Exaggerated Pancreatic Polypeptide Secretion in Pima Indians: Can an Increased Parasympathetic Drive to the Pancreas Contribute to Hyperinsulinemia, Obesity, and Diabetes in Humans?

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Vagally-mediated hyperinsulinemia is a common abnormality in various rodent models of genetic and hypothalamic obesity that have a high propensity for type 2 diabetes. We hypothesized that Pima Indians, a population with a high prevalence of hyperinsulinemia, obesity, and type 2 diabetes also have an increased parasympathetic drive to the pancreas. To test this, we measured plasma concentrations of insulin and pancreatic polypeptide (PP), a surrogate marker of pancreatic vagal tone, in lean and obese Pima Indian and Caucasian children (n = 43, 26P/17C, 7 ± 1 y) and adults (n = 92, 61P/31C, 31 ± 5 y). Pima Indian children had ~2-fold higher fasting insulin and 57% higher fasting PP concentrations than age- and sex-matched Caucasian children (*P* < .05). Although there was no difference in fasting PP concentration between Pima Indian and Caucasian adults, in response to a mixed meal, Pima Indians had a 51% higher early (30 minutes) PP concentration and 2-fold higher early insulin concentration than Caucasians (*P* < .05). PP concentrations at 60 minutes and 120 minutes after the meal were also markedly higher in both lean and obese Pima Indians compared with lean and obese Caucasians. These results suggest that Pima Indians may have an increased parasympathetic drive to the pancreas, which could lead to a primary hypersecretion of insulin and contribute to their high propensity for obesity and diabetes, as is the case in various rodent models of obesity.

THE PIMA INDIANS of Arizona have among the highest reported prevalence rates of obesity and type 2 diabetes in the world.[1] Like several other ethnic groups with a high propensity for obesity and diabetes,[2,3] Pima Indians are characterized by marked insulin resistance and hyperinsulinemia.[4,5] The hyperinsulinemia of Pima Indians appears to be an early abnormality, because Pima Indian children have higher fasting insulin concentrations than Caucasian children of similar age and weight.[6] Prospective studies have established the pathophysiologic importance of hyperinsulinemia as a high fasting insulin concentration predicts the development of both obesity and diabetes in Pima Indian children.[7,8] In Pima Indian adults, fasting hyperinsulinemia also predicts diabetes, an effect that we recently showed is independent of insulin resistance.[9] The reason for the hyperinsulinemia in Pima Indians remains unknown. To a certain extent, the higher fasting insulin concentrations is likely a secondary adaptation to the high degree of adiposity and insulin resistance.[4] This is unlikely the only explanation, however, because Pima Indians are more hyperinsulinemic than Caucasians, even after accounting for their higher degree of adiposity and insulin resistance.[9] Alternatively, the marked hyperinsulinemia in Pima Indians could, at least in part, be the result of a primary hypersecretion of insulin that might be a cause rather than a consequence of their adiposity and insulin resistance.

Fasting hyperinsulinemia is also a common abnormality of various animal models of genetic or hypothalamic obesity with a high propensity for diabetes, such as the ob/ob mouse,[10] the fa/fa rat,[11,12] and rodents with lesions of the ventromedial hypothalamus (VMH).[13-21] In these animals, the hyperinsulinemia is thought to be in large part due to an exaggerated parasympathetic drive to the pancreas, because administration of parasympathicolytic drugs such as atropine,[14,15] truncal vagotomy,[17-20] or islet cell transplantation[21] can almost completely normalize insulin levels and delay or even prevent the development of obesity and diabetes.

In humans, the parasympathetic nervous system (PNS) is also involved in the regulation of insulin secretion.[22-25] Whether an increased parasympathetic drive to the pancreas contributes to hyperinsulinemia, obesity, and diabetes in humans and whether Pima Indians and/or other obesity and diabetes prone populations may have an increased parasympathetic drive to the pancreas is unknown. However, a small study conducted some 15 years ago suggested that lean Pima Indians might have increased plasma concentrations of pancreatic polypeptide (PP).[26] While this original finding was not interpreted in the context of vagal control of insulin secretion, there is now good evidence that plasma PP concentrations can serve as a surrogate measure of the parasympathetic drive to the pancreas.[27-32] From this new point of view, an increased PP concentration in Pima Indians would be of considerable pathophysiologic interest indicating that an increased parasympathetic drive to the pancreas might contribute to their hyperinsulinemia and propensity for obesity and diabetes.

