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LOYOLA UNIVERSITY

STUDIES

ON THE INTESTINAL ABSORPTION OF HISTAMINE
I. THE EFFECTS OF VARIOUS CHEMICAL AGENTS
APPLIED TO THE MUCOSA

A THESIS

SUBMITTED TO THE FACULTY
OF LOYOLA UNIVERSITY GRADUATE SCHOOL
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MASTER OF SCIENCE

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BY

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INTRODUCTION

Histamine has been found by chemical and bacteriological methods to be present in the normal, and to a slightly greater extent, in the pathological intestinal tract. Mutch (1) isolated a histamine producing bacillus from pieces of bowel removed from human patients by surgical operation. The discovery has been made repeatedly by others in both humans and in animals, and lately Koessler and Hanke (2) have made quantitative estimates of the histamine present in the intestinal contents of normal human beings of dogs and guinea pigs.

Extensive studies have been carried out on the absorption of histamine from the intact intestine of laboratory animals. Mellanby (3), using cats, found that the histamine was absorbed from virtually all parts of the intestine, but to the greatest degree from the ileum. Meakins and Harington (4) duplicated these experiments with the cat as a laboratory animal. The latter workers noted that a segment of the intestine, whose mucosa had been damaged by temporarily stopping off the blood supply beforehand, did not absorb the histamine so readily as when the intestine was intact. Curiously enough, a physiological difference is manifest between the absorptive powers of the cat on one hand, and the dog, guinea pig and man on the other. Koessler and Hanke (2) noted that no toxic symptoms followed after feeding large amounts of histamine to guinea pigs and to dogs. Ivy (5) gave 225 mgms. to a man by stomach tube,

with no consequent toxic effects.

The fate of histamine artificially placed in the intestinal tracts of the aforementioned animals is not entirely known. Enough was absorbed from the bowel of the cat into the blood to cause toxic symptoms, but the intestine of the dog, as an example, is not so permeable. Koessler and Hanke (2) believe that histamine which is fed to a dog by stomach tube is "rendered physiologically inert in its passage through the intestinal wall." The evidence in support of this theory is that when 500 mgm. of histamine were fed to a 5 kilo dog, this histamine disappeared very rapidly without evoking a marked physiological reaction. Upon killing the animal two hours later, the stomach and intestinal contents were examined for the presence of the drug. Only one half of the histamine could be accounted for in the stomach, intestines and their contents. The other half of the histamine originally fed was evidently absorbed, but certainly not all of it as histamine, for the rate would have been so fast as to cause the severest symptoms of shock, and perhaps death. We know that histamine, if injected into the systemic circulation at a rate which has been determined by Koessler and Hanke to be .0027 mgm. per minute in dogs, will cause a pronounced fall in blood pressure. In the above experiment the absorption of histamine, if unchanged, would have been at the rate of 2.2 mgm. per minute, a speed which is inconsistent with the absence of symptoms of absorption. It was likewise found that the liver plays no important role in detoxifying

histamine, so that the only conclusion which is warranted in the light of present knowledge is that the histamine is rendered harmless by the intestinal mucosa.

It is evident, from the brief resume given, that different animals show properties of the intestinal tract toward histamine which are peculiar to their species. A high threshold for the appearance of toxic symptoms has been referred to in the guinea pig, dog and man. To lower this threshold, or in other words, to increase the rate of disappearance from the intestine of histamine artificially placed there, so that the drug will be brought to the blood as histamine, is a problem of practical and theoretical value. One possibility, suggested perhaps to many by the analogous absorption of histamine-like substances in extensive tissue destruction, is that a high threshold may be reduced when the healthy alimentary tract is injured in any way.

The degree of functional impairment suffered by the intestine when it is damaged and its relation to absorption of histamine was investigated by Meakins and Harington (4). Their conclusion, based on the results obtained with cats, was that an injured intestinal mucosa retards absorption of histamine. Most writers have accepted this conclusion to be applicable to all cases of intestinal injury. Recently, Wangensteen and Loucks (6) found that histamine absorption from a simple obstruction and from a strangulated segment of small intestine of the dog cannot be detected by the physiologic test for histamine. The

purpose of this work is to show that in certain abnormal conditions of the mucous membrane of the gut, the rate of absorption of histamine from the intestinal tract is increased, or that the threshold for the appearance of symptoms of this absorption is considerably lowered.

