Progress report

Inhibition of gastrointestinal secretion

Much interest has been shown recently in the phenomenon of inhibition of the gastrointestinal secretions. It is worth commenting on two important aspects of inhibitory phenomena.

What Do We Mean by 'Inhibition' of Secretion?

Many studies of gastric or pancreatic secretion have inferred that 'inhibition' has been demonstrated if the rate of secretion in response to some stimulus decreases, following an experimental manipulation. For example, gastric secretion of acid in dogs has been shown to be inhibited by vagal influences¹⁹ and denervation², by acid¹, fat¹⁵, or hypertonic solutions³⁴ in the intestine, and by parenteral administration of secretin²⁴, cholecystokinin²⁵, and gastrin¹⁷ as well as by high doses of cholinergic drugs¹⁸. Pancreatic secretion of electrolytes has been shown to be inhibited by vagal stimulation³, by acid⁴², and by hypertonic solutions¹⁴ in the intestine.

It has recently become clear that 'inhibition' of secretion is not always merely a matter of demonstrating that there is a dip in the plotted curve of a secretory response or observing that an organ does not secrete as satisfactorily after an experimental procedure as before. Indeed, the concept of 'inhibition' covers a whole series of situations ranging from severe and irreversible loss of response to a stimulant, through more or less rapidly reversible decrease in response to a rebound increase in the secretory response either during or after cessation of the 'inhibitory' process. Unfortunately, it is not possible to distinguish between different types of 'inhibition', not only because we do not know enough about the mechanisms of stimulation and inhibition of secretory cells to be able to interpret and identify different processes, but also simply because many of the experiments stop immediately or soon after the demonstration of a period of 'inhibition'. As an example, it is perhaps worth considering the biphasic 'inhibition-rebound' type of secretory response in a little detail.

Although the emphasis has been on the 'inhibition' in most instances in which a biphasic secretory response has been noted, it is clear that the effect of the experimental procedure must be measured on the secretory response as a whole in a response with this type of time course. The overall net change in the secretory response may then be found to be negligible⁴¹. A biphasic gastric acid secretory response has been noted during the infusion of acid into the duodenum^{11, 12, 32, 34, 41}, during the 'inhibition' of gastric acid secretion

by secretin⁴¹, and in response to supramaximal dose rates of pentagastrin in man⁴⁰. 'Inhibition' with rebound secretion of pepsin has been reported in response to histamine²⁸ and the secretion of pancreatic enzymes shows this type of biphasic response to secretin³⁹. More interestingly, the phenomenon of 'inhibition-rebound' has been recorded during processes other than secretion by exocrine glands as, for example, during the action of acetylcholine on cardiac muscle^{20, 29}; during the action of the vagus on the heart²⁷ and small-intestinal muscle⁴; following stimulation of the intramural inhibitory nerves of guinea pig taenia coli⁹ and following the inhibition of acetylcholine release by noradrenaline from guinea pig ileal muscle³¹.

It appears, therefore, that 'inhibition' may sometimes be wholly or partly compensated, while under other experimental conditions, there is no compensatory rebound and perhaps even more or less marked residual impairment of response. The use of a term like 'inhibition' therefore requires explicit definition, description, and analysis. The biphasic 'inhibition-rebound' type of response, for example, could be due to temporary depression with subsequent facilitation of the response to the secretory stimulant or, alternatively, to two phases comprising separate and successive processes of 'inhibition' and 'stimulation'. There is insufficient information from secretory processes to permit resolution of this problem, but the matter has been more intensively investigated in the case of intestinal smooth muscle. Bennett⁵ considered that the biphasic muscle contraction was due to adrenoceptor-mediated hyperpolarization, followed by rebound depolarization. An alternative interpretation suggested that the α -adrenoceptor stimulation produced a double response with primary inhibition which partly masked a secondary, more slowly developing but more persistent stimulatory action⁷. The rebound was considered to represent the unmasking of the secondary stimulant action, which was postulated to be a consequence of some change arising during the primary inhibition⁷. On the other hand, Day and Warren¹³ considered that the motor (contraction) component of the response was not a 'rebound' phenomenon at all, but resulted from the activation of cholinergic nerve endings, while the 'inhibitory' component was due to activation of non-adrenergic inhibitory neurones within the muscle wall.

A considerable amount of careful, detailed study is required so that the significance of the many situations which have been reported to represent 'inhibition' can be satisfactorily evaluated.

What Is the Mechanism of 'Inhibition' of Secretion?

The mechanism of inhibition is presumably related to, and largely dependent on, the mechanism whereby cells are stimulated. Non-specific factors, such as interference with blood supply or with normal metabolic function, have been invoked to explain secretory inhibition, but will be disregarded for the purpose of the present commentary.

Hormones and hormone-like substances have been postulated to affect cell function by at least four mechanisms.

