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Sir David Cuthbertson Medal Lecture

Metabolic cross talk between the colon and the periphery: implications for insulin sensitivity

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Until recently, a glance at a standard undergraduate textbook would have given the impression that the colon was merely a storage organ for faeces and maybe something about the absorption of electrolytes and water. In reality, the colon is a highly-metabolically-active organ, the function of which has implications not only for the remainder of the digestive tract, but also for peripheral organs such as adipose tissue (AT), liver and skeletal muscle. The present review focuses on two distinct but complementary areas: (1) the metabolic adaptation that occurs following surgical removal of colonic tissue; (2) the effect of modulating the colon *in situ* in terms of postprandial metabolism, insulin sensitivity and disease risk. Work in these two areas points to the colon being important in modulating normal tissue insulin sensitivity. The role of fatty acids is central to the insulin sensitivity hypothesis. AT acts as a daily 'buffer' for fatty acids. However, following colonic resection there is an apparent change in AT function. There is an increase in the AT lipolysis rate, resulting in the release of excess fatty acids into the circulation and consequently the take up of excess fatty acids into skeletal muscle. This resultant increase in either storage of lipid or its oxidation would result in a reduction in insulin sensitivity. The insulin-sensitising effects of high-fibre diets are also related to changes in AT function and fatty acid metabolism, but manipulating colonic tissue *in situ* allows the mechanisms to be elucidated. This research area is an exciting one, involving the potential role of SCFA (the absorbed by-products of colonic bacterial fermentation) acting directly on peripheral tissues, following the recent identification of G-protein-coupled receptors specific for these ligands.

Colon: Adipose tissue: Insulin sensitivity: SCFA

'I have finally come to the conclusion that a good reliable set of bowels is worth more to a man than any quantity of brains' Henry Wheeler Shaw (1818–1885)

Obesity, insulin resistance and type 2 diabetes are predicted to become the epidemics of the 21st century. It would be too simplistic to assume that changing any one dietary constituent would provide a strategy for prevention. However, key elements of the diet have repeatedly been linked with a reduced risk of developing chronic diseases such as type 2 diabetes and CVD: decreased SFA; decreased *trans*-fatty acids; decreased glycaemic index of digestible carbohydrates; increased non-viscous cereal fibres, such as those normally found in whole grains (Baxter *et al.* 2006). The picture is changing, with emphasis now being placed firmly on the quality of carbohydrates in the diet. Unlike the glycaemic index concept, which is primarily involved with acute changes in glycaemia caused by manipulating the proportions of rapidly- and slowly-absorbed digestible carbohydrates, non-viscous fibres are resistant to small intestinal enzymic digestion. They have negligible effects on gastric emptying, macronutrient absorption from the gut, postprandial

Abbreviations: AT, adipose tissue; GI, gastrointestinal; GLP, glucagon-like peptide; GPR, G-protein-coupled receptors; TC, total colectomy.
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glucose responses or blood lipids. However, increased consumption is linked to a reduced disease risk by a mechanism that because of the physico-chemical properties of the fibres themselves must involve colonic metabolism. For many years the colon has been overlooked by both physiologists and nutritionists; however, this oversight is now being addressed. The colon is intimately linked to the functioning of peripheral tissues distant from the gastrointestinal (GI) tract. The absence of colonic metabolism leads to insulin resistance through changes in adipose tissue (AT) metabolism; conversely, increasing colonic metabolism increases insulin sensitivity, potentially also through changes in AT metabolism. These research areas appear distinct, yet provide complementary information and an integrative approach to the investigation of the importance of the colon. This metabolic cross talk between the colon and peripheral tissues, especially AT, has the potential to provide a new interpretation for the health benefits of non-viscous fibres, in addition to providing novel insights into the role of the colon in both health and disease.

Loss of normal colonic function

Conventionally, surgical loss of colonic tissue, or total colectomy (TC), involves performing a loop-ileostomy following resection of the entire colon, with only minimal resection of the terminal ileum (<50 mm). This procedure leaves either a temporary (with follow-up surgery at a later date to reconstruct a continent ileal reservoir) or permanent stoma, which is formed from the small intestine through the abdominal wall. TC can be performed for ulcerative colitis, colon cancer, Hirschsprung's disease, Crohn's disease and familial adematous polyposis, which are diseases with very different aetiologies and progression. Quantitatively, the most common reason for this surgery is ulcerative colitis, a chronic inflammatory disease confined to the large intestine that currently affects three in 1000 of the population in the UK, with similar incidences in both Western Europe and the USA. Despite dramatic advances in both the genetic understanding of ulcerative colitis and improvements in medication, it is still estimated that ≤15% of patients will require TC at some point in their lives. Understanding the consequences for this surgery is not only an important issue for this substantial group of patients, but also gives an insight into the relationship between the colon and metabolic interactions involving other segments of the GI tract and more peripheral organs such as the liver, AT and muscle, and the disease risk that may be may posed.

Gastrointestinal adaptation

It is not surprising that surgical loss of an organ such as the colon would lead to adaptation in both the structure and function of the remaining GI tract. Multiple areas are affected: GI motility (Robertson & Mathers, 2000); bile acid metabolism (Teufel *et al*. 1988); composition of the intestinal microflora; absorption of both Na^+ and water. Following surgery, the most consistent observation in both human and animal studies is a rapid change in stomal function. Immediately following resection, post-operative diarrhoea results in fluid losses of approximately 1·0–1·5 l/d. However, there is rapid 'adaptation' leading to a dramatic drop in fluid and Na^+ loss from the stoma in a scale of days to weeks to months (Wright *et al*. 1969; Hill, 1976). This adaptation is an important initial step, without which there would be continuous and deleterious losses of electrolytes and water from the body. The initial step in adaptation following TC has been well described and involves stimulation of the adrenal cortex.

The characteristic response to the electrolyte and fluid loss is stimulation of the renin–angiotensin system and increased aldosterone production (Christl & Sceppach, 1997). Both renin and aldosterone levels have been reported to be elevated following TC (Robertson *et al*. 2005*b*), with plasma concentrations remaining elevated for several years following surgery, implying a more fundamental metabolic change. The GI tract is a well-characterised target tissue for aldosterone action, with the mineralocorticoid receptor found widely distributed (Fuller & Verity, 1990), including in the gastric parietal cells (Kato *et al*. 1999).

Increased levels of plasma aldosterone have the acute effect of activating receptors in both the GI tract and kidney tubule to enhance Na^+ re-absorption and increase the net loss of K^+ from the body. In both animals (Koyama *et al*. 1999) and man (Huber *et al*. 2001) TC results in secondary aldosteroidism as a result of the subclinical state of mild dehydration and Na^+ depletion that, despite metabolic adaptation, persists long term.

It has been established since the pioneering work of the 1960s and 1970s (Wright *et al*. 1969; Hill, 1976; Woo & Nygaard, 1978) that TC results in structural and functional changes within the remaining GI tract. More recently, the emergence of more molecular technologies have allowed a more detailed examination of the underlying mechanisms. The GI adaptation occurring following colonic resection, for simplicity, has been subdivided into two sections: (1) generalised hyperplasia of the gut; (2) specific or selective changes in levels or activities of transporters and enzymes.

