EFFECTS OF DOPAMINE AGONISTS AND ANTAGONISTS ON GASTRIC ACID SECRETION AND STRESS ULCER FORMATION.

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This thesis is dedicated
to my parents in appreciation
of their patience and encouragement

Effects of dopamine agonists and antagonists on gastric acid secretion and stress ulcer formation

Abstract

Rats given restraint stress for 3h developed a high incidence of gastric ulcers, which resemble human stress ulcers seen among severely ill patients. The pathogenesis of these lesions is not completely understood. Recently, however, research has focused on the role of central and peripheral neurotransmitters in stress ulcer pathogensis. In this study, we examined the effects of different dopamine agonists and antagonists on gastrointestinal and corticosterone responses to stress conditions. We also examined gastric secretory responses following treatment with dopaminergic drugs. The results showed that both central and peripheral dopaminergic mechanisms may be involved in mediating basal and stress-perturbed gastric function. Activation of peripheral dopamine receptors reduced the severity of ulcers (as indicated by a significant reduction in cumulative ulcer length). Stimulation of central DA receptors or augmenting central dopaminergic activity also attenuated ulcer formation. Moreover, the cytoprotective effect of dopamine on the gastric mucosa may be in part due to an inhibition of gastric acid secretion. Dopamine agonists decreased, while dopamine antagonists increased basal gastric acid secretion in rats. However, peripheral dopamine receptor blockers failed to increase gastric acid output, indicating that central dopaminergic mechanisms are likely more important than peripheral receptors in mediating gastric secretory responses.

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I. INTRODUCTION AND REVIEW OF LITERATURE

Stress ulcers are serious and life-threatening. These lesions are a common occurrence among patients admitted to hospitals for severe illnesses. Patients who bleed from gastric stress ulcers may have a mortality rate as high as 50% (Marrone and Silen, 1984). Clinical studies indicate that the incidence of stress ulcers among the elderly and infants is higher than in young adults (Katz et al., 1965, Bradley, 1967).

Early clinical studies revealed a high incidence of acute ulcers of the stomach and or duodenum in patients undergoing major surgery, (McDonnell and McCloskey, 1953; Kelly and Schueter, 1964; Fogelman and Garvey, 1966) and myocardial infarction (Andersen and Clausen, 1966). In 1964, Dunn and Nash, reported on two cases of acute gastric ulcers following caesarean section and abdominal hysterectomy. Other pathological conditions that are known to be associated with the development of acute ulcers include severe head injury (Karsch 1972; Kamada et al., 1977). Skillman and his colleagues (1969) reported on a high incidence of massive upper gastrointestinal bleeding from acute ulcers among patients admitted to intensive care units with respiratory failure, hypotension, sepsis or jaundice. Klein et al. (1973), in a retrospective study on patients with malignant diseases, demonstrated that upper gastrointestinal bleeding represented a serious problem, and that the mortality rate among those patients was 100%. The authors concluded that patients with malignant diseases

were at risk of developing gastric mucosal erosions. In most of the cases mentioned above, the patients had no previous history or current symptoms of ulcer disease and their gastrointestinal radiologic examinations were negative. In addition to these pathological conditions, acute ulcers represent a serious clinical problem for millions of patients using aspirin, non-steroidal anti-inflammatory drugs, caffeine and alcohol - all known gastric irritants.

Despite a voluminous and rapidly growing literature on acute stress ulcers, effective treatment of this disease is still lacking. This is probably due to the uncertainty in identifying the pathogenesis of the disease. Several attempts have been made to characterize the possible mechanisms involved and the following is a review of these mechanisms.

1. Gastric acidity

Considerable atttention has been focused on gastric acid secretion, however its role in stress-induced gastric ulcer disease remains a topic for considerable debate. Early reports by Fletcher et al. (1954), and Shay (1954) indicated that stress ulceration in humans was attributable to gastric hypersecretion. Several experimental studies showed stimulation of gastric acid secretion during stressful situations (Mahl, 1949). Recent studies also reported a similar conclusion. For example, Kitagawa et al. (1979) found increased gastric acid secretion in rats

following water-immersion stress. In 1981 Odonkor et al. reported that sepsis-induced gastric ulcers in dogs were associated with acid hypersecretion. These authors found that the ulcers were prevented by treatment with cimetidine, which inhibits gastric secretion. The objection to this theory is that several agents which effectively inhibit or neutralize gastric acid secretion such as cimetidine or antacids do not necessarily protect against stress-induced gastric ulcers (Pare et al., 1978 and Nemeroff et al., 1980). This conclusion was reached earlier by several other investigators. In 1960, Menguy and his group, found that increased gastric acid secretion in pylorus-ligated rats was not an important factor in the formation of stress ulcers. These results were later confirmed by Pare et al. (1973), Dai and Ogle (1974) and Desiderato and Testa (1976). Moreover, Menguy (1960), Brodie et al. (1962) and Robert et al. (1970), have shown that acid secretion was significantly reduced in experimental ulcers induced by pyloric-ligation, chronic administration of prednisolone, and exertion ulcers, respectively.

2. Gastric mucosal barrier function

The gastric mucosa maintains its integrity despite continuous exposure to potentially damaging gastrointestinal contents including, hydrochloric acid, pepsin, bile, bacteria and other toxins, as well as a host of damaging ingested substances (food particles, spices, alcohol, caffeine and non-steroidal antiinflammatory drugs).

Hollander (1954), introduced the concept of "mucosal barrier", as consisting of a layer of mucus covering a layer of epithelial cells. Code et al. (1955) described a similar barrier in the gastric mucosa which was impermeable to sodium ions. This barrier accounts for the stomach's ability to contain noxious substances without injuring itself. This is expressed as the very low permeability of the gastric mucosa to hydrogen ion and other ions including sodium. However, when this barrier is broken, acid can diffuse back into the mucosa causing serious pathophysiologic consequences which were summarized by Davenport (1967) as follows: 1. Acid back diffusion into the gastric mucosa stimulates stomach motility and pepsinogen secretion, through stimulation of the intrinsic plexuses; 2. Acid back diffusion stimulates the secretion of histamine which, in turn, stimulates gastric acid secretion. Histamine and other substances released during mucosal injury cause capillary vasodilation, plasma protein outward passage to the extracellular space as a result of increased capillary permeability and finally, mucosal edema and bleeding may occur, ranging from superficial haemorrhage to exsanguination. Figure 1 summarizes these mechanisms.

Overholt and Pollard (1968) have also shown abnormal permeability of human gastric mucosa in patients with gastric ulcer, gastritis and hypochlorhydria.

This finding was supported by Skillman et al. (1969) who reported that lethal gastroduodenal ulceration in

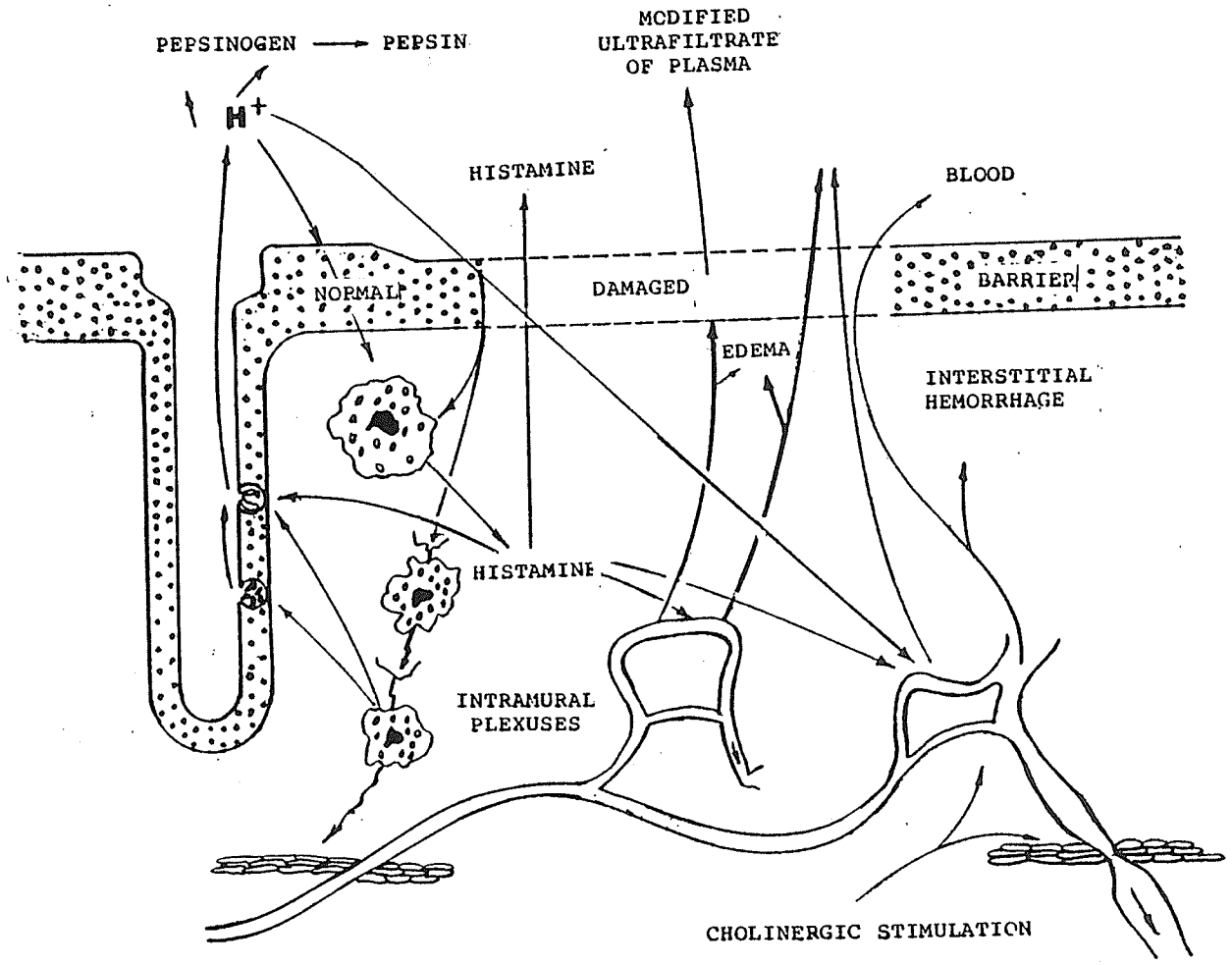


Fig.1. Pathophysiologic consequences of the back-diffusion of acid through the broken gastric mucosal barrier. (from Davenport H.W: . Salicylate damage to the gastric mucosal barrier. N Eng J Med 276: 1312, 1967).

critically ill patients (respiratory failure, sepsis, jaundice, hypotension) in whom hypersecretion of acid is not often a problem, were associated with a disruption of the gastric mucosal barrier, allowing back diffusion of hydrogen ion which, in turn, digested the mucosa.

In 1964, Davenport showed that gastric acid hypersecretion in patients with chronic gastric ulcer may be caused by acid back diffusion across damaged gastric mucosa. This author has also found that bile, synthetic taurocholate, and urea produce gastric mucosal barrier breakdown resulting in back diffusion of acid (Davenport, 1968).

