereby causing an additive or synergistic effect on the direct stimulation of the vagi, by insulin hypoglycemia, cocaine HCl was perfused over the pyloric mucosa in an attempt to negate this hypothetical mechanism.

In order to ascertain the effect of the higher centers in the brain on gastric secretory stimulation evoked by
insulin hypoglycemia, the anatomical connections, first of
the cerebral cortex and then of the diencephalon were
abolished and the results observed immediately.
METHODS

Animals used in the chronic experiments were of two types. The first type of animal was equipped with a simple Mann-Bollman fistula of the fundus of the stomach by resecting a one inch loop of jejunum and anastamosing the distal end to an incision on the anterior surface of the stomach and bringing the proximal end to the outside. Continuity of the gastro-intestinal tract was maintained by an end-to-end anastamosis of the remaining intestine. All chronic surgical procedures were carried out under nembutal anesthesia and aseptic conditions. Great care was taken to leave the vagi completely intact. The second type of dog was also equipped with a Mann-Bollman fistula of the fundus of the stomach but in addition had what is termed a Pavlov pouch of the pylorus. This is constructed by making a semi-circular incision of the muscularous perpendicular to the greater curvature at the pyloric-fundic junction. The muscularous was seperated from the mucosa by blunt dissection over the lesser curvature. Thus the vagal fibers in the muscularous of the lesser curvature were left intact leaving the pylorus completely ennervated by the vagus. The pyloric sphincter was then sectioned and brought to the surface of the abdomen. The duodenal stump was sutured and a posterior gastro-enterostomy constructed to allow emptying of the stomach.
Control experiments to determine the effects of insulin were conducted in the following manner. After a 24 hour fast, trained dogs were placed in stocks and collections of gastric secretions were made at 30 minute intervals until two consecutive collections yielded low and very nearly equal quantities of total acid. Control blood sugars were taken during this period. This period is termed the control period. At this time the insulin was administered intravenously and blood samples were taken at \( \frac{1}{2}, 1, 1\frac{1}{2}, 2, 3, \) and 4 hours following the injection of insulin. Collections of gastric juice were taken every 30 minutes until the total acid output showed a definite tendency towards the control values. Enzyme analysis for pepsin were also made on each 30 minute collection of gastric juice.

To study the effects of intravenous glucose, we injected various doses at various times following the injection of insulin.

To study the effect of the perfusion of cocaine in the pylorus, concentrations of cocaine from \(2\%\) to \(5\%\) were perfused in the pyloric pouch for 30 minutes. In order to study the time element the cocaine was perfused at four different time periods following administration of insulin. To eliminate any effect of the volume of the cocaine solution, saline was perfused throughout the experiment except for the 30 minute period during which the
cocaine was being perfused.

Free and total acid secretions of the stomach were obtained by titrating the gastric secretions with a solution of NaOH, approximately 0.03 N, using Tophers and Phenolphthalein as indicators.* Pepsin analyses were done following the Bucher modification of the Mersky-Anson hemoglobin substrate method (12). Standards were run against known quantities of crystalline pepsin as supplied by Armour Laboratories. Both pepsin concentrations and output were calculated and reported in micrograms of crystalline pepsin. The blood glucose levels were determined according to the method of Symogyi (13).

The effects of insulin hypoglycemia in the decorticate and decerebrate animal were ascertained in the following manner. Animals were equipped with a fundic fistula of the stomach as previously described. At least three days separated the surgical preparation from the control experiments which were chronic in nature. After a 24 hour fast, the dogs were anesthetized by ether inhalation. The trachea and left carotid artery were cannulated. This was necessary in order to be able to apply artificial respiration and record blood pressure. The head was fixed in an appropriate position by means of a modified Horsley-

*only total acid output is reported in the graphs and charts
Clark head holder attached to the operating table. All approaches to the cephalic brain stem (mid-brain and pons) were made by exposing the occipital lobes by an appropriate opening in the skull. The occipital pole was elevated and retracted by gentle traction with a wide rigid spatula. This procedure routinely exposes to direct visibility the dorsal surfaces of the body tentorium, the inferior colliculus and superior colliculus with a minimal loss of blood. Following this, a long hemostat was projected ventrally at the desired level and with the desired slant to envelop the brain stem. The widely opened hemostat was pushed gently down, the tips opened laterally to follow the bone of the lateral side of the cranium and downward to the bone which forms the base of the cranium. Thus, upon clamping the hemostat, complete transection of the brain stem was executed at the desired level. When the above procedure was carried out there was little bleeding along the path of the transection, and there was little tissue destruction under optimum conditions. Usually within a half hour the hemostat was opened slightly and withdrawn. After section of the brain stem the ether anesthesia was discontinued. Control collections of gastric secretion were made until two consecutive one-half hour collections yielded approximately equal quantities of total acid. Blood sugars were taken during this control period. Insulin
was then administered intravenously and effects noted on gastric acid and pepsin secretions, blood sugar, and blood pressure. After the return of the blood sugar to normal, in approximately 3 to 4 hours, a second dose of insulin was administered. 30 minutes following the second injection of insulin, the mid-brain was sectioned as described above and the same protocol followed as in the case of decortication.
PRESENTATION OF DATA

