Aminophylline Stimulates Insulin Secretion in Patients With Type 2 Diabetes Mellitus

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In healthy subjects, paracrine factors partly regulate insulin secretion and basal endogenous glucose production. Administration of pentoxifylline, an adenosine receptor antagonist, inhibits transiently endogenous glucose production in healthy humans without any changes in glucoregulatory hormone concentrations. To evaluate the modulatory role of adenosine on endogenous glucose production and basal insulin secretion in type 2 diabetes, aminophylline, a potent adenosine receptor antagonist, was administered intravenously to 5 patients with type 2 diabetes mellitus in a saline-controlled study. Endogenous glucose production was measured before and during 6 hours after administration of aminophylline/saline by primed, continuous infusion of [6,6-$^2H_2$]glucose. During both experiments, the decrease in plasma glucose concentration was similar (16% *v* 18% from basal, not significant [NS]). After aminophylline administration, basal endogenous glucose production was transiently inhibited within 15 minutes to 70% from basal, whereas it did not change significantly in the control experiment (*P* = .02). The inhibition of glucose production coincided with stimulation of insulin secretion to 144% from basal 90 minutes after the administration of aminophylline (*P* = .008). In the control experiment insulin secretion decreased gradually by 29% during 6 hours. We conclude that aminophylline inhibits endogenous glucose production in type 2 diabetes by stimulation of insulin secretion. Paracrine factors, such as adenosine, may be involved in the regulation of basal insulin secretion in type 2 diabetes mellitus.

ENDOGENOUS GLUCOSE PRODUCTION is regulated predominantly by glucoregulatory hormones, mainly insulin, and by substrate supply.[1-3] In addition to these major regulatory mechanisms, in healthy adults, there are indications that other factors are involved in the modulation of basal endogenous glucose production, a process frequently referred to as autoregulation.[3] One of these factors involves the interaction between hepatocytes and Kupffer cells via mediators, such as adenosine. Adenosine is released in all tissues, including the liver[4-7] and the pancreatic islet.[7] In vitro, adenosine stimulates glycogenolysis in hepatocytes[8,9] through binding to the A_2 adenosine receptor, whereas in the pancreatic islet, binding to its A_1 purinergic receptor leads to inhibition of insulin secretion.[10,11] In vivo, adenosine antagonists, such as pentoxyfylline, inhibit basal endogenous glucose production in healthy humans without changes in glucoregulatory hormone concentrations.[12,13] In the pancreatic islet, aminophylline, another adenosine receptor antagonist, stimulates glucose and arginine-stimulated insulin release in healthy subjects.[14,15] These data indicate that mediators, such as adenosine, are involved in the regulation of basal endogenous glucose production, as well as in regulating stimulated insulin secretion.

In patients with type 2 diabetes mellitus, basal endogenous glucose production is inappropriately increased, considering the elevated glucose and insulin concentrations. In addition, regulation of endogenous glucose production by glucose per se seems to be impaired in type 2 diabetes mellitus.[16] It is currently unknown whether paracrine factors also influence basal endogenous glucose production and insulin secretion in patients with type 2 diabetes mellitus. Therefore, we evaluated the involvement of adenosine in the regulation of basal insulin secretion and glucose production in type 2 diabetes by measuring endogenous glucose production during intravenous administration of aminophylline, an adenosine receptor antagonist, in a saline-controlled study in 5 patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Subjects

Five patients with type 2 diabetes mellitus were studied. Their clinical characteristics are shown in Table 1.

Their mean glycosylated hemoglobin level was 7.2% ± 0.5%. Except for the presence of type 2 diabetes, they were otherwise healthy and taking no other medication known to affect glucose metabolism. None had been treated with insulin. Oral antidiabetic agents (only sulfonylurea) were discontinued 72 hours before the start of each study and reinstated directly after each study. All consumed a weight-maintaining diet of at least 250 g carbohydrate for 3 days before the study. Written informed consent was obtained from all the patients. The study was approved by the Institutional Ethics and Isotope Committees.

Study Design

Each subject served as his or her own control and completed 2 study protocols separated by at least 2 weeks (Fig 1). On 1 occasion, the subjects were studied during intravenous administration of aminophylline and on the other occasion during intravenous administration of saline (control experiment). The sequence of both studies was determined by random assignment. The subjects were studied in the postabsorptive state after a 14-hour fast. A 19-gauge catheter was inserted in a forearm vein for infusion of [6,6-$^2H_2$]glucose. Another 19-gauge catheter was inserted retrogradely into a wrist vein of the contralateral arm and maintained at 60°C in a thermoregulated plexiglas box for sampling of arterialized venous blood.