To further examine this question, we measured fasting and postprandial plasma PP and insulin concentrations in a large group of Pima Indian and Caucasian adults and children.

SUBJECTS AND METHODS

Subjects

A total of 87 Pima Indians and 48 Caucasians, on whom plasma samples were obtained as part of previous studies of the pathogenesis of obesity and diabetes were included in this analysis (Table 1). All subjects were nondiabetic,[33,34] healthy according to a physical examination and routine laboratory tests, and none smoked or took medica-

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Table 1. Physical and Metabolic Characteristics of the Study Population

	Study 1							
	Pima Indians		Caucasians		Study 2		Study 3	
	Lean	Obese	Lean	Obese	Pima Indians	Caucasians	Pima Indians	Caucasians
No., sex (F/M)	7 (3/4)	8 (4/4)	7 (3/4)	8 (4/4)	46 (9/37)	16 (4/12)	26 (12/14)	17 (9/8)
Age (y)	33 ± 4^{A}	32 ± 5^{A}	32 ± 11^{A}	30 ± 7^{A}	27 ± 6	32 ± 8†	6.5 ± 1.0	6.8 ± 0.9
Height (cm)	166 ± 7^{A}	172 ± 8^{B}	169 ± 6^{B}	171 ± ^{B}	169 ± 8	171 ± 11	124 ± 9	118 ± 8†
Body weight (kg)	70.3 ± 9.6^{A}	109.0 ± 15.2^{B}	71.4 ± 9.8^{A}	109.8 ± 16.8^{B}	92.0 ± 19.6	90.7 ± 24.4	31.5 ± 10.4	24.3 ± 4.3†
BMI (kg/m^2)	24.0 ± 1.9^{A}	37.9 ± 6.6^{B}	25.4 ± 2.3^{A}	38.2 ± 4.8^{B}	32.1 ± 6.6	31.1 ± 8.9	20.1 ± 4.9	15.4 ± 1.4†
Body fat (%)	24 ± 7^{A}	35 ± 5^{B}	22 ± 9^{A}	35 ± 7^{B}	29 ± 8	27 ± 10	28 ± 8	16 ± 7‡
Fat mass (kg)	16.9 ± 5.7^{A}	38.5 ± 9.5^{B}	15.8 ± 6.2^{A}	38.3 ± 12.7^{B}	27.6 ± 11.5	26.2 ± 15.6	13.4 ± 3.7	4.7 ± 1.3†
Fat-free mass (kg)	53.4 ± 7.5^{A}	70.5 ± 7.6^{B}	55.6 ± 9.2^{A}	71.5 ± 11.5^{B}	64.4 ± 11.4	64.5 ± 12.7	18.1 ± 4.0	19.6 ± 4.4
Waist-to-thigh ratio	1.56 ± 0.15^{A}	1.66 ± 0.15^{B}	1.55 ± 0.09^{A}	1.62 ± 0.09^{B}	1.65 ± 0.15	1.49 ± 0.10‡	1.44 ± 0.11	1.44 ± 0.12†
Fasting glucose (mmol/L)	4.9 ± 0.4^{A}	5.3 ± 0.4^{B}	4.8 ± 0.4^{A}	5.1 ± 0.3^{B}	4.6 ± 0.5	4.6 ± 0.5	4.5 ± 0.4	4.9 ± 0.6‡

NOTE. Mean ± SD. Group comparisons were adjusted for age and sex. Study 1, variables not sharing a common character (A or B) are significantly different ($P < 0.05$).

Studies 2 and 3, symbols indicate significant ethnic differences († $P < .01$, ‡ $P < .001$).

tions, which affect the cholinergic system or glucose or insulin metabolism at the time of the study. The study protocol was approved by the Tribal Council of the Gila River Indian Community and by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases and all subjects (or their parents) provided written informed consent.