General hyperplasia

During intestinal adaptation the residual bowel undergoes dilation, muscle-wall hypertrophy and mucosal hypertrophy to compensate for the loss of the colon through surgery. There is an increased production of cells in the crypt, and migration of these cells within the crypt results in apparent enlargement of the villus size. The outcome is an increased potential absorptive capacity of the small intestine. Most of the work into intestinal adaptation has been undertaken following massive small-bowel resection. Although there are distinct differences between the loss of the large intestine compared with loss of the small intestine, some parallel mechanisms may exist. In animal studies colon resection leads to changes in the gastric mucosa (Hallonquist *et al*. 1998), with a generalised thickening and dilation of the mucosal surface and consequent up-regulation of the gastric acid-producing parietal cells.

Changes in the structure of the small intestine are also well documented, with an increased intestinal length and weight, mucosal thickness, villus length and villus cell count (Woo & Nygaard, 1978; Willis *et al*. 2002). The loss of colonic absorption is thus compensated by the increase in the ileal surface, with subsequent elevations in Na^+ and water absorption. The 'trigger' for this gross and generalised change in structure is poorly understood. Peptide hormones and growth factors released either locally from the GI tract and from extra-GI sites may have trophic effects on the intestine. Neurotensin, a peptide derived from endocrine cells of the jejunum and duodenum, is elevated following colonic resection (Kennedy *et al*. 1982) and has been shown to enhance mucosal weight, in addition to increasing RNA and DNA content (Evers *et al*. 1992) and so promoting intestinal adaptation (Mata *et al*. 1997). Mediators found to be crucial following massive small-bowel resection, such as glucagon-like peptide (GLP)-2, are actually decreased following TC (Kennedy *et al*. 1982), and therefore do not provide an explanation. Although other factors such as the growth hormone–insulin-like growth factor 1 axis and epidermal growth factors have been implicated in small-bowel adaptation following massive small-bowel resection (Lukish *et al*. 1997), the effects on these mediators following TC is at present unknown.

Following colonic resection there is rapid entry into a 'feed-forward loop'. Generalised hyperplasia of the upper small intestine leads to increased numbers of endocrine cells in this region, specifically cells secreting cholecystokinin (Buchler *et al*. 1988*b*), glucose-dependent insulinotropic polypeptide (Robertson *et al*. 1999) and neurotensin (Kennedy *et al*. 1982), resulting in elevated fasting and postprandial secretion of these hormones into the plasma. There is some discrepancy in the literature about whether some of these hormonal changes are in fact part of the underlying pathology of chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease), which is the case for both motilin (Greenberg *et al*. 1989) and glucose-dependent insulinotropic polypeptide (Besterman *et al*. 1983), and whether this level of adaptation occurs before colonic resection. Irrespective of the time course of endocrine up-regulation, changes in the plasma levels of these hormones lead to an adaptation of function. Hypersecretion of both cholecystokinin and glucose-dependent insulinotropic polypeptide leads to delayed motility, especially gastric motility, which may partially compensate for the loss of colonically-derived hormones such as peptide YY (Adrian *et al*. 1987) and GLP-1 (Robertson *et al*. 1999) that if left uncorrected would result in rapid intestinal transit and would potentially exaggerate the stomal losses following surgery. In addition to effects on motility, elevated glucose-dependent insulinotropic polypeptide secretion could stimulate pancreatic insulin secretion. Hyperinsulinaemia can have anabolic actions on the intestinal tract, with a demonstrated stimulation of ileal protein synthesis following ileostomy (Rittler *et al*. 2006) and specific reduction of urinary Na^+ excretion (Quinones-Galvan & Ferrannini, 1997), so addressing the underlying issue of Na^+ depletion. Thus, although the exact 'trigger' for intestinal adaptation remains to be determined, adaptation does indeed take place, enabling the remaining absorptive surface of the GI tract and transit time to increase, both of which enhance the process of absorption and Na–water balance.

Specific transporter adaptation

The most intriguing part of this overall adaptation is perhaps the ability of the remaining GI tract to selectively up regulate transporters and/or enzymes that deal with Na^+ conservation. This selectivity is intimately related to Na^+ depletion. There is selective up-regulation of the Na co-transporters, Na–K–2Cl co-transporter in the gastric mucosa (Hallonquist *et al*. 1998) and the electrogenic Na–glucose co-transporter 1 in the small intestine (Haneda *et al*. 2006), and molecular induction of all three subunits of the epithelial Na^+ channel and its cofactor prostasin (Koyama *et al*. 1999), a novel serine protease that may, in conjunction with epithelial Na^+ channel, accelerate Na^+ absorption (Adachi *et al*. 2001). Aldosterone is known to increase expression of both Na–K–2Cl and Na^+ channels in the kidney tubule, and so secondary aldosteronism is likely to be the prime candidate responsible for parallel up-regulation in the gut. In animal experiments aldosterone infused to reach a plasma concentration similar to that observed following colectomy has also been found to induce the mRNA of all three subunits of the epithelial Na^+ channel in addition to prostasin. In contrast, however, up-regulation of Na–glucose co-transporter 1 cannot be explained simply by elevated aldosterone, or indeed by dietary Na^+ depletion (Fukushima *et al*. 2005). Further examination of this finding using a microarray approach (Fukushima *et al*. 2006) has led to the characterisation of a total of 6109 intestinal genes by RT–PCR. Following TC in the rat eighty-two genes were found to be up regulated and ninety-one genes down regulated in the residual ileum. However, using a similar approach it has been found that aldosterone infusion modulates only twenty-one genes, and there is a definite interaction with dietary Na^+ depletion. Thus, although Na^+ depletion and hyperaldosteronism provide a potential explanation for specific intestinal adaptation, it is also clear that the situation is still very complex.

TC not only leads to an increase in circulating aldosterone, but also up regulates GI expression of the mineralocorticoid receptor throughout the GI tract (Fukushima *et al*. 1994). In addition, it increases expression (mRNA and protein) of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (Sato *et al*. 2005). This enzyme is important in the overall adaptation process, as it confers specificity to the non-selective mineralocorticoid receptor by converting local levels of glucocorticoids to their receptor-inactive metabolites (cortisol to cortisone), thus allowing the binding of aldosterone, which circulates at much lower concentrations. Increased expression of both mineralocorticoid receptor and 11β-hydroxysteroid dehydrogenase type 2 is required for full adaptation following TC. Thus, loss of colonic tissue leads to elevated aldosterone levels, the clinical effect of which is magnified by an increased number of mineralocorticoid receptors and increased levels of receptor binding as a result of increased

