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Review

Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes

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ABSTRACT

Type 2 diabetes (T2DM) results when increases in beta cell function and/or mass cannot compensate for rising insulin resistance. Numerous studies have documented the longitudinal changes in metabolism that occur during the development of glucose intolerance and lead to T2DM. However, the role of changes in insulin secretion, both amount and temporal pattern, has been understudied. Most of the insulin secreted from pancreatic beta cells of the pancreas is released in a pulsatile pattern, which is disrupted in T2DM. Here we review the evidence that changes in beta cell pulsatility occur during the progression from glucose intolerance to T2DM in humans, and contribute significantly to the etiology of the disease. We review the evidence that insulin pulsatility improves the efficacy of secreted insulin on its targets, particularly hepatic glucose production, but also examine evidence that pulsatility alters or is altered by changes in peripheral glucose uptake. Finally, we summarize our current understanding of the biophysical mechanisms responsible for oscillatory insulin secretion. Understanding how insulin pulsatility contributes to normal glucose homeostasis and is altered in metabolic disease states may help improve the treatment of T2DM.

Contents

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1. Introduction

Type 2 diabetes (T2DM) is associated with both a reduction in beta-cell mass and impaired beta-cell function. Less attention has been paid to beta cell function, which may begin to decline prior to the reduction in beta cell mass or the development of T2DM (Rahier et al., 2008). For example, the early loss of first phase secretion has long been considered a hallmark of T2DM (Nesher and Cerasi, 2002; Straub and Sharp, 2002; Ward et al., 1986). From a therapeutic standpoint, improving insulin secretion pharmacologically is a more realistic alternative to stimulating beta cell mass expansion, in part because the latter is likely to occur on a much slower time scale than improvements in beta cell function. Even in rodents, where robust changes in beta cell mass can occur, beta cell function changes more rapidly and more markedly than mass (Topp et al., 2007). Compensatory changes in beta cell function would be expected to be even more important in humans, where mass expansion is two orders of magnitude slower (Kushner, 2013; Saisho et al., 2013; Teta et al., 2005).

As is the case for other hormones, insulin is secreted from the pancreas in a pulsatile manner in both experimental animals and humans, and in patients with T2DM and other metabolic disorders the pattern of pulsatile release is disturbed. Thus, soon after the first report that fasting plasma insulin and glucagon levels oscillate in non-human primates *in vivo* (Goodner et al., 1977), Turner's group in the UK demonstrated that pulsatility occurs in healthy human subjects (Lang et al., 1979) and found disturbed pulsatility in subjects with T2DM (Lang et al., 1981).

The main focus of this review is the pulsatile insulin secretion of humans, particularly 'fast oscillations' in plasma insulin that have a period reported to range from 5 to 15 minutes. Readers with a special interest in ultradian insulin oscillations (period ≈ 80–180 minutes) are directed to other reviews (Polonsky, 1999).

2. Insulin levels oscillate in fasted humans

Lang and colleagues were the first to report insulin oscillations in the peripheral circulation of fasted but otherwise healthy human subjects. The oscillations they observed had a mean period of 15 minutes or so (Lang et al., 1979). Peripheral blood was sampled once per minute for a total duration of 1–2 hours. An example from their paper shows, at least initially, clear oscillations in insulin, C peptide, and glucose concentrations in peripheral blood, as shown in Fig. 1. The continuous lines depict three-minute moving averages of the data, while the dashed lines show the raw, unsmoothed data. Small oscillations in glucose are also apparent in the lower part of the figure, but are difficult to resolve.

Using records such as this, Lang et al. applied autocorrelation to aid in pulse detection. Autocorrelation involves creating a mirror image of smoothed time series data, translating it stepwise along the original data, and then calculating a correlation coefficient for each time point in the interval. Plots of these coefficients reveal peaks that occur at multiples of the dominant oscillation period(s). Although Lang et al. and other early studies of *in vivo* insulin pulsatility (Hansen et al., 1982) reported an oscillation period of 10–15 minutes, more recent studies have determined the *in vivo* period of insulin oscillations to be closer to 5 minutes. In a later section, we will discuss why limitations in the technical approaches that were available at the time are likely to explain the prolonged insulin periods originally reported in this literature.

3. Individuals with T2DM have impaired insulin pulsatility

Using the same approach, Lang et al. (1981) reported that individuals with diabetes (their mean fasting glucose was 7 mM) displayed shorter and highly irregular oscillations having a mean period of 8.8 minutes (vs. controls having a period of 10.7 minutes). Later studies confirmed the impaired insulin pulsatility of T2DM patients (e.g. Gumbiner et al., 1996, Hunter et al., 1996, Meier et al., 2013, but see Lin et al. (2002)).

O'Rahilly et al. (1988) extended these studies in individuals with T2DM to their first-degree relatives who lacked fasting hyperglycemia, to see whether pulsatility defects were an early event in the progression to diabetes. Control subjects were matched by age, gender and BMI to the relatives of patients with diabetes. While the control subjects exhibited regular insulin oscillations, these were lacking in the relatives of T2DM subjects. However, the relatives studied were already glucose intolerant and insulin resistant, and had reduced first phase insulin secretion, so the loss of pulsatility may have been secondary to reduced pulse amplitude, which may have reduced the signal-to-noise ratio.

In a similar study, Schmitz et al. studied the transition from normal to abnormal glucose tolerance to fasting hyperglycemia to determine whether the loss of first phase and pulsatile secretion was due to intrinsic beta cell defects or glucotoxicity (Schmitz et al., 1997). Insulin action and insulin pulsatility were measured in healthy offspring of T2DM patients vs. controls matched by age, gender and BMI. Approximate entropy (ApEn), a measure of the likelihood that a similar pattern of observed activity will be repeated in a given time interval, was used to gauge the level of irregularity of plasma insulin pulses; consistent with the general sense that entropy quantifies disorder, high ApEn