Study 1: Overall PP and Insulin Responses to a Mixed Meal in Adults

In a first study, plasma PP and insulin concentrations were measured in 15 Pima Indian and 15 Caucasian adults before and hourly for 4 hours after a standardized mixed meal. Subjects in this study, which was originally conducted to examine ethnic differences in fasting and postprandial plasma concentrations of acylation stimulating protein,[35] were closely matched for age, sex, and body weight with each ethnic group being comprised of 7 lean and 8 obese subjects (Table 1). Obesity was defined as a body mass index (BMI) above 30 kg/m^2 according to the 1995 World Health Organization (WHO) criteria.[36]

Study 2: Early PP and Insulin Responses to a Mixed Meal in Adults

Postprandial PP responses show a biphasic pattern with an early (10 to 30 minutes) first phase that was not assessed in study 1. This and the fact that hyperinsulinemia in Pima Indians is particularly evident at early time points after glucose ingestion[5] led us measure plasma PP and insulin concentrations in samples from a second study in 46 Pima Indian and 16 Caucasian adults before and at 30 minutes after the same standardized mixed meal. Samples for this study had been obtained from a longitudinal study of the pathogenesis of diabetes.[37]

Study 3: Fasting PP and Insulin Concentrations in Children

Because hyperinsulinemia in Pima Indians is present at a young age[6] and because vagally-mediated insulin hypersecretion is an early abnormality in animal models of obesity,[10-21] we measured fasting plasma PP and insulin concentrations in samples from a third study in 26 Pima Indian and 17 age- and sex-matched Caucasian children, all between 5 and 8 years of age (no postprandial samples were attained).

Methods

Mixed meal test. Subjects in studies 1 and 2 underwent a standardized mixed meal test as previously described.[35] In brief, at 7:00 AM after a 12-hour overnight fast, an intravenous catheter was placed in an antecubital vein for blood sampling and kept patent with a 0.9% saline infusion. Subjects rested quietly in bed throughout the test. At 8:00 AM, after 2 baseline blood samples had been drawn at −15 and 0 minutes, subjects consumed a standard test meal (toast, butter, jelly, scrambled eggs, and orange juice) containing 20% of their estimated 24-hour sedentary energy expenditure distributed as 40%, 44%, and 16% of calories from carbohydrate, fat, and protein, respectively. All subjects finished the meal within 15 minutes. Postprandial blood samples were drawn at 60, 120, 180, and 240 minutes in study 1, and additionally at 30 minutes in study 2. All blood samples were drawn with prechilled syringes, transferred into prechilled tubes and immediately placed on ice. All tubes were cold-centrifuged (+4°C) within minutes of collection and frozen until assay.

Anthropometric Measurements

In adults, body composition was estimated by underwater weighing with determination of residual lung volume by helium dilution[38] or by total body dual energy x-ray absorptiometry (DPX-L; Lunar Corp, Madison, WI).[39] In children, body composition was estimated by bioelectrical impedance (BIA model 103, RJL Systems Inc, Clinton Township, MN) or by total body dual energy x-ray absorptiometry.[39] Previously derived conversion equations[40,41] were used to make measurements comparable between methods. Waist and thigh circumferences were measured at the umbilicus and the gluteal fold in the supine and standing position, respectively, and the waist-to-thigh ratio was calculated as an index of body fat distribution.

Analytic Procedures

Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin concentrations were measured by radioimmunoassays, using either the Herbert modification[42] of the method of Yalow and Berson[43] or an automated analyzer (Concept 4, ICN, Costa Mesa, CA). Plasma concentrations of PP were determined by 2 different radioimmunoassays (Peninsula Laboratories, San Carlos, CA, in study 1; ALPCO, Ltd, Windham, NH, in studies 2 and 3).

Statistical Analyses

Statistical analyses were performed using the software of the SAS Institute (Cary, NC). Plasma concentrations of PP and insulin were log transformed to achieve a normal distribution and were compared between Pima Indians and Caucasians using general linear regression

