Published in final edited form as:

Pharmacogenet Genomics. 2013 September ; 23(9): 479–486. doi:10.1097/FPC.0b013e3283642f93.

Variation in the α_{2A} -adrenoceptor gene and the effect of dexmedetomidine on plasma insulin and glucose

Laxmi V. Ghimire, MD, Mordechai Muszkat, MD, Gbenga G. Sofowora, MD, Mika Scheinin, MD, PhD, Alastair J.J. Wood, MD, C. Michael Stein, MD, and Daniel Kurnik, MD

Departments of Medicine and Pharmacology, Division of Clinical Pharmacology (L.V.G., M.M., A.J.J.W., C.M.S., D.K.), Vanderbilt University School of Medicine, Nashville, TN; Division of Cardiovascular Diseases, Ohio State University, Columbus, OH (G.G.S.); Department of Pharmacology, Drug Development and Therapeutics, University of Turku, and Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland (M.S.); Department of Clinical Pharmacology, Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel Aviv University, Israel (D.K.)

Abstract

Objectives—Sympathetic activation inhibits insulin secretion through activation of pancreatic α_{2A} -adrenoreceptors (α_{2A} ARs). A common genetic α_{2A} AR variant (rs553668) is associated with impaired insulin secretion. α_{2A} AR-agonists would be expected to decrease insulin secretion, but their effects on glucose homeostasis in humans are poorly characterized. We examined the hypothesis that the selective α_{2A} AR-agonist dexmedetomidine (DEX) decreases plasma insulin and increases plasma glucose in humans, and that these effects are modified by genetic α_{2A} AR variants.

Methods—Healthy, fasting white (n=31) and black (n=33) subjects aged 18–45 years received 3 sequential infusions of placebo (normal saline) at 30 minute intervals followed by 3 infusions of DEX (0.1, 0.15, and 0.15 mcg/kg). Plasma insulin and glucose concentrations were measured at baseline, after placebo, and after DEX. We genotyped *ADRA2A* rs553668 and rs2484516, which characterize haplotypes 4 and 4b, respectively.

Results—DEX decreased fasting insulin concentrations by 37%, from a median value after placebo of 7.9 (interquartile range, 6.0 to 12.6) μ U/mL to 4.9 (3.5 to 7.9) μ U/mL ($P < 0.001$). Plasma glucose concentrations increased from 76 ± 6 mg/dL to 79 ± 7 mg/dL; $P < 0.001$). The rs2484516 variant allele was associated with higher baseline insulin concentrations before ($P = 0.001$) and after adjustment for potential confounders ($P = 0.014$), and a greater decrease in insulin after DEX ($P = 0.016$) that was no longer significant after adjustment for baseline concentrations and other confounders ($P = 0.58$).

Conclusions—Low-dose DEX decreased plasma insulin and mildly increased plasma glucose concentrations in healthy fasting subjects. *ADRA2A* genetic variation may affect baseline insulin concentrations and thus the insulin decrease after DEX.

Correspondence to: Daniel Kurnik, MD, Division of Clinical Pharmacology, 542 RRB, Vanderbilt University School of Medicine, Nashville, TN 37232. Phone +1-615-936 3420, Fax: +1-615 936 2746. daniel.kurnik@vanderbilt.edu.

Conflicts of interest: Dr. Scheinin has contract research relationships with Orion Corporation (Espoo, Finland), the manufacturer of dexmedetomidine, and has received speaker's fees and research support from Orion corporation. Dr. Wood is a partner in Symphony Capital, LLC, NY, USA, and a director of its portfolio companies, Symphony Evolution and Oxigene Pharma.

Introduction

Alpha_{2A} adrenergic receptors (α_2 ARs) regulate central and peripheral sympathetic activity and thus affect a variety of physiological functions such as contraction and relaxation of vascular smooth muscle, anxiety and stress-related behavior, platelet aggregation, and insulin release. Catecholamines act on postsynaptic pancreatic α_2 ARs to suppress insulin secretion [1–3]. Thus, increased sympathetic activity, e.g., under conditions of stress, results in increased blood glucose concentrations, in part by inhibiting insulin secretion.

