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Review

The possible role of the gut neuroendocrine system in diabetes gastroenteropathy

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Summary. Gastrointestinal symptoms such as nausea and vomiting, heartburn, abdominal pain, diarrhoea, constipation and faecal incontinence are common in patients with diabetes. Diabetes gastroenteropathy is a clinically relevant problem. In addition to the increased morbidity it causes, it results in severely impaired metabolic control, which in turn increases the risk of hyper-/hypoglycaemia. Moreover, the poorly controlled blood glucose level increases the risk of secondary diabetes complications, namely, retinopathy, nephropathy, neuropathy and cardiovascular affection. Gastrointestinal symptoms may also cause malnutrition in patients with diabetes, which, together with the disturbed immune defence in diabetes, may cause intercurrent infections. Gastrointestinal symptoms in patients with diabetes are attributed to disturbed gastrointestinal motility. Gastrointestinal dysmotility in diabetes is believed to be caused by autonomic neuropathy and/or hyperglycaemia. The neuroendocrine system of the gut secretes peptides/amines that play an important role in regulating gastrointestinal motility. It is conceivable, therefore, to assume that a disturbance in this regulatory system may contribute to the pathogenesis of gastrointestinal complications in diabetes. The present review gives an updated overview of the abnormalities in the gastrointestinal neuroendocrine system in diabetes, speculates upon the possible role of these abnormalities in the pathogenesis of diabetes gastroenteropathy and, finally, predicts the possible clinical implications of these findings.

Key words: Diabetes, Gastroenteropathy, Gut, Motility, Neuroendocrine system

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Introduction

The prevalence of diabetes in the western world has been estimated to be about 5-10% of the adult population (Rotter et al., 1990; Lock III, 1995). Since the discovery of insulin and its use in the treatment of patients with diabetes, the survival rate of these patients has increased markedly (Jervell, 1996). With an increasing age of patients with diabetes and with a longer duration of diabetes, it becomes clear that diabetes affects multiple organ systems, resulting in classic complications, such as retinopathy, nephropathy, neuropathy and cardiovascular affection with increased risk of myocardial infarction, stroke and limb amputation. The gastrointestinal tract is also affected in diabetes. Thus, gastrointestinal symptoms, such as nausea and vomiting, heartburn, abdominal pain, diarrhoea, constipation and faecal incontinence, are often encountered in these patients (Feldman and Schiller, 1983; Lock III, 1995; Enck et al., 1996; Schartz et al.,1996; Spångéus et al.,1999). The prevalence of these symptoms in patients with diabetes varies in different studies from 25% to 76% (Feldman and Schiller, 1983; Lock III, 1995; Enck et al., 1996; Schwartz et al., 1996; Spångéus et al., 1999). Diabetes gastroenteropathy is clinically important. In addition to increased morbidity, it may also severely impair metabolic control, which in turn increases the risk of hyper-/hypoglycaemia. Furthermore, a poorly controlled blood glucose level would increase the risk of the secondary diabetes complications mentioned above. In extreme cases, gastrointestinal symptoms may cause malnutrition in patients with diabetes (Nompleggi et al., 1989), which, together with the disturbed immune defence seen in diabetes, may cause intercurrent infections.

Gastrointestinal symptoms in patients with diabetes are attributed to a disturbed gastrointestinal motility (Abrahamsson, 1995; Camilleri, 1996; Koch, 1999). Gastrointestinal dysmotility in diabetes is believed to be caused by autonomic neuropathy and/or hyperglycaemia (Björnsson et al., 1994; Camilleri, 1996; Koch, 1999). Morphological studies have not shown abnormalities in