After obtaining a baseline sample for determination of background

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Table 1. Clinical Characteristics

Patient No.	Sex/Age (yr)	BMI (kg/m^2)	Glyc Hb (%)	FPG (mmol/L)	FPI (pmol/L)
1	M/65	28.4	7.8	8.8	75
2	F/54	29.1	8.5	11.0	95
3	F/67	33.2	7.0	8.3	80
4	M/64	32.4	7.1	8.5	210
5	M/69	21.3	5.7	7.6	115
Mean ± SE	3/2 63.8 ± 2.6	28.9 ± 2.1	7.2 ± 0.5	8.8 ± 0.6	115 ± 25

Abbreviations: BMI, body mass index; Glyc Hb, glycosylated hemoglobin; FPG, mean fasting plasma glucose concentration after a 17-hour fast; FPI, mean fasting plasma insulin after a 17-hour fast.

isotopic enrichment and plasma glucose concentration, a primed, continuous (0.22 μmol/kg/min) infusion of [6,6-$^2H_2$]glucose (99% Isotec, Miamisburg, OH) dissolved in sterile isotonic saline and sterilized by passage of the solution through a Millipore filter (0.2 mm, Minisart; Sartorius, Gottingen, Germany) was started and continued throughout the study. The priming dose was increased according to the formula derived by Hother-Nielsen et al[17]: adjusted prime = normal prime (17.6 μmol/kg) × [actual plasma glucose concentration (mmol/L)/5 (= normal plasma glucose)].

Fasting plasma glucose concentration was measured at the bedside using a Precision Q.I.D.Ô glucometer (Medisense, Abbott Laboratories, Chicago, IL). After 165 minutes of [6,6-$^2H_2$]glucose infusion, 3 blood samples were collected at 5-minute intervals for determination of the plasma glucose concentration and [6,6-$^2H_2$]glucose enrichment. Blood samples for measurement of basal plasma concentrations of insulin, C-peptide, and counterregulatory hormones were also collected after 175 minutes of isotope infusion (= 5 minutes before the intervention).

At time = 0, after a 3-hour equilibration period of [6,6-$^2H_2$]glucose infusion, either aminophylline (Euphyllin, Byk, The Netherlands, priming dose, 5.6 mg/kg infused during 20 minutes followed by 0.45 mg/kg/min) or isotonic saline was administered for 6 hours intravenously. Blood samples for measurement of plasma glucose concentration, glucose isotopic enrichment, and glucoregulatory hormones were obtained every 15 minutes for the first 2 hours after the intervention and every hour thereafter until the end of the studies. Blood samples for free fatty acids (FFA) were collected at time 0, 45 minutes and 6 hours after the intervention.

Assays

All measurements were performed in duplicate, and all samples from each individual subject were analyzed in the same run. The glucose concentration and [6,6-$^2H_2$]glucose enrichment in plasma were measured by gas chromatography/mass spectrometry using selected ion monitoring. The method was adapted from Reinauer et al[18] using phenyl-β-D-glucose as internal standard.

Plasma insulin concentration was measured by commercial radioimmunoassay (RIA) (Pharmacia Diagnostics AB, Uppsala, Sweden), C-peptide by ^{125}I-RIA (Byk Santec, Dietzenbach, Germany), plasma cortisol levels by enzyme-immunoassay on an Immulite analyzer (DPC, Los Angeles,CA), glucagon by RIA (Linco Research, St. Charles, MO), and plasma epinephrine and norepinephrine by high-performance liquid chromatography with fluorescence detection, using α-methylnorepinephrine as internal standard.

Calculations and Statistics

The rate of endogenous glucose production was calculated by the non–steady-state equations of Steele[19] in their derivative form, since it is known that in patients with type 2 diabetes, the fasting state is not a steady state.[17] The effective distribution volume for glucose was assumed to be 165 mL/kg.

Results are reported as the mean ± SEM. Baseline values for plasma glucose concentration, [6,6-$^2H_2$]glucose enrichment, and endogenous glucose production are reported as the mean of 3 samples taken at 5-minute intervals. Baseline hormone values are reported as the mean of the 2 samples taken at t = −5 minutes and t = 0.