(1) ACTION ON NERVE TERMINALS AND PROCESSES NEAR THE CELL SURFACE

α - and β -Adrenoceptors exert quite distinct actions on smooth muscle, although both may cause relaxation under physiological conditions. The

α -mediated relaxation is similar to the inhibitory action of acetylcholine on the vagal endings in the heart²¹ and may be partly a consequence of increasing permeability of the cells to potassium ions. α -Receptors are located on nerve cells associated with intestinal muscle^{8, 22}. An alternative mechanism of 'inhibition' involving α -receptors has been demonstrated by the use of adrenaline and noradrenaline, which inhibit smooth muscle activity by reducing the output of acetylcholine from cholinergic nerve endings³¹.

In this connexion, the importance of acetylcholine both to stimulation and inhibition of secretory cells does not require comment. It is not known, however, to what extent secretory processes, like neural processes, depend on depolarization (nerve discharge and ? secretion) or hyperpolarization (inhibition of nerve discharge and ? secretion), or rather on the changes in membrane permeability to ions associated with the changes in membrane potential. Nor is it known whether the gastrointestinal hormones act directly on cells or through the release of neurohumoral agents. The recent demonstration that secretin reduces blood levels of gastrin and hence, by inference, release of gastrin from secreting cells (J. Hansky, personal communication) represents a related mechanism of inhibition, since inhibition of release of a humoral transmitter at a site distant from the effector organ is not different in principle to the inhibition of release of a neurohumoral agent which is released in close proximity to the effector cell.

(2) INTERACTION WITH SPECIFIC RECEPTORS ON THE CELL SURFACE

Recent analyses of inhibition of gastric acid secretion by cholecystokinin²⁵ and secretin²⁴ have suggested that secretory inhibition can be explained in terms of competitive and non-competitive enzyme kinetics with the assumption that hormone-receptor interactions behave like (simplified) substrate-enzyme reactions. Since the experimental data fit the mathematical interpretations of enzyme kinetics in the inhibition of gastric acid secretion by the duodenal hormones in dogs, the hypothesis based on receptor theory has been afforded strong support.

However, it is important to remember the warning that 'in complex systems, interpretation of dose-response curves in terms of mechanisms of drug action must be approached with extreme caution . . . This type of curve is common to a wide variety of biological responses . . .'³⁰. Moreover, it must be emphasized that gastric inhibition by the gastrointestinal hormones and by acid in the small intestine is slight or absent in cats³⁵ and man⁴¹ so that conclusions from experiments in dogs cannot safely be extrapolated to secretory phenomena in general.

(3) SPECIFIC CHANGES IN THE PERMEABILITY OF CELL MEMBRANES NOT DEPENDENT ON RECEPTORS

Selective transport of ions has been shown to result from the action of the cyclic polypeptide hormone vasopressin¹⁰ on cell membranes. More recently, groups of polypeptide antibiotics have been shown to promote the selective passage of specific cations or anions not only across cellular and mitochondrial membranes, but even through artificial lipid membranes³⁷. The capacity to induce transport appears to depend on the cyclic structure of the antibiotics³³. In this connexion, it should be noted that secretin has recently been

found to have a cyclic conformation⁶, which is essential for functional activity, like that of vasopressin. It seems permissible to speculate that, just as different groups of cyclic antibiotics can reverse each others' actions²⁶, secretin may not only induce but inhibit transport from secretory cells by a direct effect on membrane permeability.

(4) INDUCTION OF SYNTHESIS OF TRANSPORT PROTEINS IN CELLS

Direct action on cell metabolism and protein synthesis has been shown to underlie the action of aldosterone on sodium transport¹⁶, of vitamin D on calcium transport across intestinal mucosa³⁶, and of prolactin on casein synthesis³⁸. Recently, gastrin has been shown to increase the synthesis of protein in the gastrointestinal tract²³. It is not known whether gastrin-induced stimulation of secretion is dependent on enzyme induction, although the time course of the action of gastrin on secretion is more rapid than might be expected if the process involved enzyme induction, from analogy with the action of aldosterone.

In view of the lack of information about the role of enzyme induction in the secretory processes evoked by the gastrointestinal hormones, it is not possible to judge whether any of the types of inhibition depend on interference with the normal or induced synthetic processes within the secretory cells.

In conclusion, the information available at present does not permit us to infer that inhibition of gastric or pancreatic secretion involves hyperpolarization of the secretory cells, competitive or non-competitive interactions at receptor sites or other changes in the permeability or metabolism of the secreting cells, or combinations of these effects. Indeed, the nature of the subject and of the experimental evidence available at the present time makes it difficult to be sure that the apparent differences in the mechanism of cellular action are real rather than hypothetical. What is certain, however, is that secretion and its inhibition merits further intensive investigation, since much light can be shed on fundamental problems of cellular function.

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