the abdominal vagus in patients with diabetes (Yoshida et al., 1988). Moreover, in patients with diabetes, decreased density of vagal myelinated fibres and degeneration of unmyelinated fibres have been reported in patients with and without gastrointestinal symptoms (Britland et al., 1990). In clinically based studies, the frequency of gastrointestinal dysfunction is much higher than the reported rates of autonomic neuropathy (Bucceri et al., 2002). Furthermore, autonomic neuropathy and gastrointestinal disorders have been reported as non-correlated (Clouse and Lustman, 1989; Lock III, 1995; Camelleri, 1996). Whereas acute hyperglycaemia correlates with gastrointestinal dysmotility in patients with diabetes (Björnsson et al., 1994; Camilleri, 1996; Koch, 1999), chronic hyperglycaemia does not (Merio et al., 1997; El-Salhy and Sitohy, 2001). On the other hand, the neuroendocrine system of the gut secretes peptides/amines that play an important role in regulating gastrointestinal motility (Allescher, 1991; Ekblad et al., 1991; Rangachari, 1991). It is conceivable, therefore to assume that a disturbance in this regulatory system may contribute to the pathogenesis of gastrointestinal complications in diabetes.

The present review aims at giving an updated overview of the abnormalities in the gastrointestinal neuroendocrine system in diabetes, to speculate upon the possible role of these abnormalities in the pathogenesis of diabetes gastroenteropathy, and finally, to predict the possible clinical implications of these findings.

The gut neuroendocrine system (NES)

The NES is the gastrointestinal local regulatory system. This system consists of two parts: endocrine cells scattered among the epithelial cells of the mucosa facing the gut lumen, and the peptidergic and sertonergic as well as nitric oxide-containing nerves of the enteric nerve system in the gut wall (Fig. 1). This regulatory system plays an important role in several functions, such as motility, secretion, absorption, local immune defence, micro-circulation of the gut and cell proliferation (Allescher, 1991; Debas and Mulvihill, 1991; Ekblad et al., 1991; Rangachari, 1991; McConalouge and Furness, 1994; Goyal and Hirano, 1996). This regulatory system comprises a large number of bioactive messengers (see Table 1). These bioactive substances exert their effects by endocrine mode of action (through the circulating blood to the distant target), by paracrine mode (by releasing into interstitial fluid to the nearby target), by synaptic signalling or by neurocrine means (releasing into the circulating blood from synapses). The different parts of this system interact and integrate with each other and with afferent and efferent nerve fibres of the central nervous system, especially the autonomic nervous system. The signal substances of the NES may be co-localised in the same cell or stored separately in mono-expressed cells. Examples of co-localised signal substances are PYY and enteroglucagon in colonic L-cells, serotonin and substance P in enterochromaffin (EC) cells, and VIP, which co-localises nitric oxide, gastrinreleasing peptide (GRP) and enkephalins .

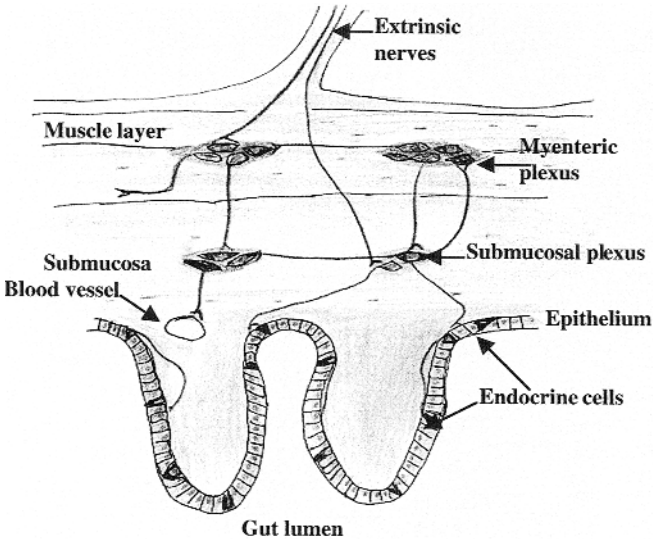

Fig. 1. Schematic drawing of the gastrointestinal neuroendocrine system.