Data were analyzed by a 2-sided nonparametric test for paired samples (Wilcoxon signed-rank test). Data within the groups were analyzed by analysis of variance (ANOVA) for randomized block design. A *P* value less than .05 was considered to represent a statistically significant difference.

RESULTS

Glucose Kinetics

Basal plasma glucose concentrations were significantly different between the 2 experiments (9.4 ± 0.7 mmol/L and 8.2 ± 0.5 mmol/L, aminophylline *v* control) (Fig 2). However, in both the control experiment, as well as after administration of aminophylline, the decrease in plasma glucose concentration during the 6-hour observation period was similar (16% and 18% from basal, not significant [NS] between both studies).

Basal endogenous glucose production was not significantly different between the 2 experiments (9.4 ± 0.9 μmol/kg/min and 9.9 ± 1.2 μmol/kg/min, aminophylline and control, respectively [NS]). During the control experiment, endogenous glucose production did not change significantly. Within 15 minutes after starting the administration of aminophylline,

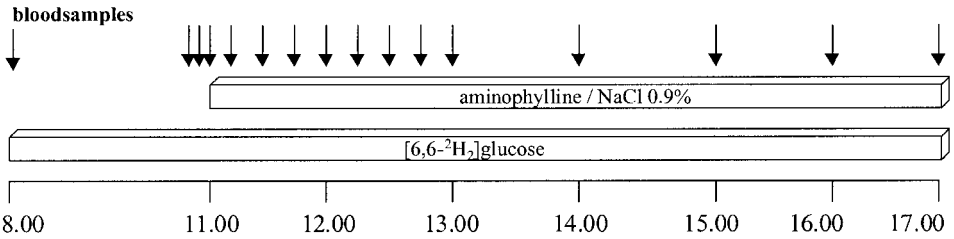

Fig 1. Study design.

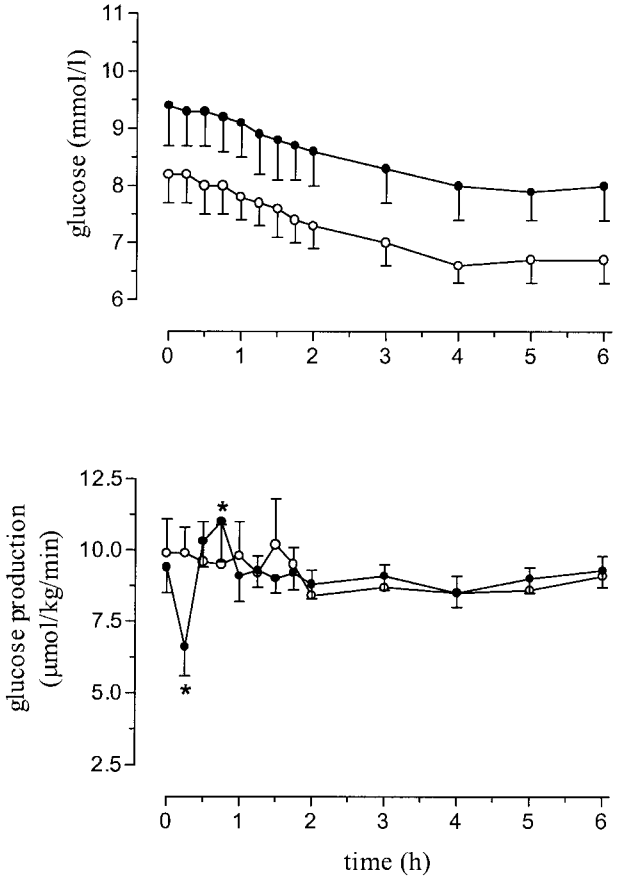

Fig 2. Plasma glucose concentration and endogenous glucose production during aminophylline (●) and saline (○). *Represents a statistically significant difference and change between the groups. Data are expressed as mean ± SEM.

endogenous glucose production was inhibited transiently to 70% from basal (nadir, 6.6 μmol/kg/min) ($P = .02$). Subsequently, glucose production increased to a maximum of 11.0 ± 1.4 μmol/kg/min, 45 minutes after the administration of aminophylline ($P = .024$ *v* control).