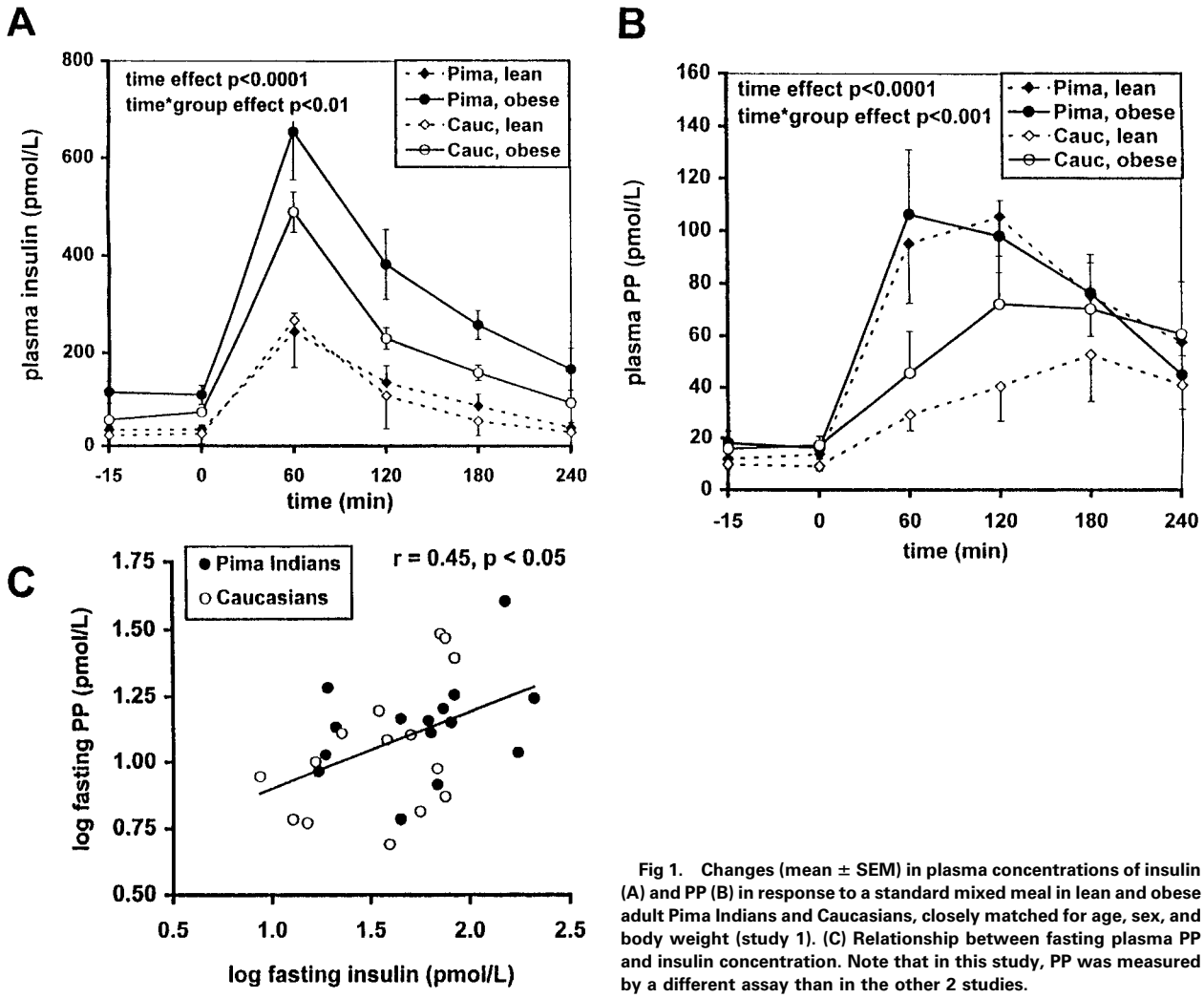

Fig 1. Changes (mean ± SEM) in plasma concentrations of insulin (A) and PP (B) in response to a standard mixed meal in lean and obese adult Pima Indians and Caucasians, closely matched for age, sex, and body weight (study 1). (C) Relationship between fasting plasma PP and insulin concentration. Note that in this study, PP was measured by a different assay than in the other 2 studies.

models with simultaneous adjustment for age and sex. Linear regression models with calculation of Pearson correlation coefficients were used to assess the relationships between different measures. Analyses of variance (ANOVA) for repeated measurements were used to examine postprandial changes in plasma PP (study 1) and insulin (studies 1 and 2) concentrations both within groups (time effect) and between groups (time*group effect). Paired *t* tests were used to test whether PP concentrations at 30 minutes after the test meal were different from those at baseline (study 2).

RESULTS

The physical and metabolic characteristics of the subjects in the 3 studies are given in Table 1.

Study 1: Overall PP and Insulin Responses to a Mixed Meal in Adults

The fasting plasma insulin concentration was higher in obese Pima Indians as compared with obese Caucasians and to lean subjects ($P < .05$, Fig 1A). At 60, 120, 180, and 240 minutes after the meal, plasma insulin concentrations were higher in obese than in lean subjects with no ethnic differences within the lean and obese groups (Fig 1A). Although the fasting plasma PP concentration was not different among the 4 groups, at 60 and 120 minutes after the meal, plasma PP concentrations were 144% and 77% higher in Pima Indians compared with Caucasians, respectively (Fig 1B). These differences were evident in both the lean and obese subgroups (Fig 1B) and in both males and females (no significant gender effect). The fasting plasma PP concentration was positively related to the fasting plasma insulin concentration (Fig 1C), a correlation that remained significant after adjustment for age, percent body fat, and the fasting plasma glucose concentration (partial $r = .51$, $P = .05$). Although postprandial PP and insulin concentrations were both positively related to their respective fasting levels, PP and insulin concentrations at postprandial time points were not correlated with one another. Neither fasting nor postprandial PP concentrations were related to measures of adiposity (BMI or percent body fat).