Table 1. Glucose metabolism following surgical colonic resection*

Underlying pathology	Subjects		Age range (years)	BMI range (kg/m^2)	Methodology	Primary result (compared with control group)	Reference
	n	M:F					
HD	16	15:1	16–26	20–37	MTT	Elevated fasting glucose and insulin	Medhus *et al.* (2001)
UC, CD, FAP	6	6:0	26–46	20–26	OGTT	Normal fasting glucose and insulin Hyperinsulinaemia and elevated C-peptide concentration during OGTT	Nauck *et al.* (1996)
UC	6	6:0	40–55	22–26	MTT	Normal fasting glucose and insulin Hyperinsulinaemia and elevated plasma glucose during MTT	Robertson & Mathers (2000)
UC	10	4:6	40–60	20–30	MTT, hyperinsulinaemic–euglycaemic clamp	Elevated fasting insulin Hyperinsulinaemic during MTT	Robertson *et al.* (2005*b*)
UC	11	6:5	22–54	Normal wt	OGTT	Elevated fasting insulin Hyperinsulinaemia and elevated plasma glucose during OGTT	Palnaes Hansen *et al.* (1997)

HD, Hirshsprung's disease; CD, Crohn's disease; FAP, familial adenatous polyposis; UC, ulcerative colitis; M, male; F, female; MTT, meal tolerance test; OGTT, oral glucose tolerance test.
*All studies are age- and BMI-matched *v.* healthy controls.

enzymic degradation of the competing substrate. Increased stimulation by aldosterone may then be responsible for the increased expression of Na^+ transporters such as epithelial Na^+ channel. Of course, the situation is likely to be far more complex, with local changes within the GI lumen that are not explained by changes in aldosterone playing an important role.

Peripheral adaptation; cause or consequence?

For many years it was assumed that any long-term effects following TC would be entirely GI. However, work that was started in the 1990s and continues today consistently demonstrates otherwise. With what is now known about the normal functioning of the colon, effects of endocrine mediators such as GLP-1 and SCFA, in addition to the well-established links between colonic fermentation of dietary fibre and chronic diseases such as type 2 diabetes and CVD, it should not be surprising that complete loss of colonic tissue would have implications for peripheral metabolism. The most consistent finding following TC in both human and animal studies is an inappropriate insulin response, both as a fasting measurement and in response to a carbohydrate challenge. The age- and gender-matched human studies addressing this issue are summarised in Table 1. The key observation from these data is that it is apparently the loss of colonic tissue that is important, not the underlying pathology that led to surgery. In the earlier discussion of GI adaptation it was suggested that inflammatory bowel disease itself may be the 'trigger' for adaptation; certainly for gut endocrinology. However, in other conditions such as Hirschsprung's disease and colon cancer, in which the underlying aetiology is different, a similar level of hyperinsulinaemia is observed. Indeed, in the single study in which glucose metabolism was assessed in patients with inactive ulcerative colitis no such dysregulation was reported (Capristo *et al.* 1999) and, of course, when TC is performed in animal models there is no underlying disease (Buchler *et al.* 1988*a*). Based on the current evidence, it is likely that any peripheral changes in metabolism, of which hyperinsulinaemia is the most prominent and easily measured, is directly related to the loss of functioning colonic tissue.

Insulin resistance

Despite the prevailing hyperinsulinaemia, there have been many reports of concomitant hyperglycaemia, which implies a level of tissue insulin resistance (Table 1). In the postprandial state glucose enters the body from the GI tract. The main tissue involved in buffering this influx of glucose is the liver, which absorbs the influx of glucose and switches off hepatic glucose production. Skeletal muscle plays a parallel role, taking up glucose under the influence of insulin. The glycaemia measured is the simultaneous balance of these mechanisms, and so more kinetic studies are required to tease apart the various aspects. In a previous study (Robertson *et al.* 2000) a double-isotope approach was employed, in which a [^{13}C]glucose isotope was fed to trace glucose uptake from the GI tract in combination with a D-[6,6^{2}H$_2$]glucose infusion to trace hepatic glucose production. Despite the potential increase in Na–glucose co-transporter 1 reported in animal models following TC (Haneda *et al.* 2006), in the human model no increase was found in the level of glucose uptake by the gut. An explanation for this finding is that the

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normal human gut already 'efficiently' absorbs lumen glucose and so absorption is not increased further by increased Na–glucose co-transporter 1 expression. Furthermore, no defect in the normal suppression of hepatic glucose output was demonstrated. The primary outcome was, however, that insulin-dependent glucose disposal in the cohort that had undergone ileostomy was only 28% that of the matched controls, an observation that was primarily a result of a reduced rate of oxidative glucose disposal (Robertson *et al*. 2000).

In elucidating a primary mechanism for this change, it is likely that the insulin resistance observed following TC reflects alterations in intermediary metabolism.

Adipose tissue function following total colectomy

The links between AT function, fatty acid metabolism and glucose uptake into insulin-sensitive tissues are now well established. Plasma NEFA concentrations are the balance between release (from the lipolysis in AT and intravascular lipolysis of dietary TAG) and uptake (re-esterified in AT and liver and oxidised in muscle heart and liver). It is now believed that abnormalities in fatty acid storage and lipolysis, with increased flux from AT to non-AT (skeletal muscle, liver, pancreas), are critical in the development of insulin resistance (McGarry, 2002).

There are several lines of evidence that suggest a direct link between TC and changes in intermediary metabolism: (1) lower levels of systemic SCFA (Scheppach *et al*. 1991) produced from colonic fermentation may modulate AT lipolysis (Crouse *et al*. 1968); (2) lower levels of GLP-1 released from the distal gut may also act directly to regulate clearance of TAG-rich lipoproteins (Beck, 1989); (3) there may be a direct or indirect relationship with secondary hyperaldosteronism or the resultant hypokalaemia (Catena *et al*. 2006).

The understanding of the metabolic consequences of TC has been enhanced by the use of arterio–venous balance techniques that can determine directly the metabolic flux across the tissue of interest (AT or skeletal muscle). TC results in dysregulation of fatty acid metabolism, resulting in an increased level of AT lipolysis (Fig. 1) and increased NEFA and glycerol efflux into the plasma (Robertson *et al*. 2005*b*).

Acetate, quantitatively the most important of the SCFA, has been shown *in vivo* to suppress AT lipolysis, resulting in a suppression of both NEFA and glycerol levels (Suokas *et al*. 1988; Akanji *et al*. 1989). It is well established that the colon is an important exogenous source of plasma acetate; plasma levels in subjects who have undergone ileostomy are 50% lower than those of controls (Scheppach *et al*. 1991). Thus, the first potential mechanism is simply that lipolysis is increased after TC because of lower circulating levels of acetate. The second potential mechanism involves GLP-1. In animal and *in vitro* studies GLP-1 has been shown to have potent effects on the expression of lipoprotein lipase and potentially also AT lipolysis. However, the results of many studies are often confounded by the interplay between GLP-1 and insulin, and many of the effects relating to AT lipolysis may

