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Impaired Increase of Plasma Abscisic Acid in Response to Oral Glucose Load in Type 2 Diabetes and in Gestational Diabetes

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ABSTRACT

The plant hormone abscisic acid (ABA) is present and active in humans, regulating glucose homeostasis. In normal glucose tolerant (NGT) human subjects, plasma ABA (ABAp) increases 5-fold after an oral glucose load. The aim of this study was to assess the effect of an oral glucose load on ABAp in type 2 diabetes (T2D) subjects. The increase of ABAp in response to glucose was found to be abrogated in T2D patients compared to NGT controls. A similar result was observed in the women with GDM compared to pregnant NGT controls; 8–12 weeks after childbirth, however, fasting ABAp and ABAp response to glucose were restored to normal in the GDM subjects, along with glucose tolerance. These results indicate an impaired hyperglycemia-induced ABAp increase in T2D and in GDM and suggest a beneficial effect of elevated ABAp on glycemic control.

Introduction

The phytohormoneabscisic acid (ABA) lies at the interface between abiotic stress and metabolic signaling in plants, regulating vital functions [1]. Interestingly, ABA was found to play a conserved role as a "stress hormone" also in lower Metazoa, regulating animal responses to temperature and light [2, 3], and in mammals, regulating the activation of innate immune cells [4, 5] and glucose homeostasis [6–8].

ABA also stimulates GLUT4-mediated glucose uptake by adipocytes and myoblasts [7]. ABA role in glucose homeostasis prompts the hypothesis that diabetes mellitus is associated with an impaired ABA response

Methods

Study subjects and sampling procedures

The study of ABAp in T2D included a total of 50 subjects. Eleven of them had impaired fasting glucose levels and underwent a standard oral glucose tolerance test (OGTT) for diagnostic purposes after overnight fasting. Plasma samples were collected immediately before (time zero) and 15, 30, 60, 90, and 120 minutes after ingestion of 75 g glucose. Two-ml plasma samples for each time point were immediately frozen in the presence of 4 vol distilled methanol for subsequent ABAp measurement. Glucose, insulin, and ABAp were then measured in 9 out of the 11 subjects, who were diagnosed with T2D on the basis of the result of the OGTT.

Out of the 16 women studied, 9 were diagnosed with GDM, based on the finding of plasma glucose values ≥180 mg/dL or ≥153 mg/dL 1 or 2 hours after the glucose load, respectively [11]. None of the women reported a change in her dietary habits after childbirth.

In the retrospective part of the study, ABAp was measured in frozen plasma samples from 20 severely obese patients who had undergone BPD within a clinical study and had their blood withdrawn 1 week before and 1 month after surgery [12]. Nine subjects had T2D before BPD, while the others had normal FPG levels and served as controls. FPG and insulin concentrations had been determined at the time of sample collection.

The area-under-the-curve (AUC) values of plasma ABA, glucose and insulin were calculated with the trapezoidal rule, from the concentrations measured at the time points indicated in the legends to Table 1and Table 2.

1. Impaired increase of the ABAp during OGTT in T2D patients.

	NGT	T2D	p
N	7	9	
Age (years)	58.1±6.2	60.2±10.2	0.642
BMI (kg/m²)	30.2±6.1	27.7±4.4	0.342
FPG (mg/dL)	95.4±12.6	145.8±39.6	0.007
Fasting ABAp	0.97±0.36	1.75±1.02	0.040
(nM)	0.99 (0.38–1.54)	1.61 (0.35–3.42)	
ABA AUC (nmol/L*min)	121.7±33.9	68.3±44.3	0.019
Glucose AUC (mg/dL*min)	18550±4422	30694±6129	<0.001
Insulin AUC (mU/L*min)	6998±910	8192±2724	0.155

Impaired increase of the ABAp during OGTT in T2D patients.

Higher fasting ABAp in T2D patients compared to NGT controls.

	NGT	T2D	p
N	27	21	
BMI (kg/m²)	26.3±6.3	29.9±7.7	0.197
FPG (mg/dL)	84.6±32.4	140.4±57.6	0.003
Fasting ABAp (nM)	0.74±0.45	1.68±1.44	0.003
	0.66 (0.13–1.72)	1.15 (0.19–4.77)	0.013

Higher fasting ABAp in T2D patients compared to NGT controls.