3. Endogenous gastric mucosal prostaglandins.

Currently, prostaglandins, which have been isolated in large quantities from human gastric mucosa (Bennett et al., 1977) are believed to play a major role in the protection of the gastrointestinal mucosa against physical and chemical trauma (Robert, 1979). Under normal conditions, the gastric mucosa has been found to produce prostaglandins (Konturek et al., 1981). Recent reports indicate the existence of reduced antral and corpus mucosal prostaglandin biosynthesis, as determined by radioimmunoassay, in patients with gastric ulcer (Wright et al., 1982; Kobayashi et al., 1982). Robert et al. (1968) were the first to report that the incidence of gastric ulceration in rats subjected to pyloric ligation is reduced if animals were given subcutaneous injections of prostaglandin E1. Prostaglandins

are also reported to protect against mucosal necrosis caused by absolute ethanol and boiling water (Robert et al., 1979), as well as by nonsteroidal antiinflammatory drugs (NSAID's) such as aspirin (Cohen, 1978).

There has been some difference of opinion concerning the mechanism by which prostaglandins protect against gastric mucosal ulcers. Some authorities have maintained that prostaglandins simply stimulate the production of mucus (Bickel and Kauffman, 1981) which results in an increased pH gradient across the surface mucus layers. Other mechanisms have been suggested including: stimulation of the gastric sodium pump (Robert, 1979); tightening of the gastric mucosal barrier (Bolton and Cohen, 1979); stimulation of bicarbonate production (Garner and Heylings, 1979); and inhibition of acid secretion (Karim and Fung, 1976). These authors reported that intravenous administration of prostaglandins E1 and A1 to human volunteers consistently reduced both basal and stimulated acid secretion. The prostaglandins do not inhibit secretory activity when they are given by mouth, but their methylated derivatives (methyl and dimethyl prostaglandins E2) are active by the oral route and they are much more potent than the parent compound (Robert et al., 1981).

4. Gastric Mucosal Blood Flow

Gastric mucosal blood flow appears to maintain the integrity of the gastric mucosa by removing, diluting or

buffering back diffusing acid (Spiro, 1985). Another advantage of maintaining an adequate blood flow is to deliver nutrients and oxygen to the mucosal cells. Reduced mucosal blood flow has been observed following hemorrhagic shock (Shirazi et al., 1977) and after endotoxin-induced ulcers in pigs (Richardson et al., 1973). The current hypothesis appears to be that during stress, vascular perfusion of the stomach may be reduced, causing the mucosal cells to become anoxic and malnourished and thus become vulnerable to the damaging effect of the acidic gastric contents.

5. Energy Deficit

The hypothesis that stress ulceration may be caused by a deficiency in gastric mucosal energy was substantiated by the work of Menguy et al. (1974) who investigated the effects of hypovolemic shock-induced stress ulcers on the energy metabolism of the gastric mucosa of rats. They found a fall in the levels of ATP and ADP in the mucosa 15 minutes after the establishment of hemorrhage. The fall in ATP levels was higher in the corpus than that observed in the antrum. Instillation of sodium taurocholate into the rabbit stomach during hemorrhagic shock inhibited gastric mucosal ATPase and uncoupled oxidative phosphorylation of gastric mucosal mitochondria which resulted in an increase in the severity of stress ulcers (Menguy and Masters, 1976).

6. Mucosal Cell Renewal

Another proposed endogenous mechanism that may contribute to mucosal defense against injury is the rapid rate of replacement of desquamated epithelial cells from the mucosal surface by new cells formed by the proliferation of mucus neck cells of the gastric glands. In 1982, Svanes and his colleagues have demonstrated that in vitro exposure of frog gastric mucosa to 1M NaCl caused complete destruction of the surface epithelial cells within 10 minutes. These cells became completely restored within four hours by new cells which migrated from the proliferative zone (between the gastric gland and surface epithelium). The authors also reported that the epithelial restoration was enhanced at high pH and inhibited at low intra-luminal pH (<4.0).

It has also been shown by Eastwood and Quimby (1982) that in the rat, chronic administration of aspirin (120 mg/kg/day) for four weeks, stimulated epithelial proliferation in the fundic mucosa, but had no effect in the antrum. The authors suggested that epithelial proliferation may be the mechanism responsible for these epithelial changes.

Models of Stress Ulcer

Several experimental approaches have been described to produce stress ulcer in animals. It is imperative that experimentally-induced stress gastric ulcers are reliably produced and closely resemble human ulcers seen in clinical settings after a variety of acute conditions. As early as 1936, Selye has reported that when an animal is exposed to

stress (such as might be produced by physical injury, irradiation, surgical injury, infection, fatigue, intoxication with sublethal doses of drugs, or exposure to cold), it responds in a characteristic fashion. The response to stress may be local at (the site of stress) or a general non-specific response. According to Selye, who called the latter response the general adaptation syndrome, this response may be divided into three successive phases. The "alarm" (immediate) reaction is the first stage in which there is an increase in size of some organs including the spleen, liver, thymus, lymph nodes, loss of muscular tone, fall in body temperature and formation of acute erosions in the digestive tract, particularly in the stomach. The second phase is the stage of resistance, while the final stage is called the stage of exhaustion. The last stage is only seen if the stressor is sufficiently intense or prolonged to exhaust the physical mechanisms responsible for initiating and maintaining the process of resistance.

In a stress situation, impulses from the cortex reach the hypothalamus and produce secretion of corticoids, which provide the means of resistance and assist in the return of physiological normalcy following exposure to stress. A failure of resistance is thought to lead to "diseases of adaptation", such as rheumatic fever, gout, rheumatoid arthritis, hypertension and depression. Selye's views were at first embraced indiscriminately by many researchers. For example, an early study by Hench and his colleagues (1949),

showed that corticosterone and adrenocorticotrophic hormone (corticotrophin, ACTH) both brought about a rapid relief of the symptoms of rheumatoid arthritis. These data apparently supported Selye's hypothesis that many human disorders result from a failure of mechanisms mediated by the adrenal cortex and controlled by the hypothalamic-pituitary system, the activity of which enables the organism to adapt to the stress (physical, chemical or nervous) of everyday life. However, over the next three decades, much evidence against the notion of "non-specifity" accumulated and Selye's original ideas were seriously challenged.

One of the earliest techniques used to induce experimental ulcers in animals is restraint or acute immobilization, which consists of placing the animal (usually rodents) into a confined space, by means of surgical tape, window screen, or a metal box with movable sides and ends (Rossi et al., 1956; Robert et al. 1966). Brodie and his colleagues used this technique to induce experimental ulceration in rats, and they deserve considerable credit for improving and establishing parameters for this model.

Over the years, the restraint technique has become a powerful and reliable method for experimental ulcer formation as well as being used for testing the effectiveness of various anti-ulcer drugs.

Brodie et al. (1962), reported that fasting prior to restraint, enhances the production of gastric lesions in

rats. The authors also found that this technique was species-specific (rats and mice were more susceptible to ulcer formation than hamsters, rabbits, guinea pigs or monkeys).

In 1977, Vincent et al. described a modification of the restraint technique. They combined restraint of rats in the supine position for 3 hr with placing them in a cold environment (4^{o}-6^{o}C). This procedure resulted in true ulcer formation (that is ulcers which penetrate the muscularis mucosae, Glavin, 1980). Until this time, most restraint-induced ulcers were usually superficial and did not penetrate the muscularis mucosae.

A modification of the restraint procedure was also described by Takeuchi et al., (1976). Their method is called water immersion stress and consists of immersion of restrained pyloric-ligated rats in water at 23^{o}C for 3 hr. The authors reported that this method induced a high incidence of stress ulcers.

Another model of experimental ulcer, but especially of chronic ulcers, is known as activity-stress. In this procedure rats are placed in a running wheel activity cage and fed for only one hour a day while having continuous access to the wheel. Animals so treated developed gastric ulcers in the glandular portion of the stomach within 4 to 12 days (Pare and Houser, 1973; Pare, 1974; Pare, 1975; Pare, 1976; Pare, 1980). This procedure leads to increased running activity with some rats running as much as 10 miles

per day (Pare, 1975). Activity stress ulcers may penetrate through the muscularis mucosae and thus may differ from restraint ulcers which are usually superficial. The deep penetration of activity-stress erosions is probably partially due to the chronic nature of these ulcers, that is, they develop slowly over a period of several days, whereas restraint ulcers are produced within 2 to 24 hours, depending upon the ambient temperature.

Electric shock has also been used to induce stress ulcers in rats. However, more interesting results have been reported when monkeys were used. In 1958, Porter et al. found that monkeys placed in a situation where they had to control electric shock delivery to themselves and to a nearby monkey by pressing a bar, developed severe ulceration. This model was known as the "executive monkey" procedure. Several attempts have been made to replicate these results but without success (Natelson et al., 1977).

Haemorrhagic shock has also been reported to cause gastric ulcers. Harjola and Sivula (1966) described acute gastric mucosal ulceration in rabbits following haemorrhagic shock. They explained these changes as being the result of vasoconstriction of the gastric mucosa due to haemorrhage.

These findings were supported by the work of Guilbert et al. (1969) who found a high incidence of microscopic and gross acute multiple gastric erosions in the dog following haemorrhagic shock (40 mmHg for 4.5 hr, followed by reinfusion of shed blood). On the other hand, these authors

suggested the possibility that altered gastric mucosal barrier function caused by the refluxing duodenal content with subsequent ulceration of the stomach, may be the salient pathogenic factor. Since both pyloric ligation, which prevents duodenal content from flowing back into the stomach, and inhibition of trypsin, which prevents the release of hydrolytic enzymes, significantly reduced both the incidence and severity of the hemorrhage-induced gastric ulceration, it appears that this explanation has some support.

Septic shock produced in dogs by intraperitoneal injection of a mixture of bacteria and bile, resulted in the development of bleeding gastric erosions within two days (Ondonkor et al., 1981). In an early study by Penner and Bernheim (1960), the injection of bacterial endotoxin into the cerebral ventricles or the subdural space caused the formation of ulcers in the stomach and duodenum of rats. This result was contradicted by Rosoff and Goldman (1968) who found that bacterial flora produced by oral administration of polymyxin B to experimental animals provided protection against acute restraint-induced ulcers.

As early as 1932, Cushing reported that gastroduodenal ulcers were frequently observed in patients with neurological trauma. Similar forms of ulcers were experimentally produced by electrical stimulation of various areas of the hypothalamus in monkeys (French et al., 1952) and cats, (Feldman et al., 1961).

One of the most commonly used methods to induce gastric ulcers in experimental animals is by pharmacological procedures, including the use of drugs that are known to produce gastroduodenal damage as a side effect in humans. The use of chemicals to produce ulcers is popular because of the many features shared by stress and pharmacologically-induced ulcers, such as their rapid onset, rapid healing with discontinuation of the stress condition or the drug, and the fact that they are both multiple and superficial (Giampaolo et al., 1978).