Abnormalities in the NES in diabetes

The abnormalities observed in diabetes are based largely on studies done on animal models of diabetes; only a very few studies were done on patients with diabetes. The reason is obvious; whereas gut endocrine cells can be studied in forceps biopsies obtained during endoscopy, transmural biopsies are needed to investigate the neuroendocrine substances in the enteric nervous system. The latter are almost impossible to obtain, as the condition of diabetic patients never calls for gastrointestinal resections.

The changes observed in the NES in diabetes have been detected either by morphological or by biochemical methods. Morphological changes are mostly represented by alteration in the density of cells and/or nerve fibres. These changes represent change in the anatomical units producing the bioactive signal substances and require time to develop and endure over a period of time. An increase in the density of a certain cell type would indicate an increase in the signal substance produced by this particular cell type and *vice versa*. The other types of changes observed are expressed as changes in the concentration of a signal substance in tissue extracts of gut segments. These changes develop rapidly in response to changes in the physiological conditions but last briefly. An increase in the level of a particular signal substance implies an increase in the synthesis of this substance, which might or might not be accompanied by an increased release. A decrease of a signal substance, on the other hand, would imply either decreased synthesis or a high rate of synthesis and release.

The changes in the NES in diabetes seem to be dynamic. These changes can be divided into three categories: changes occurring before the onset of diabetes, changes after the onset of diabetes and changes occurring in long-term diabetes. The abnormalities in the NES after long-term diabetes appear to be those of clinical importance in connection with diabetes gastroenteropathy.

Gut endocrine cells

In animal models of human diabetes type 1 (non-obese diabetic mice), the changes in the density of endocrine cell types and the levels of endocrine peptides in tissue extracts have been investigated systematically in different segments of the gut (El-Salhy, 1988, 1999, 2001a,b; El-Salhy et al., 1998; El-Salhy and Spångéus, 1998a; Spångéus and El-Salhy, 1998b). Furthermore, the various endocrine cell types in different segments of the gastrointestinal tract have been investigated in patients with long-term diabetes type 1 (El-Salhy and Sitohy, 2001). The outcome of this study has been correlated to gastrointestinal symptoms and gastric emptying as well as electrogastrography (El-Salhy and Sitohy, 2001).

Table 1. Overview of the most important neuroendocrine peptides and other signal substances in the neuroendocrine system of the gut.