Study 2: Early PP and Insulin Responses to a Mixed Meal in Adults

As in study 1, the fasting plasma insulin concentration was higher in Pima Indians than in Caucasians (Fig 2A and B, $P < .01$), a difference that remained significant ($P < .05$) after

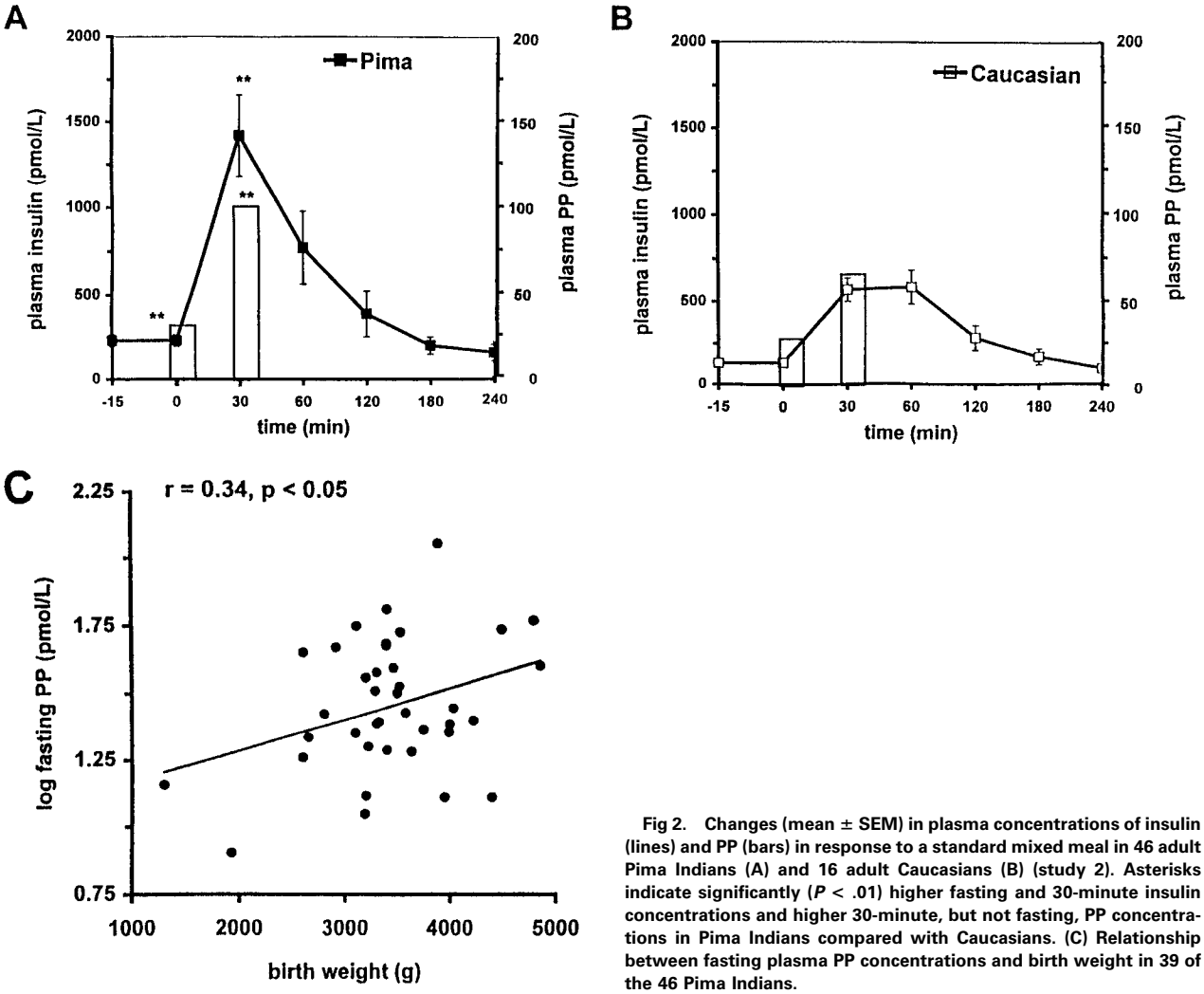

Fig 2. Changes (mean ± SEM) in plasma concentrations of insulin (lines) and PP (bars) in response to a standard mixed meal in 46 adult Pima Indians (A) and 16 adult Caucasians (B) (study 2). Asterisks indicate significantly ($P < .01$) higher fasting and 30-minute insulin concentrations and higher 30-minute, but not fasting, PP concentrations in Pima Indians compared with Caucasians. (C) Relationship between fasting plasma PP concentrations and birth weight in 39 of the 46 Pima Indians.

