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Introduction
Insulin, which is secreted from pancreatic β cells, is the key hormone in regulating glucose metabolism. Insulin secretion is a highly dynamic process regulated by complex mechanisms. It is regulated by nutrient status, hormonal factors such as gastrointestinal hormone incretins (i.e., glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinothropic polypeptide [GIP; originally termed “gastric inhibitory polypeptide”]), and neural factors (1–5). In addition, the regulation of insulin secretion is a multi-tiered process, occurring at the level of the single β cell, the pancreatic islet, the whole pancreas, and the intact organism. Thus, in vivo, the dynamics of insulin secretion is the consequence of an integration of all of these systems.

Fundamental mechanism of insulin secretion
Stimulus-secretion coupling is an essential biologic event in pancreatic β cells. Ca²⁺, ATP, cAMP, and phospholipid-derived signals such as diacylglycerol and inositol 1,4,5-triphosphate are the major intracellular signals in insulin secretion (6, 7). Glucose-stimulated insulin secretion (GSIS) is the principal mechanism of insulin secretion. Glucose is transported into the β cell by glucose transporters, and then metabolized, leading to increases in the ATP concentration (or ATP/ADP ratio), closure of ATP-sensitive K⁺ (KATP) channels, depolarization of the β cell membrane, and opening of the voltage-dependent Ca²⁺ channels (VDCCs), thereby allowing Ca²⁺ influx (8). The resultant rise in intracellular Ca²⁺ concentration ([Ca²⁺]i) in the β cell triggers insulin secretion. In addition to this KATP channel–dependent pathway, which triggers GSIS, there is also a KATP channel–independent pathway that amplifies the effects of Ca²⁺ on exocytosis (9) and does not require an additional increase in [Ca²⁺].

Dynamics of insulin secretion
It is well known that the insulin concentration in the blood oscillates even during postabsorptive periods (10, 11). There are two major oscillatory secretion patterns, ultradian oscillations (pulsatile secretion), which have a period of 1–2 hours and may be due to a feedback loop between glucose production and insulin secretion (12), and more rapid oscillations, which have a period of 10–15 minutes (13). Insulin is more effective at reducing blood glucose levels if it is delivered in pulses rather than continuously (14). Oscillatory insulin secretion has also been detected in vitro in isolated dog pancreas and pancreatic islets from dogs (15–17). Thus, oscillation of insulin secretion is likely caused by intrinsic β cell mechanisms and modified by exogenous signals such as hormonal and neuronal inputs. Oscillations in [Ca²⁺], rather than metabolism in the β cell are thought to be the direct cause of these oscillations in insulin secretion (17).

Hyperglycemic clamps and experiments in isolated pancreatic islets have demonstrated that glucose induces insulin secretion in a biphasic pattern: an initial component (first phase), which develops rapidly but lasts only a few minutes, followed by a sustained component (second phase) (18–20). Loss of first-phase secretion and reduced second-phase secretion are characteristic features of type 2 diabetes mellitus (T2DM); it is well known that a decrease in the first phase of GSIS is found in the early stage of T2DM and also in impaired glucose tolerance (IGT) (18, 21). Thus, in order to understand the pathogenesis and pathophysiology of these diseases, it is important to clarify the cellular and molecular mechanisms responsible for the alterations in the dynamics of insulin secretion. Biochemical experiments and capacitance measurement have suggested that secretory vesicles generally exist in functionally distinct pools and that sequential release of these pools underlies the dynamically separable components of exocytosis (22). Pancreatic β cells contain at least two pools of insulin secretory granules that differ in release competence: a reserve pool (RRP), which accounts for the vast majority of granules, and a readily releasable pool (RNP), which accounts for the remaining granules (less than 5%). The prevailing hypothesis is that the release of RRP granules accounts for the first phase of GSIS, and that mobilization of a subsequent supply of new granules for release by mobilization accounts for the second phase (22).

Recently, investigation of insulin granule dynamics has been refined by use of the total internal reflection fluorescence microscopy (TIRFM) system. TIRFM is a technology that provides a means to selectively excite fluorophores in an aqueous or cellular environment near a solid surface (within 100 nm) without exciting fluorescence from regions farther from the surface. The unique features of TIRFM analysis have enabled numerous applications in biochemistry and cell biology (23–26).