Drug-induced gastric ulcers include administration non-steroidal antiinflammatory compounds such as aspirin (Brodie and Hooke, 1971; Lev et al., 1971; Cooke, 1973), phenylbutazone (Dascalakis, 1971), and indomethacin, which has also been shown to produce ulcers in the upper gastrointestinal tract in rats and humans. These ulcers were not prevented by cimetidine, atropine, or vagotomy (Satoh et al., 1981). Other ulcerogenic drugs include corticosteroids (Robert and Nezamis, 1964; Kelly and Robert, 1969), reserpine (Weiner, 1980) cysteamine (Selye and Szabo, 1973; Robert et al., 1974; Szabo, 1978), and propionitrile (Szabo and Selye, 1972). Cysteamine and propionitrile have been shown to produce marked increase in gastric acid secretion (Szabo et al., 1979), probably due to their ability to stimulate gastrin release (Lichtenberger et al., 1977), and to delay gastric emptying (Poulsen et al., 1982). Alcohol is also known to produce ulcers (Davenport,

1967; Eastwood and Erdman 1978). Clinical reports indicate a high incidence of ulcers among alcoholics (Hagnell and Wretmark, 1957). Recently Szabo et al. (1985) showed that multiple daily doses of the dopaminergic neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) incuded duodenal ulcers in the rat. In this study, Szabo and his group, found a significant reduction of pancreatic bicarbonate, amylase and trypsin as well as a decrease in gastric acid and pepsin output. They therefore concluded that these ulcers are not due to acid hypersecretion, but were associated with decreased neutralization of acid in the duodenum. Among currently used experimental ulcer models, procedures which combine restraint and cold are considered "good" experimental tools for inducing peptic ulcer disease in animals. These models satisfy the requirements of a reliable model for ulcer formation including: penetration through the muscularis mucosae, production of ulcers at specific locations of the gastrointestinal tract and response to currently available therapy (drugs, surgery) for peptic ulcer disease. Satisfaction of these criteria make the cold restraint stress model valuable for use in examining the cause, course and consequence of ulcer disease (Glavin, 1980; Pare and Glavin, 1986).

Neurogenic factors in stress ulcer formation:

Support for the importance of catecholamines in experimental ulcer formation comes from their role in

mediating responses of the sympatho-adrenal system. Such evidence was provided by the results of pharmacological analyses of the application of selective blockers of α- and β-adrenergic receptors as well as the application of presynaptic sympatholytic agents. The involvement of the sympathetic nervous system in the formation of ulcers of different origins (surgical and chemically induced) has been well documented. Depletion of catecholamines, for example by guanethidine, reserpine or 6-hydroxydopamine (6-OHDA), and surgical sympathectomy by spinal cord transection or adrenalectomy, have been found to induce gastric ulcers and/or potentiate ulcer formation by other methods (Lau and Ogle, 1979; Esplagues et al., 1982; Taylor and Nabi, 1982 and Hernandez et al., 1984).

The theory that the sympathetic nervous system has an important role in the gastrointestinal tract was reinforced by the histological findings of Costa and Gabella (1971) who indicated that the gastric mucosa is richly innervated by adrenergic fibres. Ahlquist and Levy (1959), however, showed that in the dog, adrenergic relaxation of the gut was mediated by stimulation of α- and β-adrenoreceptors. Lands et al. (1967) found that most of the adrenoreceptors in the gut are of the β1-subtype, since practolol specifically blocked these receptors. Identification of the exact subtype of adrenergic receptors which are involved in the pathogenesis of gastric ulcers is still controversial.

A recent study by Esplagues et al. (1982) on the effects of β-adrenoreceptor stimulation on gastric ulcers induced by several models including stress, pyloric-ligation, histamine, indomethacin, reserpine, polymyxin-B, and gastric distension, found that pretreatment of the rats with isoprenaline or salbutamol, significantly inhibited stress-induced gastric ulcers. This effect was abolished by propranolol but not by atenolol. The authors thus suggested that the response to β-adrenoreceptor stimulants was mediated by β_2-receptors. Salbutamol was also found to reduce acute ulcer formation in rats treated with histamine, polymyxin-B, indomethacin and in pyloric-ligated rats. These findings were confirmed by Orlando et al. (1985) who indicated that stress-induced gastric ulcers could be prevented by α- and β-adrenoreceptor agonists. Drugs such as cysteamine which apparently act as sympatholytic compounds, have a significant ulcerogenic effect in the stomach and duodenum (Szabo et al., 1982).

Although the mechanism(s) by which sympathomimetic agents provide protection against ulcer formation is still unknown, some investigators pointed to the inhibition of acid secretion as one of the effects of adrenoreceptor stimulation. Debnath et al., (1974), reported a dose-dependent effect of propranolol on gastric acid secretion and gastric ulcers in pylorus-ligated rats. Small doses of propranolol increased total volume, acid output and pepsin secretion along with and <u>increase</u> in the incidence of

ulcers, whereas high doses were inhibitory. Canfield and Price (1981) found that isoprenaline inhibited gastric acid secretion in response to pentagastrin in concious rats with Heidenhain pouches. This inhibition was abolished by propranolol and butoxamine and partially reversed by practolol.

Neuropeptides in stress-induced gastric ulcers

Several neuropeptides have been implicated in the pathogenesis of stress gastric ulcer formation. Most of these peptides have already been identified in the brain and in peripheral tissues including the gastrointestinal tract. Nemeroff et al. (1982) reported that intracisternal injection of neurotensin, significantly inhibited cold restraint stress ulcers in the rat. The cytoprotective effect of neurotensin was found to be both dose-related and route-specific. High intracisternal doses and intravenous administration of the peptide failed to provide protection against gastric stress ulcers. Osumi et al. (1978) have demonstrated that intraventricular application of neurotensin caused an inhibition of gastric acid secretion. Whether the inhibition of gastric acid secretion is involved in neurotensin-induced cytoprotection is unknown. In 1982, Szabo and his group found that somatostatin, a peptide known to be released by central administration of neurotensin, prevented the formation of cysteamine-induced duodenal ulcers in rats. Other investigators have reported that centrally administered β-endorphin completely prevented

stress gastric ulcers in the rat (Hernandez et al., 1983). Other neuropeptides that have been implicated in the cytoprotective effect on stress-induced gastric ulcers include: bombesin (Tache et al., 1979) and substance P (Hernandez et al., 1983). In contrast, other neuropeptides have been found to aggravate stress-induced gastric ulcers such as vasoactive-intestinal polypeptide (VIP) and thyrotropin-releasing hormone (TRH) (Hernandez et al., 1983).

Gastrointestinal Physiology

The stomach is the most complicated portion of the alimentary tract. It receives about 2500 ml of fluid per day from the cells lining the stomach. This fluid contains the enzymes, pepsin and rennin and has a low pH of 1.5-2.5 due to the presence of hydrochloric acid.

The stomach can be divided into three parts: the fundus, the body and the pylorus, each of which contains a particular type of gland. The cardiac area, is a 1 to 4 cm wide zone which guards the esophageal orifice, also known as the cardiac sphincter (Brooks, 1970).

The fundic area is the largest area of the stomach and accounts for 60 to 80% of the total mucosal surface area.

Histologically, the stomach consists of four layers: The outer serous coat consists of peritoneum. The muscular coat consists of three layers: the outer longitudinal, the middle circular and the inner oblique layer. The next layer

is called the submucous coat, followed by the layer of the muscularis mucosae and a supporting stroma of connective tissue. Finally, there is the mucous membrane which is thrown out into large folds when the stomach is empty and these folds tend to disappear when the stomach is distended. Hence, this folded arrangement of the mucous membrane provides a substantial protective device to prevent damage from stretch or distention. The surface of the gastric mucosa is covered with a thick layer of tenacious mucus which is secreted by the surface epithelial cells. This layer varies in thickness from 0.5 mm to 2.5 mm. Under the surface layer of epithelium, are located simple tubular glands which secrete gastric juice.

Histologically, as well as functionally, the glands are not the same. They differ in different parts of the stomach, but they are all tubular in structure and extend to the muscularis mucosae where they terminate in a blind bulbar end, known as fundus of the gland. The main tubular part of the gland is called the body. The neck of the gland connects the body to the isthmus, which communicates with the gastric crypt.

The cardiac glands tend to be short and secrete mucus, although some pepsinogen cells are also present. The fundic glands tend to be slender and straight with a narrow lumen. These glands are composed of the following: (a) the mucous neck cells which secrete the mucus; (b) the chief (peptic cells) in the body of the glands. These cells are

basophilic and secrete pepsin and contain zymogen granules which are precursors of pepsin (pepsinogen). In addition, the chief cells probably produce gastrin, rennin, and a gelatin-splitting enzyme, gelatinase; and (c) oxyntic (parietal) cells. They are found pressed at the bed by chief cells and are oval in shape. They secrete hydrochloric acid (HCl) and may also secrete "intrinsic factor", which is a glycoprotein required for normal intestinal absorption of vitamin B12 (Ganong, 1985).

Secretion of gastric juice.

The secretion of gastric juice is controlled by both nervous and chemical mechanisms. Stimulation of the vagus nerves causes secretion of gastric juice and an increase in gastric motility. It is for this reason that vagal fibres to the stomach are sometimes sectioned in cases of intractable gastric ulcer. Gastric secretion is associated with the intake of food and occurs in three stages, known as the cephalic, gastric, and intestinal phases, depending upon the location of the stimulus.

The cephalic phase of gastric secretion occurs before food enters the stomach. Psychological factors are involved at this stage because unappetizing foods do not elicit this type of gastric secretion (which is sometimes called "appetite juice".)

The gastric phase of secretion occurs while food is in the stomach. It is apparently caused by substances in the food which stimulate the gastric mucosa (secretogogues).

Meats, proteins, as well as alcohol and caffeine, are effective secretogogues. They cause the release of gastrin from the gastric mucosa into the blood stream, which in turn causes the release of gastric juice when it reaches the gastric mucosa. The intestinal phase refers to the secretion of gastric juice that continues several hours after chyme has left the stomach. It is probably due to release of gastrin-like hormone from the gastric mucosa. Gastric secretion can be inhibited by the presence of certain substances in the duodenum. For example: (1) introduction of alkali directly into the duodenum inhibits gastric secretion and (2) the presence of fats in the duodenum inhibits gastric secretion (both the gastric and intestinal phases). This inhibitory action of fat is due to the release of the intestinal hormone, enterogastrone.

Mechanisms of secretion of hydrochloric acid

Hydrochloric acid is secreted by the oxyntic cells (or parietal cells). These cells also secrete Castle's intrinsic factor which regulates the absorption of vitamin B12. The parietal cells are present in the fundus and the body of the stomach. Many theories explaining the formation of HCl are being proposed. One theory, which was suggested by Davenport, Davies and others, explains the formation of HCl in a simplified manner. According to this theory, the H^+ and OH^- ions are formed by ionization from water and other metabolites. H^+ ions are then passed out of the oxyntic cells into the canaliculus of the gastric gland.

This is an active process, the energy for which is derived from aerobic and anerobic glycolysis. The transport is also dependent on oxidative phosphorylation and may involve adenosine triphosphate. The secretion of HCl stops when energy conversion is blocked by, for example, dinitrophenol. For each H^+ ion released, one OH^- ion is held back inside the cell. This OH^- combines with H^+ ion released from the dissociation of H_2CO_3 into HCO_3^- and H^+, the HCO_3^- being released in the circulation. The H_2CO_3 is formed in the cell by the combination of CO_2 and H_2O and this reaction is catabolised by the enzyme carbonic anhydrase, found in large amounts in the gastric cells. Blocking the action of carbonic anhydrase by acetazolamide stops the formation of HCl, and thus, this enzyme is believed to play an important role in HCl formation. A new model for the formation and transport of gastric acid suggests that H^+ ions formed in the parietal cells from ionization of water are secreted into the gastric juice in exchange for K^+ by the action of the H^+-K^+ ATPase at the apical membrane of the gastric cell (the membrane facing the secretory canaliculi). Chloride ions (Cl^-) move against their electrochemical potential gradient from the extracellular fluid into the parietal cell in exchange for HCO_3^-. Some investigators believe that the entry of Cl^- ions depends on the presence of Na^+ in the serosal fluid. The existance of the Na^+ gradient depends on the enzyme Na^+, K^+-ATPase located in the basolateral plasma membrane (Kutchai, 1983).