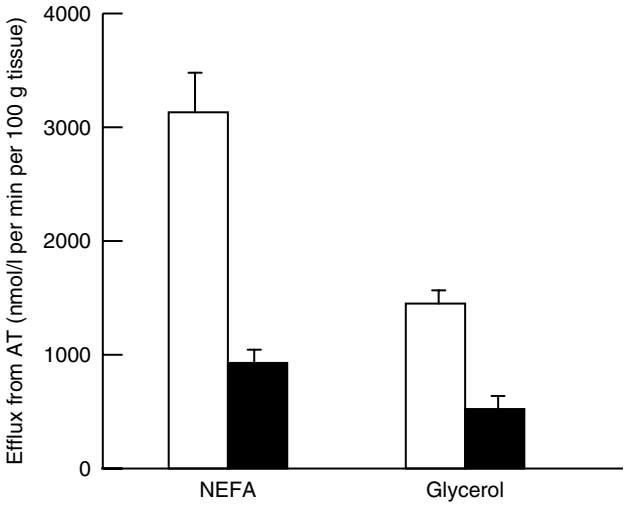

Fig. 1. Increased net efflux of fatty acids and glycerol from subcutaneous adipose tissue (AT) as a measure of lipolysis in patients following total colectomy (□) and in matched control subjects (■). Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for the patients following total colectomy: for NEFA, $P = 0{\cdot}019$; for glycerol, $P = 0{\cdot}02$. (Data taken from Robertson *et al.* 2005*b*.)

actually be a result of increased insulin secretion. In a single human AT microdialysis study (Bertin *et al*. 2001) in which this possibility was actually assessed *in vivo* by infusing GLP-1 directly into subcutaneous AT, no direct effect on AT lipolysis was found. Although the GLP-1 concentration is reduced by 50% following TC (Robertson *et al*. 1999), it is unlikely to be a primary cause of the resultant insulin resistance. The third proposed mechanism is the result of the most fundamental change in metabolism following TC, the secondary aldosteronism. In a recent study (Catena *et al*. 2006) hyperinsulinaemia and insulin resistance were found in patients with primary aldosteronism unrelated to hypertension, which rapidly resolved following either surgery or treatment with aldosterone antagonists. It is possible therefore that aldosterone itself might be the primary cause of insulin resistance, although currently there is little evidence in the literature for a direct causal link. In animal studies aldosterone treatment has been found to increase plasma NEFA levels, consistent with an effect on AT lipolysis (Kirsten *et al*. 1977), and aldosterone added to human adipocytes *in vitro* reduces insulin-dependent glucose uptake by 30% (Kraus *et al*. 2005). The relationship between aldosterone and glucose metabolism is poorly understood, but in the light of recent findings linking both primary and secondary aldosteronism with insulin resistance and hyperinsulinaemia, more work to elucidate this metabolic link is warranted.

Skeletal muscle metabolism

Perhaps as a direct consequence of the increased flux of fatty acids from AT there is an increased uptake of fatty acids directly into skeletal muscle following TC (assessed by arterio–venous sampling). Uptake of fatty acids by

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muscle requires transfer across the membrane by proteins such as fatty acid transporter CD36. Following TC the increased uptake of fatty acids by muscle is further enhanced by an increased tissue expression of CD36 (Robertson *et al*. 2005*b*). Under resting conditions the delivery of fatty acids to the mitochondria for β-oxidation is regulated by their rate of tissue uptake (which is increased) and so the increased rate of fatty acid oxidation observed after TC is perhaps as expected (Robertson *et al*. 2000). It is widely accepted that fatty acid competition with glucose for substrate oxidation leads to the inhibition of pyruvate dehydrogenase, phosphofructokinase and hexokinase II (Randle *et al*. 1963) activity. The result is decreased glucose transport and phosphorylation, in addition to independent effects on insulin receptor signalling caused by accumulation of intramyocellular lipid metabolites, which impair insulin action despite prevailing hyperinsulinaemia (Morino *et al*. 2006; Fig. 2).

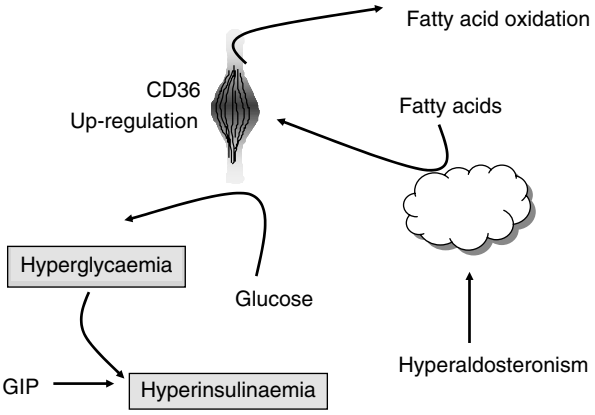

Fig. 2. Potential link between hyperinsulinaemia, insulin resistance and total colectomy. The primary 'change' in adipose tissue (AT) metabolism may be initiated by either elevated levels of aldosterone or reduced levels of acetate and/or propionate in the peripheral circulation, leading to a reduced buffering capacity and/or increased lipolysis within AT. There is increased uptake of fatty acids into skeletal muscle, increased fatty acid oxidation and, as a result, reduced insulin-mediated glucose uptake. The hyperinsulinaemia itself may result from the combination of increased plasma fatty acid levels, hyperglycaemia and elevated glucose-insulinotropic polypeptide (GIP) secretion.

Vascular function, aldosterone and leptin

The uptake of a substrate and its efflux from a tissue is mediated primarily by the rate of blood flowing through it, which serves to maintain the effective concentration gradient. TC results in an increase in both muscle and AT blood flow, measured using independent methodology (Robertson *et al*. 2005*b*). This peripheral change in vascular function may again be inter-related with Na^+ depletion and elevated aldosterone levels. Aldosterone has been shown to elevate forearm (muscle) blood flow by increasing NO release from the vascular endothelium (Schmidt *et al*. 2003). The change in AT blood flow is perhaps more intriguing. Leptin levels are elevated following TC (Robertson *et al*. 2005*b*), and hyperleptinaemia has been linked to increased sympathetic outflow to many tissues including AT. An increased level of leptin-induced NO release from the vascular endothelium could potentially explain the increased AT blood flow following TC. The mechanism for elevated leptin in these patients is, however, unclear. Active inflammatory disease has been linked to both low (Karmiris *et al*. 2006) and elevated (Barbier *et al*. 2003) leptin concentrations and mRNA expression in AT. Aldosterone treatment has been shown to elevate leptin expression (by 5000%) in isolated adipocytes (Kraus *et al*. 2005), which may provide an underlying link. Alternatively, recent studies have demonstrated gastric production of leptin, which has historically been considered to be an adipokine produced by white AT. Gastric chief cells are capable of secreting leptin directly into the circulation (Cammisotto *et al*. 2005), although the precise contribution to circulating concentrations is unknown. As there is hyperproliferation of the gastric mucosa following TC, the gastric production of leptin may also be enhanced, which could partly contribute to the observed hyperleptinaemia.