Hormone Concentrations

Baseline values of insulin, C-peptide, and counterregulatory hormones were not different between the 2 studies (Figs 3 and 4). In the control experiment, plasma insulin and C-peptide concentrations decreased gradually in all patients by 28% from baseline (111 ± 26 to 79 ± 21 pmol/L, $P = .01$) and by 32% from baseline (1,310 ± 89 to 884 ± 249 pmol/L, $P = .001$).

After administration of aminophylline, plasma insulin, as well as C-peptide concentrations, increased in all patients by 44% from baseline (117 ± 24 to a maximum at t = 1.5 hours of 169 ± 31 pmol/L, $P = .008$ *v* control) and by 24% from baseline (1,334 ± 244 to 1,648 ± 245 pmol/L, $P = .003$). At the end of the aminophylline study, plasma insulin concentrations were still significantly higher than in the control experiment (114 ± 22 *v* 79 ± 21 pmol/L) ($P = .008$ at t = 6 hours, aminophylline *v* control). Plasma C-peptide concentrations declined more rapidly and were not significantly different from the control experiment at the end of the study (1,168 ± 214 *v* 884 ± 244 pmol/L) ($P = .06$ *v* control).

Basal plasma levels of glucagon, cortisol, adrenaline, and noradrenaline were not significantly different between the 2 studies, and no significant differences were observed during both experiments, although there was a trend for an increase in plasma cortisol after the start of the aminophylline infusion ($P = .061$) (Fig 4).

Basal levels of FFA were not different between the 2 studies (0.78 ± 0.03 *v* 0.70 ± 0.06 mmol/L, aminophylline *v* control). During the control experiment, plasma FFA concentrations did not change significantly (0.78 ± 0.03 to 0.88 ± 0.08 mmol/L), whereas during administration of aminophylline, plasma FFA concentrations increased 33% (to 0.93 ± 0.11 mmol/L, $P = .034$).

Aminophylline serum concentrations were all in the range of 10 to 20 mg/L at t = 30 minutes, t = 2 hours, as well as at t = 6 hours.

DISCUSSION

Administration of aminophylline to patients with type 2 diabetes mellitus stimulated insulin secretion, reflected in the increased insulin and C-peptide levels. This was associated

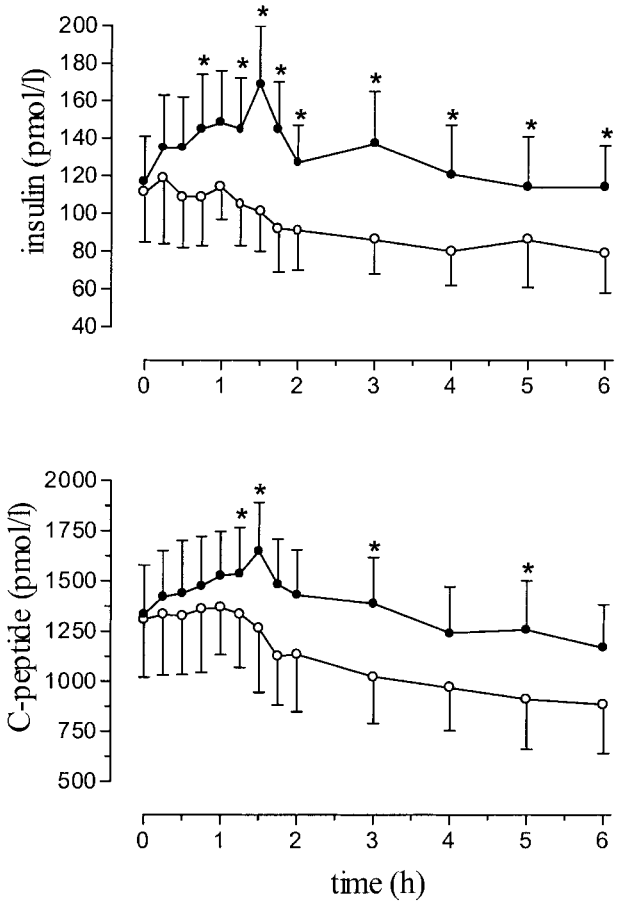

Fig 3. Plasma insulin and C-peptide concentrations during aminophylline (●) and saline (○). *Represents a statistically significant difference between the groups. Data are expressed as mean ± SEM.