Effects of hormones, chemicals and drugs on gastric secretion:

Hormones from different endocrine glands influence gastric secretion. Glucocorticosteroids, secreted by the adrenal cortex following stimulation by ACTH, increase acid and pepsin secretion by the stomach, but decrease the mucus secretion, thus making the stomach more susceptible to ulceration. Epinephrine and norepinephrine, on the other hand, decrease gastric secretion. Hypophysectomy causes characteristic changes in the chief cells of the gastric glands, consisting of a decrease in the size of nucleus and loss of most of the pepsinogen granules. Secretion of hydrochloric acid is also reduced.

Insulin has an effect on the gastric glands similar to that of stimulation of the vagi. In addition, the release of gastrin is reduced by insulin.

Serotonin, possibly secreted by certain enterochromaffin cells in the intestinal mucosa, inhibits gastric secretion, particularly that activated reflexively or by cholinergic drugs.

Histamine is a powerful stimulant of acid secretion and it has been used in clinical investigations in order to assess the ability of the stomach to secrete acid. Pentagastrin is preferred for this purpose because of fewer and less severe adverse reactions. Histamine is found in cells in the gastric mucosa known as "histaminocytes" which resemble mast cells. The mechanisms involved in the

activation of these cells are unclear. Histamine, when released from these cells, acts directly on the parietal cells through H2 receptors, that are linked to adenylate cyclase. The stimulatory effect of histamine on gastric secretion is not affected by atropine.

Caffeine and alcohol are strong secretory stimulants, producing a gastric juice of high acidity and rich in mucin. Gastrin, which is released from the pyloric antrum by entry of the contents of the stomach, stimulates pepsin and HCl secretions. Parasympathomimetics, such as acetylcholine, carbachol, methacholine and neostigmine are secretory stimulants. Secretory depressants include alkali, acids, atropine, hyoscine.

Reserpine increases acid production when given in high doses for a long period of time. The mechanism of action of reserpine on acid secretion is not clear. Figure 2 summarizes pro- and anti-secretory agents.

Dopamine in the pathogenesis of gastroduodenal ulcers:

Although reports concerning the association between gastric ulcers and Parkinson's disease (a condition caused by a marked depletion of dopamine in the corpus striatum) appeared in the early 1960's, no attention was directed toward the possible relationship between ulcer formation and dopamine deficiency. Schwab (1961), was the first to report a high incidence of "gastrointestinal malfunctions" manifested as active ulcers or ulcer-like syndromes among Parkinson's patients. This author suggested that Parkinson

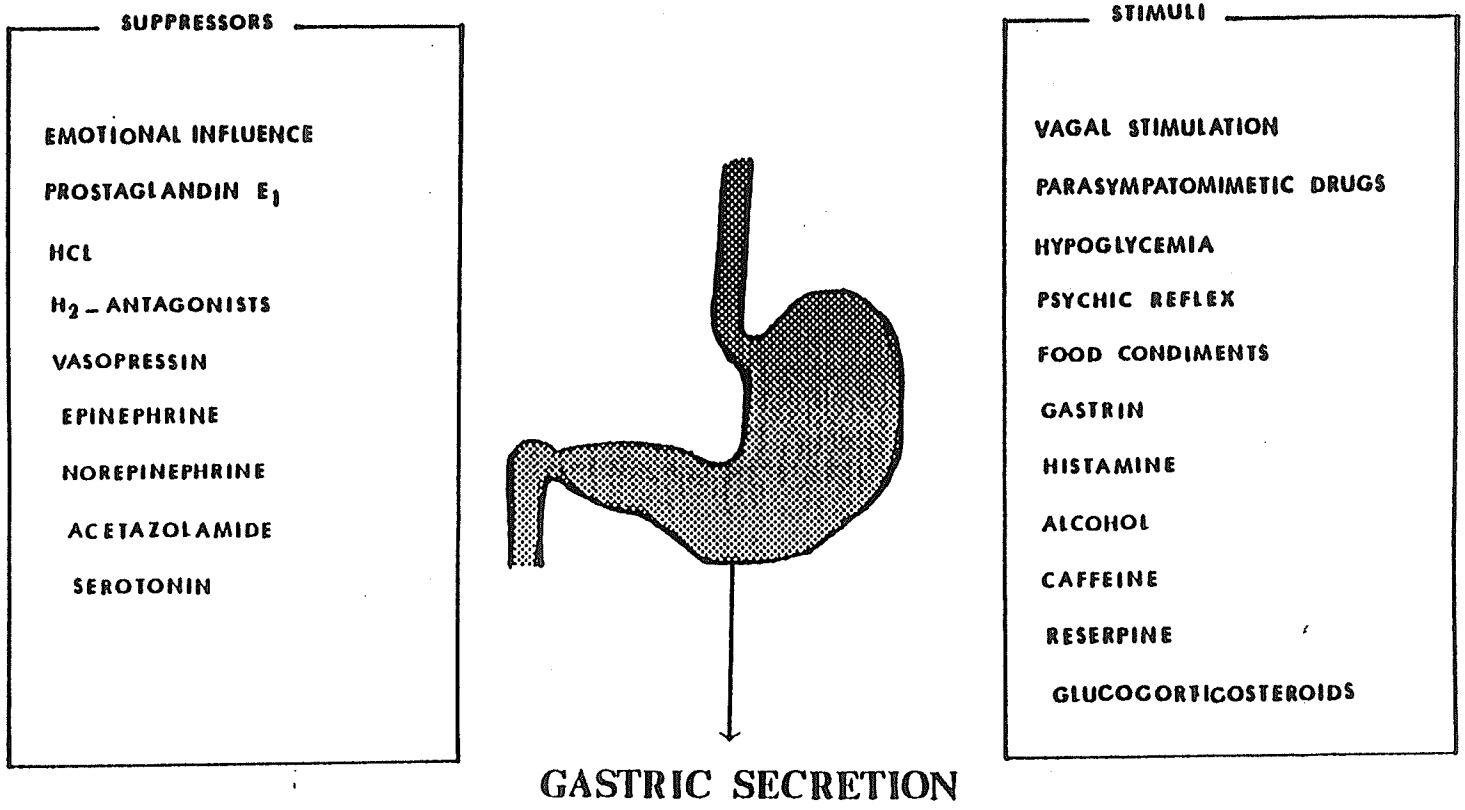


Fig.2. Effects of hormones, chemicals and drugs on gastric secretion

patients were more vulnerable to ulcer formation than were healthy people of the same age group. Similar observations were reported by Strang (1965) who showed that gastroduodenal ulceration occurred more frequently among patients who were subsequently diagnosed as having Parkinson's disease. In this report, Strang also indicated that anti-Parkinsonism medications (anticholinergics) provided protection against ulceration. Recently Szabo and his colleagues (1985) reported that the Parkinson-inducing drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), produced duodenal ulcers when given orally or subcutaneously to rats.

The ulcerogenic effect of MPTP was prevented by pretreatment with dopamine agonists (e.g. bromocriptine, lergotrile) or monoamine oxidase inhibitors (e.g., pargyline, l-deprenyl) administered p.o. 30 minutes before each dose of MPTP. Glavin et al. (1986) reported that l-deprenyl administered into the cerebral ventricles in microgram quantities or intraperitoneally in larger (milligram) doses, significantly reduced stress gastric ulcer formation in rats. Moreover, several authors have shown that disorders associated with dopamine excess and/or hyperactivity such as schizophrenia, are rarely associated with duodenal ulcers (Pollak and Kreplick, 1945; Hinterhuber and Hochenegg, 1975).

Many researchers have shown a protective effect afforded by the pharmacological activation of dopamine-

receptors against ulcer formation due to restraint-stress (Strocchi et al., 1976; Lauterbach and Mattes, 1977; Groisman et al., 1984); Hernandez et al. 1984) activity-stress (Hara and Ogawa, 1984); cysteamine (Szabo, 1979); pyloric-ligation (Sikiric et al., 1985); and several ulcerogenic drugs including aspirin, phenylbutazone, and reserpine (Parmar et al., 1984).

Dopamine is found in both central and peripheral presynaptic vesicles, and large quantites of this neurotransmitter have been located in the gastrointestinal tract, especially in the duodenal mucosa (Landsberg et al., 1975). Christensen and Brandsborg, (1974) demonstrated that dopamine is present in large amounts in human gastric juice during basal conditions. Similar findings were reported earliers by Haggendal (1967). Recently, dopamine has been demonstrated to be present in peripheral nerves and the spinal cord (Lackovic et al., 1981). Biochemical evidence has also shown a significant increase in [^{3}H]-DA binding in the gastric mucosa after cold-restraint stress, during which approximately, 30% of the rats had gastric ulcers (Hernandez et al., 1986).

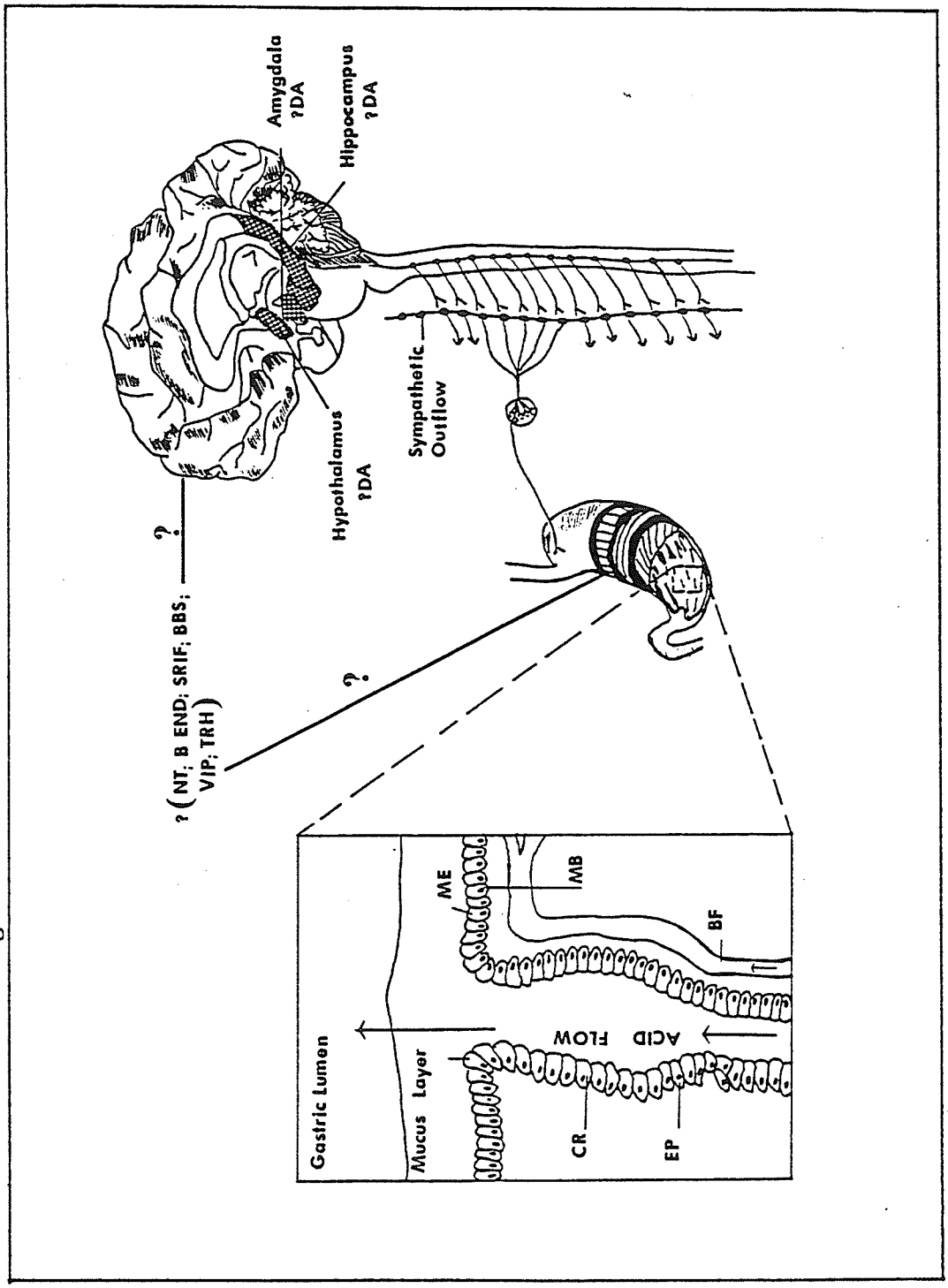
The mechanism(s) of action of dopamine in the pathogenesis of gastroduodenal ulceration is/are not completely understood. Szabo and his colleagues (1979; 1982) have extensively studied the anti-ulcer effects of dopamine (DA) in duodenal ulcer formation. They found that cysteamine-induced duodenal ulcers in rats were prevented by