Colon *in situ?*

If the hypothesis is correct, that having no colon is a risk factor of insulin resistance, then the contrary view would be that having an 'active' colon would actually be preventative. The colon contains an active microflora that can efficiently metabolise most substrates. However, both in terms of quantity and health benefits, carbohydrates are the most important of these substrates. The carbohydrates entering the colon are those that are resistant to small intestinal digestion, and in the colon they are fermented to produce SCFA. The observed pattern of SCFA production is the result of a complex process involving primary saccharolytic fermenters and secondary cross-feeders. Typically, acetate:propionate:butyrate is 60:20:20. However, the corresponding proportions reached within the post-hepatic circulation would be 90:10:0, with butyrate preferentially metabolised by colonocytes. The classification of carbohydrates and dietary fibre will not be addressed here, but an important factor to consider when discerning the metabolic effects of the so-called dietary fibres is the physiochemical properties they confer. Viscous fibres change the lumen environment and so have a beneficial effect on lumen glucose diffusion and subsequent absorption from the GI tract, and have a direct impact on the glycaemic index. Although there is increasing evidence for the importance of glycaemic index in determining disease risk (Aston, 2006), the strongest epidemiological data still exist for a link between the ingestion of non-viscous (no effect on glycaemic index) fibre and a lower incidence of both type 2 diabetes and CVD. In order to fully assess the relationship it is important to look at experimental data for which the effects of glycaemic index and colonic fermentation can be fully separated, and for which insulin sensitivity has been assessed using appropriate methodology. When these two criteria are taken into account, the situation becomes more evident (Table 2). In all recent studies that have used euglycaemic–hyperinsulinaemic

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Table 2. Effects of cereal fibre ingestion on insulin sensitivity, assessed by euglycaemic–hyperinsulinaemic clamp

Subjects	Design	Dietary intervention	Effect*	Reference
Seventeen, overweight or obese (all female) NGT	Randomised cross-over, clamp at end of each intervention	31·2 g oat fibre/d for 3 d *v.* placebo	M value: 6·85 *v.* 6·06 for fibre compared with placebo $P = 0{\cdot}003$	Weickert *et al.* (2006)
Ten, normal weight (six female) NGT	Randomised cross-over, clamp at end of each intervention	30 g resistant starch/d for 4 weeks *v.* placebo	M value: 9·7 *v.* 8·5 for fibre compared with placebo $P = 0{\cdot}027$	Robertson *et al.* (2005*a*)
Eleven, overweight or obese (six female) IGT	Randomised cross-over, clamp at end of each intervention	Six to ten servings whole or refined grains per d for 6 weeks	M value: mean of 0·07 higher following whole-grain intervention $P<0{\cdot}05$	Pereira *et al.* (2002)
285, adolescents (130 female)	Epidemiological, clamps at age 13 and 15 years	127 FFQ, subjects split into tertiles of whole-grain intake	M value across tertiles of intake: 13·3 *v.* 12·3 *v.* 11·5 from highest to lowest $P = 0{\cdot}01$	Steffen *et al.* (2003)

NGT, normal glucose tolerance; IGT, impaired glucose tolerance.
*M value is the glucose disposal rate during the final 20 min of a 180 min euglycaemic–hyperinsulinaemic clamp expressed in mg glucose/min per kg, with the exception of the Pereira *et al.* (2002) study, which is expressed as mmol glucose/min per kg.

clamp methodology to assess insulin sensitivity as 'gold-standard' for this measurement fermentable carbohydrate in the diet has been shown to enhance tissue insulin sensitivity.

Colonic effects on fatty acid metabolism

As stated previously, following TC changes in insulin sensitivity are likely to be mediated via changes in intermediary metabolism; specifically, by changes in AT function. There are several key areas that could be mediated via colonic fermentation: (1) a change in AT lipolysis, and the buffering capacity of AT; (2) a change in adipocyte size and differentiation; (3) a change in adipokine release. The concept of ectopic fat storage and its detrimental effects on insulin sensitivity is also now well established (Yki-Jarvinen, 2002). A hyperlipolytic state within subcutaneous AT will result in an increased flux of plasma fatty acids and TAG accumulation in other peripheral tissues such as the liver, muscle, pancreas and heart, directly affecting metabolic function (Fig. 3). Despite this association, insulin resistance cannot always be directly attributed to changes in ectopic fat (Goff *et al*. 2005), and so whether the insulin-sensitising effects of fermentable carbohydrate observed during each of the studies shown in Table 2 is directly or indirectly related to fat distribution is at present unknown. Thus, the outstanding questions in relation to carbohydrate fermentation and intermediary metabolism are: does colonic fermentation affect AT metabolism; does colonic fermentation affect fatty acid metabolism and TAG accumulation in other insulin-sensitive tissues.

Effects of SCFA on adipose tissue

Although many studies have reported changes in NEFA concentration after feeding fermentable carbohydrate (Ferchaud-Roucher *et al*. 2005; Brighenti *et al*. 2006), Robertson *et al*. (2005*a*) were the first to demonstrate a direct effect on fatty acid and glycerol flux from subcutaneous AT using arterio–venous sampling across AT in human subjects. With current advances in technology, it is now known that both acetate and propionate circulate in measurable micromolar concentrations in plasma (Robertson *et al*. 2005*a*), and so direct metabolic effects on peripheral tissues must now be considered. Carbohydrate fermentation elevates the plasma levels of both these SCFA, with direct uptake into subcutaneous AT (Robertson *et al*. 2005*a*). It was previously considered that only acetate reaches the circulation beyond the liver

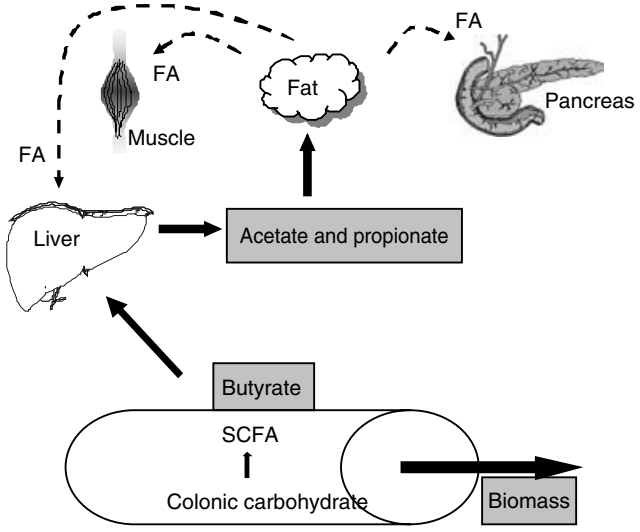

Fig. 3. Interaction between colonic fermentation and ectopic fat distribution. Colonically-produced acetate and propionate appears in the post-hepatic circulation, where there is direct interaction with adipose tissue (AT) to inhibit the rate of TAG lipolysis. An increased buffering capacity of AT would decrease the peripheral uptake of fatty acids (FA) into other insulin-sensitive tissues such as the liver, muscle and pancreas, with the potential to affect both ectopic fat storage and organ function.

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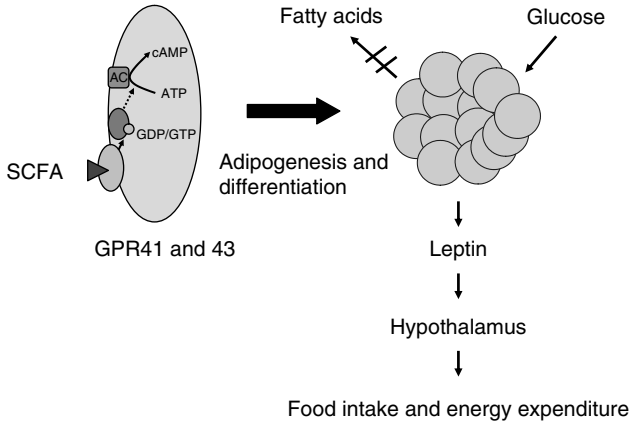

Fig. 4. Role of SCFA as ligands for adipocyte G-protein-coupled receptors (GPR) 41 and 43. AC, acetyl-CoA carboxylase.

