Ultradian Oscillations of Insulin Secretion in Humans

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Ultradian rhythmicity appears to be characteristic of several endocrine systems. As described for other hormones, insulin release is a multioscillatory process with rapid pulses of about 10 min and slower ultradian oscillations (50–120 min). The mechanisms underlying the ultradian circhoral oscillations of insulin secretion rate (ISR), which arise in part from a rhythmic amplification of the rapid pulses, are not fully understood. In humans, included in the same period range is the alternation of rapid eye movement (REM) and non-REM (NREM) sleep cycles and the associated opposite oscillations in sympathovagal balance. During sleep, the glucose and ISR oscillations were amplified by about 150%, but the REM-NREM sleep cycles did not entrain the glucose and ISR ultradian oscillations. Also, the latter were not related to either the ultradian oscillations in sympathovagal balance, as inferred from spectral analysis of cardiac R-R intervals, or the plasma fluctuations of glucagon-like peptide-1 (GLP-1), an incretin hormone known to potentiate glucose-stimulated insulin. Other rhythmic physiological processes are currently being examined in relation to ultradian insulin release. Diabetes 51 (Suppl. 1):S258–S261, 2002

In addition to the rapid insulin pulses that recur every 5–10 min, slow and large ultradian oscillations of insulin secretion with a period range of 50–120 min have been described in both humans and animals. These oscillations are best seen in situations of insulin stimulation, and have been observed after meal ingestion (1), during continuous enteral nutrition (2), and during intravenous glucose infusion (3). They are closely associated with similar oscillations of plasma glucose concentration. Figure 1 shows the insulin secretion rate (ISR) profile estimated from plasma C-peptide levels as proposed by Eaton (4) and the concomitant glucose profile obtained in one subject studied during continuous enteral nutrition with a 10-min blood-sampling procedure. ISR was estimated by deconvolution analysis from plasma C-peptide concentrations.

FIG. 1. Plasma glucose concentration and ISR profiles in one representative subject studied during continuous enteral nutrition with a 10-min blood-sampling procedure. ISR was estimated by deconvolution analysis from plasma C-peptide concentrations.

The precise mechanisms that generate the ultradian insulin oscillations are not fully understood. In particular, it is not established whether the glucose oscillations have an active role in the origin of the ISR oscillations or whether the latter are independently generated by an intrapancreatic pacemaker. ISR oscillations persist after pancreas transplantation (13) or in denervated islet cell autografts (14), which suggests that their origin does not depend on the central nervous system; also, they do not seem to involve the counterregulatory hormones (3). Based on a mathematical model, it has been hypothesized that they could result from instability in the insulin-glucose feedback loop (15,16). This nonlinear model,
which is based on different time-delayed feedback loops (glucose stimulates insulin secretion, insulin stimulates glucose uptake and inhibits hepatic glucose production, and glucose stimulates its own uptake), exhibits self-sustained oscillations when a constant glucose infusion is simulated and is consistent with several experimental data. Yet, it does not account for the existence, in some type 2 diabetic patients (7), of glucose pulses in the absence of any concomitant oscillations. The existence of an intrapancreatic pacemaker cannot be excluded. Chou et al. (17) have identified low-frequency insulin oscillations in perfused rat pancreatic islets with a period ranging from 50 to 100 min. Ultradian rhythms have also been described for numerous physiological processes—hormonal release, such as norepinephrine (18), as well as behavioral, gastrointestinal, and sleep processes (12)—indicating that other control mechanisms, although not exclusive, may be involved.

**Relationship with the rapid oscillations.** To analyze the relationship between the two rhythmic components of ISR, plasma insulin was measured with a 2-min blood-sampling procedure in four subjects studied during continuous enteral nutrition for 8 h. A deconvolution method based on a biexponential disappearance rate of insulin, assuming half-lives for insulin of 2.8 and 5 min with a fractional slow component of 28% (19), was used to quantify the dynamics of insulin secretion. The plasma insulin and estimated ISR profiles from one subject are represented in Fig. 2, which shows that the slow insulin oscillations are partly due to a slow rhythmic amplification of rapid ISR pulses. Spectral analysis of the deconvoluted ISR profiles confirmed the presence of two significant rhythmic components: one with a mean periodicity of 48–96 min, the other with a mean periodicity of 6–12 min. Altogether, these results indicate that the temporal organization of insulin secretion is analogous to that of luteinizing hormone or growth hormone, for which the presence of both rapid and slow secretory pulses has been demonstrated (20,21).

