The role of amylin in the physiology of glycemic control

W. A. Scherbaum
Diabetes Research Institute, Heinrich Heine University, Düsseldorf, Germany

Key words: Amylin, glycemic control, diabetes mellitus, pramlintide

Summary: Amylin is a 37-amino acid peptide hormone, discovered in 1987, which is co-located and co-secreted with insulin by the pancreatic β-cells in response to nutrient stimuli. Like insulin, there is a deficiency of amylin in people with type 1 diabetes, while the changes in plasma amylin concentrations in people with impaired glucose tolerance and type 2 diabetes parallel those of insulin. It is well established that insulin regulates glycemic control by promoting glucose disposal. This paper reviews evidence from studies in animals and people with diabetes that amylin regulates the inflow of glucose to the circulation by delaying nutrient delivery and, thus, the appearance of meal-derived glucose, and also suppresses glucagon secretion in the postprandial period. It is suggested, therefore, that the actions of amylin complement those of insulin, and that the problems of glycemic control which continue to exist in people with diabetes, despite insulin replacement therapy, may be attributable to a deficiency in amylin. Preclinical and clinical studies with pramlintide, a synthetic analogue of human amylin, are also included in this brief review.

Introduction

Diabetes mellitus has traditionally been considered to be associated with insulin deficiency resulting from the destruction or dysfunction of the pancreatic β-cells. While type 1 diabetes is associated with an absolute insulin deficiency arising from β-cell destruction, type 2 diabetes is characterised by both relative insulin deficiency, which tends to increase over time, and significant insulin resistance in peripheral target tissues (Bennett, 1994). Despite a number of advances in the management of diabetes, including refinements in insulin replacement therapy, the majority of patients still experience considerable difficulty in achieving optimum glycemic control. For example, fewer than 5% of the patients with type 1 diabetes who participated in the Diabetes Control and Complications Trial were able to achieve normal HbA1c concentrations, despite receiving intensive insulin therapy in an optimised environment that is not generally available in routine clinical practice (DCCT Research Group, 1993).

In 1987, it was found that the pancreatic β-cells produce and co-secrete a second hormone, amylin, along with insulin (Cooper et al., 1987). Initial studies of the possible actions of amylin, using supraphysiological concentrations of the hormone, suggested that it might be implicated in the development of insulin resistance (Cooper et al., 1988; Leighton and Cooper, 1990; Young et al., 1990). Still other experimental and clinical investigations, using amylin at physiological concentrations, support the idea that the hormone plays an important role in normal glucose homeostasis. This article reviews the evidence that amylin acts as a partner hormone with insulin in glycemic regulation.

Characterisation of amylin

Amylin was discovered in 1987 when it was isolated from amyloid deposits obtained at post-mortem from the pancreas of patients with type 2 diabetes (Cooper et al., 1987). It is a 37-amino acid peptide hormone
that is co-packaged with insulin in the secretory granules of the pancreatic β-cells (Moore and Cooper, 1991; Rink et al., 1993), and the two hormones are co-secreted in response to nutrient stimuli and other secretagogues (Hartter et al., 1991; Moore and Cooper, 1991). Studies in humans have demonstrated that the plasma concentrations of insulin and amylin rise and fall in parallel following meals (Koda et al., 1995). Amylin circulates at picomolar concentrations: in normal human subjects, fasting plasma amylin concentrations are 4–8 pmol/L, rising to 15–25 pmol/L following an oral glucose load or a meal (Butler et al., 1990; Hartter et al., 1991).

Insulin and amylin are products of separate genes. Insulin is the product of a gene located on chromosome 11 (Owerbach et al., 1980), while amylin is produced from a discrete locus on chromosome 12 (Cockburn et al., 1989).

**Amylin in people with diabetes**

It has been discovered that the secretion of amylin is altered in individuals with abnormalities in their β-cell function, such as those with diabetes mellitus and impaired glucose tolerance (IGT). Basal amylin concentrations are markedly reduced in people with type 1 diabetes, and there is no increase in secretion in response to nutrient ingestion. Typically, plasma amylin concentrations fall below the limits of assay sensitivity within this population (Koda et al., 1992).

The changes in amylin secretion in people with IGT and type 2 diabetes parallel those of insulin secretion. People with IGT (Koda et al., 1995) and early type 2 diabetes (Fineman et al., 1994) have elevated plasma amylin concentrations, but the secretion of both insulin and amylin falls as the β-cells become exhausted (Leahy, 1990; Ludvik et al., 1991). Consequently, people with type 2 diabetes have a diminished amylin response (Fineman et al., 1996; Sanke et al., 1991). Thus, despite the differing aetiologies of type 1 and late-stage type 2 diabetes, both groups of patients exhibit decreased secretion of amylin and insulin.