A study by Spadolini (7) suggested that the functional derangement due to a damaged mucosa, in certain instances at least, will permit an increased rate of passage of histamine from the bowel into the circulation. Spadolini injured the intestines of dogs with chloroform, and attributed depressing and tetanic symptoms which later occurred, to the freer passage of toxic substances to the blood by virtue of the damage instituted. A study was made, in acute experiments upon dogs, of the effect upon histamine absorption brought about by injury to the intestinal mucous membrane by chloroform. Moreover, the study was continued, using other chemical agents to injure the mucosa, attempting in this way to learn if the increased permeability in the case of this drug is due solely to the damage inflicted.

METHOD

Chemical agents which are known to be destructive to epithelium were employed. These agents were injected into the intestinal tracts of dogs which were under the influence of an anesthetic. The dogs had previously been deprived of all food for 24 hours or longer. It was necessary to learn by experience the use of the proper concentrations of the chemicals which would be necessary to promote the intestinal injury without producing any undesired systemic effect, e.g. a low blood pressure. Some of these solutions were injected into the duodenum, others into the colon, and in earlier experiments, an injection of normal saline followed the introduction of chemical agents as a control measure.

Sodium barbital was preferred as an anesthetic because when under its influence there was little fluctuation of blood pressure and respiration. A small amount of ether was administered sometimes while the bowel was manipulated. The nature of some of the drugs employed as injuring agents required an anesthetic which could be removed during the absorption of the drug. When alcohol was intended for use in damaging the intestinal mucosa, ether was the choice for anesthesia. Certain concentrations of chloroform in oil, however, when used to injure the intestinal epithelium, left the blood pressure and respiration unaffected while the animal was under the influence of barbital narcosis. The dose of sodium barbital given was 0.3 to 0.35 gm. per kilo of body weight, and this was administered,

After solution in water, by stomach tube.

The technique in preparing the animal varied as the work progressed. A rubber catheter was introduced into the duodenum through an incision made above the pylorus, and through this catheter the various drugs and the histamine were injected. Later there was evidence that some of the solutions injected were regurgitated from the small intestine back into the stomach. This was prevented in future work by transecting the catheter about 6 cm. from the tip, and uniting the two segments by means of a short glass tube. The catheter was inserted into the duodenum as before, but when the glass tube was felt to be at the pyloric valve, a tight ligature was placed about the bowel at that point. In some experiments, peristalsis of the intestine was suspected as propelling the solutions aborally so fast that no local action could be produced. For this reason an incision was made in the intestine, about 18 inches below the pylorus, and a cork which had a groove cut into it perpendicular to its long axis, was inserted in the oral direction into the lumen of the gut. A ligature applied about the intestine held the cork securely in place when tightened over the groove, and prevented any fluid from coming into contact with a part of the tissue injured by the ligature. The bile duct was ligated in most cases when hydrochloric acid or alcohol was used. The reason for this precaution is obvious, because these substances might act as cholagogues, and the bile could then dilute the fluids injected,

and so obscure results.

When injections were made into the colon, the catheter was inserted into that organ through an incision near the end of the ileum, and ligated so that there could be no reflux into the ileum. The colon of a dog is quite short, and one of our experiments was spoiled because some of the solutions injected flowed from the anus. The anus was closed in later work by means of single sutures, and the solutions were injected very slowly so that no distention of the segment would follow.

Some of the histamine, the dichloride, was obtained from Dr. M.T. Hanke of the University of Chicago. Another preparation used was the histamine acid phosphate or ergamine preparation of Burroughs Wellcome Co., New York. The dichloride has about twice as much active principle as the acid phosphate, and therefore 5 mgm. per kilo of body weight of the former, and 10 mgm. per kilo of the latter substance were injected after being dissolved in 10 to 20 cc. of warmed normal saline. All solutions were heated to 40 degrees before injection.

As criteria of histamine absorption, recourse was had to the most invariable and easily elicited signs which are at present known. Of these, the change in blood pressure, is perhaps the most noteworthy, and then the alteration in respiration. A definite interval of time was permitted after the injection of the chemicals so that the blood pressure, if it was influenced in any way, could return to normal or near normal before the histamine injection. Pancreatic secretion is known

to be affected by histamine when in the blood in certain concentrations. In most of our work we cannulated the pancreatic duct of Santorini for a possible normal secretion, and to note the effect of histamine upon such a secretion. No quantitative measurements of gastric juice were made, although at the end of every experiment, when a necropsy was performed to study the condition of the segment worked upon, an examination was made of the stomach, and it was always found to be dilated with fluid when there was other evidence that histamine had been absorbed.