Recent studies have drawn attention to the importance of α_2 AR-mediated inhibition of insulin release, and the importance of genetic variations that may affect this response [4]. Studying a congenic rat model of type 2 diabetes, human pancreatic β cells, and insulin responses to intravenous glucose, Rosengren et al. showed that increased α_2 AR expression and signaling resulted in decreased insulin release [5]. In humans, this observation was replicated by studying subjects carrying the common *ADRA2A* rs553668 polymorphism, a gene variant associated with increased *ADRA2A* mRNA and protein expression. Carriers of this variant had impaired insulin secretion and an increased risk of type 2 diabetes compared to non-carriers [5].

Since α_2 ARs inhibit insulin secretion, α_2 AR agonists would be expected to decrease plasma insulin concentrations. Dexmedetomidine is a selective α_2 AR agonist (without selectivity for any of the α_2 -subtypes α_{2A-C}) that is widely used in clinical practice for short-term sedation and analgesia during surgery and in the intensive care setting. In mice, dexmedetomidine caused a significant decrease in plasma insulin and an increase in glucose concentrations [6]. However, there is little and inconsistent information regarding the effect of dexmedetomidine on insulin concentrations in humans [7, 8]. This could be clinically relevant, considering that dexmedetomidine is generally used in high-risk clinical settings frequently associated with insulin resistance and hyperglycemia.

We therefore set out to define the effect of dexmedetomidine on plasma insulin concentrations in humans. We studied healthy subjects in order to avoid the confounding effects of illness and concomitant medications. As a secondary outcome, we also examined whether a common α_2 AR genetic variant (rs553668), known to be associated with decreased insulin secretion, and a related variant (rs2484516) affect insulin responses to dexmedetomidine.

Methods

Subjects

The current study is part of a larger project designed to identify parameters contributing to interindividual variability in responses to dexmedetomidine, and the methods have been described in detail previously [9–11]. The Institutional Review Board of Vanderbilt University Medical Center approved the study, and all subjects gave written informed consent. Among 73 subjects participating in the original study, plasma insulin and glucose concentrations were available for 64 subjects, who constitute the study cohort for the present study. The cohort included unrelated healthy white and black subjects, aged 18–45 years, without any significant medical conditions as confirmed by medical history, physical examination, and routine laboratory tests. Participants received a standard diet (providing 150 mmol of sodium, 70 mmol of potassium, and 600 mmol of calcium daily, and free of alcohol and caffeine) for 5 days before the study day. All subjects were free of medications and dietary supplements for at least 2 weeks before the study.

Study Procedure

This placebo-controlled, single masked study was performed at the Vanderbilt University Clinical Research Center. After an overnight fast, intravenous cannulae were placed in antecubital veins bilaterally, one for blood collection and the other for drug infusion. After supine rest for 30 minutes, blood pressure (BP) and heart rate were measured from the left brachial artery with a semi-automated device (Dinamap[®] MPS; GE Medical Systems, Waukesha, WI, USA), and a venous blood sample was taken for DNA extraction and measurement of baseline plasma catecholamine, insulin and glucose concentrations. After baseline measurements, six infusions (each infusion lasted 10 minutes and was followed by a 20 minutes observation period) were administered. Placebo (normal saline) was infused during cycles 1–3, and dexmedetomidine (Precedex[®], Abbott Laboratories, Abbott Park, IL, USA) at doses of 0.1, 0.15, and 0.15 mcg/kg body weight, respectively, during cycles 4–6 (cumulative dose, 0.4 mcg/kg). Blood samples were drawn ten minutes after the last placebo infusion and the last dexmedetomidine infusion for the determination of plasma catecholamines, dexmedetomidine concentrations, and plasma insulin and glucose concentrations.

Plasma glucose and insulin determination

Plasma glucose concentrations were measured in triplicate using the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Plasma insulin concentrations were determined by radioimmunoassay (RIA) [12] using the porcine insulin RIA kit (Millipore, St. Charles, MO, USA), with a coefficient of variation of 7–11% at the relevant concentrations.