Revising previous models, our group used TIRFM to analyze insulin granule dynamics induced by various stimuli in detail, using primary cultured mouse pancreatic β cells (25). In contrast to the findings of Ohara-Imaizumi et al. (27), we found three different modes of insulin exocytosis based on the dynamics of insulin granules: mode 1, in which preloaded granules are immediately fused to the plasma membrane by stimulation (old face); mode 2, in which

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: J Clin Invest. 2011;121(6):2118-2125. doi:10.1172/JCI45680.
granules are newly recruited by stimulation and immediately fused to the plasma membrane (restless newcomer); and mode 3, in which granules are newly recruited by stimulation but are first docked and then fused to the plasma membrane (resting newcomer) (Figure 1 and ref. 25). Our group further demonstrated a biphasic pattern of glucose-induced insulin granule exocytosis, and found that both phases of glucose-induced insulin granule exocytosis are caused primarily by restless newcomer (25). In contrast, most potassium-induced insulin granule exocytosis that occurs immediately and transiently after stimulation results from release by old face. This was confirmed by sequential stimulation by glucose and potassium using two protocols: first, glucose stimulation followed by potassium stimulation, and then the reverse (28).

The difference in the granules involved in the first phase of glucose-induced fusion events and those involved in potassium-induced fusion events is noteworthy. Our group recently demonstrated that interaction of Rim2α with the vesicle protein Rab3 is required for docking of insulin granules but not for either potassium-induced or glucose-induced insulin granule exocytosis (29). Docking is considered to be a braking state that prevents the fusion of granules to the plasma membrane (26, 29). Stimulation of pancreatic β cells with high concentrations of potassium induces supraphysiologic levels of [Ca^{2+}], that can force insulin granule exocytosis by overwhelming the braking state. We hypothesize that glucose stimulation may not elicit fusion events by old face because the rise in [Ca^{2+}], induced by glucose is insufficient to overwhelm the braking state, in contrast to that induced by potassium. While potassium-induced insulin secretion requires only the Ca^{2+} signal, glucose-induced insulin secretion requires Ca^{2+} and other signals including metabolites (30), permitting different modes of insulin granule exocytosis induced by the two stimuli.

Based on these data, we propose a new model of GSIS, in which both the first and second phases are caused by newly recruited granules without docking (restless newcomer) (Figure 2). These granules are more than 50 nm away from the plasma membrane but are readily releasable. Although both phases of insulin secretion are caused by these granules, the mechanisms of the first and second phases of insulin secretion are distinct, and the two phases are caused by granules of separate pools. It is known that the actin cytoskeleton is a highly dynamic and complex structure that is remodeled in response to various stimuli (31), and the dynamics of insulin granules by glucose stimulation could also be affected by actin remodeling. Indeed, glucose stimulation triggers transient F-actin remodeling to allow access to the plasma membrane (32, 33). Since most insulin granules reside in a region deeper than the F-actin barrier, and F-actin remodeling could mobilize granules to t-SNARE proteins at the plasma membrane (34), it is likely that actin remodeling is involved in the second phase of GSIS. Moreover, a recent study found that inhibition of RhoGDI enhanced the second phase of GSIS through activation of Cdc42 (35). The finding that Cdc42 promotes actin polymerization (36) further supports the hypothesis that dynamics of the actin network regulate the second phase of GSIS. However, the role of F-actin in the first phase of insulin secretion is still unknown, and it is possible that the roles of the actin cytoskeleton differ in the first and second phases of insulin secretion.

Some insulin granules are known to partially fuse to the plasma membrane, release small molecules, and then undergo endocytosis (termed “kiss-and-run exocytosis”) (37, 38). However, since crystallized insulin cannot pass the small pore formed by kiss-and-run exocytosis, the full fusion of granules is required for the release of insulin (39). The interaction of insulin granules with VDCC, which...
promotes the local increase of $[\text{Ca}^{2+}]$, at the fusion site, is proposed to be involved in the full fusion (38).