SIGNAL SUBSTANCE	ENDOCRINE CELLS	NERVE FIBRES	ACTION	REFERENCE
Secretin	+	-	Simulates pancreatic bicarbonate and fluid secretion; inhibits gastric emptying and inhibits contractile activity of small and large intestines	Leiter et al., 1994; Walsh, 1994
Vasoactive active polypeptide (VIP)	-	+	Stimulates gastrointestinal and pancreatic secretion; relaxes smooth muscles in the gut and causes vasodilation	Dockray, 1994a
Gastric inhibitory peptide (GIP)	+	-	Incretin; inhibits gastric acid secretion	Pederson, 1994; Walsh, 1994
Gastrin	+	-	Stimulates gastric acid secretion and histamine release; trophic action on gastric mucosa; stimulates contractions of lower oeosphageal sphincter (LES) and antrum	Walsh, 1994
Cholecystokinin (CCK)	+	+	Inhibits gastric emptying; stimulates gallbladder contraction and intestinal motility; stimulates pancreatic exocrine secretion and growth; regulates food intake	Liddle, 1994; Walsh, 1994
Enteroglucagon	+	-	Inhibits gastric acid secretion and pancreatic secretion	Walsh, 1994
Pancreatic polypeptide (PP)	+	-	Inhibits pancreatic secretion; stimulates gastric acid secretion; relaxes the gallbladder and stimulates motility of the stomach and small intestine	Mannon and Taylor, 1994; Walsh, 1994
Peptide YY (PYY)	+	-	Delays gastric emptying; inhibits gastric and pancreatic secretion; ileal brake mediator; vasoconstrictor	Mannon and Taylor, 1994; Walsh, 1994
Neuropeptide Y (NPY)	-	+	Inhibits pancreatic and intestinal secretion; decreases gastrointestinal motility; vasoconstrictor	Mannon and Taylor, 1994; Walsh, 1994
Somatostatin	+	+	Inhibits intestinal contraction, inhibits gut exocrine and neuroendocrine secretion	Chiba and Yamada, 1994
Neurotensin	+	+	Stimulates pancreatic secretion; inhibits gastric secretion; delays gastric emptying and stimulates colon motility	Shulkes, 1994
Substance P	+	+	Stimulates smooth muscle contraction, vasodilator; inhibits gastric acid secretion	Dockray, 1994b
Motilin	+	-	Induces phase III MMC (migrating motor complex), stimulates gastric emptying and stimulates contraction of LES	Poitras, 1994
Gastrin-releasing peptide (GRP)	-	+	Releases gastrin, somatostatin, and some other endocrine peptides; stimulates pancreatic secretion and smooth muscle contraction	Bunnett, 1994
Enkephalin	+	+	Inhibits gastric and pancreatic secretion; delays gastric emptying and intestinal transit	Dockray, 1994c
Galanin	-	+	Inhibits gastric, pancreatic and intestinal secretion; delays gastric emptying and intestinal transit; supresses postprandial release of some neuroendocrine peptides	Rökaeus, 1994
Serotonin	+	+	Stimulates gastric antrum and small intestinal and colonic motility; accelerates gastric emptying and both small and large intestinal transit	Lindberg, 1995; Tally, 1992; Ohe et al.,1994
Nitric oxide (NO)	+	+	Smooth muscle relaxation	Whittle, 1994

+, present; -, absent

Moreover, endocrine cells in streptozotocin-induced diabetes have been studied in rodents (Portela-Gomes et al., 1990; Nwokolo et al., 1992). The results of these studies are summarised in Table 2. Changes in the gut endocrine cells appear early in the pre-diabetic period, where insulin cell density declines in the pancreatic islets and insulinitis continues. When the destruction of insulin cells is complete and insulin deficiency and hyperglycaemia develop, i.e. at the onset of diabetes, some of the changes in the endocrine cells remain, while others occur in response to altered metabolic conditions. After a long duration of the diabetic state and adaptation to the new metabolic rearrangement, abnormalities in the endocrine cells can be seen. These abnormalities differ in some aspects, however, between animal models of human diabetes type 1 and patients with diabetes. This difference may be due to these animal models not resembling human diabetes type 1 in all aspects, or to the fact that the diabetic patients examined had a longer duration of diabetes than the animal models studied. The abnormalities observed after a long duration of diabetes type 1 are a high density of serotonin cells in all the gut segments, a high density of duodenal secretin (Fig. 2) and GIP cells and of colonic PYY cells. Moreover, the density of colonic enteroglucagon and somatostatin cells is low.

The changes in gastrointestinal endocrine cells differ between the obese diabetic mice (ob/ob) (Spångéus and El-Salhy, 1999) and (db/db) (Pinto et al., 1995), both being used as animal models of human diabetes type 2 (Table 2). The low density of colonic serotonin cells is, however, common in both animal models. The concentrations of colonic PYY and somatostatin in tissue extracts are high in ob/ob diabetic mice with a