adjustment for percent body fat. Also, as in study 1, the fasting PP concentration was not significantly higher in Pima Indians than in Caucasians (33.1 ± 20.5 *v* 18.4 ± 7.5 pmol/L) (Fig 2A and B). However, 30 minutes after ingestion of the meal, Pima Indians had not only a more than 2-fold higher insulin concentration, but also a 51% higher PP concentration than Caucasians (Fig 2A and B). In 39 of the 46 Pima Indians in whom birth weight data were available, fasting PP concentrations were positively related to birth weight (Fig 2C), a correlation that remained significant after adjustment for body weight at the time of the study (partial $r = .37$, $P < .05$). As in study 1, neither fasting nor postprandial PP concentrations were related to BMI or percent body fat.

Study 3: Fasting PP and Insulin Concentrations in Children

Compared with the age- and sex-matched Caucasian children, Pima Indian children were significantly taller and heavier and had higher fat mass, but similar fat-free mass. The fasting insulin concentration was higher in Pima Indian than in Caucasian children ($P < .001$, Fig 3A), a difference that remained significant after adjustment for the higher percent body fat and the lower fasting glucose concentration (Table 1). The fasting PP concentration was 57% higher in Pima Indian than in Caucasian children ($P < .05$, Fig 3B). As with adults, the fasting PP concentration was positively related to the fasting insulin concentration (Fig 3C). However, unlike in adults, PP concentrations were also positively related to percent body fat ($r = .45$, $P < .01$), and the relationship between fasting PP and insulin concentrations was no longer significant after adjustment for percent body fat (partial $r = .13$, not significant).

DISCUSSION

In the present study, we hypothesized that the Pima Indians of Arizona, a population with marked hyperinsulinemia[4,5,9] and a very high propensity for obesity and type 2 diabetes[1] have an increased parasympathetic drive to the pancreas. To test our hypothesis, we measured fasting and postprandial plasma concentrations of PP in Pima Indian and Caucasian children and adults. We found that Pima Indian children had not only markedly higher fasting insulin concentrations, but also higher fasting PP concentrations than age- and sex-matched Caucasian children. Although there were no differences in fasting PP

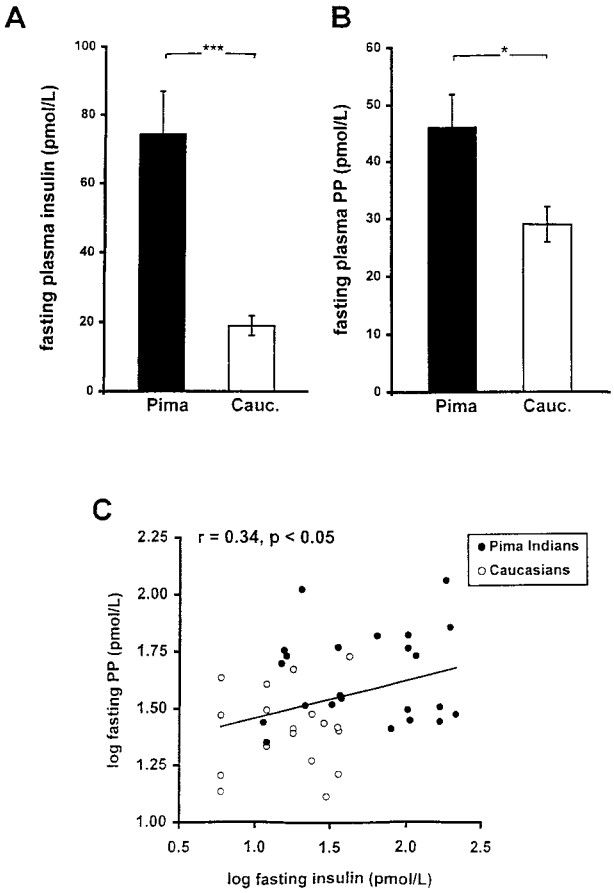

Fig 3. Fasting plasma insulin (A) and PP (B) concentrations in Pima Indian and Caucasian children matched for age and sex (* *P* < .05. ** *P* < .01) (study 3). (C) Relationship between fasting plasma PP and insulin concentrations.