(research primarily related to the acute influence of alcohol consumption on plasma acetate concentrations), and so the effects of acetate in inhibiting lipolysis have been known for about 40 years (Crouse *et al*. 1968). However, the role of SCFA in relation to adipocyte metabolism has regained momentum since the recent elucidation of their role as ligands for the previously-orphaned G-protein-coupled receptors (GPR) 41 and 43 (Brown *et al*. 2003; Fig. 4). Both GPR41 and 43 are expressed on adipocytes as well as on cells of the GI tract and on immune cells (granulocyte–macrophage progenitor cells). *In vitro* work using both a mouse adipocyte cell line and mouse AT in primary culture (Xiong *et al*. 2004) has shown that SCFA increase leptin expression; propionate having a more potent effect than acetate. In contrast, GPR43 appears to be involved both in AT adipogenesis and as a regulator of adipocyte development and differentiation (Hong *et al*. 2005) in 3T3-L1 cells. Unlike GPR41, GPR43 is stimulated by both acetate and propionate. The potential for SCFA, at physiological concentrations, to have effects on adipocyte cell size, and differentiation, without a change in overall adiposity is intriguing. Adipocyte size correlates well with whole-body insulin sensitivity and is considered to be more reliable than any other single measure of adiposity (Weyer *et al*. 2000). There are not only potentially acute differences in the lipolytic activity between larger and smaller adipocytes, with inhibited suppression of lipolysis (more fatty acids available for uptake into ectopic fat depots or oxidised?), but larger adipocytes have more macrophage infiltration and secrete more of the pro-inflammatory cytokines IL-6, TNFα, angiotensinogen and C-reactive protein and less of the beneficial adipokines leptin and adiponectin. Large adipocytes are indicative of a failure in AT proliferation and/or differentiation.

Interestingly, in terms of the traditional view of fatty acid impairment of insulin action, the well-established anti-lipolytic effects of SCFA also now appear to be directly mediated by GPR43. The signalling cascade is comparable with that of insulin, with activation of the adipocyte cGMP-inhibited cAMP phosphodiesterase reducing cellular cAMP levels, which leads to inactivation of the cAMP-dependent protein kinase and net dephosphorylation of hormone-sensitive lipase (Hong *et al*. 2005).

SCFA also appear to stimulate fat accumulation in adipocytes, potentially by stimulating both PPARγ2 and the enzymes acetyl CoA carboxylase and fatty acid synthase (Lee & Hossner, 2002), which control the initial rate-limiting step in AT lipogenesis. If these findings are a true representation of what occurs *in vivo* in man, carbohydrate fermentation, via its effects on plasma levels of acetate and propionate, could increase fat deposition within AT and hence reduce ectopic fat depots. The physiological importance of these primarily animal-based *in vitro* studies remains to be determined, but it is clear that there is a need for more human-based investigation.

Effects of SCFA on body fat distribution

The role of ectopic fat distribution in the aetiology of insulin resistance is well accepted, and any factor that can affect the fatty acid-buffering capacity of AT could impact on TAG storage in non-adipose sites and hence body fat distribution. Despite the potential effects on the adipocyte mentioned previously, there is limited evidence for the effects of acetate or propionate on ectopic fat distribution. One reason is presumably the technological limitations in assessing fat depots *in vivo*. A number of animal studies have reported that feeding diets high in fermentable carbohydrate results in a change in body composition (Pawlak *et al*. 2004), with a decrease specifically in intra-hepatic lipid levels, as determined by magnetic resonance spectroscopy (PW So, WS Yu, AP Goldstone, JD Bell and GS Frost, unpublished results). However, these studies are confounded by changes in the relative glycaemic index of the test diets and so the results cannot be clearly interpreted as being a result only of fermentation or increased SCFA production.

Future directions

To the author's knowledge, there have been no experiments designed specifically to assess the potential effects of carbohydrate fermentation on adipocyte size and fat distribution. As such, all the data currently available in this area are severely confounded by the effects of glycaemic index (Lerer-Metzger *et al*. 1996; Kabir *et al*. 1998*a*,*b*) on these variables. Well-designed studies, preferably in human subjects, are required to demonstrate definitively this link between the colon and AT metabolism *in vivo*.

Summary

There is a theoretical mechanism that could link the colon with insulin sensitivity via the production of SCFA. In simplistic terms, acetate and propionate have beneficial effects on AT metabolism, serving to lower plasma fatty acid release, increase fat deposition and, because of changes in adipogenesis, result in smaller adipocytes that release higher levels of leptin and adiponectin and lower levels of pro-inflammatory adipokines. The increased

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buffering capacity of the subcutaneous AT results in less substrate competition with glucose, lower levels of fat oxidation and lower ectopic fat accumulation in tissues such as the liver, pancreas and muscle. Like all physiological systems, however, the specific interactions involved are far more complex. Unravelling these interactions will not only increase the understanding of the aetiology of insulin resistance itself, but in the future may allow the formulation of functional foods that could specifically change colonic fermentation, providing a potential strategy to decrease the risk or progression of chronic disease at a population level.

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References

Adachi M, Kitamura K, Miyoshi T, Narikiyo T, Iwashita K, Shiraishi N, Nonoguchi H & Tomita K (2001) Activation of epithelial sodium channels by prostasin in Xenopus oocytes. *Journal of the American Society of Nephrology* **12**, 1114–1121.

Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS & Bloom SR (1987) Release of PYY after resection of small bowel, colon and pancreas in man. *Surgery* **100**, 715–719.

Akanji AO, Bruce MA & Frayn KN (1989) Effect of acetate infusion on energy expenditure and substrate oxidation rates in non-diabetic and diabetic subjects. *European Journal of Clinical Nutrition* **43**, 107–115.

Aston LM (2006) Glycaemic index and metabolic disease risk. *Proceedings of the Nutrition Society* **65**, 125–134.

Barbier M, Vidal H, Desreumaux P, Dubuquoy L, Bourreille A, Colombel JF, Cherbut C & Galmiche JP (2003) Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. *Gastroenterologie Clinique et Biologique* **27**, 987–991.

Baxter AJ, Coyne T & McClintock C (2006) Dietary patterns and metabolic syndrome – a review of the epidemiological evidence. *Asia Pacific Journal of Clinical Nutrition* **15**, 134–142.

Beck B (1989) Gastric inhibitory polypeptide: a gut hormone with anabolic functions. *Journal of Molecular Endocrinology* **2**, 169–174.

Bertin E, Arner P, Bolinder J & Hagstrom-Toft E (2001) Action on glucagon and glucagon-like peptide 1 (7–36) amide on lipolysis in human subcutaneous adipose tissue. *Journal of Clinical Endocrinology and Metabolism* **86**, 1229–1234.