Plasma catecholamine determination

Blood was collected into cooled heparinized tubes which were immediately placed on ice until centrifuged at 4 °C for 10 minutes at 3,000 rpm. Plasma was separated and stored at –20 °C in tubes containing 40 µL of reduced glutathione (6%) until assayed. Norepinephrine and epinephrine concentrations were measured by high performance liquid chromatography using electrochemical detection with dihydroxybenzylamine as internal standard [13].

Plasma dexmedetomidine determination

Plasma dexmedetomidine concentrations were determined by reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection (PE Sciex API4000, PE Sciex, Foster City, CA) with deuterium-labeled medetomidine as internal standard, as previously described [14, 15].

Genotyping

We genotyped for *ADRA2A* rs553668, a variant previously associated with increased suppression of insulin release [5, 16] and a tag SNP for a haplotype we previously designated as haplotype 4 [17]. We also genotyped for rs2484516, a variant that identifies a subgroup of haplotype 4 (haplotype 4b) [17]. Genotyping was performed by allelic discrimination with TaqMan 5'-nuclease assays on an ABI 7900 HT real-time PCR system (Applied Biosystems, Foster City, CA) using validated TaqMan probes. For genotyping quality control, we included 6 samples with known genotypes previously determined by direct sequencing [16], and all control samples yielded concordant genotypes. Genotype distributions were tested for deviation from Hardy-Weinberg equilibrium with the use of chi-square tests with one degree of freedom.

Data and statistical analysis

Our main outcomes were differences in serum insulin and glucose concentrations between the placebo and the dexmedetomidine study phase (insulin and glucose). Serum insulin concentrations were not normally distributed, and we therefore used logarithmic transformation of insulin concentrations (LogInsulin) for statistical analysis. LogInsulin and glucose concentrations were compared among the study periods (baseline, placebo, dexmedetomidine) by repeated measures ANOVA with post-hoc analysis using Bonferroni's multiple comparisons test.

As a secondary outcome, we examined the association of *ADRA2A* genotypes with insulin and glucose concentrations at baseline, and with insulin and glucose after dexmedetomidine. For this purpose, we used multiple linear regression analyses, with Log insulin and glucose concentrations (or insulin and glucose) as dependent variables and rs553668 and rs2484516 as independent variables, without and with adjustment for potential confounders (age, sex, race, BMI, corresponding baseline or post-placebo values for outcomes insulin and glucose, and plasma dexmedetomidine concentration [for outcomes assessed after the dexmedetomidine infusions]). Genotypes were coded as numbers of variant alleles (0–2) assuming an additive mode of inheritance. Data are expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR). In these exploratory analyses, we did not adjust for multiple comparisons, and P-values <0.05 were considered statistically significant. Statistical analyses were performed using the statistical software SPSS (SPSS v. 21, SPSS Inc., Chicago, IL, USA).

Results

Subjects

We studied 64 healthy subjects, and their demographic characteristics, baseline measures, and genotypes are shown in Table 1. For both *ADRA2A* variants, genotyping results yielded minor allele frequencies within the expected range, and the genotype distributions conformed to Hardy-Weinberg equilibrium in each racial group (all $P>0.05$).

Insulin and glucose concentrations during study phases

Insulin ($P<0.001$) and glucose concentrations ($P<0.001$) differed significantly among the three study phases (baseline, placebo, and dexmedetomidine). The median insulin concentration increased moderately by a median of 19% after placebo infusions, from 6.8 $\mu\text{U/mL}$ to 7.9 $\mu\text{U/mL}$, ($P<0.001$; Table 2, Figure 1). After dexmedetomidine, plasma insulin decreased to 4.9 $\mu\text{U/mL}$, a median decrease from placebo of 2.9 $\mu\text{U/mL}$ (37%, $P<0.001$; Table 2, Figure 1). Insulin concentrations after dexmedetomidine were also significantly lower compared to baseline ($P<0.001$). Glucose concentrations remained stable during the placebo phase, but increased slightly after dexmedetomidine from 76 ± 6 to 79 ± 7 mg/dL ($P=0.001$; Table 2).

