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A Review: The Agents and Actions of Sympathetic Nerve and Catecholamine Inhibition of Gastric Mucosal Function

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Abstract

The role of the sympathetic nerve supply to the gastric mucosa in gastric physiology is discussed. It is concluded that they are inhibitory to gastric acid secretion, mucosal blood flow, pepsin secretion, gastric oxygen consumption and that these nerves also decrease the serum gastrin concentration. Sympathetic nerve stimulation always reduces the mucosal blood flow and it is suggested therefore, that the inhibition of gastric secretion could be secondary to vasoconstriction mediated by noradrenaline release. The evidence for these conclusions is considered alongside the available histological evidence. It is concluded that the remaining hurdle is to place these phenomena within our knowledge of gastric physiology.

It is generally agreed that sympathectomy increases the gastric output of acid and pepsin [1–4]. However several groups of early workers produced contrary results [5–9]. It is clear that electrical stimulation of the splanchnic nerves reduces gastric activity. This has been shown for gastric muscle activity [10–12], gastric acid secretion [13, 14], gastric mucosal blood flow [12–15] and total blood flow [15, 16]. Gastric oxygen consumption is also inhibited [16]. Pepsin secretion is not reduced if the sympathetic nerves are stimulated about 70 minutes after the start of vagal stimulation [12], but is if stimulated about 180 minutes after the beginning of vagal stimulation [17]. Recently these observations of the effect of the sympathetic nerves on gastric function have been extended to include the hormone gastrin [18]. Splanchnectomized dogs have larger serum gastrin responses to feeding as well as acid and pepsin responses [18]. Electrical sympathetic nerve stimulation reduces the serum gastrin response to food material in antral pouches, and the simultaneously occurring acid and mucosal blood flow responses are also inhibited [19]. We can conclude that under certain conditions, the sympathetic nerve supply does inhibit gastric function. The mechanisms of these inhibitory actions are not nearly so clear.

Some workers have observed the effects of circulating catecholamines on gastric secretion. However, these studies usually involved the IV infusion of these materials which leads to variable results. For example, IV isopropylnoradrenaline is said by some to inhibit gastric acid secretion [20, 21] but others who have administered this material intra-arterially to the stomach have shown it to be both a vasodilator in the gastric mucosa [14] and to increase the gastric acid response to exogenous gastrin [22]. Blood flow does limit the acid secretory rate [23] and a vasodilator presumably increases the acid response by bringing more nutrients or stimulant or by flushing away metabolites. The discrepancy between the results obtained with IV and IA infusion can probably be explained by effects on arterial blood pressure (BP). In the IA infusion experiments the BP did not change [13] but IV isopropylnoradrenaline presumably produced a fall in arterial BP which would then reduce the perfusion of the gastric mucosal circulation and inhibit acid secretion. IV adrenaline [24] and noradrenaline [25] do reduce gastric acid secretion, but when given increase arterial BP. This must surely alter the relationship between acid secretion and mucosal blood flow. JACOBSON [25] reported that IV infusion of noradrenaline in conscious dogs during either histamine or gastrin stimulated acid secretion,

produced a reduction in both acid output and mucosal blood flow. The ratio R of

$$\frac{\text{gastric juice amidopyrine}}{\text{arterial plasma amidopyrine}} = \frac{\text{clearance}}{\text{volume rate of secretion}}$$

fell during this period, a fact the author suggests indicates a primary action of noradrenaline on the gastric vasculature, leading to a secondary reduction in acid secretion. However, to interprete R as the ratio of blood flow to acid secretion requires the assumption that acid concentration remains constant during all forms of stimulation and inhibition. Indeed Jacobson's results, when calculated as the ratio of gastric clearance to acid secretion, show a rise during noradrenaline inhibition of gastrin stimulated acid secretion. This either indicates a primary inhibition of the parietal cell mechanism or a secondary relative increase in mucosal blood flow perhaps as a result of the noradrenaline effect on BP.

Stimulation of the splanchnic (sympathetic) nerves in anaesthetized cats does not reduce the acid, pepsin or mucosal blood flow responses to electrical vagal stimulation if the arterial BP is allowed to rise. In this experimental series the BP increased during sympathetic nerve stimulation and neither acid nor mucosal blood flow were reduced by greater than 15%. However if the rise in BP is prevented, the acid and mucosal blood flow responses are inhibited [13], an observation which suggests a vasoconstrictor action but not the agent responsible.

But pepsin secretion is not inhibited whether the BP increases or remains constant [13]. During the first 70 minutes, of vagal stimulation the pepsin response increases [13] and then steadily declines [13] for about 80 minutes [13, 17, 26], sympathetic nerve stimulation after this time, about 180 minutes after the start of vagal stimulation, does inhibit pepsin secretion [17]. After this prolonged vagal stimulation, pepsin secretion may depend on newly synthesized pepsin which probably relies on the mucosal blood supply much more than does secretion of preformed granules of pepsinogen [11, 26]. This again points to the inhibitory action of the sympathetic nerves being dependent on a vasoconstrictor mechanism.

Whatever the action of these inhibitory mechanisms, the agents apparently do not include catecholamines from the adrenal medulla, because the degree of inhibition of acid secretion is not affected by adrenalectomy [13]. But the inhibition was largely reversed by guanethidine [13]. The major action of this drug is to prevent release of noradrenaline from postganglionic sympathetic nerve endings [27] which, together with the evidence from the adrenalectomy experiments, suggests that the inhibitory pathway is dependent on noradrenaline release from sympathetic nerve terminals in the gastric mucosa [13].

