Commentary

Treating diarrhoea: what might the pituitary offer?

Administration of cholera toxin to an animal can protect it against subsequent administration of the toxin or viable *Vibrio cholerae*. This protection is usually explained in terms of neutralisation of the toxin by secretory IgA before it penetrates the intestinal mucosa. In 1984 Lange and Lönnroth reported that extracts from hypophysis, brain and jejunal mucosa, obtained from rats immunised with cholera toxin administered intravenously or orally, attenuated fluid secretion induced by cholera toxin in jejunal loops. This effect was not seen with extracts from other organs (pancreas, spleen, adrenal glands) or from control rats. The antiserotory activity of the pituitary material, known as antiserotory factor (ASF), increased as the number of immunisations increased. ASF was found to be a protein with a molecular mass considerably lower than that of IgA. This observation and the origin of ASF suggested that it is not secretory IgA. Subsequently, Lange and Lönnroth reported that ASF was also found in bile and milk from rats immunised with cholera toxin. Further studies demonstrated antiserotory activity in the pituitary in rats, pigs and humans who had not been immunised against cholera toxin.

Conventional biochemical separation techniques were used initially to try to isolate and characterise ASF. The ASF bioassay comprises inhibition of cholera toxin induced fluid secretion in rat jejunal loops. The apparent molecular mass of ASF varied widely from 16 to 60 kDa in different reports, as did its isoelectric point, suggesting that there were more than one ASF. Eventually an ASF was cloned from human pituitary glands (recombinant ASF, rASF). rASF was found to be a new protein comprised of 382 amino acids with a molecular mass of 41.14 kDa. This substance was used to inhibit cholera toxin induced fluid secretion at a dose of $10^{-11}$ mol given intravenously to 200–250 g rats. On immunohistochemical examination of the pituitary gland, rASF was detected in cytoplasmatic granules in a moderate number of adenohypophysic cells.

ASF effects both the transport of intestinal fluid and also the histological changes induced by certain enterotoxins. In a previous report and in one published in this issue (see page 642), Lange, Lönnroth and collaborators have investigated the effects of ASF on the histological changes induced by *Clostridium difficile* toxin A in the rat intestine. This toxin causes severe damage to the intestinal mucosa within hours, including villous destruction and mucosal bleeding. The toxins produced by *C difficile* are probably of great importance in the pathophysiology of pseudomembranous enterocolitis. In the previous report two ASFs were isolated from the rat pituitary gland, one of which was effective in preventing the development of damage to the intestinal mucosa. In this issue rASF was tested in the same animal model using *C difficile* toxin A. Furthermore, Johansson et al studied the effect of rASF on the secretion and tissue damage caused by okadaic acid, a substance involved in food poisoning caused by shellfish. rASF was effective in preventing fluid secretion induced by both agents. The histological damage induced by toxin A is largely prevented by rASF, given either intravenously or intraluminally. No effect was seen on mucosal damage caused by okadaic acid. Hence, ASF not only attenuates fluid secretion but also influences the histological damage caused by toxin A. Similar effects have been reported for drugs interfering with the activity of the enteric nervous system (ENS), suggesting that the ENS is involved in the development of tissue damage.

What triggers the formation of pituitary ASF? The studies by Lange, Lönnroth and collaborators indicate that the triggering event is net intestinal fluid secretion. This has been shown for several enterotoxins and for secretion induced by hyperosmolar solutions of sorbitol, mannose, glycine, and alanine. Surprisingly, the isoelectric points of the ASFs found in the pituitary gland varied if, for example, a sorbitol or a glycine solution was placed in the intestinal lumen. The induction of ASF by cholera toxin was abolished in vagotomised rats.

The studies by Lange, Lönnroth and collaborators would suggest that ASF is an endogenous compound(s) produced when the intestinal epithelium secretes instead of absorbs fluid, as the early studies on rats indicated that ASF was produced only after the induction of intestinal secretion. In later studies pituitary glands from pigs and humans were used without prior knowledge of the secretory state of the gut. On the basis of the early studies one may infer a servo system with sensors for net tissue fluid flux in the intestinal mucosa, which, via vagal afferents, induces the formation and release of ASF. Such a control system would serve the purpose of reducing the potential life threatening effects of intestinal secretagogues. There is one observation that does not comply with the proposed feed back system. Lange and Lönnroth showed repeatedly that ASF is only effective in attenuating intestinal secretion if it is given before the administration of the secretagogue. However, in this issue, using rASF, they report that ASF has an antiserotory effect after the induction of a secretory state.

The cellular mode of action of ASF is not known. The observations reported so far do not provide a coherent picture. Giving ASF intraluminally inhibits fluid secretion in both the treated and adjacent jejunal loops. ASF has no effect on electrolyte transport in the isolated intestinal mucosa in vitro. ASF inhibits GABA ($\gamma$-aminobutyric acid) and chloride ion transport across neuronal plasma membranes from Deiters’ nuclei. The rate of incorporation of cholera toxin into the intestinal epithelium is increased by the action of ASF. On the basis of these observations, the following sites of action for ASF have been proposed: (1) downregulation of adenylate cyclase; (2) attenuation of the activation of the ENS by cholera toxin; (3) inhibition of fluid secretion via action on epithelial ion channels; (4) interference with cholera toxin binding to its receptor on the intestinal epithelial cells.

To summarise, studies on ASF so far have not produced a coherent picture of its physiological functions at either the organ or the cellular level. The availability of rASF...
should make it possible to elucidate in detail the functions of this protein. However, individual observations are interesting and potentially very important. ASF has been shown to be an effective antsecreatory agent when tested in several secretory states, even when given orally. Furthermore, as shown in the study by Johansson et al, rASF prevents mucosal damage following exposure to C difficile toxin A.

Diarrhoeal diseases still constitute a major global health problem despite the introduction of oral rehydration therapy. Thousands of children die every day as a result of fluid loss across the gastrointestinal mucosa. Research is under way to produce effective vaccines against the microbes causing the most common types of diarrhoea, yet the pharmacological arsenal of treatments for diarrhoea is limited. ASF or related compounds may represent a new class of antsecreatory drugs.

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