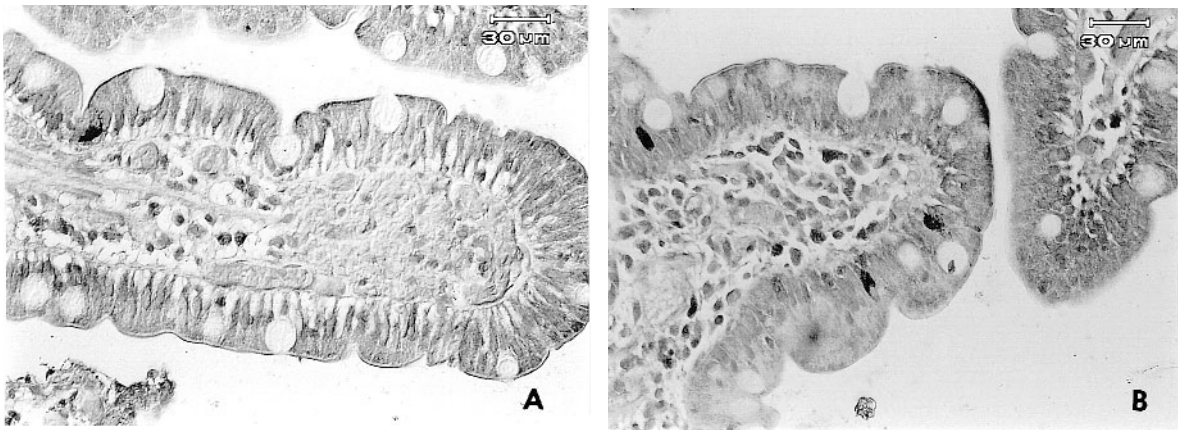

Fig. 2. Secretin-immunoreactive cells in the duodenum of a healthy volunteer **(A)** and in a diabetic patient. **(B)** x 260

Table 2. An overview of the abnormalities observed in the mucosal endocrine cells in diabetes.

GUT SEGMENT	SIGNAL SUBSTANCE	DIABETES TYPE 1				DIABETES TYPE 2		
		NOD mice		Chemically-induced diabetes	Diabetic patients	Obese diabetic mice (ob/ob)		Obese diabetic mice (db/db)
		Cell density	RIA	Cell density	Cell density	Cell density	RIA	Cell density
Stomach	Gastrin/CCK	D L	N L U	L	U	n	L E	H
	Somatostatin	D L	D L U	L	U	n	L U	L
	Serotonin	N n	NK	n	d	n	NK	H
Small intestine	Secretin	N H	I H d	NK	E	n	L U	NK
	GIP	D L	I H U	NK	E	n	LU	NK
	CCK/gastrin	D L	I H U	NK	U	n	LU	NK
	Motilin	NK	NK	NK	NK	NK	L	NK
	Somatostatin	N n	N L d	NK	U	n	LU	L
	Serotonin	D L	NK	L	E	L	NK	H
Large intestine	PYY	N L	D L U	NK	E	L	L E	H
	PP	NK	NK	NK	U	NK	NK	NK
	Enteroglucagon	I n	NK	NK	d	L	NK	L
	Somatostatin	NK	D I U	NK	d	NK	L E	L
	Serotonin	I n	NK	H	E	L	NK	L

I: Increased; D: decreased; N: not altered in pre-diabetic mice. H: high level; L: low level; n: unchanged level in diabetic animal models with short term diabetes. E: high level; d: low level; U: unchanged levels in animal models and humans with long-term diabetes; NK: Not known

long duration of diabetes (El-Salhy, 2001a,b, unpublished data). To the best of my knowledge, the gut endocrine cells have not been investigated in patients with diabetes type 2.

The effect of the diabetic state on the gene-expression of PYY and enteroglucagon co-localisation in L-cells, and serotonin and substance P in EC cells, has been investigated in animal models of human diabetes type 1 and 2, namely NOD mice and ob/ob obese diabetic mice (Spångéus et al., 2000, 2001). It has been found that, although the numbers of PYY and enteroglucagon cells are changed, the balance between