The sympathetic nerve inhibition of gastric acid secretion and mucosal blood flow is apparent against a wide range of excitatory stimuli with reductions in the responses to electrical vagal stimulation [13], IV infusion of high [14] and low [13] doses of gastrin pentapeptide, high doses of histamine [14] (IV) or to stimulation with meat extract suspension [19] in antral pouches. This range of stimulants against which the sympathetic nerves can exert their inhibitory action suggests that the inhibition is directed at points after the stimulation of the parietal, peptic and G cell mechanisms. Because pepsin secretion is inhibited under certain conditions only, it is more difficult to conceive of an antisecretory mechanism against secretory cells as being the method of sympathetic nerve inhibition.

Mucosal blood flow is consistently reduced [12, 13, 16, 19] whether accompanied by acid secretion or not [14]. The vasodilator response to isopropylnoradrenaline is reduced by sympathetic nerve stimulation which confirms the presence of a vasoconstrictor pathway to the gastric mucosa. Sympathetic nerve stimulation during IV infusion of high doses of histamine always reduces the mucosal blood flow but only inhibits acid secretion if the blood flow reaches a critical level. It is known that high doses of histamine produce an extra vasodilatation in the gastric mucosa [14, 28–30], over and above that linked to parietal cell activity [30]. If the sympathetic nerves reduce the blood flow to a value expected if gastrin were the stimulant, then acid secretion is inhibited [14]. This data, and the observation that if the BP is allowed to rise during sympathetic nerve stimulation, there is no inhibition, suggests that extra mucosal blood flow can reverse the inhibition. This could be used as an argument that a reduction in blood flow was the mecanism of the inhibition.

Gastric oxygen consumption was tested during sympathetic nerve stimulation to test the

antisecretory hypothesis. Oxygen consumption decreased in parallel with acid secretion [16] and there was no change in oxygen extraction [16]. If we assume that the sympathetic nerves inhibit gastric secretion by a vasoconstrictor action then the parietal cells could conceivably attempt to extract more oxygen from the circulation in an attempt to continue secretion. However, they do not [16] which may indicate an antisecretory action of the sympathetic nerves. But the parietal cells may be extracting as much oxygen as possible to start with, nearly 70% [16], and it may be impossible to extract more.

So far, it looks as though sympathetic nerve activity inhibits acid secretion by reducing mucosal blood flow.

The inhibition of mucosal blood flow is progressive, being greater during the 2nd 10-minute period of splanchnic stimulation than the first [13]. This is apparently in contrast to some blood flow studies which show the phenomenum of autoregulatory escape after about 1 minute of sympathetic nerve stimulation. In the example we are considering here, the stomach, there is likely to be a reactive hyperaemia as the result of acid and pepsin secretion which may oppose the vasoconstrictor action of the sympathetic nerves and only gradually result in a reduced mucosal blood flow. Whatever the mechanism of this gradual reduction in mucosal blood flow, it is reproducible [13, 14, 16].

The sympathetic nerve supply to the upper abdomen (splanchnic nerves) does appear to contain efferent inhibitory fibres. They may be part of a physiological mechanism because the frequency of stimulation used in the electrical stimulation experiments was 10 Hz. This is the value required to produce maximal vasoconstriction [31] in susceptible blood vessels. 10 Hz stimulation reduces gastric acid and pepsin secretory rates, mucosal blood flow and serum gastrin in the cat [19]. Section of the splanchnic nerves increase these responses in dogs [18].

The microanatomical evidence is of some help in determining the mechanism of sympathetic nerve inhibition of gastric function. The small arteries at the base of the cat gastric mucosa are adrenergically innervated [32]. Direct observation of the small arterioles which make up the submucosal plexus of the rat gastric mucosa shows them to be reduced to 72% of the control diameter [33] when the sympathetic nerves were stimulated, and these blood vessels are known to have adrenergic innervation [34]. This is consistent with the observation that the per cent arterial haemoglobin concentration was reduced during splanchnic nerve stimulation [16], which suggests that there is a net precapillary constriction in the abdomen, and also perhaps in the whole body, mediated by adrenaline release from the adrenal medulla. If there is an increase in precapillary resistance in the gastric mucosa then this might help to localize the site of action of the sympathetic nerve inhibitory effect. This agrees with the histological evidence [32]. If sympathetic nerves inhibited both blood vessels and parietal cells then the transmitter would have to overflow from the arterioles at the base of the gastric mucosa into the capillary bed and thereby inhibit the parietal cells [16, 32]. The decreased blood flow would presumably reduce any dilution of the noradrenaline by the mucosal blood flow. However, the transmitter at the blood vessel sites may be released into the tissue fluid and then diffuse to the parietal cells. If gastrin is taken up by cells at the base of the gastric pits and if these cells release a local hormone, e.g. histamine, then the adrenergic innervation might inhibit parietal cell activity at a non-blood vessel site. In contrast though, there is some histological evidence from rabbit and guinea-pig, to suggest that there are adrenergic nerve fibres supplying the glands in the gastric mucosa [35].

It does seem therefore, that there are pathways in the sympathetic nerves to the upper abdomen which inhibit gastric mucosal function. The mechanism, at least in part, depends on a vasoconstrictor action of the sympathetic nerves [14] and this may be sufficient to account for the inhibitory phenomenum. The agent of the inhibition is probably noradrenaline [13].

The remaining hurdle is the need to place this inhibitory effect within our knowledge of gastric physiology. The sympathetic nerve pathways in the upper abdomen are very complicated [36], and it may be some time before this effect is fully understood.

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