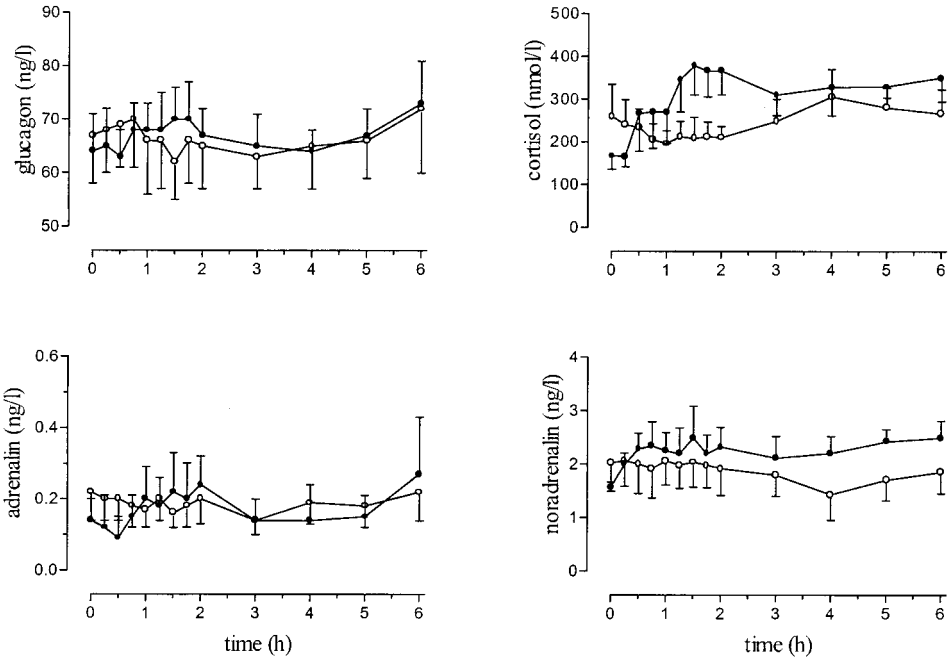

Fig 4. Plasma glucagon, cortisol, adrenalin, and noradrenalin concentrations during aminophylline (●) and saline (○). *Represents a statistically significant difference between the groups. Data are expressed as mean ± SEM.

with a transient decrease in endogenous glucose production of 30% without affecting plasma glucose concentrations. Because aminophylline is an adenosine receptor antagonist, these data indicate that adenosine may inhibit postabsorptive insulin secretion in patients with type 2 diabetes mellitus.

The effects of aminophylline on insulin secretion were described in the late 1960s by Cerasi et al.[14] Aminophylline, infused for 1 hour before a glucose infusion test, did not influence basal insulin secretion, but augmented glucose-induced insulin secretion significantly in a subgroup of healthy subjects, but not in patients with type 2 diabetes.[14] Later, similar effects of aminophylline on arginine-stimulated insulin secretion were found by Pontiroli et al[15] in healthy subjects. Recently, adenosine-specific G-protein–linked membrane receptors with different subtypes, A_1,A_{2a}, A_{2b}, and A_3, were found. The subtypes, which are products of separate genes, differ in their influence on cell metabolism and tissue distribution.[20] In the pancreatic islet, the A_1 receptor predominates and in the liver, the A_2 receptor. Whereas A_1 and A_3 receptors transduce signals via G_i and G_o, the A_2 receptor interacts with G_s. Binding of extracellular adenosine to its receptor may lead to either inhibition or stimulation of adenylate cyclase, dependent on the tissue of action. Bertrand et al[10] proposed that the physiologic role of adenosine in the pancreatic islet is to attenuate the amplification of insulin release, induced via cyclic adenosine monophosphate (cAMP).[10] The effect of aminophylline on basal insulin secretion in vivo in humans has been studied in healthy subjects in only 3 studies. Cathcart-Rake et al[21] studied 13 healthy subjects during administration of aminophylline with similar plasma aminophylline levels compared with the present study (10 to 20 μg/mL). They observed small increases in plasma glucose levels without any changes in plasma concentrations of insulin or other glucoregulatory hormones.[21] In accordance, Jenkins and Marlin[22] found no short-term effect of low-dose aminophylline (30 minutes at an infusion rate of 0.2 mg/kg/min) on glucose or insulin concentrations in 4 healthy volunteers. In contrast, Vestal et al[23] studied 6 postabsorptive healthy males during 4 different infusion rates of aminophylline, reaching theophylline concentrations between 4.5 and 20 μg/mL, respectively. They observed dose-related increases in plasma concentrations of glucose and insulin.[23] Endogenous glucose production was not measured in any of those studies. Finally, another adenosine receptor antagonist, pentoxifylline, did not alter plasma insulin concentrations during an observation period of 7 hours in healthy subjects.[12,13] Thus, in healthy humans, the effects of adenosine-receptor antagonists on basal insulin are limited. The role of adenosine thus appears to be different under basal versus insulin-stimulated conditions. We therefore performed these experiments in patients with type 2 diabetes mellitus, who are characterized by stimulated basal insulin secretion.