Determinants of insulin and glucose concentrations at baseline

The *ADRA2A* rs2484516 variant was significantly associated with baseline fasting insulin. Carriers of one variant allele had 85% higher median plasma insulin concentrations than non-carriers, and the single subject with 2 variant alleles had 4.2-fold higher insulin concentrations ($P=0.001$; Table 3, Figure 2). This association remained statistically significant after adjustment for age, race, sex, and BMI ($P=0.014$; Table 3). In our cohort, the variant allele was present only in black subjects, and a sensitivity analysis in the subgroup of black subjects still showed a significant association between rs2484516 and baseline insulin (adjusted $P=0.027$). After placebo infusions, the association between rs2484516 and insulin concentrations was still evident, although somewhat weaker

($P=0.032$; adjusted $P=0.16$). Among the non-genetic covariates, only higher BMI was associated with baseline insulin concentrations ($\beta=0.03$, 95% CI, 0.01 to 0.04, adjusted $P=0.002$).

The rs2484516 genotype was also associated with baseline glucose concentrations ($P=0.009$), with carriers of variant alleles having higher glucose concentrations (Table 3). This association, however, was of borderline statistical significance after adjusting for covariates ($P=0.055$).

The second *ADRA2A* variant examined, rs553668, was associated with neither baseline insulin (adjusted $P=0.46$) nor glucose concentrations (adjusted $P=0.31$; Table 3).

Determinants of changes in insulin and glucose concentrations after dexmedetomidine

After dexmedetomidine, insulin concentrations decreased by a median of 2.9 $\mu\text{U/mL}$ (IQR, 1.9 to 5.0 $\mu\text{U/mL}$; range, -1.0 to 19.4 $\mu\text{U/mL}$). There was a positive association between higher insulin concentrations after placebo and a greater drop in insulin after dexmedetomidine (Spearman's rank correlation coefficient $\rho=0.71$; $P<0.001$). The rs2484516 genotype was associated with the decrease in insulin after dexmedetomidine infusion (β insulin; $P=0.016$, Figure 2), but this association was no longer statistically significant after adjustment for baseline insulin and other covariates ($P=0.58$; Table 4). Other than insulin concentration after placebo ($P<0.001$), no other covariate was significantly associated with β insulin in the adjusted analysis.

The mean baseline glucose concentration increased marginally after dexmedetomidine by a mean of 2.4 ± 5.7 mg/dL (range, -9 to 18 mg/dL; $P<0.001$; Table 2). Neither rs2484516 (adjusted $P=0.30$) nor rs553668 genotypes (adjusted $P=0.48$) were associated with the increase in blood glucose (Table 4). Among other covariates, lower glucose concentrations after placebo ($P<0.001$) was significantly associated with a greater β glucose in the adjusted analysis, while older age ($P=0.026$), white race ($P=0.012$), and higher dexmedetomidine plasma concentrations ($P=0.023$) showed weak associations with β glucose.

As reported previously in this cohort [11], dexmedetomidine decreased systolic and diastolic blood pressure and plasma norepinephrine and epinephrine concentrations significantly compared to baseline values (all $P<0.001$; Table 2). However, there was no significant correlation between the decrease in insulin or the increase in glucose and these other measures of dexmedetomidine effect (all P values >0.21).

Discussion

The major finding of this proof-of-principle study is that dexmedetomidine significantly decreased plasma insulin and increased plasma glucose concentrations in healthy human subjects, extending findings from *in vitro* and animal studies to humans. Among two candidate genetic variants in the target receptor of dexmedetomidine, the $\alpha_2\text{AR}$, rs2484516 was associated with higher baseline insulin concentrations and a greater decrease of insulin after dexmedetomidine, largely a reflection of the higher baseline concentrations.

$\alpha_2\text{AR}$ s are important physiological mediators of catecholamine-induced suppression of insulin secretion [4]. *In vitro* studies with pancreatic beta cells showed that $\alpha_2\text{AR}$ agonists such as clonidine and dexmedetomidine reduced the membrane docking of insulin granules and reduced glucose-stimulated insulin release [5]. These responses could be reversed by pharmacological blockade of $\alpha_2\text{AR}$ s with yohimbine. Animal studies confirmed the inhibitory role of $\alpha_2\text{AR}$ s on insulin secretion: *adra2a* knockout mice had increased insulin secretion [6], and mice with selective pancreatic β cell overexpression of *Adra2a* were

glucose-intolerant and had a pronounced reduction in insulin secretion, and consequent hyperglycemia, in response to an α_2 AR agonist [18].