pretreatment with bromocriptine, lergotrile, and apomorphine, whereas both the severity of the ulcers and mortality rate were increased by the dopamine antagonist haloperidol. Szabo and his group suggested that the protective effect of dopamine and dopamine-like drugs may involve inhibition of gastric secretion and duodenal acid neutralization along with a decrease in gastric motility or increased mucosal blood flow. Recently, Pihan et al., (1985) have shown that duodenal ulcerogens (cysteamine, propiontrile, mepirizole and MPTP) decreased duodenal motility. The authors suggested that alterations of duodenal motility may contribute to changes in the acid handling capacity of the proximal duodenum. Pipkin et al. (1985), however, reported that dopamine agonists SK&F 82526 and SK&F 89124 (selective peripheral DA1 and DA2 receptor agonists) had no effect on acid output or mucosal blood flow due to pentagastrin or topical application of aspirin.

The anti-secretory effects of dopamine and dopamine agonists have been studied by Valenzuela et al. (1979) in humans and by Hirst et al. (1976) in cats. Both research groups found that dopamine infusion significantly reduced acid secretion in a dose-dependent manner. Costall et al. (1985) demonstrated that apomorphine consistently reduced both the volume and acid concentration of gastric secretion in rats with chronically indwelling gastric cannulas. The role of dopamine on gastric acid secretion, however, remains controversial. In a recent study by Taylor and Nabi Mir

(1982), it was found that dopamine did not exert an inhibitory affect on gastric acid secretion in pylorus-ligated rats. Nemeroff and his associates (1982) recently suggested that acid secretion was not a critical for the development of cold-restraint-induced gastric ulcers. These observations were supported by Hernandez et al., (1984) who found that the gastric pH of rats treated with apomorphine and methylphenidate was not different from placebo-treated controls. Despite indications that certain peripheral (gut) and central (brain) neurotransmitters, including DA, seem to be involved in stress-ulcer formation (summarized in Figure 3), the role of central and peripheral dopaminergic mechanisms in cold-restraint stress ulceration has not been widely examined. The present studies were conducted in an attempt to determine whether peripherally administered dopamine agonists and antagonists as well as specific dopamine receptor agonists or selective monoamine oxidase type B inhibitors given into the cerebral ventricles, would modify the ulcerogenic effect of cold restraint-stress. In addition, the effects of these compounds on conscious, non-stimulated basal gastric acid secretion in rats were examined, in order to extend these studies to include one of the proposed pathogenic mechanisms involved in the induction of stress gastric ulcers.

Fig. 3. PATHOGENESIS OF STRESS ULCERS



Legend, Fig. 3 Pathogenesis of stress ulcers. DA = Dopamine; NT = Neurotensin; B-END = B-Endorphin; SRIF = Somatostatin; BBS Bombesin; VIP = Vasoactive intestinal polypeptide; TRH = Thyrotropin-releasing hormone; MB = Mucosal bicarbonate; ME = Mucosal energy; CR = Cell renewal; EP = Endogenous prostaglandins; BF = Mucosal blood flow.

II. MATERIALS AND METHODS

Gastric cannulation and collection of gastric acid secretion

Male Sprague-Dawley rats weighing 200-300 g were used. Rats were implanted with chronic indwelling stainless steel gastric cannula (sodium pentobarbital anesthesia 65 mg/kg i.p.) as described previously (Pare et al., 1977). A postoperative period of 14 days was allowed, during which cannulae became firmly anchored and produced no complications. Before each experiment, rats were deprived of food for at least 18 h but allowed water ad libitum. Immediately prior to sample collection, the cannula plug was removed and the stomach rinsed with 20-30 ml of distilled water. The cannula was left open and the stomach allowed to drain for 30 min prior to three consecutive 1 h gastric secretion collection periods Figure 4 illustrates this preparation. Following collection, the cannula plug was replaced and 96 h elapsed between successive collections from the same animal. Samples were centrifuged at 2500 x g for 10 min to remove residual debris, the pH determined, and 1.0 ml aliquots of the supernatant titrated to pH 7.0 with 0.01N NaOH. Acid output was expressed as mEq/100g body weight/h.

The first 1 h collection consisted of a pre-drug injection baseline. At the beginning of the second hour, all collection vials were changed and injections (1.0 ml) of vehicle; bromocriptine mesylate (Sandoz) at doses of 1.0, 2.0 and 4.0 mg/kg ip; bupropion HCl (Burroughs-Wellcome) at

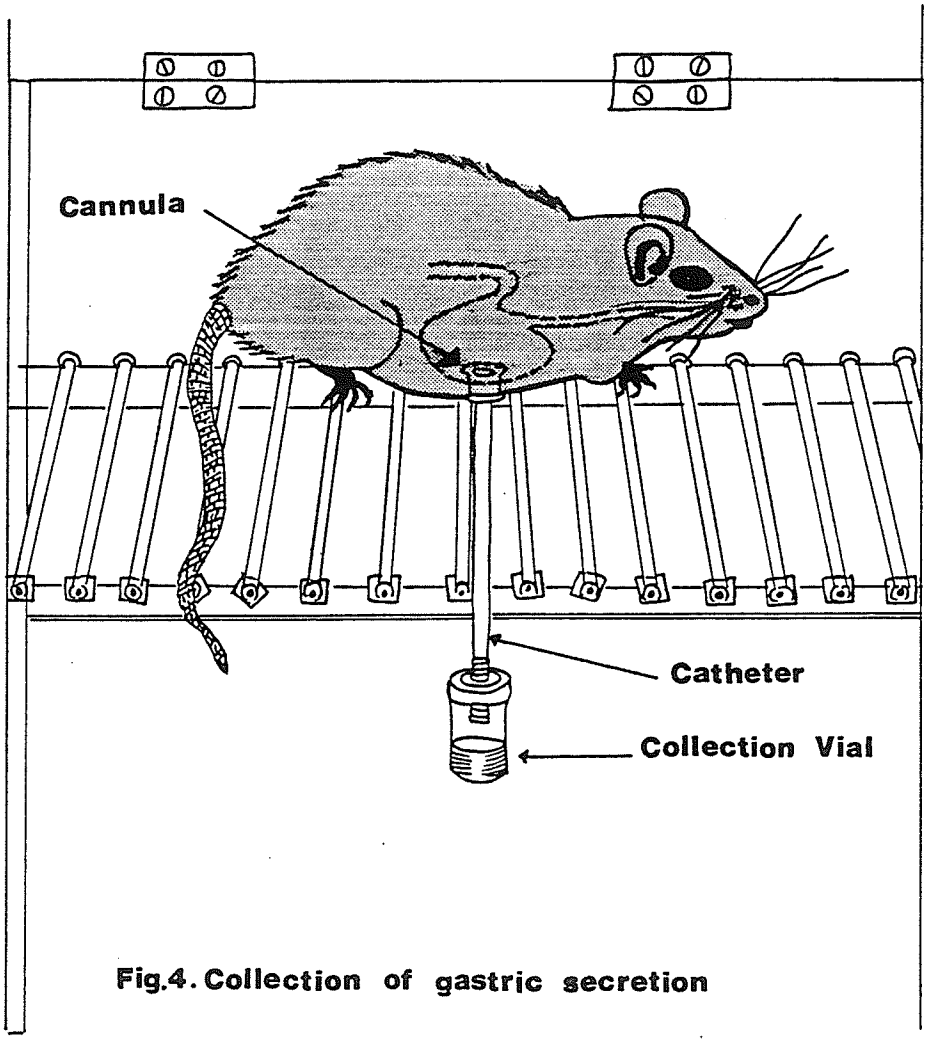


Fig.4. Collection of gastric secretion

doses of 12.5, 25.0 and 50.0 mg/kg ip; haloperidol (McNeil) at doses of 0.1, 0.25 and 0.50 mg/kg ip; domperidone HCl (Janssen) at doses of 0.50, 1.0 and 2.0 mg/kg ip; metoclopramide HCl (Nordic) at doses of 5.0, 10.0 and 20.0 mg/kg ip and pimozide (McNeil) at doses of 0.25, 0.50 and 1.0 mg/kg ip were administered. The following vehicles were used: for bromocriptine, 4% (v/v) ethanol; for bupropion, distilled water; for haloperidol, McNeil lactic acid vehicle, pH < 4.0; for pimozide, tartaric acid/distilled water; and for domperidone and metoclopramide, distilled water. At the beginning of the third hour, vials were again changed, and a post-drug injection collection period of 1 h started. All rats were tested over five collection periods, separated by 96 h, in the following order: vehicle, first (lowest) dose, second dose, third (highest) dose, and again a vehicle. Thus, each animal served as its own control and all drug injections were preceded and followed by a vehicle injection collection period.

Intracerebroventricular cannulation and drug administration

Male Sprague-Dawley rats weighing between 200 and 300 g at the time of surgery were used. Animals were anesthetized with sodium pentobarbital (65 mg/kg) supplemented with intraperitoneal (ip) chloral hydrate 160 mg/kg (Valenstein, 1961) and placed in a Stoelting stereotaxic apparatus. Standard stereotaxic surgery was used for the implantation

of a 23 gauge cannulae into the right lateral ventricle at A-P 5.8, M-L 1.4, and D-V + 4.0 mm, (Costall et. al., 1985). Following surgery, rats were housed individually with free access to food and water. After a 5-7 day recovery period, animals were deprived of food for 24 h and were tested in experiments where drugs were infused intracerebroventricularly (icv) with a Sage Instruments infusion pump in volumes of 10 ul over a 5 min period. Infusions occurred 30 min prior to restraint.