RESULTS

CONTROL EXPERIMENTS

Four animals were used as controls. These dogs were placed under sodium barbital anesthesia. Histamine in saline solution was led into the duodenum of each of these dogs with no subsequent signs of absorption. To test the potency of the histamine used, 1 mgm. was introduced intravenously in dog 57A. The blood pressure fell 60 mm. within 20 seconds, and dropped from 140 mm. before the injection to 68 mm. within 2 minutes after the injection. There was a slow return toward the original pressure.

CHLOROFORM

Two animals were used in this series. The site of injection was the duodenum. A positive result was obtained with two dogs, 56A and 63A. The original blood pressure of 56A was 120 mm. A mixture of 10 cc. chloroform and 10 cc. paraffin oil was injected into the duodenum, and 48 minutes later, 50 mgm. histamine dichloride was introduced. The blood pressure fell to 88 mm. within 2 minutes after the histamine injection (Fig. 1). The blood pressure was 58 mm. 14 minutes later, and 1½ hours after, it had returned to 130 mm. The respiratory change was from the normal rate of 21 respirations per minute to an average of about 12 per minute. Post-mortem examination revealed the duodenum to be quite hyperemic and the stomach filled with fluid.

The blood pressure of dog 63A fell from 108 mm. to 94 mm. in $3\frac{1}{2}$ minutes after the injection of 25 mgm. of histamine dichloride. To promote injury, 3 cc. of chloroform and 7 cc. paraffin oil was injected previously. The time lapse between injection of the irritant and histamine was 37 minutes. The fall in blood pressure as a response to histamine absorption was immediate, though not so profound as in the preceding animal. The return toward normal required about 25 minutes.

HYDROCHLORIC ACID

Hydrochloric acid was injected into the duodenum in the case of five dogs, and into the colon of one instance. Of the first five animals, three showed the effects of histamine absorption after a solution of 0.4% HCl, in amounts from 20 to 35 cc. were led into the duodenum. In dog 65A (Fig. 2) the blood pressure fell from 128 mm. before the histamine, to 92 mm. within one minute after, and to 84 mm. within 10 minutes after the histamine introduction. The respiration changed from the thoracic to the abdominal type, and defecation took place soon after the injection. Dog 88A showed a drop in pressure of 16 mm. within one minute, and a total fall of 26 mm. in $3\frac{1}{2}$ minutes. The respiratory change was doubtful. No pancreatic secretion was obtained either before or after the histamine absorption. The fall in blood pressure in dog 91A was 18 mm. within 1 minute after the histamine injection, but the respiratory change in this dog was much more apparent than in any other

animal, for the breathing changed from the long and easy to the short and spasmodic type. No pancreatic secretion was obtained. The HCl had caused the mucous membrane to be hyperemic in each of these instances. Histamine was evidently also absorbed from the colon of dog 89A, for the drop in pressure after histamine introduction was 20 mm. in $1\frac{1}{2}$ minutes, and a maximum fall of 32 mm. was realized in about 15 minutes. There was no pancreatic secretion. The colon was found to be very slightly hyperemic.

A negative result was obtained with dog 67A. An injection of 40 cc. of 0.3% acid was made into the duodenum, and later on the histamine solution was introduced. The bile duct was not ligated, nor was the pancreatic duct cannulated. In dog 69A, the drop after histamine injection was so slight that it might readily be confused with the result of a reflex action, and the experiment was therefore inconclusive.

MUSTARD OIL

This substance was used with no apparent success. In one dog, 77A, 20 cc. of a $1/5$ of 1% solution were injected into the duodenum, followed 13 minutes later by 90 mgm. of histamine acid phosphate. The blood pressure did not change, nor did the post-mortem examination reveal any ischemia or hyperemia of the mucosa. A stronger concentration, 20 cc. of a 0.5% solution injected into dog 78A also failed to aid in increasing the rate of histamine absorption. The blood pressure before the injection of mustard oil was 108 mm. and about 45 minutes later, or

just before the histamine introduction, it had fallen to about 72 mm. The gradual fall then in progress was not modified by the injection of histamine. The mucosa, as seen at necropsy, was not involved.