In keeping with findings from *in vitro* studies, α_2 AR agonists such as dexmedetomidine inhibit insulin secretion in mice [6]. In small studies in humans, clonidine decreased fasting plasma insulin and increased fasting plasma glucose concentrations both after a single dose and during chronic treatment [19, 20]. However, small studies with dexmedetomidine, the α_2 AR-agonist that has largely replaced clonidine in the intensive care units (ICU), have yielded inconclusive results, presumably because of small sample sizes and the many confounders in the ICU study setting (e.g., effects of acute disease, surgery, and multiple concomitant medications) [8, 21]. In contrast, in the current study, even at dexmedetomidine dose rates that were less than half of the median therapeutic rate of 0.8 mcg/kg*hr⁻¹) [22], we found a robust 37% reduction in plasma insulin concentrations, a finding concordant with the known effects α_2 AR agonists on insulin secretion *in vitro* and in animal models. Several reasons may account for these discordant findings.

We studied healthy subjects under controlled conditions, thus improving our chance to detect an effect of dexmedetomidine without the confounding effects of disease, surgery, and concomitant medications. Our study was performed under highly controlled conditions, including a 10-hour fast and a standardized pre-study diet. Moreover, our sample size was comparatively large for a translational study.

Reduced insulin secretion after dexmedetomidine would be expected to facilitate an increase in plasma glucose concentrations. Indeed, we found a statistically significant increase in glucose concentrations, but of a magnitude too small to be of clinical importance. A previous meta-analysis of the effects of dexmedetomidine on blood glucose found no increased risk of hyperglycemia (RR 1.05, 95% CI 0.64–1.71, P=0.85) in 695 ICU patients pooled from 3 studies, but large heterogeneity among the studies limited comparability [23]. In contrast, in a randomized controlled trial of 375 critically ill patients receiving either dexmedetomidine or midazolam for sedation, hyperglycemia occurred more frequently in patients receiving dexmedetomidine (56.6% vs. 42.6%; P=0.02) [24]. Thus, in healthy fasting subjects with intact homeostatic mechanisms, inhibition of insulin secretion by low doses of dexmedetomidine as used in our study appears to result in only small increases in fasting blood glucose; in contrast, inhibited insulin secretion may result in greater increases in blood glucose under conditions that promote insulin resistance or require increased insulin secretion to maintain normoglycemia (e.g., stress, sepsis), conditions typically encountered in ICU patients receiving dexmedetomidine.

As expected, α_2 AR activation by dexmedetomidine reduced plasma catecholamine concentrations and blood pressure significantly, but the magnitudes of these reductions were not significantly correlated with the decreases in insulin. One possible explanation for this observation is that physiological homeostatic responses act to mask the correlation between these responses.

The *ADRA2A* rs553668 variant has been associated with increased α_2 AR expression, reduced insulin secretion, a higher prevalence of impaired glucose tolerance and diabetes, and enhanced cardiovascular responses to dexmedetomidine [5, 11]. In the present study, we did not find any association between the rs553668 genotype and plasma insulin and glucose concentrations or their responses to dexmedetomidine. Since the differences in fasting insulin concentrations between subjects without and with 2 variant alleles of rs553668 were approximately 12%–17% in very large study populations [5], our study was likely underpowered to detect differences of this magnitude, considering the small number of variant allele carriers.

The rs553668 variant, which characterizes the *ADRA2A* haplotype 4, is a 3'-UTR downstream variant and may be only a marker of *ADRA2A* expression rather than the causal variant [16]. The rs2484516 is a 5'-UTR tagSNP for a subgroup of haplotype 4 [17], and we therefore also investigated the possible association of this variant with glucose homeostasis. rs2484516 was associated with higher fasting insulin concentrations and a greater reduction after dexmedetomidine (largely reflecting the higher baseline values). Thus, the effect on baseline serum insulin was opposite to that previously described for rs553668.