concentrations between Pima Indian and Caucasian adults, in response to a mixed meal, Pima Indians had markedly higher early and late phase PP responses than Caucasians. These findings are consistent with the hypothesis that Pima Indians have an increased parasympathetic drive to the pancreas, which might contribute to their hyperinsulinemia and high propensity for obesity and diabetes.

The secretion of PP has been recognized as a unique indicator for studies of vagal control of endocrine systems.[28] In animals and humans, vagotomy decreases fasting PP concentrations and almost completely abolishes the PP response to food intake and other secretory stimuli.[26-30] In patients with long-standing diabetes, PP responses decrease in direct proportion to the loss of peripheral sensation, leading to the suggestion that PP secretion might be used as a sensitive marker in the quantification of autonomic (vagal) neuropathy.[28] In contrast, electrical stimulation of the vagus nerve dose-dependently increases circulating PP concentration in pigs.[28] Moreover, basal PP concentrations and gastric acid secretion fluctuate in parallel with a periodicity similar to the ultradian rhythm of the autonomic nervous system.[25] Based on these and other findings, PP concentrations are considered to be a useful surrogate measure of the parasympathetic drive to the pancreas.[25,27,44]

Preliminary evidence that Pima Indians might have an exaggerated PP response to food intake was reported some 15 years ago, but this finding was based on comparison with a rather small reference group of lean Caucasians and was not interpreted in the context of parasympathetic innervation of the pancreas. The results of our first study not only demonstrate that Pima Indians have markedly higher postprandial PP responses than Caucasians, but also that this ethnic difference is evident in both lean and obese subjects and in both males and females.

Because hyperinsulinemia in Pima Indians is most prominent at early time points after glucose ingestion[4] and because the postprandial PP response is known to follow a biphasic pattern with an early first phase (initial 30 minutes) and a prolonged second phase (30 minutes to 6 hours),[25,26] we measured plasma insulin and PP concentrations in samples from a second study that were taken at an earlier postprandial time point. We found that 30 minutes after the meal, Pima Indians not only had a markedly higher insulin concentration than Caucasians, but also a 51% higher PP concentration. Thus, both first and second phase PP secretion is exaggerated in Pima Indians.

In animal models of obesity such as in rats with ventromedial hypothalamic lesions, vagus-mediated insulin hypersecretion represents one of the earliest detectable metabolic abnormalities that precedes weight gain and glycemic deterioration.[8-19] Because hyperinsulinemia in the Pima Indians is also present at a young age,[7] we measured fasting plasma concentrations of PP and insulin in samples from a third study in Pima Indian and Caucasian children. We found that by the age of 5 to 8 years, Pima Indian children were not only substantially more obese and had higher fasting insulin concentrations, but also had 57% higher fasting PP concentrations. The anthropometric differences in this study have to be interpreted with caution, as some of the Caucasian children were selected from a study in twins, which likely contributed to their lower body weight at birth and later in life. It is known, however, that even after controlling for perinatal factors, Pima Indian children are heavier and fatter than age- and sex-matched Caucasian children.[6] Furthermore, the ethnic differences in fasting insulin and PP concentrations remained significant after adjustment for percent body fat. Assuming that fasting PP concentrations are an indicator of basal vagal-pancreatic tone, then our findings in children suggest that an increased parasympathetic drive to the pancreas is an early abnormality in Pima Indians, detectable at a young age and even under basal conditions.

The above findings are of considerable pathophysiologic interest. Consistent with metabolic abnormalities found in animal models of genetic and hypothalamic obesity,[8-19] Pima Indians appear to have complex disturbances in autonomic regulation that may include not only low sympathetic nervous system activity,[5] but also an increased parasympathetic drive to the pancreas. This leaves the possibility that central (eg, hypothalamic) factors might be responsible, in part, for the hyperinsulinemia and propensity for obesity and diabetes in Pima Indians. Although there is strong evidence that exaggerated PP secretion is reflective of an increased parasympathetic drive to the pancreas,[27-32] our study does not ultimately prove this notion, nor does it provide direct evidence that this abnormality