The basal values of glucose production and hormone levels were similar in both experiments. Plasma glucose levels, however, were slightly lower in the control experiment. Nonetheless, this does not affect our conclusion with respect to the effect of aminophylline on insulin secretion. During short-term starvation, insulin secretion decreases in patients with type 2 diabetes[24,25] as in healthy subjects, in contrast to the observed increase in plasma insulin concentrations during aminophylline infusion found in our postabsorptive patients with type 2 diabetes mellitus. In healthy subjects, pentoxyfylline, another adenosine receptor antagonist, inhibits glucose production without any effect on plasma glucose concentration or glucoregulatory hormones.[12,13] In patients with type 2 diabetes mellitus, the inhibitory effect of aminophylline on basal glucose production was similar to that in healthy subjects, but was associated with increased insulin levels. Despite a significant increase in insulin concentrations and transient decrease in the

production of glucose, plasma glucose concentrations declined at a similar rate during aminophylline administration, as during the control experiment. Apparently, the rate of glucose uptake decreased in response to aminophylline administration. This is in accordance with recent in vitro data indicating that adenosine can stimulate insulin-stimulated glucose uptake[26] by enhancing the increase in GLUT4 at the cell surface of rat skeletal muscle, a process that can be blocked by administration of adenosine deaminase.[27] Administration of an adenosine receptor antagonist, such as aminophylline, can thus increase peripheral insulin resistance.

Plasma FFA levels increased during aminophylline administration despite increased insulin levels, increasing peripheral insulin resistance even further. These observations are in line with inhibitory effects of adenosine on lipolysis,[28,29] as well as with inhibition of phosphodiesterase by aminophylline.[30] Increased FFA levels can also result from enhanced lipolysis through sympathetic stimulation, since adenosine may also inhibit norepinephrine release from sympathetic nerve endings.[31] Plasma norepinephrine levels did not increase significantly after aminophylline administration, but it is well known that these levels markedly underestimate sympathetic activation. Finally, increasing FFA concentrations have a direct stimulatory effect on insulin secretion.[32]

Since increasing portal insulin concentrations inhibit basal glucose production, it is likely that in our patients with type 2 diabetes, the inhibitory effect on glucose production is the result of stimulation of insulin secretion by aminophylline. However, the rapid and transient inhibition of glucose production did not completely coincide with the increase in insulin levels, whereas previously in patients with type 2 diabetes, we observed a close correlation in time between a decrease in peripheral insulin and C-peptide concentrations and an increase in glucose production.[33] Moreover, aminophylline was found to induce a decrease in hepatic blood flow,[34] which would also result in sudden changes in percent enrichment and therefore in calculated rates of endogenous glucose production. Adenosine-specific receptors, however, are present in the liver. An additional direct intrahepatic effect of adenosine on basal endogenous glucose production can therefore not be excluded.

This potential inhibitory effect of aminophylline on endogenous glucose production in vivo in humans is different from the stimulatory effect on glucose production found in rats in vivo. Aminophylline increased hepatic glucose production, as well as insulin secretion in rats.[35] This difference between humans and rodents suggests interspecies differences in post-absorptive glucoregulation, a feature that has been documented with respect to the glucoregulatory effects of another paracrine mediator, prostaglandines.

Aminophylline appears to have multiple effects and inhibits phosphodiesterase, in addition to blocking adenosine receptors. It is unlikely, however, that the inhibition of endogenous glucose production was due merely to inhibition of phosphodiesterase by aminophylline. For instance, Rizza et al[36] showed that theophylline stimulated rather than inhibited endogenous glucose production in the presence of glucagon in healthy subjects.

In conclusion, aminophylline stimulates insulin secretion associated with transient inhibition of endogenous glucose production in patients with type 2 diabetes mellitus. This observation indicates that basal insulin secretion is actively inhibited in patients with type 2 diabetes mellitus by mechanisms that involve factors, such as adenosine.

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