Demonstration of a Dawn Phenomenon in Normal Human Volunteers

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SUMMARY

To ascertain whether the dawn phenomenon occurs in nondiabetic individuals and, if so, whether it is due to an increase in glucose production or a decrease in glucose utilization, we determined plasma concentrations of glucose, insulin, C-peptide, and counterregulatory hormones, as well as rates of glucose production, glucose utilization, and insulin secretion at one-half-hourly intervals between 1:00 and 9:00 a.m. in eight normal volunteers. After 5:30 a.m., plasma glucose, insulin, and C-peptide concentrations all increased significantly; rates of glucose production, glucose utilization, and insulin secretion also increased (all $P < 0.05$). Plasma cortisol, epinephrine, and norepinephrine increased significantly from nocturnal nadirs between 4:00 and 6:30 a.m. Plasma growth hormone, which had increased episodically between 1:00 and 4:30 a.m., decreased thereafter nearly 50% ($P < 0.05$). Plasma glucagon did not change significantly throughout the period of observation. These results indicate that a dawn-like phenomenon, initiated by an increase in glucose production, occurs in nondiabetic individuals. Thus, early morning increases in plasma glucose concentrations and insulin requirements observed in IDDM and NIDDM may be an exaggeration of a physiologic circadian variation in hepatic insulin sensitivity induced by antecedent changes in catecholamine and/or growth hormone secretion. DIABETES 1984; 33:1150–53.

The dawn phenomenon is a condition, originally described in patients with insulin-dependent diabetes mellitus (IDDM), in which plasma glucose concentrations and/or insulin requirements that were stable throughout the night abruptly increase between 5:00 and 9:00 a.m. in the absence of antecedent hypoglycemia.[1–8] The condition is said to occur in up to 75% of IDDM patients, although its severity may vary from patient to patient and from day to day in the same patient.[8] Recently, this condition has also been found to occur with similar frequency and severity in both insulin-treated and non-insulin-treated patients with non-insulin-dependent diabetes mellitus (NIDDM).[8]

The mechanisms responsible for this phenomenon have not been established. Circulating concentrations of glucose counterregulatory hormones appear to be normal,[3,5–7] and suppression of the early morning increase in plasma cortisol does not prevent its occurrence.[5,7] Although evidence has been presented suggesting that an increase in insulin clearance may be responsible,[7] other possible mechanisms, such as altered sensitivity to nocturnal surges in growth hormone secretion[9] or early morning catecholamine release,[10] have not been excluded. Furthermore, it is not known whether increases in hepatic glucose production or decreases in peripheral glucose utilization are primarily involved.

The frequency with which this condition occurs in both NIDDM and IDDM patients suggests that it could simply represent an exaggeration of a normal diurnal rhythm in glucose homeostasis. Although glucose tolerance is known to undergo a circadian variation in both diabetic and nondiabetic subjects,[11,12] it has generally not been possible to identify early morning increases in plasma glucose or insulin concentrations suggestive of a dawn phenomenon in nondiabetic individuals.[13–16] Recently, however, Schmidt et al.,[17] using a continuous blood withdrawal technique, were able to demonstrate about a 30% increase in plasma insulin concentrations between 4:00 and 8:00 a.m. in nondiabetic subjects. These investigators postulated that this early morning increase in plasma insulin may represent the same chronobiologic phenomenon that occurs in diabetic patients who have the dawn phenomenon.

To test this hypothesis and the possible mechanism responsible for it in terms of changes in glucose production and glucose utilization, we determined plasma glucose, in-

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sulin, C-peptide, and counterregulatory hormone concentrations as well as rates of glucose turnover and insulin secretion in eight normal volunteers at one-half-hourly intervals from 1:00 a.m. through 9:00 a.m. Our results indicate that a phenomenon qualitatively similar to the dawn phenomenon occurs in nondiabetic individuals and that it is initiated by an increase in hepatic glucose production.

MATERIALS AND METHODS

Subjects. Informed, written consent was obtained from 8 male volunteers, aged 23–36 yr, who were within 10% of their ideal body weight and had no family history of diabetes mellitus. The subjects had been on a weight maintenance diet containing at least 200 g carbohydrate for a week before experiments.