contributes to the marked hyperinsulinemia in Pima Indians, as it does in animal models of obesity. While the finding of a positive relationship between the fasting insulin and PP concentrations in both children and adults suggests that fasting insulinemia may be influenced by the basal vagal tone, the ethnic difference in insulin and PP concentrations is most prominent in the postprandial period in which insulin and PP concentrations were unrelated. This does not necessarily argue against a role of vagal activity in meal-related insulin secretion, however, given that postprandial insulin secretion is affected by numerous other factors such as the rate of gastric emptying and the degree of underlying insulin resistance. In fact, several lines of evidence indicate an important role of vagal tone in the postprandial insulin secretion in humans. Blockade of the parasympathetic drive to the pancreas by vagotomy or atropine not only completely blocks postprandial PP responses, but also dose-dependently attenuates meal-induced insulin secretion in humans.[22,23] In contrast, cholinergic activation increases PP concentration and augments insulin secretion.[25] As pointed out,[45] interpretation of such studies is complicated by the simultaneous effect of the vagus nerve on gastric emptying. Interestingly, patients with Prader-Willi syndrome, a rare form of hypothalamic obesity, have remarkably low fasting and postprandial PP and insulin concentrations,[46] suggesting a hypothalamic defect that is associated with a reduced parasympathetic drive to the pancreas. In common forms of human obesity, increased,[46] normal,[45] and decreased[47,48] PP concentrations have been reported, indicating that human obesity is not invariably associated with an increased parasympathetic drive to the pancreas.

Interestingly, increased PP concentrations have previously been reported in a remote unacculturated American Indian tribe in the Brazilian Amazon.[49] An increased parasympathetic drive to the pancreas might therefore be a phenotypic expression of the "thrifty genotype,"[49] which is commonly invoked to explain the high propensity for diabetes and obesity in populations that have rapidly transitioned from a traditional rural lifestyle to a Westernized one such as the Pima Indians. As early as 1962, Neel[50] suggested that expression of these thrifty gene(s) would result in a "quick insulin trigger" that favors energy storage in times of feast as a survival advantage in times of famine.

More recently, an alternative hypothesis has emerged according to which exposure to intrauterine factors such as hyperglycemia, hypercortisolemia, or malnutrition during fetal life may lead to a programming of propensity for adulthood disease such as diabetes (the "thrifty phenotype" hypothesis).[51] In Pima Indians, both low and high birth weights are associated with increased risk of diabetes.[52] The finding of a positive, albeit rather weak, correlation between fasting PP concentration and birth weight in Pima Indians might thus suggest that high birth weight is associated with an increased parasympathetic drive to the pancreas later in life. High birth weight is typical of offspring of mothers with diabetes or glucose intolerance, presumably because of compensatory fetal hyperinsulinemia. Studies in rodents[53,54] have shown that fetal or neonatal hyperinsulinemia leads to structural disorganization of the ventromedial hypothalamus associated with hyperinsulinemia and increased propensity to obesity and diabetes later in life. Based on these findings, it might be proposed that fetal hyperinsulinemia could cause subtle hypothalamic defects leading to reduced sympathetic and increased parasympathetic tone, which in turn, may predispose to hyperinsulinemia, obesity, and diabetes later in life.

If an increased parasympathetic drive to the pancreas contributes to hyperinsulinemia, and possibly to the development of obesity and diabetes, in some human populations, as the case in some rodent models, then the question arises whether vagal hyperinsulinemia should be attenuated. In humans with hypothalamic obesity, truncal vagotomy leads to a marked reduction in the hyperinsulinemia associated with weight loss.[55] In patients with more common forms of obesity, attenuation of hyperinsulinemia as achieved by vagotomy[56,57] or nonvagal mechanisms such as treatment with diazoxide[58] also seems to favor weight loss. In the end, long-term intervention studies are required to test whether attenuation of (vagally-mediated) insulin hypersecretion might be an option in the prevention of obesity and/or diabetes in humans.

In summary, the present study demonstrates that Pima Indians have not only higher fasting and early postprandial insulin concentrations, but also a markedly exaggerated PP response to food intake compared with Caucasians. In Pima Indian children, fasting plasma concentrations of both insulin and PP are higher than in Caucasian children. These results suggest that Pima Indians have an increased parasympathetic drive to the pancreas. Whether this abnormality contributes to the high prevalence of hyperinsulinemia, obesity, and diabetes in this population, as it does in animal models of obesity with high diabetes propensity remains to be elucidated.

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