**Regulation of dynamics of insulin secretion by cAMP signaling**

It is well known that the insulin secretory response is much greater after oral than after i.v. glucose administration, even when plasma glucose levels are matched. This phenomenon, called the “incretin effect,” is mediated by two gastrointestinal hormones, GLP-1 and GIP (40). GLP-1 and GIP are released in response to the ingestion of nutrients from gastrointestinal endocrine L cells and K cells, respectively (41). Both of these hormones potentiate GSIS (42, 43) by activation of cAMP signaling in pancreatic β cells (44–46). cAMP acts in the insulin secretory process at various steps (1, 47, 48). In normal mouse pancreatic islets, in vitro concentration dependency of GSIS displays a sigmoid curve (49), in which glucose concentration exceeding 6 mM is required for triggering insulin secretion. GLP-1 and GIP are known to potentiate both the first and second phases of GSIS from perfused pancreas (50). In addition, it has been reported that although single β cells dispersed from rat pancreatic islets are often found to be glucose-insensitive, as assessed by electrical activity, GLP-1 endows these cells with glucose competency, probably by modulating $K_{\text{ATP}}$ channel activity (51). These findings suggest a mechanism by which cAMP induces glucose responsiveness of pancreatic β cells. We recently reported that small and step-wise increases in the glucose concentration from 2.8 to 12.5 mM do not trigger insulin secretion from perfused mouse pancreas (48). However, in the presence of the cAMP analog 8-Br-cAMP or GLP-1, insulin secretion is readily evoked in response to such small increases in glucose concentration. Thus, cAMP signaling is critical not only for potentiation of GSIS, but also for induction of glucose responsiveness. Treatment with GLP-1 induces a delayed but measurable GSIS response, even in $K_{\text{ATP}}$ channel–deficient (Kcnj11$^{-/-}$) mice (47), indicating that some of the effect of GLP-1 in induction of glucose responsiveness is independent of the $K_{\text{ATP}}$ channels. In contrast, induction of glucose responsiveness by GIP in Kcnj11$^{-/-}$ mice is much less than that by GLP-1, which indicates that the action of GIP is critically dependent on $K_{\text{ATP}}$ channels (47). Differential effects of GLP-1 and GIP on insulin secretion are also found in a clinical setting. For example, treatment with GLP-1 improves insulin secretion in T2DM, whereas GIP does not (52). These and other data suggest that cAMP signaling in distinct intracellular compartments mediates the distinct cellular responses in pancreatic β cells (53). Interestingly, a recent study showed that the mouse β cell line MIN6-K20, which does not exhibit either GLP-1 or GIP responsiveness in monolayer culture, clearly exhibits responsiveness almost comparable with that of normal mouse islets when pseudoislets (exhibiting three-dimensional structure) are formed by the cell line. These data suggest that β cell–β cell interaction is critical for induction of cAMP responsiveness (54).

**Role of cAMP signaling in insulin granule dynamics**

Although cAMP potentiates GSIS, how cAMP acts in the exocytotic processes of recruitment, docking, and fusion of secretory granules is not clear. Our group has examined regulation of insulin granule dynamics by cAMP signaling using the TIRFM system (25). 8-Br-cAMP alone did not increase the number of docking granules or elicit fusion events but clearly potentiated both the first and second phases of glucose-induced insulin granule exocytosis. 8-Br-cAMP enhanced the exocytosis by increasing the number of restless newcomers, suggesting that activation of cAMP signaling increases the size of the pools (both RRP and RP) of insulin granules and/or facilitates recruitment of insulin granules from the pools to the plasma membrane.

It has been shown that cAMP oscillations occur in pancreatic β cells (55–57). A close temporal and causal interrelationship between the increase in cytoplasmic $\text{Ca}^{2+}$ and cAMP levels following membrane depolarization has been reported (55, 56). A recent study demonstrated that glucose metabolism directly controls cAMP signaling (57), suggesting that cAMP oscillations regulate dynamics of insulin granule exocytosis.