Following 3 h of cold restraint (Glavin, 1980), all rats were killed by decapitation. Trunk blood was collected into heparinized tubes, centrifuged at 5000 x g for 20 min and the plasma stored frozen at -70^{o}C until analyzed for corticosterone levels (Van der vies, 1961). This method depends on the reading of the fluorescence of the steroid in a mixture of sulfuric acid and ethanol. The stomachs were immediately excised following the 3 h restraint, opened along the greater curvature, rinsed and cleaned with distilled water followed by 10% formaldehyde and examined for ulcers by an observer unaware of experimental treatments. The number and the cumulative length (expressed in millimeters) of the ulcers were recorded. Drugs used were: l-dopa (Sigma) at doses of 0.1, 0.5, 1.0 and 2.0 ug; l-deprenyl (Research Biochemicals Inc.) at doses of 0.1, 1.0, or 2.0 ug; domperidone HCl (Janssen) at doses of 0.5, 1.0 and 2.0 ug and threo-dl-p-hydroxymethylphenidate (a gift from Dr. D. Hernandez, School of Veterinary Medicine,

University of North Carolina) at doses of 1.0, 5.0 and 10.0 ug. Domperidone and threo-dl-p-hydroxymethylphenidate were dissolved in distilled water and 0.9% w/v NaCl solution (saline) respectively. L-dopa, however, was dissolved in 0.2% ascorbic acid solution, as antioxidant, and neutralized to pH 7.4 with 20 mM phosphate buffer. Control rats received the appropriate vehicle injections.

Stress-induced gastric ulceration:

Adult male Sprague-Dawley rats (200-300 g) were housed in a controlled environment animal facility and fed laboratory chow with water ad libitum. Before starting the experiments, all rats were deprived of food but not water for 24 h. Rats were then randomly divided into equally sized groups and given a single injection of the following drugs: l-dopa (Sigma) at doses of 0.5, 1.0, 2.0 mg/kg ip and 2.0 mg/kg ip for 4 days; l-deprenyl (Research Biochemicals Inc.) at doses of 0.1, 1.0 and 2.0 mg/kg ip; domperidone HCl (Janssen) at doses of 0.125, 0.25, 0.5, 1.0 or 2.0 mg/kg and sulpiride (Ravizza, s.P.a; Italy) at doses of 5.0, 10.0 and 20.0 mg/kg ip. The solutions were freshly prepared before injections. The control animals received an equivalent volume of the corresponding vehicle. Thirty minutes after drug injections, all rats were restrained and placed supine in a cold (4-6^{o}C) environment for 3 h as described previously (Glavin, 1980) and which is shown in Figure 5. Following the restraint period, rats were sacrificed by decapitation, the stomachs removed and

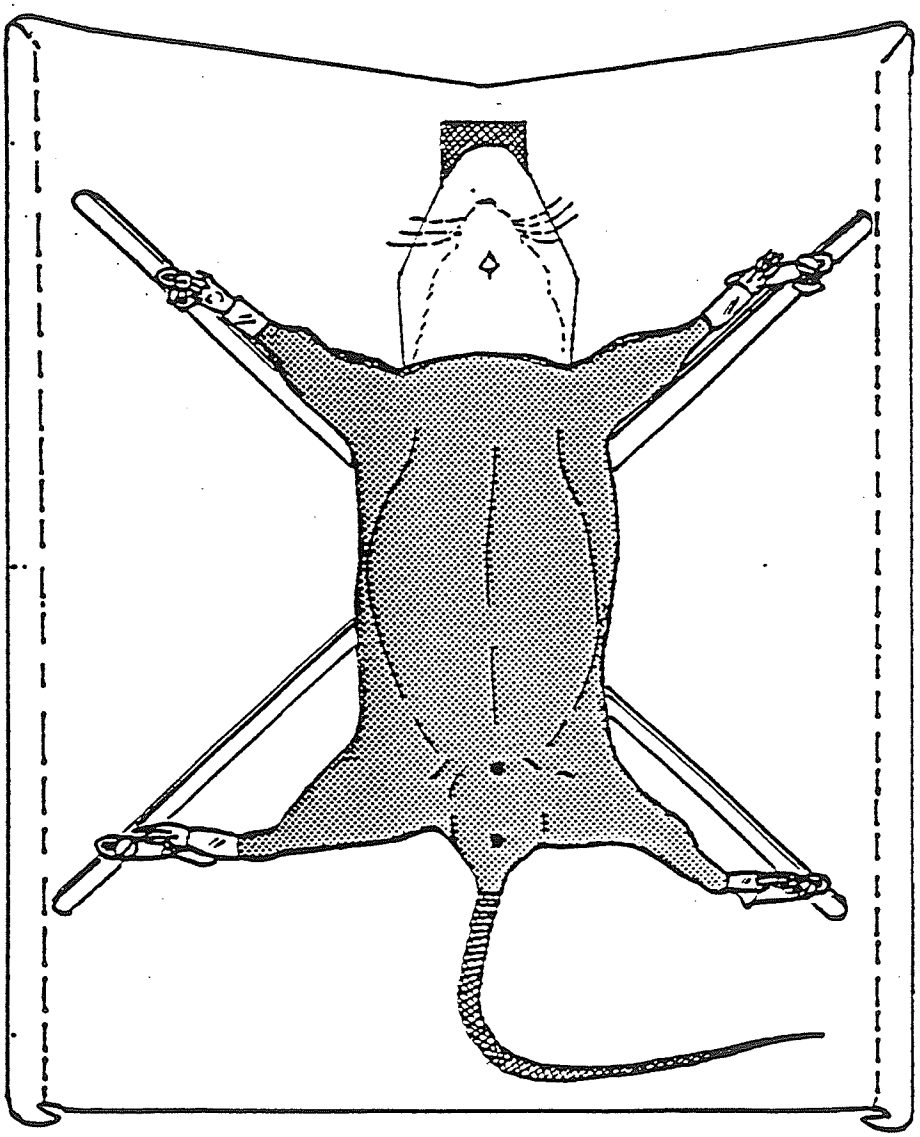


Fig.5. Immobilzation restraint showing rat in the supine position with the limbs tied to a restraint board.

examined for gastric ulcers. Both the incidence, defined as the mean number of ulcers per rat, and the severity, defined as the cumulative length (mm) of ulceration were recorded.

In all experiments, groups of rats consisted of 5 to 8 animals per group. Data are expressed as mean $\pm$ S.E.M. Data were analyzed by analysis of variance followed by post-hoc Tukey tests. Statistical significance was considered at the 0.05 and 0.01 levels.

III. RESULTS

Stress Ulceration Studies:

A. Effects of peripheral aministration of dopamine agonists and antagonists on stress-induced gastric ulceration in rats.

Intraperitoneal injections with l-dopa induced a decrease in the severity of stress ulceration. The reduction was both dose- and frequency-dependent. L-dopa at doses of 1.0 or 2.0 mg/kg and 2.0 mg/kg for 4 days produced a statistically significant ($p<0.01$) decrease in ulcer severity compared with the control group given an equivalent amount of the vehicle (Table I). However the most effective dose appeared to be 1.00 mg/kg, which was more effective than 2.0 mg/kg given once or repeated daily for 4 days. Table I also shows that all doses of intraperitoneally administered l-deprenyl, a specific monoamine oxidase type B inhibitor, significantly attenuated stress ulcer formation. In comparison with l-dopa, l-deprenyl was effective at even smaller doses (0.10 mg/kg). Moreover, 1.0 mg/kg was the most effective dose in terms of reducing the severity of stress ulceration. In contrast, injections of the dopaminergic antagonist domperidone 30 minutes prior to cold-restraint, worsened the stress ulcer condition. There was a slight, non-significant increase in the severity of ulcers with small doses of domperidone (0.125 and 0.25 mg/kg). However, larger doses of 0.50 and 1.00 mg/kg

Table I Effects of intraperitoneal administration of l-dopa and l-deprenyl on stress ulcer formation.

Drug	Dose	Mean (±SEM) Number of Ulcers	Mean (±SEM) Ulcer Length (mm)
L-Dopa	vehicle	12.0 (3.6)	29.0 (7.8)
	0.5 mg/kg	7.4 (2.2)	22.8 (5.2)
	1.0 mg/kg	2.8 (0.6)	7.8 (2.8)*+
	2.0 mg/kg	4.8 (1.0)	11.8 (2.4)*+
	2.0 mg/kgx 4 days	12.8 (2.5)	17.6 (2.8)*
L-Deprenyl	vehicle	21.7 (3.5)	40.8 (3.9)
	0.1 mg/kg	4.6 (1.6)	7.0 (3.5)**
	1.0 mg/kg	4.3 (1.5)	6.0 (3.0)**
	2.0 mg/kg	4.0 (2.0)	7.6 (4.6)**

* Significantly less than vehicle, $p<0.01$.

\+ Significantly less than l-dopa 0.5 mg/kg, $p<0.01$; and l-dopa 2.0 mg/kg x 4 days; $p<0.05$.

** Significantly less than vehicle, $p<0.01$.

significantly ($p<0.01$) aggravated experimental gastric ulcer development. With the highest dose of domperidone tested (2.0 mg/kg), ulceration was not different from that seen with vehicle or 0.125 mg/kg but the number of ulcers and their severity were less than those observed with 0.50 and 1.0 mg/kg treated rats (Table II). Domperidone was tested in an attempt to assess the involvement of peripheral dopamine receptors in mediating stress effects, since, unlike other dopaminergic blockers, domperidone reportedly does not cross the blood-brain barrier.

Sulpiride, a dopaminergic antagonist with prominent presynaptic blocking properties, produced a significant preventive effect on stress ulcer formation at a dose of 20.0 mg/kg, which was the highest dose tested (Table II). This finding is in agreement with that of Strocchi et al (1976) who reported that in the Sprague-Dawley strain, peripherally administered sulpiride had an inhibitory effect on restraint ulcers over a dose range of 5-20 mg/kg. The effects of metoclopramide, a dopamine receptor antagonist, given intraperitoneally were dose-related. A small dose, (5.0 mg/kg) was associated with a significant decrease in stress ulceration, while a dose of 20.0 mg/kg markedly increased ulcer severity.

Effects of intracerebroventricular administration of dopamine agonists and antagonists on stress ulcer formation:

Table III shows the effects of l-dopa (icv) on stress

Table II Effects of Dopamine Agonists and Antagonists on Stress Ulcer Formation

Drug	Dose	Mean (±SEM) Number of Ulcers	Mean (±SEM) Ulcer Length (mm)
Domperidone	vehicle	12.0 (3.6)	29.0 (7.8)
	0.125 mg/kg	15.0 (3.5)	31.6 (9.5)
	0.25 mg/kg	16.0 (3.1)	32.7 (6.7)
	0.50 mg/kg	21.0 (5.1)	43.3 (10.2)*
	1.00 mg/kg	22.0 (3.0)	41.7 (1.9)*
	2.00 mg/kg	16.3 (3.3)	31.3 (1.8)
Sulpiride	5.0 mg/kg	15.0 (1.5)	38.3 (4.8)
	10.0 mg/kg	12.0 (2.0)	28.3 (2.6)
	20.0 mg/kg	9.7 (1.7)	19.0 (6.6)**
Metoclopramide	5.0 mg/kg	8.7 (0.9)	16.0 (6.0)+
	10.0 mg/kg	10.8 (1.4)	22.8 (4.8)
	20.0 mg/kg	9.7 (2.7)	38.0 (6.6)++

* Significantly greater than vehicle and domperidone 0.125, 0.25 and 2.0 mg/kg; $p<0.01$.