**The physiology of glucose homeostasis**

Insulin plays a key role in stimulating the uptake and metabolism of glucose by the tissues (Wallum et al., 1992) and, as a result, discussions of the physiology of glycemic regulation have tended to focus on the importance of glucose disposal in the maintenance of glucose homeostasis. However, glycemic regulation depends upon ensuring that there is a balance between the rate of glucose inflow to the circulation and the rate of glucose disposal, though the importance of regulating glucose inflow has only recently been recognised.

There are two sources for glucose inflow: the meal-derived glucose that follows the ingestion of carbohydrates, and endogenous glucose production by the liver during the fasted state, a process stimulated by glucagon secreted from the pancreatic α-cells (Lefèvre, 1995).

The results of studies in experimental animals support the idea that amylin complements the stimulatory actions of insulin on glucose disposal, by regulating glucose inflow via two main mechanisms. First, there is good evidence that amylin delays the delivery of nutrients to the small intestine and, thus, modulates the inflow of meal-derived glucose to the circulation (Brown et al., 1994; Young et al., 1995; Young et al., 1996b). More recently, it has been shown that amylin can also suppress postprandial glucagon secretion (Gedulin et al., 1997a; Gedulin et al., 1997b), and this may, in turn, help to reduce hepatic glucose production following nutrient ingestion.

As discussed in the remainder of this review, amylin deficiency in people with diabetes may result in accelerated nutrient delivery and loss of the suppression of hepatic glucose production, leading to excessive glucose inflow to the circulation. These abnormalities would then contribute to the chronic hyperglycemia, particularly during the postprandial period, which is seen in patients with diabetes, despite insulin therapy (Service et al., 1972).

**Effect of amylin and the amylin analogue, pramlintide, on meal-derived glucose**

The delivery of ingested food to the small intestine is the rate-limiting step in the absorption of meal-derived glucose (Ferrannini and DeFronzo, 1992). Studies of the physiological actions of amylin in animals (Brown et al., 1994; Clementi et al., 1996; Young et al., 1995; Young et al., 1996b) have shown that it dose-dependently restrains the delivery of nutrients to the small intestine and, thus, slows the inflow of meal-derived glucose to the circulation. Similarly, in patients with type 1 diabetes who received either an intravenous infusion (Kong et al., 1997a) or subcutaneous injections (Kong et al., 1997b) of the synthetic human amylin analogue, pramlintide (Colburn et al., 1996; Janes et al., 1996), in addition to their usual morning dose of insulin, there was a delay in nutrient delivery to the small intestine and, in turn, to the peripheral circulation. This restraining effect of pramlintide on nutrient delivery slowed the appearance of meal-derived glucose (Kong et al., 1997b), and thus reduced the postprandial glycemic excursion in patients with type 1 (Fig. 1a) (Kolterman et al., 1995) and type 2 diabetes (Thompson et al., 1997). However, pramlintide does not reduce hyperglycemia following an intravenous glucose load (Fig. 1b) (Kolterman et al., 1995), indicating that effects of
amylin on the disposition of exogenous glucose are mediated via the gastrointestinal tract.

It has recently been demonstrated that rodent models of diabetes mellitus appear to have faster rates of gastric emptying than normal rats (Green et al., 1997; Young et al., 1995). Similarly, people with type 1 and type 2 diabetes who, as discussed above, are amylin deficient, show evidence of accelerated rates of nutrient delivery compared with healthy subjects (Frank et al., 1995; Nowak et al., 1995; Phillips et al., 1991; Schwartz et al., 1996). This results in a rapid inflow of meal-derived glucose to the circulation, which may contribute to the postprandial hyperglycemia that is seen in people with diabetes (Pehling et al., 1984). Thus, it appears that amylin may regulate nutrient delivery and, by so doing, help to match the rate of absorption of meal-derived glucose with that of insulin-mediated glucose disposal to maintain stable blood glucose concentrations.

Delaying the delivery of nutrient-derived glucose could be problematic in people with diabetes, increasing their risk of developing hypoglycemia. However, studies in rats have shown that hypoglycemia reverses the restraining effect of amylin on nutrient delivery, thereby ensuring that blood glucose levels are maintained within normal limits (Young et al., 1996a; Young et al., 1996c). Although this effect remains to be demonstrated in humans, it does support the hypothesis that the effects of amylin on nutrient delivery are indeed those of a hormone.