**Role of Epac2A/Rap1 signaling in the regulation of dynamics of insulin secretion**

cAMP regulates the potentiation of insulin secretion by a PKA-dependent mechanism and by a PKA-independent mechanism.

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**Figure 2**

Existing and new models of GSIS in the normal state. (A) In the existing model of GSIS, the first phase of insulin secretion results from a RRP composed of docked insulin granules (old face); the second phase of secretion results from a RP composed of granules located farther away (resting newcomer) that are newly recruited upon stimulation, docked, and fused to the plasma membrane. (B) In the new model, both phases consist of insulin granules that are recruited upon stimulation and immediately fused to the plasma membrane (restless newcomer). A RRP responsible for the first phase is located more than 50 nm from the plasma membrane, yet is immediately releasable. The second phase of insulin secretion involves exocytosis of insulin granules from a RP associated with the cortical actin network regulated by glucose-evoked signals in a mechanism yet to be elucidated.
It has been proposed that SUs also bind to a putative receptor expressed on insulin granules (gSURs) and that gSURs couple with the granular chloride channel CIC-3 (70–72). Acidification of insulin granules enhanced by CIC-3 might facilitate GSIS in pancreatic β cells (73–75).

**Clinical implications of dynamics of insulin secretion**

**Obesity and insulin resistance.** Clinically, obesity is characterized by insulin resistance and hyperinsulinemia. Hyperinsulinemia results from increased insulin secretion, decreased insulin clearance (particularly hepatic insulin extraction), or a combination of these two factors (76–79). One study indicates that insulin secretion is increased in moderate obesity under basal conditions over a 24-hour period on a mixed diet and in response to i.v. glucose and is highly correlated with BMI, while hepatic insulin clearance does not differ in normal and obese subjects, suggesting that increased insulin secretion is the major determinant of hyperinsulinemia (78). However, in patients with more marked basal hyperinsulinemia and during intense stimulation of insulin secretion, a reduction in insulin clearance also contributes to the greater increase in peripheral insulin concentrations (78, 79).

Because insulin secretion is related to insulin sensitivity (S_i) as a hyperbolic function (80, 81), compensation of insulin secretion for S_i is usually estimated from the disposition index (DI), which is calculated as the product of S_i and the first-phase acute insulin secretory response to i.v. glucose (AIRg), using the frequently sampled i.v. glucose tolerance test (ref. 82 and Figure 4). It has been shown that S_i progressively and significantly decreases with obesity, whereas AIRg rises, and thus DI declines significantly among obese family members (83). A study of obese youth with normal glucose tolerance, IGT, and T2DM indicated that the first-phase insulin response to glucose and DI progressively decrease with the degree of impairment of glucose tolerance, with a more profound defect in obese subjects with T2DM involving both the first- and second-phase insulin responses (84). In addition, because the early-phase insulin secretory defect is not found in subjects with simple obesity (obesity in the absence of metabolic syndrome) and progressive decline of glucose tolerance is only seen in subjects with decreased insulin secretion (85), the glucose intolerance would seem to be evoked not by obesity itself but by the insulin secretory defect, especially in the first phase.

The temporal pattern of insulin secretion and the secretory pulses that occur every 1.5–2 hours in normal subjects are maintained in obese subjects, although the amplitude of these pulses postprandially is greater in obese subjects (78). Rapid oscillations also occur in obese subjects with a periodicity similar to that of normal subjects (10–12 minutes). Thus, the intrinsic regulatory mechanism of the dynamics of insulin secretion appears to be normal in an obese state, and the increase in insulin secretion in obese subjects is not likely due to hyperresponsiveness to various stimuli in individual β cells but rather to the larger functional β cell mass (Figure 5A).

In a mouse model with β cell–specific disruption of the insulin receptor, loss of acute-phase insulin secretion in response to glucose but not to arginine (86) suggests that insulin signaling in pancreatic β cells itself is critical to GSIS. In humans, extreme insulin resistance syndrome associated with a primary defect in insulin signaling due to mutations of the insulin receptor gene has been reported (87). Lack of insulin signal transduction in the peripheral tissues is responsible for the continuous elevation of plasma glucose levels after glucose challenge. However, these patients show hyperinsulinemia following glucose stimulation despite the defect in insulin signaling in the
β cells (88). Thus, the significance of insulin signaling in human β cells in the dynamics of acute insulin secretion remains unclear.