Besterman HS, Mallinson CN, Modigliani R, Christofides ND, Pera A, Ponti V, Sarson DL & Bloom SR (1983) Gut hormones in inflammatory bowel disease. *Scandinavian Journal of Gastroenterology* **18**, 845–852.

Brighenti F, Benini L, Del Rio D, Casiraghi C, Pellegrini N, Scazzina F, Jenkins DJ & Vantini I (2006) Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. *American Journal of Clinical Nutrition* **83**, 817–822.

Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D *et al.* (2003) The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *Journal of Biological Chemistry* **278**, 11312–11319.

Buchler M, Malfertheiner P, Eiberle E, Friess H, Nustende R, Schusdziarra V, Feurle GE & Beger HG (1988*a*) Pancreatic trophism following colectomy in rats: the potential role of gastrointestinal hormones. *Pancreas* **3**, 477–483.

Buchler M, Malfertheiner P, Friess H, Eiberle E & Beger HG (1988*b*) Gut-peptide mediated adaptive response of the exocrine pancreas. *Scandinavian Journal of Gastroenterology* **151**, Suppl., 114–122.

Cammisotto PG, Renaud C, Gingras D, Delvin E, Levy E & Bendayan M (2005) Endocrine and exocrine secretion of leptin by the gastric mucosa. *Journal of Histochemistry and Cytochemistry* **53**, 851–860.

Capristo E, Mingrone G, Addolorato G, Greco AV & Gasbarrini G (1999) Glucose metabolism and insulin sensitivity in inactive inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* **13**, 209–217.

Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G, Novello M, Favret G, Melis A, Cavarape A & Sechi L (2006) Insulin sensitivity in patients with primary aldosteronism: a follow-up study. *Journal of Clinical Endocrinology and Metabolism* **91**, 3457–3463.

Christl SU & Sceppach W (1997) Metabolic consequences of total colectomy. *Scandinavian Journal of Gastroenterology* **222**, Suppl., 20–24.

Crouse JR, Gerson CD, DeCarli LM & Lieber CS (1968) Role of acetate in the reduction of plasma free fatty acids produced by ethanol in man. *Journal of Lipid Research* **9**, 509–512.

Evers BM, Izukura M, Townsend CM, Uchida T & Thompson JC (1992) Neurotensin prevents intestinal mucosal hypoplasia in rats fed an elemental diet. *Digestive Diseases and Sciences* **37**, 426–431.

Ferchaud-Roucher V, Pouteau E, Piloquet H, Zair Y & Krempf M (2005) Colonic fermentation from lactulose inhibits lipolysis in overweight subjects. *American Journal of Physiology* **289**, E716–E720.

Fukushima K, Haneda S, Funayama Y, Watanabe K, Kouyama A, Takahashi KI, Owaga H, Shibata C & Sasaki I (2006) An approach to analyse mechanisms of intestinal adaptation following total proctocolectomy. *Journal of Gastrointestinal Surgery* **10**, 662–671.

Fukushima K, Sasano H, Sasaki I, Nagura H, Funayama Y & Matsuno S (1994) Increased expression of mineralocorticoid receptor in human ileum after total colectomy: immunohistochemical and immunoblotting studies. *Tohoku Journal of Experimental Medicine* **173**, 383–390.

Fukushima K, Sato S, Naito H, Funayama Y, Haneda S, Shibata C & Sasaki I (2005) Comparative study of epithelial gene expression in the small intestine among total proctocolectomized, dietary sodium-depleted, and aldosterone infused rats. *Journal of Gastrointestinal Surgery* **9**, 236–244.

Fuller PJ & Verity K (1990) Mineralocorticoid receptor gene expression in the gastrointestinal tract: distribution and ontogeny. *Journal of Steroid Biochemistry* **36**, 263–267.

Goff LM, Bell JD, So PW, Dornhorst A & Frost GS (2005) Veganism and its relationship with insulin resistance and intramyocellular lipid. *European Journal of Clinical Nutrition* **59**, 291–298.

Greenberg GR, Buchan AMJ, McLeod RS, Preston P & Cohen Z (1989) Gut hormone profile after reconstructive surgery for ulcerative colitis. *Gut* **30**, 1721–1730.

Hallonquist H, Cima RR, Klingensmith ME, Purdy MJ, Delpire E, Zinner MJ & Soybel DI (1998) Selective increase in gastric mucosal mRNA encoding basolateral Na-K-2Cl cotransporter following ileostomy in the rat. *Journal of Gastrointestinal Surgery* **2**, 238–243.

Haneda S, Fukushima K, Funayama Y, Shibata C, Takahashi K, Ogawa H, Nagao M, Watanabe K & Sasaki I (2006) Fecal stream is essential for adaptive induction of glucose-coupled sodium transport in the remnant ileum after total proctocolectomy. *Journal of Gastrointestinal Surgery* **10**, 1051–1059.

Hill G (1976) *Ileostomy: Surgery, Physiology and Management*. New York: Grune and Stratton.

Hong YH, Nishimura Y, Hishikawa D, Tsuzuki H, Miyahara H, Gotoh C *et al.* (2005) Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* **146**, 5092–5099.

Huber FX, Lucas M, Stern J, Hinz U, Haack D, Heuschen U & Herfarth C (2001) Changes in glucocorticoid and mineralocorticoid hormone levels due to compensation for ileostomy levels. *International Journal of Surgical Investigation* **2**, 369–375.

Kabir M, Rizkalla SW, Champ M, Luo J, Boillot J, Bruzzo F & Slama G (1998*a*) Dietary amylose-amylopectin starch content affects glucose and lipid metabolism in adipocytes of normal and diabetic rats. *Journal of Nutrition* **128**, 35–43.

Kabir M, Rizkalla SW, Quignard-Boulangé A, Guerre-Millo M, Boillot J, Ardouin B, Luo J & Slama G (1998*b*) A high glycemic index starch diet affects lipid storage-related enzymes in normal and to a lesser extent in diabetic rats. *Journal of Nutrition* **128**, 1878–1883.

Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T & Kouroumalis EA (2006) Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflammatory Bowel Diseases* **12**, 100–105.

Kato K, Sasano H, Ohara S, Sekine H, Mochizuki S, Mune T, Yasuda K, Nagura H, Shimosegawa T, Toyota T & Krozowski Z (1999) Co-expression of mineralocorticoid receptors and 11beta-hydroxysteroid dehydrogenase 2 in human gastric mucosa. *Journal of Clinical Endocrinology and Metabolism* **84**, 2568–2573.

Kennedy HJ, Sarson DL, Bloom SR & Truelove SC (1982) Gut hormone responses in subjects with a permanent ileostomy. *Digestion* **24**, 133–136.

Kirsten R, Nelson K, Ruschendorf U, Seger W, Scholz T & Kirsten E (1977) Effects of aldosterone on lipid metabolism and renal oxygen consumption in the rat. *Pflugers Archiv* **368**, 189–194.

Koyama K, Sasaki I, Naito H, Funayama Y, Fukushima K, Unno M, Matsuno S, Hayashi H & Suzuki Y (1999) Induction of an epithelial Na+ channel in the rat ileum after proctocolectomy. *American Journal of Physiology* **276**, G779–G784.