Protocol. Subjects were admitted to the Metabolic Unit between 9:00 and 9:30 p.m., having had their last meal between 6:00 and 6:30 p.m. Subjects were placed at bedrest, and between 9:30 and 9:45 p.m. an antecubital vein on each arm was cannulated with an 18-gauge catheter (Abbott Ireland, Ltd., Sligo, Republic of Ireland). One vein was used for a primed (11 μCi), continuous (0.11 μCi/min) infusion of 3-^{3}H-glucose (New England Nuclear, Boston, Massachusetts) for isotopic determination of glucose production and utilization. The contralateral vein was used for intermittent blood sampling. All subjects remained asleep between midnight and 8:00 a.m.

Blood samples were taken at one-half-hourly intervals from 1:00 a.m. through 9:00 a.m. for determination of plasma glucose (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, California), glucose radioactivity,[18] insulin,[19] C-peptide,[20] glucagon,[21] growth hormone,[22] cortisol,[23] epinephrine,[24] and norepinephrine.[24] Rates of glucose production and glucose utilization were calculated according to a modification of the equations of DeBodo et al.[25] and were smoothed according to the method of Miles et al.[26] Insulin secretory rates were calculated based on changes in plasma C-peptide concentrations using a modification[27] of the model of Eaton et al.[28] Data in text and figures are given as means ± SEM. Statistical evaluations were performed using paired *t*-tests corrected for repeated measures.[29]

RESULTS

Plasma glucose, insulin, and C-peptide concentrations and rates of glucose production, glucose utilization, and insulin secretion (Figure 1). Plasma glucose concentrations remained relatively constant between 1:00 and 5:30 a.m. (89 ± 3 mg/dl) after which they increased slightly in all subjects to a maximum of 92 ± 3 mg/dl ($P < 0.05$). Plasma insulin (17 ± 2 μU/ml at 1:00 a.m.) decreased slightly until 5:30 a.m. (15 ± 2 μU/ml) after which it increased to a maximum of 18 ± 3 μU/ml at 9:00 a.m. ($P < 0.05$).

Glucose production decreased from 1.76 ± 0.14 mg/kg/min at 1:00 a.m. to 1.47 ± 0.12 at 5:30 a.m. ($P < 0.05$); afterward, it increased to a maximum of 1.64 ± 0.13 mg/kg/min at 9:00 a.m. ($P < 0.05$). Rates of glucose utilization followed a similar pattern, increasing significantly after 5:30 a.m. from 1.48 ± 0.12 to 1.68 ± 0.13 mg/kg/min at 9:00 a.m. ($P < 0.01$).

Plasma C-peptide decreased throughout the night to a nadir at 6:00 a.m. of 1.2 ± 0.15 ng/ml ($P < 0.05$) and subsequently increased to a maximum of 1.39 ± 0.14 ng/ml at 7:00 a.m. ($P < 0.01$). The calculated rates of endogenous insulin secretion followed a similar pattern, increasing from a nadir of 230 ± 30 μU/kg/min to a maximum of 300 ± 40 μU/kg/min at 7:00 a.m. ($P < 0.05$).