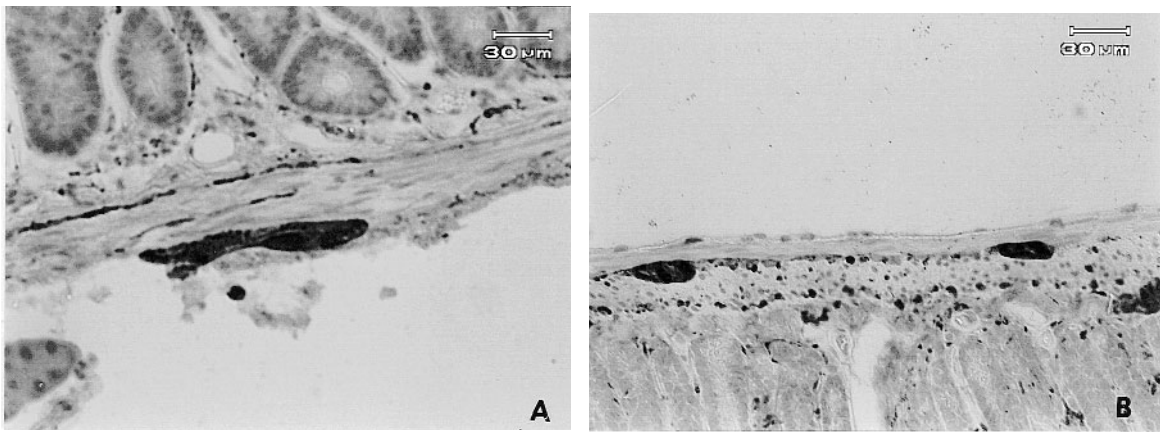

Fig. 3. Protein gene-producct (PGP) 9.5 - immunoreacctive myenteric ganglia and nerve fibres in muscularis propria in the duodenum of the control **(A)** and of non-obese diabetic mouse. **(B)** x 260

Table 3. Summary of the changes found in the enteric nervous system in animal models of human diabetes.

GUT SEGMENT	SIGNAL SUBSTANCE	DIABETES TYPE 1						DIABETES TYPE 2		
		NOD mice			Chemically-induced diabetes			Obese diabetic mice		
		Nerve cells	Nerve fibres	RIA*	Nerve cells	Nerve fibres	RIA*	Nerve cells	Nerve fibres	RIA*
Stomach	Somatostatin	NK	NK	L U	NK	NK	H	NK	NK	L U
	Substance P	NK	n	L U	NK	NK	L	n	n	L U
	VIP	H	L	L E	NK	NK	NK	L	n	L U
	NPY	n	n	L U	NK	NK	NK	n	n	n U
	Neurotensin	NK	NK	n U	NK	NK	NK	NK	NK	L
	Galanin	n	n	L U	NK	NK	NK	NK	NK	n U
	GRP	NK	NK	NK	L	NK	NK	NK	NK	NK
	Nitric oxide	L	n	NK	NK	NK	NK	n	L	NK
	Serotonin	NK	NK	NK	NK	NK	NK	NK	NK	NK
Small intestine	Somatostatin	NK	NK	n d	NK	NK	NK	NK	NK	L U
	Substance P	NK	n	L U	NK	NK	L	n	n	L d
	VIP	n	n	H U	L	I	H	L	L	n U
	NPY	n	n	n U	NK	NK	NK	n	n	n U
	Neurotensin	NK	NK	n U	NK	NK	NK	NK	NK	n U
	Galanin	n	n	n U	NK	NK	NK	n	L	n U
	Enkephalin	NK	NK	H	NK	NK	NK	NK	NK	NK
	GRP	NK	NK	NK	NK	NK	NK	NK	NK	NK
	Nitric oxide	L	n	NK	n	NK	NK	n	n	NK
	Serotonin	NK	NK	NK	L	L	L	NK	NK	NK
Large intestine	Somatostatin	NK	NK	L U	NK	NK	NK	NK	NK	L E
	Substance P	NK	L	L U	NK	NK	NK	n	n	L d
	VIP	n	n	L d	H d	H d	H d	n	n	L d
	NPY	n	n	L U	n U	n U	L U	n	n	L U
	Neurotensin	NK	NK	n U	NK	NK	NK	NK	NK	n U
	Galanin	n	n	L E	NK	NK	NK	n	H	L U
	GRP	NK	NK	NK	NK	NK	NK	NK	NK	NK
	Nitric oxide	n	n	NK	n	NK	NK	n	n	NK
	Serotonin	NK	NK	NK	H	H	H	NK	NK	NK