** Significantly less than the vehicle and sulpiride 5.0 and 10.0 mg/kg; $p<0.01$.

\+ Significantly less than the vehicle, $p<0.01$ and less than metoclopramide 10.0 mg/kg; $p<0.05$.

++ Significantly greater than the vehicle and metoclopramide 5.0 and 10.0 mg/kg; $p<0.01$.

Table III. Effects of intracerebroventricular (icv) administration of l-dopa on stress ulcer formation.

Dose	Mean (±SEM) Number of Ulcers	Mean (±SEM) Ulcer Length (mm)
vehicle	19.3 (0.9)	40.7 (6.7)
0.1 ug	17.7 (8.2)	38.3 (1.2)
0.5 ug	10.7 (1.2)	20.0 (4.2) *
1.0 ug	9.3 (3.2)	10.0 (4.6) * +
2.0 ug	12.3 (2.9)	11.3 (1.8) * +

* Significantly less than vehicle and l-dopa 0.1 ug; ($p<0.05$).

\+ significantly less than l-dopa 0.1 ug, $p<0.05$.

ulcer formation. Intracerebroventricular injection of l-dopa significantly ($P<0.05$) reduced the severity of cold-restraint ulcers in the groups receiving 0.1, 1.0 and 2.0 ug. Rats given l-dopa at a dose of 1.0 ug developed the least amount of gastric ulcer disease. The ulcer-mediating effects of icv injection of l-deprenyl and domperidone are shown in Table IV. Domperidone given i.c.v. led to significant protection against stress ulceration. This cytoprotective effect was demonstrated by all doses tested (0.5, 1.0 or 2.0 ug). L-deprenyl administration into the cerebral ventricles also caused a significiant inhibition of gastric ulceration induced by cold restraint and to a greater extent than that seen with domperidone.

Although intraperitoneally administered l-deprenyl was also found to significantly reduce stress ulceration (Table I), the drug given icv in microgram quantities was far more effective in reducing ulcers than when administered ip at a larger dose (Table IV).

P-hydroxymethylphenidate (a hydroxylated analog of methylphenidate) was also effective (Table IV). An intracerebroventricular infusion of this compound (1.0, 5.0 and 10 ug) 30 minutes prior to cold-restraint stress significantly reduced the cumulative length of the observed stress ulcers, but to a lesser degree than seen with l-deprenyl.

Table IV. Effects of intracerebroventricular (icv) administration of l-deprenyl, p-hydroxyymethyl-phenidate and domperidone on stress ulcer formation.

Drug/Dose		No. of Ulcers	Cumulative Ulcer Length (mm)
Vehicle		23.6 (3.6)	44.1 (3.8)
l-deprenyl	0.1 ug	3.5 (2.5)	5.0 (3.0) *
	1.0 ug	6.7 (2.3)	2.7 (1.9) *
	2.0 ug	2.5 (2.0)	2.5 (1.8) *
p-hydroxymethyl-phenidate	1.0 ug	14.3 (5.3)	20.3 (1.8) +
	5.0 ug	8.3 (4.3)	13.7 (7.2) +
	10.0 ug	8.7 (4.3)	23.3 (14.2) +
Domperidone	0.5 ug	12.7 (5.2)	26.7 (2.7) +
	1.0 ug	12.0 (5.2)	18.7 (1.8) +
	2.0 ug	11.6 (1.8)	20.7 (6.3) +

* Significantly less than the vehicle, $p<0.01$.

+ Significantly less than the vehicle, $p<0.05$.

Gastric acid secretion studies

Effects of dopamine agonists and antagonists on gastric acid secretion in rats.

Graded doses of the dopaminergic agonists tested caused a significant inhibition of gastric acid output. Bromocriptine at doses of 1.0, 2.0 and 4.0 mg/kg ip and bupropion at doses of 12.5, 25.0 and 50.0 mg/kg markedly reduced total acid output (mEq/ml/100g/h). On the other hand, the dopamine receptor antagonists haloperidol (0.25, and 50.0 mg/kg ip) and pimozide (0.50 and 1.00 mg/kg) significantly increased the acid output. Haloperidol, 0.1 mg/kg, did not increase acid output, nor did pimozide at doses of 0.25 mg/kg. Moreover, the lowest dose of haloperidol (0.1 mg/kg) and pimozide (0.25 mg/kg) only slightly increased gastric acid secretion as compared with the pre-and post-drug vehicle injection values (Table V).

The peripherally acting dopamine receptor antagonist domperidone, produced a significant inhibition of gastric acid secretion at 2.0 mg/kg, which was the highest dose tested. In addition, this inhibition was only significant during the second hour of collection; that is, the hour immediately following its administration (Table VI).

Table V Effects of Dopamine Agonists and Antagonists on Gastric Acid Secretion (Mean ± SEM)

Drug	Dose	Acid Output (mEq/ml/100 g)	
Bromocriptine	vehicle-pre	13.75 (1.12)	
	1.0 mg/kg	0.23 (0.03)	*
	2.0 mg/kg	0.86 (0.10)	*
	4.0 mg/kg	11.14 (0.51)	*
	vehicle-post	12.23 (0.81)	
Bupropion	vehicle-pre	13.43 (0.80)	
	12.5 mg/kg	11.26 (0.20)	**
	25.0 mg/kg	0.06 (0.01)	**
	50.0 mg/kg	0.40 (0.20)	**
	vehicle-post	13.40 (0.53)	
Haloperidol	vehicle-pre	12.98 (1.10)	
	0.10 mg/kg	13.43 (1.22)	
	0.25 mg/kg	21.63 (2.31)	+
	0.50 mg/kg	21.29 (4.71)	+
	vehicle-post	13.22 (1.71)	
Pimozide	vehicle-pre	13.33 (0.91)	
	0.25 mg/kg	13.80 (1.20)	
	0.50 mg/kg	28.10 (2.20)	++
	1.00 mg/kg	26.22 (1.31)	++
	vehicle-post	12.91 (0.88)	

* significantly less than bromocriptine vehicle-pre and vehicle-post; $p<0.01$.

** significantly less than bupropion vehicle-pre and vehicle-post; $p<.01$.

\+ significantly greater than haloperidol vehicle-pre, haloperidol 0.10 mg/kg and vehicle-post; $p<.01$.

++ significantly greater than pimozide vehicle-pre, pimozide 0.25 mg/kg, and vehicle-post; $p<.01$.

Table VI Effects of Domperidone on Gastric Acid Secretion

(Meq/ml/100g/h) (Mean±SEM)

Dose	hour 1	hour 2	hour 3
vehicle	19.6 (2.2)	16.3 (2.8)	19.8 (3.5)
0.025 mg/kg	21.7 (3.1)	22.5 (3.8)	24.5 (4.1)
1.0 mg/kg	20.9 (2.6)	22.6 (3.8)	20.3 (3.7)
2.0 mg/kg	23.6 (4.3)	10.9 (1.1)*	18.5 (3.2)
vehicle	15.5 (2.1)	12.6 (2.3)	17.0 (3.2)

* significantly less than hour 1 and hour 3 for domperidone 2.0 mg/kg and all other doses of domperidone and vehicle hour 2 ($p<0.05$).

Effects of dopamine agonists and antagonists on plasma corticosterone responses to cold-restraint stress.

We evaluated the effects of representative dopamine agonists and antagonists on stress-induced changes in plasma corticosterone level, which is known to increase during stress situations due to activation of the hypothalmic-pituitary-adrenal axis (Keim and Sigg, 1977). The results of these studies are summarized in Table VII and Table VIII.

Plasma corticosterone levels were markedly and significantly reduced in restrained rats pretreated with the MAO B inhibitor l-deprenyl, given both intraperitoneally at a dose of 2.0 mg/kg and intracerebroventriculary at a dose of 2.0 ug/kg. These doses of l-deprenyl were also found to produce a signficant inhibition of stress ulcer formation. Domperidone, in a dose of 1.0 ug icv, also resulted in a significant reduction of plasma corticosterone level ($P<0.05$).

Intracerebroventricular infusion of the indirectly acting dopamine agonist, threo-dl-p-hydroxymethylphenidate, however, had no significant effect on plasma corticosterone levels. L-dopa administered intraperitoneally at doses of 0.5, 1.0, 2.0 mg/kg and 2.0 mg/kg daily for 4 days also significantly ($p<0.01$) reduced plasma corticosterone relative to control groups injected with the vehicle and exposed to 3 hr cold-restraint stress and relative to to non-stressed animals (Table VIII).

Table VII Effects of l-deprenyl ip and icv and domperidone icv on plasma corticosterone responses to restraint-cold stress (mean ± SEM)

Drug/Dose	Corticosterone (ug%)
Vehicle ip	69.8 (6.3)
l-deprenyl 0.1 mg/kg i.p.	75.5 (7.7)
1.0 mg/kg i.p.	71.7 (6.8)
2.0 mg/kg i.p.	53.6 (5.3)*
Vehicle icv	61.2 (5.7)
l-deprenyl 0.1 ug icv	66.7 (8.1)
1.0 ug icv	67.3 (7.9)
2.0 ug icv	49.0 (5.8)*
Domperidone 0.5 ug icv	60.2 (6.1)
1.0 ug icv	48.5 (5.4)+
2.0 ug icv	61.6 (6.3)

* Significantly less than vehicle and all other doses of l-deprenyl ($P<0.05$)

+ Significantly less than vehicle and all doses of domperidone.

In order examine whether peripheral dopamine receptors were involved in modifying the animal's response to stress we administered the peripheral dopaminergic blocker, domperidone in a dose of 0.125, 0.25, 0.50, 1.0 and 2.0 mg/kg intraperitoneally to rats 30 minutes prior to cold-restraint stress. Analysis of domperidone data showed both an increase in plasma corticosterone levels at a dose of 2.0 mg compared to the control stressed group and a decrease at a dose of 0.25, and 1.0 mg/kg ip.

Table VIII Effects of domperidone and l-dopa on plasma corticosterone responses to stress (Mean ± SEM)

Drug/Dose		Corticosterone (ug%)
vehicle only (no stress)		39.8 (5.3)
vehicle & stress		69.8 (6.3)
Domperidone & stress	0.125 mg/kg i.p.	58.4 (5.8)
	0.25 mg/kg i.p.	47.6 (7.1)**
	0.50 mg/kg i.p.	64.9 (6.9)
	1.0 mg/kg i.p.	44.1 (6.2)**
	2.0 mg/kg i.p.	82.9 (4.9)*
l-dopa & stress	0.5 mg/kg i.p.	20.9 (4.0)+
	1.0 mg/kg i.p.	27.8 (4.1)+
	2.0 mg/kg i.p.	24.6 (4.5)+
	2.0 mg/day/4 days	24.8 (3.7)+

* Significantly greater than vehicle only and vehicle + stress ($P<0.01$).

\+ Significantly less than vehicle only ($P<0.05$) and less than vehicle + stress ($P<0.01$).