Results

Impaired increase of plasma ABA after glucose load in T2D subjects

Consistent with the experimental evidence supporting a role of ABA in promoting glucose disposal, ABAp increases following an oral glucose load in healthy individuals [7].

Diminished increase of ABAp after oral glucose load in GDM is followed by postpartum restoration of the ABAp response to hyperglycemia and resolution of diabetes

Diminished increase of ABAp after oral glucose load in GDM and reversal to normal after childbirth.

		NGT			GDM		
N		**7**			**9**		**p**
BMI (kg/m²)		**24.9±3.1**			**25.5±4.9**		**0.767**
Age (years)		**37.0±3.7**			**37.1±1.4**		**0.934**
	prepartum		**postpartum**	**prepartum**		**postpartum**	**p**
FPG (mg/dL)	**72.4±7.2**	*p* = **0.117**	**67.9±9.3**	**80.7±5.8**	*p* = **0.007**	**70.3±11.1**	**0.015*** 0.631#
Fasting ABAp (nM)	**1.15±0.69**	*p* = **0.011**	**2.33±1.49**	**0.54±0.62**	*p* = **0.0002**	**2.39±0.98**	**0.043*** 0.708#
ABA AUC (nmol/L*min)	**191.2±78.3**	*p* = **0.113**	**298.3±105.2**	**79.4±56.9**	*p* = **0.011**	**376.5±98.9**	**0.033*** 0.113#
Glucose AUC (mg/dL*min)	**12604±256**	*p* = **0.686**	**12116±2182**	**15546±2066**	*p* = **0.022**	**12258±3084**	**0.015*** 0.914#
Insulin AUC (mU/L*min)	**5984±2942**	*p* = **0.284**	**4911±1889**	**7465±3406**	*p* = **0.015**	**5438±3641**	0.237* 0.894#

Diminished increase of ABAp after oral glucose load in GDM and reversal to normal after childbirth.

Interestingly, pre-partum fasting ABAp was significantly lower in GDM subjects (0.54±0.62 nM, n = 10) compared to NGT controls (1.15±0.69 nM, n = 12, *p* = **0.043). After childbirth, ABAp increased significantly in both NGT and GDM subjects, in the latter ones reaching control values (**Table 3).

Increased basal ABAp and decreased fasting glycemia in obese NGT and T2D subjects after BPD.

Discussion

The main finding of the prospective part of this study is that the increase in ABAp that normally occurs after an oral glucose load is impaired both in patients with T2D and in women with GDM.

Concerning the tissue source of plasmatic ABA, pancreatic β-cells and adipocytes are both capable of releasing ABA upon stimulation with glucose *in vitro* [7], and the higher cell mass of the adipose tissue might make it an important determinant to fasting ABAp, particularly in obese subjects. Interestingly, the limited (approximately 10 and 15% in NGT and T2D subjects, respectively) reduction of body weight that occurred in both NGT and T2D subjects within the first month after BPD was associated with an increase, not a decrease, of ABAp (Table 4). This observation suggests an inhibitory effect on ABA secretion of one or more adipokines released from adipose tissue that is most readily lost after BPD.

BPD causes a substantial reduction in nutrient absorption in the small intestine [13]. Therefore, an alternative possibility is that stimulation of enteroendocrine cells by excess non-absorbed nutrients may result in an increased release of GLP-1 [14, 15], which in turn can stimulate ABA secretion from β-pancreatic cells [7]. Both hypotheses open new intriguing areas of investigation.

The higher mean value and wider distribution of the fasting ABAp in the T2D subjects compared to the NGT controls (Table 2) do not appear to be correlated with age or BMI in the T2D group and may reflect a heterogeneity of ABA-related dysfunctional mechanisms occurring in T2D, such as resistance to the glycemia-lowering effect of ABA (causing higher-than-normal basal ABAp levels), or impairment of the molecular mechanisms regulating the increase of ABAp in response to hyperglycemia (causing ABAp levels to be in the normal range despite hyperglycemia). At variance with what observed in T2D subjects, the fasting ABAp of the GDM subjects was lower compared to the NGT controls: this observation may suggest insufficient ABA release in response to hyperglycemia as the common pathogenetic mechanism underlying ABA dysfunction in GDM.

The demonstration that plasma ABA is altered/abnormal in T2D and GDM suggests a role for the dysregulation of ABAp response to hyperglycemia in the pathophysiology of these conditions and warrants further studies to test the new mechanistic hypotheses arising from this study.

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