Symbols are the same as in Table 2. *: Radioimmunoassay of tissue extracts in the case of peptides and serotonin as measured by high-performance liquid chromotography .

the co-expressing of PYY and enteroglucagon and the mono-expressing cells seems to be preserved (Spångéus et al., 2000). Moreover, it has been reported that there is a decreased expression of substance P in serotonin-immunoreactive cells in both the antrum and the duodenum in diabetic animals of both type 1 and type 2 diabetes, as well as a change in the number of mono-expressed cells. There is, however, no such pattern in the colon (Spångéus et al., 2001).

The enteric nervous system

The myenteric plexus of an animal model of human diabetes type 1 (NOD) mice (Spångéus and El-Salhy, 1998a) and an animal model of human diabetes type 2 (ob/ob) mice (Spångéus and El-Salhy, 2001) has been investigated by a general marker for nerve elements. In NOD mice, the number of myenteric ganglia in the duodenum has been found to be decreased both in pre-diabetic and diabetic mice (Fig. 3) (Spångéus and El-Salhy, 1998a). Furthermore, in both pre-diabetic and diabetic NOD mice the relative volume density of nerve fibres has been reported to be reduced in muscularis propria of the duodenum (Spångéus and El-Salhy, 1998a). Neither the number of myenteric ganglia, nor the relative volume density of nerve fibres in muscularis propria have been found to be altered in the antrum or colon of these animals (Spångéus and El-Salhy, 1998a). Similarly, in rats with streptozotocin-induced diabetes, gastric nerve fibre density has been found unaltered (Nwokolo et al., 1992). No changes have been found in the myenteric plexus of diabetic obese (ob/ob) mice in the antrum, duodenum or colon (Spångéus and El-Salhy, 2001).

The changes in the peptidergic, sertonergic and nitric oxidergic innervation have been investigated in NOD and obese diabetic mice (El-Salhy, 1998, 1999, 2001, 2002; El-Salhy and Spångéus, 1998b,c; Spångéus and El-Salhy, 1998a, 2001; Spångéus et al., 2000) and in chemically-induced diabetes (Di Guilio et al., 1889; Lincolin et al., 1984; Bellman and Conlon, 1985; Loch et al., 1986; Belai et al., 1988, 1990, 1991; Gorio et al., 1992; Wrzos et al., 1997; Burnstock et al., 1997). The results of these studies are summarised in Table 3. Substance P concentrations have been measured in rectal biopsies during colonscopy of 27 diabetic patients (15 with type 1 diabetes and 12 with type 2 diabetes). Of these patients, 16 suffered from chronic severe constipation and 11 diabetic patients (three with type 1 diabetes and eight with type 2 diabetes) had normal bowel movements (Lysy et al., 1993). The authors have found that rectal mucosal contents of substance P in diabetic patients (constipated and non-constipated) are higher than in non-diabetics. One should keep in mind, however, that substance P measured in this work represents mainly substance P in EC-cells and, to some extent, substance P in nerve elements in the lamina propria and probably the superficial part of muscularis mucosa.