The results of the control experiments are shown in Graphs I and II and the data tabulated in fig. I. It may readily be seen that the acid output of the stomach is increased as the blood sugar level is diminished by the action of the insulin. The latent period was calculated in the following manner. There was no stimulation of the acid secretion in the first 30 minutes following the injection of insulin. However, in the following 30 minutes there was a marked quantity of acid secretion, therefore, the latent period must be between 30 and 60 minutes. This is due to two factors: (1) a threshold level of hypoglycemia must be reached before stimulation can occur and, (2) there undoubtedly is a short time lag due to mechanical drainage of the secretions of the stomach. I shall assume, arbitrarily, the latent period to be from 40 to 50 minutes. The level of hypoglycemia which must be obtained must likewise be concluded rather arbitrarily. The point of the curve where the rising acid secretions intersect the falling blood sugar level indicates a threshold level of 30-40 mg.%. However, if 10-15 minutes be allowed for mechanical drainage the level will be found to be in the range of 40-50 mg.%, for all practical purposes. The duration time of the stimulus may then be determined simply by determining the length of time during which the blood sugar level is below 45 mg.%.,
following a single injection of insulin. This was found to be 120 minutes and 135 minutes for doses of 0.8 and 1.3 units of insulin per Kg. intravenously, respectively. From the data presented it is impossible to determine the duration of the response except by extrapolation since most of the experiments were terminated after 4 hours. It is obvious, however, that even after four hours or 240 minutes, the output and concentration of acid in the gastric secretions is far above the control level.

In order to determine the effect of hypoglycemia on the gastric secretory response due to insulin two types of experiments were conducted. Using the experiments cited previously as control experiments the same protocol was used except that large quantities of glucose (0.2-1.0 Gm./Kg.) was administered before and at the height of insulin hypoglycemia. The results are shown very clearly in Graphs III, IV, V, and VI. It may readily be concluded from Graph III that the blood glucose level was elevated above the threshold level within the latent period of insulin, thus completely negating the effects of the stimulus. One and one-half hours following the injection of insulin, the exogenous glucose seems to have either been stored or excreted. The moderate hypoglycemia that followed is an inadequate stimulus since it did not remain at the threshold level for a sufficient length of time to cause a gastric secretory response. Graph IV shows the same effect in causing a delay of the
onset of hypoglycemia. It is interesting to observe that the exogenous glucose was either stored or excreted within the time of the duration of the stimulus, thus an adequate stimulus ensues with a resulting stimulatory effect on gastric secretion.

Graph V is a representation of the effect of intravenous glucose administered after gastric secretion has been stimulated by insulin hypoglycemia. This experiment shows very clearly the reciprocal relationship between hypoglycemia and hypersecretion and hyperglycemia and hyposecretion.

The determination of the effect of cocaine HCl perfused in an enervated pouch of the pylorus on the secretory effect of insulin hypoglycemia was carried out in the following manner. Because of the possible time effect, 4 types of experiments were conducted: (1) cocaine perfused from 0-30 minutes after injection of insulin, (2) 30-60 minutes after insulin, (3) 60-90 minutes after insulin, and (4) 90-120 minutes after insulin. The graphical representation of typical experiments are shown in graphs VI, VII, VIII, and IX. If graph VI is compared with the control graph (II), it may be observed that the stimulation of acid secretion due to insulin hypoglycemia may be somewhat delayed although there is no gross apparent change in the shape of the curve. Graph VII, when compared with the control graph (II) shows no suggestion
of an inhibition of gastric secretion, also it must be mentioned that the graph is the result of a single experiment and the apparent increased response to insulin hypoglycemia, is within the bounds of the control experiments on the particular animal. Graph VIII represents the results obtained when cocaine HCl was perfused from 60-90 minutes following insulin administration and graph IX the results obtained when cocaine HCl was perfused from 30-60 and 90-120 minutes following insulin administration. As in previous experiments there is very little or no change from the control experiments as shown in graph II.

The effect of the higher brain centers on gastric stimulation evoked by insulin hypoglycemia are shown in graph X. As may readily be observed, there is no stimulation of gastric secretion following abolition of the cerebral cortex in spite of a marked hypoglycemia. This observation is made more striking in view of the fact that immediately following section of the mid-brain a moderate flow of gastric secretion ensues.
SUMMARY

It has been shown that insulin hypoglycemia stimulates gastric secretion in the normal animal. Quantitative analysis of the data obtained indicates that there is a latent period for this effect of approximately 45 minutes, the threshold level of hypoglycemia is approximately 45 mg.%, and that the duration of the response is longer than the duration of the stimulus, suggesting the presence of the phenomena of "after discharge."

