Possible Links Between Amylin and Diabetes

Amylin is released into the blood stream along with insulin

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Around the turn of the 20th century, the pathologist Opie noted that amyloid deposits were present in the islets of Langerhans in patients with non-insulin-dependent diabetes mellitus (NIDDM); however, until recently the composition of these deposits was unknown. In the last few years two groups have succeeded in purifying and characterizing the protein composing the amyloid deposits (1,2). What they found was a peptide that is now known as either amylin or islet amyloid polypeptide. Amylin is a 37 amino acid peptide made in the β-cell of the islet where it is processed and packaged in secretory granules together with insulin. In response to stimuli that trigger the secretion of insulin, amylin is released into the blood stream along with insulin (3,4). The discovery of this peptide has raised a great number of questions about diabetes and the role that amylin might play in this disorder. Several basic issues need to be answered regarding amylin. 1) What controls the expression of amylin? 2) What is its normal physiological action? 3) What role might amylin play in the pathogenesis of NIDDM? Although at present we do not know the definitive answers to these questions, several interesting observations have been made following its discovery that have stimulated speculation about the possible roles amylin might play in carbohydrate metabolism and diabetes.

Although small amounts of amylin have been found in the GI tract and other tissues, the β-cell in the islet is the main source of this peptide in the body. Plasma amylin levels have been measured and are estimated to be from 1 to 14% of the molar amount of insulin (5–7). This range probably reflects differences in the assay from different labs, rather than actual variations in the relative amounts of amylin. Amylin secretion is regulated in parallel with the secretion of insulin. Thus, in patients with insulin-dependent diabetes and insulin deficiency, amylin deficiency also is present. In patients with glucose intolerance and hyperinsulinemia, amylin levels are elevated. In NIDDM with lower insulin levels, amylin levels also are decreased. Thus, in each of these situations amylin levels change in concert with variations in insulin.

Once amylin is secreted from the β-cell and enters the circulation, the major question is what does it do. Currently, no convincing evidence has been produced that identifies a specific receptor unique for amylin in any tissue. However, potential effects of amylin have been observed in vivo and in vitro in skeletal muscle and liver (8–10). Amylin also has been shown to have potent hypocalcemic effects (11). One of the most striking actions that has been shown is in muscle where amylin inhibits glycogen synthesis and enhances glycogen breakdown (12,13).

Both of these effects oppose the actions of insulin in muscle and represents one of the changes found in the insulin-resistant state of NIDDM. However, one of the main problems currently is the amount of amylin that is required to observe these effects. Levels that are probably 10–100 times higher than circulating levels of amylin have been used to induce these effects. Thus, one of the major questions is whether these effects are physiologically relevant or instead represent pharmacological actions of amylin. If similar actions can be demonstrated at physiological levels, amylin might play an important role in carbohydrate metabolism, modifying insulin actions and providing a mechanism to promote the delivery of glucose-derived carbon to tissues other than muscle.

Does amylin have any role in the pathogenesis of NIDDM? Again the answers are not yet available; however, it is possible that amylin could promote problems associated with NIDDM that occur either in the islet or peripheral tissues. Both insulin resistance and a relative β-cell failure play a role in the development of NIDDM (14). An insulin-resistant state is initially present, but is compensated by increased insulin secretion. In some individuals the β-cell is not able to continue to secrete the increased amounts of insulin necessary to overcome the peripheral insulin resistance and a relative insulin deficiency is present. At this point glucose intolerance progresses to frank diabetes.

Could the peripheral insulin resistance be triggered by increased levels of amylin? It seems unlikely that the

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initial step in the development of insulin resistance is related to amylin caused by the low levels of amylin present at that time; however, with the compensatory rise in insulin levels there would be a progressive rise in circulating amylin levels. It is possible that at some point the levels of amylin would contribute to the worsening of the insulin-resistant state. On the other hand, it is still not clear if the increased amounts of amylin would be high enough to lead to the insulin resistance that has been observed in experimental animals.

Amylin also could play a role in the pathogenesis of NIDDM within the islet, interfering with normal β-cell function by the progressive deposition of amyloid. The amyloid deposits appear to be composed of the same species as that normally secreted by the islet and probably does not result from any grossly altered processing of the peptide. Mutant amylins that might be prone to precipitate as amyloid also do not appear to account for the deposits in the islet.

Steiner et al. (15) examined the sequence of the amylin gene in 25 NIDDM subjects and did not find any variants in the coding region of the gene. It is possible that increased secretion of amylin that occurs along with the hyperinsulinemia of glucose intolerance would promote the deposition of amyloid, the native structure of normal amylin being prone to precipitation at high concentrations. In individuals in which amyloid deposition is triggered, NIDDM ultimately develops. The event that leads to the amyloid is still not known, because many subjects with glucose intolerance and high levels of amylin secretion do not appear to develop amyloid deposits and NIDDM. When present, islet amyloid could contribute to the functional impairment of the β-cell in the islet.

If either the peripheral or islet effects of amylin are significant in the pathogenesis, what can be done to interfere with this process? It is clear that the best alternative would be to selectively suppress the expression of amylin, relative to insulin. In both cases, the harmful effects of amylin would be related to the increased expression that occurs along with the increased insulin expression to compensate for insulin resistance. Currently, no condition has been found to independently regulate the expression of these two genes; however, the regions of the genes that control the expression of both insulin and amylin are sufficiently different that it may be possible to identify agents that selectively regulate the amylin gene.

What might be the consequences of upsetting the balance between insulin and amylin expression? This is unclear. We know that insulin administration without amylin has been used for more than 50 yr in the treatment of insulin-dependent diabetes and has been reasonably successful. Amylin is not essential for life as is insulin, but could play a role in modifying the actions of insulin. As such, amylin might be an effective adjunct in the treatment of insulin-dependent diabetes. Potentially, this could result in fewer problems with hypoglycemia, as well as altered storage of glucose as glycogen and fat in different tissues. Young (16) has recently shown that amylin administration to rats with streptozocin-induced diabetes helps replete glycogen stores in the liver.

Other alternatives also exist to inhibit amylin-mediated effects in NIDDM. If the amylin-promoted insulin resistance could be blocked by an amylin antagonist, the progression of insulin resistance might be halted at an early stage. However, although the antagonist would block peripheral effects of amylin it would not prevent the amyloid formation in the islet. To prevent the deposition of islet amyloid, a better understanding is needed of the events that promote this process. Certainly other factors beyond the increased secretion of amylin from the β-cell also play a role in this process.

The identification and characterization of amylin has stimulated a lot of possibilities regarding the pathogenesis of NIDDM and potential avenues to interfere with this process. However, the proof that amylin actually plays a role in this process is not yet available. Indeed, it is possible that the real physiological actions of amylin have not yet been uncovered. Further studies are required to determine whether amylin, amylin antagonists, or amylin regulators will play a role in the management of diabetes. Although there are many options to be explored, amylin may or may not explain many of the enigmas regarding the pathogenesis of NIDDM.

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