**Relationship with sleep and sympathovagal activity.** Beside a circadian rhythm, sleep presents an ultradian component, which is responsible for the alternation of the two basic sleep states, non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. The REM-NREM cycles, which are associated with inverse fluctuations of sympathovagal balance (22,23), have a mean periodicity of 80–20 min close to that reported for ISR.

Using spectral analysis of the sleep electroencephalographic (EEG) activity, which provides a dynamic description of sleep processes, it has been demonstrated that the delta wave activity (0.5–3.5 Hz), which characterizes the depth of sleep, oscillates with a similar period (24).

We previously established (25) that the oscillations of plasma glucose and ISR are amplified by about 150% during sleep without any modification of their frequency (Fig. 1). This amplification is not an endogenous circadian clock effect since it occurs whatever the time of sleep. To better evaluate the temporal link of the glucose and ISR oscillations with the internal structure of sleep and its ultradian component, we used spectral analysis of sleep EEG. Concomitantly, spectral analysis of cardiac R-R intervals over 5-min periods was used to calculate various indexes of heart rate variability, thought to reflect the sympathovagal balance. In particular, we calculated the ratio between the power densities in the low-frequency (LF: 0.04–0.15 Hz) to the high-frequency (HF: 0.15–0.50 Hz) bands.

To establish the time courses of plasma glucose levels, ISR estimated from plasma C-peptide, and heart rate variability indexes during the different sleep states, we selected for each of nine subjects studied during continuous enteral nutrition, uninterrupted NREM sleep episodes containing slow-wave sleep (SWS). Figure 3 illustrates the mean normalized profiles of sleep pattern obtained in the nine subjects, together with the concomitant LF/HF ratio, ISR, and plasma glucose profiles. As expected, the oscillation of delta wave activity, which reflects sleep deepen-
glucose or ISR profile varied in opposite ways, with a predominant lightening, and the oscillation of LF/HF ratio were
entered in delta wave activity trigger neither ISR nor glucose oscillations. Inspection of the individual profiles confirmed that the fluctuations of insulin secretion were not systematically associated with concomitant oscillations in delta wave activity. Conversely, sleep deepening was associated with a valley, a peak, an increase, or a decrease in ISR, which explains the smooth aspect of the averaged curves.

**IS R oscillations and glucagon-like peptide-1.** Glucagon-like peptide-1 (GLP-1) is a peptide hormone secreted by the intestinal mucosa in response to meal or glucose ingestion (26). It is known to act as an incretin hormone, potentiating glucose-stimulated insulin release and has been shown to increase β-cell sensitivity to oral glucose excursions in patients with impaired glucose tolerance (27). GLP-1 itself is secreted in a pulsatile manner with a high-frequency periodicity (28). In order to establish whether GLP-1 secretion also presents ultradian fluctuations that could modulate the ISR oscillations, GLP-1 plasma levels and ISR were determined in six healthy male subjects (20–26 years) studied during continuous enteral nutrition with a 10-min blood-sampling procedure. GLP-1 (7–36 amide) was measured by radioimmunoassay with an intra-assay variation coefficient of 6% (Peninsula, San Carlos, CA). Plasma GLP-1, ISR, and glucose profiles obtained in one subject are illustrated in Fig. 4. Contrasting with the regular oscillations observed for glucose and ISR, the GLP-1 profile exhibited irregular fluctuations. Pulse analysis revealed the presence of 5.0 ± 0.8 significant pulses during the 8-h experiment. These pulses had a mean period of 45–70 min depending on the subject. Their relative amplitude was 22.8 ± 2.1%. Coincidence analysis did not reveal any systematic association between the GLP-1 fluctuations and the insulin or the glucose oscillations.

**CONCLUSION**

Insulin secretion is characterized by a complex temporal organization with two distinct rhythm components, rapid pulses being associated with slower ultradian oscillations that are best seen when insulin secretion is stimulated. Ultradian rhythms with similar periods have been identified for numerous physiological processes with no evident coupling with ISR oscillations, which does not support the view of one common pulse generator. Whatever the mechanisms involved, different data suggest that the ISR circoral rhythm has functional significance.

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