It is shown that hyperglycemia definitely inhibits the gastric secretory response due to insulin hypoglycemia.

It is suggested that there is a definite synergistic relationship between direct vagal stimulation of the fundic glands and the gastrin mechanism.

The effects of insulin hypoglycemia on gastric secretion may be greatly modified by the higher centers in the brain. Section of the cerebral cortical pathways inhibits this effect completely while subsequent section of the hypothalamic pathways tends to make the response normal.
CONCLUSION

In view of the previously mentioned experiments it can be concluded that insulin hypoglycemia does stimulate the production of gastric secretion, both acid and pepsin. This effect must originate in the vagal nucleus of the medulla and can be modified by higher centers in the brain as well as hyperglycemia. The effect of insulin hypoglycemia possibly works synergistically with other stimuli. It has been shown that at an insulin dosage of 0.8 and 1.3 units per Kg., given intravenously, the latent period is approximately 45 minutes. This is due to two main factors: (1) the lag in time to allow for mechanical drainage of the secretions after they have been stimulated and, (2) the time necessary to lower the blood glucose level to a stimulating or threshold level. The threshold blood glucose level was found to be approximately 45 mg.%. The duration time of the stimulus was found to be 120 and 135 minutes for doses of 0.8 and 1.3 units per Kg., respectively. The duration of the response was found to be in excess of 200 minutes and therefore it can be stated that the presence of the phenomena of "after discharge" is definitely indicated. It is suggested that this phenomena of "after discharge" occurs in the diencephalon, since, after abolition of this area by surgical means, the time necessary for the duration of the response is lessened.
The effects of administration of higher doses of glucose intravenously have been shown. If the reason for stimulation of gastric secretion following insulin is the resulting hypoglycemia, it naturally follows that high blood glucose levels will inhibit or abolish the effect. If the glucose is administered within the latent period of the action of insulin, the exogenous glucose does inhibit the stimulation of gastric secretion. However, if the exogenous glucose is excreted or stored within the time of the duration of the stimulus, the blood level of glucose will decrease to a level which is sufficient to stimulate gastric secretion. If the exogenous glucose is given during the height of the secretory response a short but definite decrease in gastric secretion is observed. The effect of hyperglycemia may well be attributed to decreasing the irritability of the vagal nucleus, but it is impossible to prove definitely. The effect may also be peripherally as shown by Day and Komarov (8).

The possibility of a synergistic phenomena between direct vagal stimulation of the parietal cell and by indirect stimulation via the gastrin mechanism is shown. In many of the experiments the response to insulin hypoglycemia appeared to be delayed when accompanied by perfusion of cocaine HCl in the enervated pyloric pouch. The decrease in acid production appeared to be much more rapid.
when cocaine HCl was perfused in the pylorus. These two mentioned observations may be interpreted to mean that there is a positive potentiation between direct vagal and indirect stimulation of gastric glands. This potentiating phenomena is best illustrated at the very beginning and near the end of the blood glucose curve following insulin administration. The fact that it does not appear during the peak of hypoglycemia may be due to the fact that the stimulation due to insulin at this time is so strong that it over-rides or masks the gastrin potentiating mechanism. Thus it may be concluded that the vagus could very well ennervate the gastrin producing glands of the pylorus and potentiate the gastric secretory response due to direct stimulation of the vagus.

The effect of the higher brain centers on gastric secretion induced by insulin hypoglycemia appears to be very marked in the experimental animal immediately following section of the brain. From the experiment shown it may be concluded that the mid-brain is primarily an inhibitory center for gastric secretion and that the cortex serves as an inhibitor to the inhibitory center in the mid-brain. In summary, gastric secretion can be stimulated in the intact animal and in the animal following section of the mid-brain but cannot be stimulated in the animal following section of the cerebral cortex.
1. Pavlov and Shumov-Simanovski, Vratch No. 41, 1890


3. La Barre and de Cespedes, Sur l'origine parasymphathique de l'hyperscretion gastrique consecutive a l'administration d'insulin, Compt. rend. Secc. de biol. 106: 484-486, Feb. 20, 1931


7. Lecompte, P., Inhibition of Gastric Secretion by Intra-Duodenal Glucose, La Cellule 17: 297, 1900


11. Jogi, Strom, and Uvnas, Effect of CNS Secretions on Gastric Secretion Induced by Insulin Hypoglycemia, Acta Physiologica Scandinavica 17: 212, 1949