T2DM. T2DM is characterized by impaired insulin secretion and/or insulin resistance. However, insulin secretory capacity is the major factor contributing to the development of T2DM because neither hyperglycemia nor glucose intolerance develops in insulin-resistant patients, so long as sufficient insulin is secreted from β cells in a timely fashion in response to various stimuli. Genetic variation between populations likely contributes to differences in insulin secretory capacity, and thus to the proclivity to develop T2DM. For example, although obesity (defined by a BMI of greater than 30) is less prevalent in Japan than the US, the prevalence of T2DM is similar in both countries (89).

In addition, Welch et al. reported that all patients with T2DM in a European population exhibited decreased SI (90), whereas Taniguchi et al. found that SI in Japanese T2DM is distributed from low to high values (91). In contrast, AIRg was decreased in Japanese patients with T2DM, while AIRg in those of European descent varied.

Impaired insulin secretion may be due to β cell dysfunction, reduced β cell mass, or both. Whether β cell dysfunction or reduced β cell mass precedes clinical onset of diabetes remains an open question. However, in mice, surgical and chemical reductions of β cell volume demonstrate that the functional adaptation of the normal β cell prevents a rise in fasting glucose or reduction in the first phase of insulin secretion (92, 93), suggesting that β cell dysfunction, rather than a decrease in β cell mass, is likely to be more closely associated with the pathophysiology of T2DM.

The insulin secretory response to glucose has been studied using i.v. bolus glucose administration and hyperglycemic clamp, the former suitable for evaluation of the early phase (first phase) of insulin secretion, the latter suitable for evaluation of the second phase (94, 95). The first phase of AIRg (81) is often used to evaluate β cell function. As mentioned above (and shown in Figure 4), AIRg is related to the degree of SI as a hyperbolic function (81, 82).

It is accepted that abnormal dynamics of insulin secretion selec-
tive for glucose stimulation, especially the first phase of the insulin response to i.v. glucose, is already reduced in the early stages of T2DM (96, 97), first-degree relatives of patients with T2DM (98, 99), and those with IGT and their first-degree relatives (91, 100, 101). In addition, even across the range of normal fasting glucose levels, the first-phase response decreases as the glucose level increases (97, 102). Furthermore, as glucose tolerance decreases, for any degree of $S_g$, the first-phase response is lower in those with lower glucose tolerance (97). As mentioned above, since the early phase of insulin secretion is determined by the RRP, a reduction in its size and/or impaired exocytosis of RRP granules might develop in IGT and in the early stages of T2DM (Figure 5B). The RRP is completely depleted, and the RP is markedly reduced in the developed stage of T2DM (Figure 5C). Signaling mechanisms underlying exocytosis of insulin granules from the RRP and the RP may also be defective in T2DM. Clarification of the mechanisms regulating insulin granule exocytosis from the RRP as well as the size of RRP should be helpful for understanding a defect in the first phase of GSIS in T2DM.

The pulsatile nature of insulin secretion is maintained in patients with T2DM, with the number of pulses similar to that in healthy control subjects (103). Pulses are detected even in patients with very low rates of insulin secretion, suggesting that the rhythmic secretion is a fundamental characteristic of β cell function that is retained even when there is a severe loss of secretory reserve (103). However, in patients with T2DM, the pulses after meals are less frequent, are irregular, and have a significantly lower amplitude, resulting in a marked disruption in the dynamics of post-meal insulin secretion. Interestingly, pulsatility and/or rapid oscillation of insulin secretion is lost or disordered in first-degree relatives of T2DM patients who show minimal glucose intolerance or normal glucose tolerance, and subjects with IGT (104–107). A loss of coordinated insulin secretory responses to oscillatory glucose infusion is found in subjects with IGT, indicating a defect in the ability of the β cell to properly sense and respond to parallel changes in the plasma glucose level (107). Moreover, a recent mouse study revealed that the molecular clock in β cells has a role in rhythmic control of insulin secretion and that ablation of the pancreatic clock can trigger the onset of T2DM (108). These findings suggest that abnormalities in the dynamics of insulin secretion are an early manifestation of β cell dysfunction that precedes the development of T2DM.