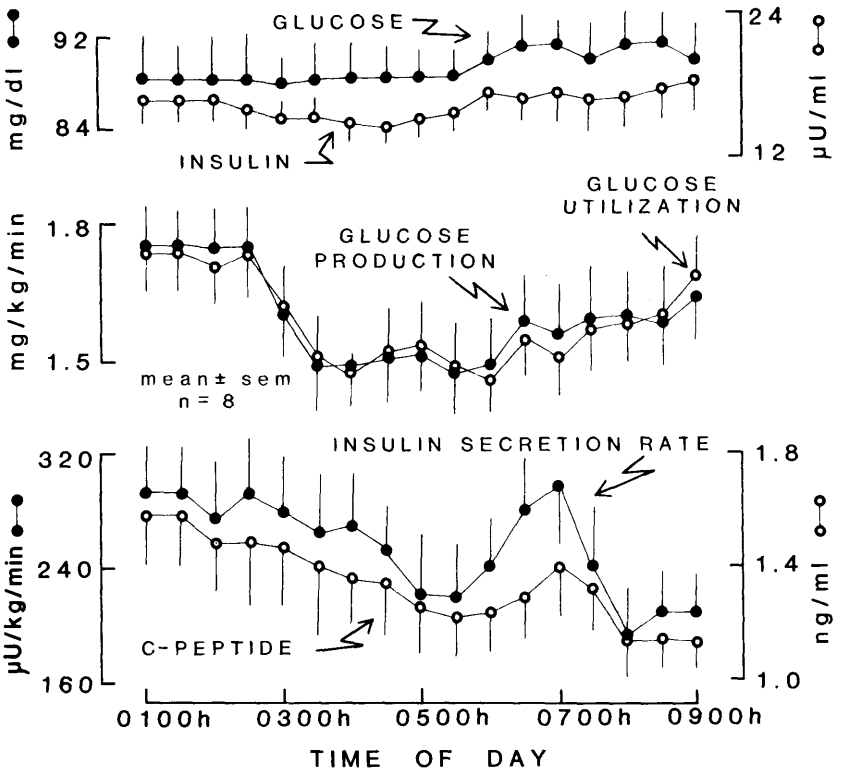

FIGURE 1. Plasma glucose, insulin, and C-peptide concentrations and rates of glucose production, glucose utilization, and insulin secretion between 1:00 and 9:00 a.m. in nondiabetic volunteers.

Plasma glucagon, cortisol, growth hormone, epinephrine, and norepinephrine concentrations (Figure 2). Plasma glucagon concentrations did not change significantly throughout the study. As expected, after decreasing slightly through the night, plasma cortisol increased after 3:00 a.m. (6.2 ± 0.6 μg/dl) to a maximum (13.9 ± 1.5 μg/dl) at 7:30 a.m. ($P < 0.01$). Intermittent increases in plasma growth hormone were observed in all subjects between 1:00 and 6:00 a.m.; afterward, such increases were observed in only 2 of the 8 subjects. Consequently, the mean plasma growth hormone concentration between 1:00 and 5:00 a.m. (3.5 ± 0.5 ng/ml) was nearly twice as great as that between 5:00 and 9:00 a.m. (1.9 ± 0.2 ng/ml, $P < 0.05$).

Plasma epinephrine concentrations remained constant until 3:30 a.m. (42 ± 6 pg/ml) after which they progressively increased to a maximum at 8:00 a.m. of 73 ± 6 pg/ml ($P < 0.01$). Plasma norepinephrine concentrations decreased in all subjects between 1:00 a.m. (185 ± 8 pg/ml) and 5:00 a.m. (164 ± 18 pg/ml, $P \leq 0.05$), but then progressively increased to a maximum of 289 ± 25 pg/ml at 9:00 a.m. ($P < 0.01$).

DISCUSSION

Our results demonstrate that a phenomenon occurs in normal individuals that is qualitatively similar to the dawn phenomenon observed in patients with NIDDM and IDDM.[1-8] We found increases in plasma insulin, C-peptide, and calculated insulin secretory rates accompanied by increases in plasma glucose concentrations that began shortly after 5:00 a.m. in normal volunteers. Our subjects remained asleep between midnight and 8:00 a.m., thus eliminating the stress of awaking as a possible explanation of these findings.

The increases in insulin secretion rates (~30%) that we observed are of similar magnitude to the increases in plasma insulin observed by Schmidt et al. in normal volunteers during a similar period of observation,[17] but are less than the increases in insulin requirements that have generally been observed after 5:00 a.m. during closed-loop insulin infusion in NIDDM and IDDM patients.[3,5,7,8] The latter could be due to the algorithms of the closed-loop devices, the lag time between changes in plasma glucose and compensatory alterations in insulin infusion rates, or greater sensitivity to factors responsible for the dawn phenomenon in diabetic patients.

The failure of other studies[13-16] to demonstrate early morning increases in plasma glucose or insulin concentrations in nondiabetic individuals is probably the result of infrequent sampling intervals and the imprecision of the assays used in these studies. Indeed, Schmidt et al.[17] had to resort to continuous blood sampling and larger sample volumes in their insulin assay to detect a significant increase in plasma insulin. In our study, we relied predominantly on changes in plasma C-peptide to detect changes in insulin secretion.