SODIUM FLUORID

Sodium fluorid was injected into the colon of one dog and into the duodenum of another. In dog 79A, 25 cc. of a 1.0% solution of NaFl were led into the colon, followed 50 minutes later by 50 mgm. of histamine acid phosphate. The original blood pressure of the animal was very low, about 60 mm., and the histamine did not appreciably change this. The mucosa of the colon seemed intact. Conditions were more favorable in dog 80A for histamine absorption. 20 cc. of 2.5% NaFl led into the duodenum caused a watery defecation and the blood pressure fell from 146 mm. to 100 mm. in 30 minutes. Histamine accelerated the slow fall somewhat, and the pressure dropped from 100 mm. to 90 mm. in 9 minutes. The pancreas did not secrete before or after the histamine absorption. A thick, gluey mucous was apparent in the intestine on later examination, and also a slight hyperemia in the lower part of the small bowel.

CARBON TETRACHLORIDE

Three animals were given CCl₄ and two positive results were realized. Dog 81A was given 25 cc. CCl₄ into the duodenum, and 23 minutes later, 45 mgm. acid phosphate. The blood pressure fell slowly after histamine injection for about 21 minutes, descending within this time from 104 mm. to 76 mm.,

and then suddenly it dropped 26 mm. within 2 minutes. Such a sudden fall is typical of a rapid histamine absorption, but it usually follows immediately after histamine introduction. There was no pancreatic secretion whatsoever from the dog.

Into the duodenum of dog 87A, 15 cc. of CCl_4 were injected, followed 58 minutes later by 50 mgm. histamine acid phosphate. The blood pressure fell 16 mm. in 3 minutes, and 10 minutes later was 37 mm. lower than the original level. No pancreatic secretion was obtained, nor was there any noticeable change in respiration. The gut of this animal and of the previous one mentioned showed hyperemia due to the CCl_4 . Another dog, 86A, had such a low blood pressure even before giving CCl_4 into the duodenum, that no change was noted due to the histamine.

ALCOHOL

Dogs under barbital anesthesia are easily killed when alcohol is later introduced into the alimentary tract. When alcohol was to be put into the intestine, ether was the anesthetic employed.

Dog 74A showed a drop in blood pressure of 30 mm. one minute after 30 mgm. histamine dichloride had been injected. 30 cc. of 20% alcohol had been injected into the duodenum 16 minutes before this time, and the blood pressure was then 140 mm. The blood pressure was at 56 mm. 13 minutes after histamine injection. The respiratory change was not conclusive. About one

hour after the first histamine injection, when the blood pressure had returned to 120 mm., 30 cc. of 10% alcohol were led into the duodenum once more, followed two minutes later by 60 mgm. histamine acid phosphate. The blood pressure fell to 112 mm. in 3 minutes, and then rose slowly again to the former level. The post-mortem investigation showed the duodenum to be hyperemic.

Another attempt which was successful was made with dog 83A. 20 cc. of 25% alcohol were injected into the duodenum and 13 minutes later, 28 mgm. of histamine dichloride were introduced. The original blood pressure was 98 mm. and the histamine injection caused the blood pressure to fall to 84 mm. in one minute. It was still at 84 mm. after ten minutes, and then began slowly to rise. The respiration did not change. There was no pancreatic secretion, and the duodenum, after the dog had been killed, was seen to be slightly hyperemic.

A less marked result was obtained with 72A. The blood pressure, which was 104 mm. before histamine injection, fell very slowly and was 88 mm. 9 minutes later. It regained the height of 104 mm. in about $\frac{3}{4}$ hour. A negative result was obtained with dog 82A whose original pressure, before histamine introduction, was 86 mm., and it did not change when histamine was led into the duodenum. There was no pancreatic secretion from any of these animals. The mucosa in each of these dogs was rendered hyperemic by the alcohol.

Four attempts were made to "force" absorption of hist-

amine from the colon by means of alcohol. Three of these attempts gave positive results. A 30% solution of alcohol was injected into the colon of dog 75A, and 8 minutes later, 27 mgm. histamine dichloride were injected. The blood pressure fell to 82 mm. from 140 mm. in $\frac{1}{2}$ minute, and to 66 mm. in 20 minutes. No decided change could be distinguished in the respiration. Defecation took place after histamine injection. The cecum appeared normal upon later inspection. The result was not so accentuated with dog 76A, into whose colon 20 cc. of a 15% solution had been led. Five minutes later, 30 mgm. histamine dichloride were introduced into the colon and the pressure fell in $\frac{1}{2}$ minute from 132 mm. to 116 mm., and further to 80 mm. in 20 minutes. The respiratory change was not convincing. The large intestine was later found to be normal, and the stomach was dilated with fluid. Neither of these animals gave a pancreatic secretion. When alcohol and histamine solution were injected into the colon of dog 84A, some of the fluid was found to have escaped from the gut through the anus. No fall in blood pressure was noted here, and on examination, we found no apparent hyperemia in the colon. The anus was closed by means of sutures in dog 85A, and 20 cc. of 30% alcohol was led into the colon, and 20 minutes later it was followed by 55 mgm. histamine acid phosphate. The original blood pressure was 108 mm., and this fell to 53 mm. in one minute. The individual respirations (Fig.3) decreased in size, and the normal pancreatic secretion of a drop every 5 to 7 minutes was not changed. The

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mucosa of the colon was quite bloody when examined after the animal had been killed.