Effects of incretins and incretin-related drugs on the dynamics of insulin secretion

The incretin effect is estimated to underlie approximately 60%–70% of insulin secretion in response to glucose in normal healthy subjects (109). Studies using hyperglycemic clamps and i.v. bolus glucose administration indicate that incretin-related agents including GLP-1, GIP, the GLP-1 receptor agonist exenatide, and the GLP-1 analog liraglutide augment both the first and second phases of the insulin secretory response to glucose, with the most predominant effect on the first phase (110). The timing of administration results in differential effects of incretins or incretin-related drugs on the dynamics of insulin secretion (110, 111). Although the effects of i.v. infusion of GLP-1 and GIP on potentiation of insulin secretion in response to glucose are similar (112) and additive in normal healthy subjects (113), they have distinct insulinotropic effects in T2DM. GLP-1 infusion can readily normalize hyperglycemia in patients with T2DM (114). On the other hand, the insulinotropic effect of GIP is markedly impaired in patients with T2DM, and GIP infusion in diabetic patients elicits just 40% of the normal insulin secretory response (109, 114–116). Acute i.v. infusion of GLP-1 (110), liraglutide (117), and exenatide (118) improves insulin secretory response to i.v. glucose in patients with relatively mild T2DM by enhancing both the first and second phases of insulin secretion. The first phase of the insulin response is also improved in patients with T2DM after treatment with liraglutide for 14 weeks, as assessed by i.v. glucose tolerance test. Interestingly, in patients with T2DM, the defect in amplification of the second-phase insulin response to glucose by GIP is more pronounced than that in amplification of the first phase (119). Thus, although both GLP-1 and GIP act on insulin secretion through cAMP signaling in pancreatic β cells as described above, these hormones have distinct effects on the dynamics of GSIS.

In vitro, the dynamics of GSIS are usually assessed by a large and rapid increase in glucose concentration, e.g., an immediate increase from 3–4 mM to 16–20 mM glucose. However, such a drastic change in glucose concentration is unlikely to occur in the physiological state in vivo. As described above, although small and stepwise increases in the glucose concentration do not trigger insulin secretion in perfused pancreas, activation of cAMP signaling evokes insulin secretion even in this setting (45). Thus, in addition to potentiation of GSIS, incretins and incretin-related drugs might contribute to triggering the first phase of GSIS in the physiological state in vivo, since circulating levels of GLP-1 and GIP rise concomitantly with blood glucose after meal ingestion.

Conclusion

Since the first report of biphasic insulin secretion in response to glucose by Curry et al. (19), the dynamics of insulin secretion have been studied extensively in both normal and disease states such as diabetes and obesity using in vitro and in vivo systems. It is generally accepted that the abnormalities in the dynamics of insulin secretion, especially a defect in the first phase of GSIS, represent an early event in the development of T2DM. While studies so far have focused primarily on phenomenology of the dynamics of insulin secretion, the underlying cellular and molecular mechanisms can now be investigated by various approaches. Clarification of these mechanisms should yield novel therapeutic strategies as well as further understanding of the pathogenesis and pathophysiology of obesity and T2DM.

Acknowledgments

We are grateful to Kenneth Polonsky of the University of Chicago for careful reading of, and helpful suggestions for, the manuscript, and Mitsuo Fukushima of Okayama Prefectural University for helpful discussion. We also thank Grace Honkawa for assistance in the manuscript. This work was supported by a CREST grant from the Japan Science and Technology Agency and Grant-in-Aid for Scientific Research and by a grant for the Global Centers of Excellence Program “Global Center of Excellence for Education and Research on Signal Transduction Medicine in the Coming Generation” from the Ministry of Education, Culture, Sports, Science and Technology. The Obesity Review Series is supported in part by unrestricted educational grants from Merck & Co. and the Life Sciences Institute of the University of Michigan.

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