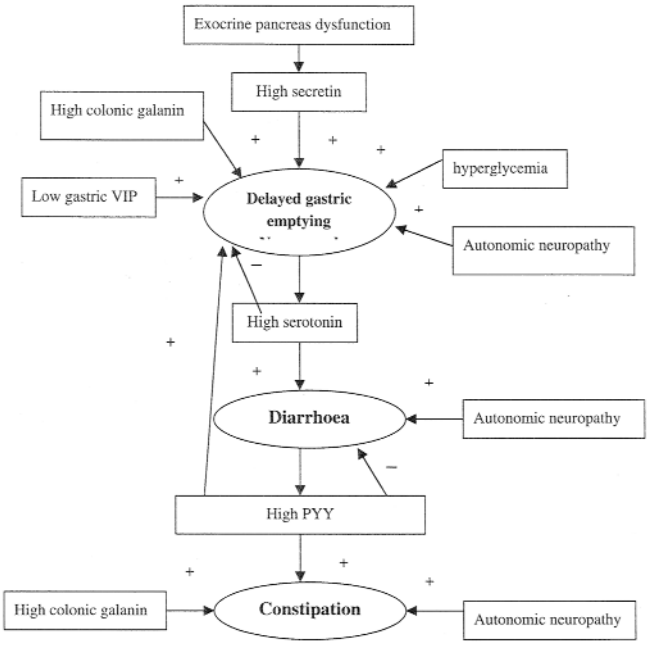

Fig. 4. Schematic presentation of the possible role of neuroendocrine peptides/amines in the development of gastrointestinal disorders in diabetes (see text). +=increase; -= decrease.

The possible role of the NES in the pathogenesis of diabetes gastroenteropathy

It is clearly seen from the previous presentation that the changes in the neuroendocrine system in connection with diabetes are multiple and start before the onset of diabetes type 1 with the decline of insulin production and probably at the very beginning of insulin receptor resistance in type 2 diabetes. This is not surprising, as the gut neuroendocrine signal substances interact and integrate with each other and with the endocrine system, as well as with the autonomic and central nervous systems. Looking upon the alteration in the neuroendocrine signal substances in different studies and over the course of diabetes, it seems that secretin, serotonin and PYY are the key signal substances in diabetes gastroenteropathy. To some extent, gastric VIP seems to be involved. Colonic galanin appears to play a major role in the manifestation of gastroenteropathy in type 1 but not type 2 diabetes.

Impairment of pancreatic exocrine function has been found in patients with diabetes (Camilleri, 1996). This impairment may, as a feedback mechanism, lead to an increase in duodenal secretin cells and probably their synthesis and secretion. The increased secretin level, together with hyperglycaemia and probably autonomic neuropathy, cause a delayed gastric emptying. Low gastric VIP and high colonic galanin inhibit further gastric emptying. As a response to delayed gastric emptying, serotonin cells (and probably level) increase

to accelerate gastric emptying. The increase in serotonin would result in diarrhoea. PYY cells and levels in the colon increase to counter the diarrhoea. The increased level of PYY, in turn, would worsen gastric emptying and could cause constipation. Depending on the balance between serotonin and PYY levels, the patient can have either diarrhoea or constipation as the predominant symptom (Fig. 4). Admitting that this seems to be highly speculative, it could serve, however, as a working hypothesis for further studies.

Clinical implications

The cause of diabetes gastroentropathy seems to be multifactorial, where autonomic neuropathy, hyperglycaemia and disorders of the neuroendocrine system appear to be important factors. There is no way at the present time to correct autonomic neuropathy in diabetic patients. Normoglycaemia is already a goal that both patients and physicians are endevouring to achieve. This leaves us the gut neuroendocrine system disorders as a possible target for treatment of diabetic gastroenteropathy. The accumulated data of the changes in gastrointestinal neuroendocrine signal substances in diabetes could, therefore, be beneficial in clinical practice. Thus, in cases where a gut signal substance increase or decrease is desirable, diet that regulates this substance synthesis and release can be followed, or a receptor agonist or antagonist can be utilised. (Agonists and antagonists to most neuroendocrine signal substances are available). Among these substances are serotonin agonists and antagonists that are now under clinical trial in other gastrointestinal motility disorders.

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