Presumably, an increase in arterial glucose concentrations was the major factor responsible for the increase in insulin secretion that we observed. This supposition is supported by the small increase that we found in venous plasma glucose concentrations. Such an increase in circulating glucose levels could have resulted from either an increase in glucose production or a decrease in glucose utilization. The fact that both glucose production and glucose utilization increased

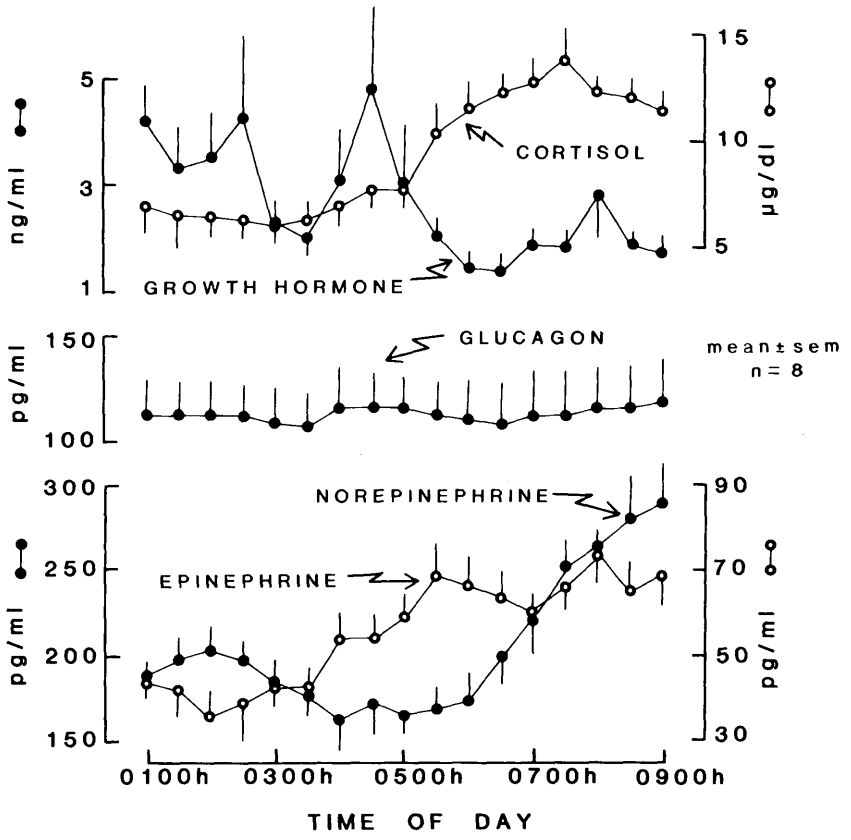

FIGURE 2. Plasma glucagon, cortisol, growth hormone, epinephrine, and norepinephrine concentrations between 1:00 and 9:00 a.m. in nondiabetic volunteers.

after 5:00 a.m. in the present study indicates that the increase in plasma glucose concentration was due to an increase in glucose production rather than to a decrease in glucose utilization.

The underlying mechanism for the dawn phenomenon has not been established. Recent studies[5,7] indicate that the early morning increase in plasma cortisol is probably not involved. An early morning increase in insulin clearance[7] also seems an unlikely mechanism in view of the increases in plasma insulin found by Schmidt et al.[17] and ourselves along with the increases in plasma C-peptide demonstrated in the present studies. Our observations, as well as those of Skor et al.[7] and Stene et al.,[9] of increases in plasma catecholamines (mainly norepinephrine) at a time anticipated to precede or coincide with initiation of the dawn phenomenon raise the possibility that adrenergic mechanisms may have been involved. Finally, it is also possible that surges in growth hormone secretion that occurred earlier in the evening may have subsequently decreased the sensitivity of the liver to insulin.[30] Either factor could have initiated an increase in glucose production, which was followed by an increase in insulin secretion as plasma glucose concentrations rose. Further studies are needed to explore these potential mechanisms.

In summary, the present studies demonstrate that rates of glucose production and insulin secretion increase after 5:00 a.m. in normal volunteers. These observations suggest that the dawn phenomenon observed in patients with diabetes mellitus may simply be an exaggeration of a normal circadian variation in hepatic sensitivity to insulin.

Note added in proof. Campbell et al.[31] and Arias et al.[32] have recently reported that nocturnal surges in growth hormone cause the dawn phenomenon in IDDM.

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