RESULTS OBTAINED WITH GUINEA PIGS

Four attempts were made to reproduce the absorption of histamine from the intestines of dogs upon guinea pigs. In these animals the asphyxia, the result of stimulation of the bronchial musculature, is the most notable phenomenon of histamine absorption. We used urethane, 1 gm. per kilo of weight, as anesthetic with three guinea pigs, injecting it into the peritoneal cavity. Solutions of 30% alcohol were injected into the small intestine of two animals and into the cecum of a third. This was followed a little later by 2.5 to 3 mgm. histamine dichloride. No asphyxia followed. A fourth animal was anesthetized with ether to preclude any involvement of the respiratory apparatus which might follow urethane narcosis. Upon similar administration of alcohol and histamine, no change in the animal was noted. All of the animals died when a fraction of a milligram of histamine was injected into the femoral or mesenteric vein.

DISCUSSION

The fall in blood pressure was in all cases the most conspicuous result of histamine absorption. This drop was sharp in most instances, followed soon after by a small rise, and a little later by a more gradual fall than the first. Recovery toward the normal pressure, when it did occur, always took place after a comparatively long time, from 20 minutes to an hour. A full discussion of the curve of depression due to the presence of histamine in the blood is given by Dale and Laidlaw (8). The apparent difference in intensity of the effect of histamine on the different animals used cannot be explained satisfactorily. The rate of absorption seems not to be directly proportional to the amount of injury of the mucosa, for this has not been found by the experiments to be true. We must consider here also the altered physiological condition of the entire organism which may influence in one way or another the threshold of histamine absorption from the injured gut.

The other phenomena issuing from absorption of histamine are less conclusive because they are less sharply defined than the change in blood pressure. The respiratory effect on dogs is not so profound as it is on guinea pigs or rabbits (9). Nevertheless, on several occasions cited, the absorption of the drug was accompanied by the change in respiration attributed to constriction of the bronchial musculature. Gastric secretion is increased when small amounts of histamine are in the blood, while under the same conditions, pancreatic secretion is

not influenced at all. Conversely, if a large amount of histamine is present in the blood at any one time, pancreatic secretion is stimulated and gastric secretion is inhibited (10). This is in accordance with the above experiments, the results of which would indicate that in no instance was the absorption fast enough to cause pancreatic secretion if there had normally been none, or to increase it if there was a normal flow from the duct.

Gastric secretion is known to follow upon alcohol administration by mouth when the alcohol solutions are not too concentrated. It is commonly considered that the secretion is due to the direct stimulating action upon the mucosa by the alcohol in the stomach or in the blood by reason of its absorption from the intestine. The results given above suggest that the alcohol may affect the mucous membrane of the alimentary tract so that histamine-like substances which are normally prevented from passing through the intestinal wall, may now find their way into the circulation and act as secretagogues upon the gastric glands.

The experiments indicate that damage to the mucosa of the alimentary tract will not invariably retard absorption of toxic substances. If the mucosa, as Koessler and Hanke believe, is the agent whereby the histamine contained in the intestine is detoxified, this property of the mucous membrane may be weakened or lost by the action of some chemicals which are occasionally taken into the intestine.

The results upon guinea pigs indicate further the difference in the physiology of the intestinal tract toward histamine absorption in different species of animals. With this type of laboratory subject it is difficult to obtain the same ideal conditions for any possible absorption because of the large amount of material present at all times in the alimentary tract.

SUMMARY

The anesthetized but otherwise normal dog shows no systemic effect from the introduction of histamine into the intestine (confirming Koessler and Hanke).

When the intestinal mucosa is exposed to certain chemicals, namely chloroform, hydrochloric acid, sodium fluorid, carbon tetrachlorid and alcohol, it becomes more permeable to histamine.

Mustard oil has been tried with inconclusive results.

There was no evidence of absorption in the guinea pig of histamine from the intestine which had previously been exposed to alcohol.

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