**Effect of amylin and the amylin analogue, pramlintide, on glucagon secretion**

Hepatic glucose production, which is regulated by glucagon, maintains basal blood glucose concentrations within the normal range of 70–100 mg/dl during the postabsorptive period (Lefèbvre, 1995). In normal individuals, glucagon secretion is inhibited in the postprandial period, resulting in a reduction in hepatic glucose output (Lefèbvre, 1995). In contrast, there is inadequate suppression of postprandial glucagon secretion in people with diabetes (Baron et al., 1987; Dinneen et al., 1995; Frank et al., 1995), resulting in inappropriate hepatic glucose production, which in turn contributes to the postprandial hyperglycemia that is a characteristic of such patients (Firth et al., 1986; Pehling et al., 1984).

There is evidence that, in addition to its effects on nutrient delivery, amylin also helps to regulate glucose inflow by suppressing glucagon secretion. Studies in rats have shown that the arginine-stimulated secretion of glucagon is reduced by the administration of physiological concentrations of amylin (Gedulin et al., 1997b) (Fig. 2). In contrast, administration of either a
Amylin acts in concert with insulin to limit postprandial hyperglycemia

Neutralising antibody or a specific amylin antagonist increases endogenous glucagon secretion in rats (Gedulin et al., 1997a). Two studies in people with type 1 diabetes have found that postprandial glucagon secretion was reduced following pramlintide administration (Fineman et al., 1997; Nyholm et al., 1997), and that this was associated with a reduction in postprandial hyperglycemia (Nyholm et al., 1997). Taken together, the findings of these studies suggest that the loss of amylin secretion in people with diabetes may lead to inadequate postprandial suppression of glucagon secretion, despite insulin treatment, and that this is a contributory factor in postprandial hyperglycemia.

Excess glucagon secretion during the postprandial period in people with diabetes may also adversely affect the normal counterregulatory mechanisms for the prevention of hypoglycemia. Nuclear magnetic resonance studies have shown that the hepatic glycogen stores are depleted in people with diabetes (Hwang et al., 1995), and it has been suggested that this may be responsible for the impaired hepatic glucose production that is seen in response to glucagon secretion in these individuals (Ørskov et al., 1991). Thus, the loss of amylin secretion in people with diabetes may contribute to deficiencies in the normal counterregulatory mechanisms for glucose homeostasis that defend the body against hypoglycemia.

Conclusions

In recent years there has been increasing awareness that glucose homeostasis depends not only on insulin-mediated glucose disposal, but that regulation of glucose inflow is also important for the maintenance of normoglycemia. Interestingly, studies with the pancreatic peptide hormone amylin, which is produced and co-secreted with insulin by the β-cells, suggest that it may complement the glucose-disposing actions of insulin by regulating glucose inflow. In particular, amylin and its synthetic human analogue pramlintide have been shown to reduce postprandial hyperglycemia in animal models of diabetes mellitus and in people with type 1 and type 2 diabetes, respectively, by both restraining nutrient delivery and suppressing glucagon secretion.

As with insulin, there is a deficiency of amylin production in people with diabetes. This deficiency may contribute to some of the problems with glycemic regulation that are seen in these individuals, including the rapid inflow of meal-derived glucose during the postprandial period, as well as hyperglucagonemia and the impaired hepatic response to glucagon stimulation. It may also help to explain the failure of insulin therapy to normalise glycemic control in patients with diabetes, even when administered according to intensive regimens. Thus, amylin replacement therapy may provide new opportunities for improving glycemic control in people with diabetes.
References


Cooper GJS, Leighton B, Dimitriadis GD, Parry-Billings M, Kowalchuk JM, Howland K, Rothbard JB, Willis AC, Reid KB: Amylin found in amyloid deposits in human Type 2 diabetes mellitus may be a hormone that regulates glycogen metabolism in skeletal muscle. Proc Natl Acad Sci USA 85: 7763–7766, 1988


Koda JE, Fineman MS, Kolterman OG, Caro JF: 24 hour plasma amylin profiles are elevated in IGT subjects vs. normal controls. Diabetes 44 (Suppl. 1): 238A, 1995 (Abstract)


Moore CX, Cooper GJS: Co-secretion of amylin and insulin from cultured islet β-cells, modulation by nutrient secretagogues, islet hormones and hypoglycemic agents. Biochem Biophys Res Commun 179: 1–9, 1991


Young AA, Gedulin BR, Rink TJ: Dose-responses for the slowing of gastric emptying in a rodent model by glucagon-like peptide (7-36) NH2, amylin, cholecystokinin, and other possible regulators of nutrient uptake. Metabolism 45: 1–3, 1996b


Prof. Dr. W. A. Scherbaum
Diabetes Research Institute
Heinrich Heine University
Auf’m Hennekamp 65
D-40225 Düsseldorf