Kraus D, Jager J, Meier B, Fasshauer M & Klein J (2005) Aldosterone inhibits uncoupling protein-1, induces insulin resistance and stimulates proinflammatory adipokines in adipocytes. *Hormone and Metabolic Research* **37**, 455–459.

Lee SH & Hossner KL (2002) Coordinate regulation of ovine adipose tissue gene expression by propionate. *Journal of Animal Science* **80**, 2840–2849.

Lerer-Metzger M, Rizkalla SW, Luo J, Champ M, Kabir M, Bruzzo F, Bornet F & Slama G (1996) Effects of long-term low-glycaemic index starchy food on plasma glucose and lipid concentrations and adipose tissue cellularity in normal and diabetic rats. *British Journal of Nutrition* **75**, 723–732.

Lukish J, Schwartz MZ, Rushin JM & Riordan GP (1997) A comparison of the effect of growth factors on intestinal function and structure in short bowel syndrome. *Journal of Pediatric Surgery* **32**, 1652–1655.

McGarry JD (2002) Banting Lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* **51**, 7–18.

Mata A, Gomez de Segura IA, Largo C, Codesal J & De Miguel E (1997) Neurotensin increases intestinal adaptation and reduces enteroglucagon-like immunoreactivity after large-bowel resection in rats. *European Journal of Surgery* **163**, 587–593.

Medhus AW, Bjornland K, Emblem R, Haug E & Husebye E (2001) Are patients with Hirschsprung's disease prediabetic? *Metabolism* **50**, 1389–1390.

Morino K, Petersen KF & Shulman GI (2006) Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes* **55**, Suppl. 2, S9–S15.

Nauck MA, Siemsgluss J, Orskov C & Holst JJ (1996) Release of glucagon-like peptide 1 (GLP-1 [7–36 amide]), gastric inhibitory polypeptide (GIP) and insulin in response to oral glucose after upper and lower intestinal resections. *Zeitschrift für Gastroenterologie* **34**, 159–166.

Palnaes Hansen C, Andreasen JJ & Holst JJ (1997) The release of gastric inhibitory peptide, glucagon-like peptide-I, and insulin after oral glucose test in colectomized subjects. *Scandinavian Journal of Gastroenterology* **32**, 473–477.

Pawlak DB, Kushner JA & Ludwig DS (2004) Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *Lancet* **364**, 778–785.

Pereira MA, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL & Seaquist ER (2002) Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *American Journal of Clinical Nutrition* **75**, 848–855.

Quinones-Galvan A & Ferrannini E (1997) Renal effects of insulin in man. *Journal of Nephrology* **10**, 188–191.

Randle PJ, Garland PB, Hales CN & Newsholme EA (1963) The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* **i**, 785–789.

Rittler P, Scheifer B, Demmelmair H, Koletzko B, Vogesar M, Alpers DH, Jauch KW & Hartl WH (2006) The effect of hyperglycemic hyperinsulinemia on small intestinal mucosal protein synthesis in patients after surgical stress. *Journal of Parenteral and Enteral Nutrition* **30**, 97–107.

Robertson MD, Bickerton AS, Dennis AL, Vidal H & Frayn KN (2005*a*) Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. *American Journal of Clinical Nutrition* **82**, 559–567.

Robertson MD, Bickerton AST, Dennis AL, Vidal H & Frayn KN (2005*b*) Enhanced metabolic cycling in patients following colonic resection for ulcerative colitis. *Journal of Clinical Endocrinology and Metabolism* **90**, 2747–2754.

Robertson MD, Livesey G, Hampton SM & Mathers JC (2000) Evidence for altered control of glucose disposal after total colectomy. *British Journal of Nutrition* **86**, 813–819.

Robertson MD, Livesey G, Morgan LM, Hampton SM & Mathers JC (1999) The influence of the colon on postprandial glucagon-like peptide 1 (7–36) amide concentration in man. *Journal of Endocrinology* **161**, 25–31.

Robertson MD & Mathers JC (2000) Gastric emptying rate of solids is reduced in a group of ileostomy patients. *Digestive Diseases and Sciences* **45**, 1285–1292.

Sato S, Fukushima K, Naito H, Funayama Y, Suzuki T, Sasano H, Krozowski Z, Shibata C & Sasaki I (2005) Induction of 11beta-hydroxysteroid dehydrogenase type 2 and hyperaldosteronism are essential for enhanced sodium absorption after total colectomy in rats. *Surgery* **137**, 75–84.

Scheppach W, Pomare EW, Elia M & Cummings JH (1991) The contribution of the large intestine to blood acetate in man. *Clinical Science* **80**, 177–182.

Schmidt BMW, Oehmer S, Delles C, Bratke R, Schneider MP, Klingbeil A, Fleischmann EH & Schmieder RE (2003) Rapid nongenomic effects of aldosterone on human forearm vasculature. *Hypertension* **42**, 156–160.

Steffen LM, Jacobs DR Jr, Murtaugh MA, Moran A, Steinberger J, Hong CP & Sinaiko AR (2003) Whole grain intake is associated with lower body mass and greater insulin sensitivity among adolescents. *American Journal of Epidemiology* **158**, 243–250.

Suokas A, Kupari M, Heikkila J, Lindros K & Ylikahri R (1988) Acute cardiovascular and metabolic effects of acetate in men. *Alcoholism, Clinical and Experimental Research* **12**, 52–58.

Teufel M, Kleeberg J, Flach A, Reifferscheid P & Niessen KH (1988) Late results following partial and total colectomy in infancy. *Klinische Padiatrie* **200**, 30–35.

Weickert MO, Mohlig M, Schofl C, Arafat AM, Otto B, Viehoff H, Koebnick C, Kohl A, Spranger J & Pfeiffer AF (2006) Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. *Diabetes Care* **29**, 775–780.

Weyer C, Foley JE, Bogardus C, Tataranni PA & Pratley RE (2000) Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia* **43**, 1498–1506.

Willis S, Kisielinski K, Klosterhalfen B & Schumpelick V (2002) Morphological and functional adaptation of the small intestine after colectomy and ileal pouch-anal anastomosis in rats. *International Journal of Colorectal Disease* **17**, 85–91.

Woo ZH & Nygaard K (1978) Small-bowel adaptation after colectomy in rats. *Scandinavian Journal of Gastroenterology* **13**, 903–910.

Wright HK, Cleveland JC, Tilson MD & Herskovic T (1969) Morphology and absorptive capacity of the ileum after ileostomy in man. *American Journal of Surgery* **117**, 242–245.

Xiong Y, Miyamoto N, Shibata K, Valasek MA, Motoike T, Kedzierski RM & Yanagisawa M (2004) Short chain fatty acids stimulate leptin production in adipocytes through the g protein-coupled receptor GPR41. *Proceedings of the National Academy of Sciences USA* **100**, 1045–1050.

Yki-Jarvinen H (2002) Ectopic fat accumulation; an important cause of insulin resistance in humans. *Journal of the Royal Society of Medicine* **95**, Suppl. 42, 39–45.