** Significantly less than vehicle + stress ($P<0.01$).

IV. DISCUSSION

Stress situations have been reported to produce a noticeable increase in dopaminergic activity in specific brain regions. Bannon and Roth (1983) and Wantanabe (1984) reported that during immobilization-stress, dopaminergic activity was significantly increased in the mesocortical and mesolimbic DA neurons in the rat. According to these authors, as well as others (Groisman et al., 1984), an increase in dopaminergic activity and/or stimulation of DA receptors in the central nervous system may be contributing factors in the production of stress-induced gastrointestinal pathology.

In our studies, we found that the dopamine agonists, l-dopa and threo-dl-p-hydroxymethylphenidate (a hydroxylated peripherally-acting analog of methylphenidate) which, according to Patrick et al. (1981), stimulates release of dopamine and hence increases synaptic transmission, both reduced gastric stress ulcers in a dose-dependent manner. These data are compatible and strongly supportive of the results obtained by many other investigators and suggest that both direct and indirect dopamine agonists provide protective effects against stress ulcers and, furthermore, that these effects are mediated via peripheral DA receptors. Hernandez et al. (1984; 1984) reported that the dopamine agonists, apomorphine, d-amphetamine, methylphenidate and threo-dl-p-hydroxymethylphenidate given peripherally, reduced both the incidence and the severity of cold-restraint stress-induced gastric ulcers. Gupta et al (1983)

and Lauterbach and Mattes (1977) have shown that infusion of small doses of dopamine either iv or icv, reduced the development of mucosal erosions in response to cold restraint and hypoxia-immobilization stress.

In addition, pretreatment with dopamine agonists was found to protect against chemically-induced gastric and duodenal ulcers. Szabo and his associates (1979;1983) reported that bromocriptine and lergotrile virtually abolished cysteamine-induced duodenal ulcers. This group has also described a similar preventive effect of bromocriptine, lergotrile and the monoamine oxidase inhibitors pargyline and l-deprenyl on ulcers induced in rats by subcutaneous or oral doses of MPTP, a neurotoxin known to deplete CNS dopamine and which produces duodenal ulcers (Szabo et al., 1985).

In the present study, the fact that l-dopa administered in microgram quantities into the cerebral ventricles, prevented stress ulcer formation more effectively than when given in larger doses intraperitoneally, indicates that the cytoprotective effect of l-dopa is mediated by the central nervous system and may involve activation of the inhibitory presynaptic DA2 receptors.

The MAOB inhibitor l-deprenyl significantly reduced both the number and severity of stress ulcers when administered ip or icv. The drug was more effective when given icv than ip, which suggests that augmenting central

dopamine activity plays a major role in stress-induced gastrointestinal pathology. Although in the rat brain only 45% of the total MAO activity is of the B sub-type (Houslay et al., 1976), this population may be more sensitive than peripheral MAOB to the action of l-deprenyl. The exact mechanism by which l-deprenyl enhances the central dopaminergic activity is still controversial. Harsing et al. (1979) and Azzaro and Desmarest (1982) suggested that l-deprenyl inhibited DA uptake in the striatum and forebrain in the rat. In addition, high concentrations of l-deprenyl enhanced both the resting and KCl-induced release of dopamine in isolated rat striatum (Harsing and Vizi, 1984).

Sulpiride, a dopamine receptor antagonist which is reported to be 4 to 8 fold more selective at blocking central presynaptic DA receptors than post-synaptic receptors (Costall et al., 1980), exerted differential effects on stress ulceration. Whereas small doses aggravated ulcer development, larger doses inhibited ulcer formation. There may be a preferential inhibition of pre- or postsynaptic DA receptors depending upon the dose of sulpiride used, so that at low doses, only presynaptic DA receptors were blocked while at larger doses, the less sensitive DA receptors located on postsynaptic membranes became inactive ultimately decreasing central dopaminergic transmission. Our sulpiride data confirm those of Strocchi et al. (1976) who reported a similar dose-dependent effect of the drug on restraint ulcer in the rat. However, these

authors interpreted the ulcer-preventing effect of sulpiride as likely being related to restoration of the balance between dopamine and norepinephrine at the hypothalamic level. Restraint stress, according to Lidbrink et al. (1972), produced an enhancement of NE turnover especially at the hypothalmic level and a decrease of DA turnover in the neostriatum, the limbic forebrain and the median eminence.

A selective blocker of peripheral dopamine receptors, domperidone, potentiated stress ulceration when given ip to rats. However, intracerebroventricular infusion of domperidone significantly decreased stress ulcer formation. This finding confirms the hypothesis that blockade of peripheral and specific populations of central dopamine receptors, produces a potentiating effect on gastric ulcers due to stress. The effects of metoclopramide given intraperitoneally were biphasic. Metoclopramide, a dopaminergic antagonist which has both central and peripheral DA receptor blocking activities, potentiated stress-ulcers at high doses and decreased ulcer formation at lower doses. However, the ulcer-potentiating effect of the drug was more significant than its antiulcer effect. Thus, it may be assumed that at high doses, metoclopramide blocked peripheral DA receptors. In addition, the effects of metoclopramide on the gastric mucosa may not be directly linked to blockade of peripheral dopamine receptors, but may involve other pathways, for example, activation of cholinergic neurotransmission. Hay (1975) suggested that the

action of metoclopramide on gastric motility in guinea pigs was mediated by an increase in the amount of acetylcholine release at the post-ganglionic cholinergic nerve endings.

Although the etiology of stress-induced gastric ulceration in the rat stomach has been studied by many investigators, the exact pathophysiology is still completely unknown. Shay suggested that the secretion of hydrochloric acid increased during stress because of increased vagal activity and corticosterone secretion from the adrenal cortex (Shay, 1954). However, subsequent studies revealed that gastric hyperacidity was not a critical factor in the initiation of these ulcers. Brodie et al. (1962) and Dai and Ogle (1973) found that acute stress was associated with a significant reduction of gastric acid output. Moreover, stress ulcers in rats were neither inhibited by antacids nor potentiated by the administration of a mixture of hydrochloric acid and pepsin (Takagi and Okabe, 1970).

Sympathomimetic agents have been shown to decrease gastric acid secretion in rats. This effect was attributed to stimulation of β-adrenoreceptors (Bass and Paterson, 1967; Lundell and Svensson, 1974). Esplagus et al. (1982) showed that salbutamol significantly reduced the severity of pyloric-ligation ulcers and that this antiulcer effect was accompanied by a moderate but not statistically significant decrease in the volume of gastric juice. However, the acid concentration ($mEqH^+/h$) was significantly reduced and thus

they concluded that these effects were mediated via β_2-adrenoreceptor activation.

The mechanism(s) of the beneficial action of dopamine agonists on stress-induced gastric ulcer is/are not completely understood. To clarify the role of dopamine receptors in the pathogenesis of ulcers, we studied the effects of several DA agonists and antagonists on gastric acid secretion in rats with chronic gastric cannulas. The results showed that dopamine agonists bromocriptine and bupropion produced a dose-dependent inhibition of basal gastric acid output. In contrast, the dopamine antagonists, haloperidol and pimozide, significantly stimulated gastric acid secretion. When animals were treated with domperidone, a dopamine antagonist which does not penetrate the blood-brain barrier, no significant change was observed during the first hour collection and only a small reduction was observed at a dose of 2.0 mg/kg during the second hour collection. Metoclopramide, on the other hand, had no significant effect on gastric acid secretion. These results indicate that central rather than peripheral dopamine receptors are involved in the modulation of gastric acid secretion by bromocriptime, bupropion, haloperidol and pimozide. Previous reports have shown differential effects of bromocriptine on acid secretion. Acute administration of bromocriptine enhanced gastric acid secretion in man (Caldara et al., 1979) and in the cat (Hirst et al., 1976). Szabo and his group, however, showed that bromocriptine and

lergotrile suppressed gastric acid output in cysteamine-treated rats (Szabo, 1979). The potentiation of gastric acid secretion by bromocriptine was attributed to α-adrenergic and/or serotonergic antagonism by this drug (Caldara et al., 1970; Hirst et al., 1976). Costall et al. (1985) studied the effect of the dopamine agonist apomorphine on rat gastric acid secretion and found that the drug reduced both the volume and acid concentration of the gastric secretion. Moreover, they suggested that the effect of apomorphine on acid volume was mediated via β_2-adrenoreceptors while that on acid concentration involved action on neuroleptic-sensitive receptors, since these actions were antagonized by pretreatment with β_2-adrenoreceptor antagonists ICI 118551, haloperidol and metoclopramide respectively. Valenzuela et al. (1976;1979) have shown that intravenous infusion of dopamine produced a dose-dependent inhibition of gastric acid secretion in man and in the dog. This inhibitory effect was reversed by pretreatment with haloperidol. Pipkin et al. (1985) studied the effects of the selective peripheral DA_1 and DA_2 receptor agonists SK&F 82526 and SK&F 89124 on gastric acid output in rats and found no significant effect with either of these compounds and, as a result, they excluded the possibility that peripheral DA receptors were involved in the regulation of gastric acid secretion. Basal and submaximal pentagastrin-stimulated gastric secretion were significantly decreased after acute intramuscular administration of D-

sulpiride, an antidopaminergic drug, given to healthy men (Caldara et al., 1983).

Our corticosterone data showed a significant alteration of the plasma levels in response to stress following the administration of drugs which increase endogenous dopamine activity, including l-dopa and l-deprenyl, which reduced plasma corticosterone, probably due to activation of DA receptors at a central level.

There have been controversial reports concerning the role of biogenic amines including noradrenaline, histamine and indoleamines in the regulation of stress-induced ACTH secretion and, as a result, increased plasma corticosterone production. Van Loon et al. (1971) have reported that noradrenaline had an inhibitory effect on ACTH release. These results were supported by Ganong (1974) who reported a similar inhibition in basal circadian and stress-induced ACTH secretion. However, Bhargava et al. (1972) and Nakai et al (1973) have indicated a facilitatory action on adrenocorticotrophic hormone release by stimulation of central adrenoreceptors.

Summary and Conclusion:

In summary, the results indicate that the dopamine agonists and dopaminergic enhances l-dopa, threo-dl-p-hydroxymethylphenidate and the monoamine oxidase type B inhibitor l-deprenyl administered both peripherally and into the cerebral ventricles, significantly inhibited stress ulcer formation in rats. Pretreatment with the dopamine agonists bromocriptine and bupropion and the dopamine antagonists haloperidol and pimozide, all of which can either stimulate or block both central and peripheral DA receptors, markedly decreased or increased the gastric acid output, respectively. However, domperidone, which selectively blocks peripheral DA receptors, had little effect on acid secretion. The effects of dopamine agonists and antagonists on plasma corticosterone responses to stress were complex. For example, both l-dopa and l-deprenyl administered ip and icv significantly attentuated plasma corticosterone. Domperidone icv also produced a similar effect, but when given ip, plasma corticosterone levels were decreased at lower doses but elevated at higher doses of this agent. Thus it may be concluded that: (a) both central and peripheral dopaminergic activity is involved in mediating stress-induced gastric pathology; (b) activation of peripheral and inhibition of some central DA receptors is a putative mechanism responsible for protecting the gastric mucosa against stress ulcers and (c) inhibition of gastric acid secretion, which appears to involve activation of

central DA receptors, may be one of the mechanisms responsible for protecting the gastric mucosa. However, further investigation is required to determine if the cytoprotective effect was due to direct activation of DA receptors or whether it involves alteration of endogenous substances and/or mechanisms which contribute to maintaining the integrity of the gastric mucosa such as prostaglandins or gastric mucosal blood flow.

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