In our cohort, rs2484516 was present only in black subjects. Previous studies have suggested ethnic differences in the association of *ADRA2A* variants with glucose homeostasis. While there was a robust and reproducible association between rs553668 and markers of glucose homeostasis or type 2 diabetes mellitus in Caucasians [16], this association was inconsistent in Han Chinese, a population with a more than 3-fold higher prevalence of the rs553668 minor allele variant (approximately 50%) [25, 26]. Black subjects have a 2-fold higher prevalence of the rs553668 variant compared to whites (30% and 15%, respectively, according to HapMap data) and a different *ADRA2A* haplotype structure [17]. Thus, marker-phenotype associations derived in one race may not be automatically extrapolated to populations of different racial compositions. Future studies of the functional effects of the rs2484516 variant on other α_2 AR-related outcomes in black populations will be of interest.

Our study had several strengths and limitations. We used dexmedetomidine because it is 8-fold more selective as an α_2 AR agonist compared to clonidine, a mixed α_1/α_2 -AR agonist. However, there is no agonist available for clinical use which is selective for the α_2 AR subtype. In this proof-of-concept study, we studied healthy subjects in a highly controlled setting to avoid the confounding effects of environmental factors, disease, and concomitant drugs in order to improve the signal-to-noise ratio. Thus, our finding of reduced insulin levels after dexmedetomidine cannot be automatically extrapolated to critically ill patients and to the non-fasting state, and the clinical significance of our finding is unclear. However, increased blood glucose levels in ICU patients receiving dexmedetomidine are compatible with our observations [24].

The order of the placebo and dexmedetomidine infusions was fixed because the effects of dexmedetomidine were likely to be long-lasting. Thus, we cannot exclude a temporal contribution to the effects observed. In fact, despite an overnight fast of approximately 10 hours, there was a small increase in insulin concentrations during the 90 minute placebo phase, while glucose concentrations remained unchanged, possibly reflecting diurnal variation in plasma insulin concentrations. The decrease in insulin concentrations after dexmedetomidine was about twice the magnitude of the increase during placebo, suggesting that this decrease was indeed drug-mediated. Moreover, a mere fasting-induced decrease in plasma insulin would have been associated with decreased blood glucose, rather than the increase that we observed.

We measured fasting insulin concentrations, and the baseline insulin values were appropriately low. Insulin secretion increases considerably after a meal, and dexmedetomidine's inhibitory effect on postprandial or glucose-stimulated insulin secretion is likely to be of greater magnitude than that on fasting insulin. Thus, our findings may underestimate dexmedetomidine's effect on glucose homeostasis in non-fasting states. Similarly, the dexmedetomidine dose in our study was low (approximately 0.3 mcg/kg*hr⁻¹), less than half of that typically required for sedation in the ICU setting (median dose rate = 0.8 mcg/kg*hr⁻¹) [22], and our findings may thus underestimate the effect of dexmedetomidine at higher doses. Additionally, we measured insulin plasma concentrations

as a marker for insulin secretion without accounting for insulin clearance. However, since dexmedetomidine decreased blood pressure, thus possibly reducing hepatic insulin clearance and increasing plasma insulin concentrations, our findings may in fact underestimate the inhibition of insulin secretion by dexmedetomidine. Finally, our genetic association study was exploratory, and the small sample size in some genotype groups did not allow more definitive analyses such as validation of our findings in subcohorts and correction for multiple comparisons.

In conclusion, the selective α_2 -AR agonist dexmedetomidine decreased fasting plasma insulin and increased glucose concentrations in healthy subjects. The *ADRA2A* rs2484516 SNP may be associated with higher fasting insulin and a greater decrease after dexmedetomidine in black subjects. Future studies examining the effect of dexmedetomidine on glucose homeostasis in the clinical setting and of rs2484516 and rs553668 on other markers of glucose homeostasis and α_2 -AR-mediated outcomes will be of interest.

Acknowledgments

Sources of Funding: This work was supported in part by NIH grant HL056693 and by the National Center for Research Resources Grant UL1 RR024975-01, which is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06.

References

1. Hamburg S, Hendler R, Sherwin RS. Influence of small increments of epinephrine on glucose tolerance in normal humans. *Ann Intern Med.* 1980; 93:566–568. [PubMed: 7001974]
2. Rizza RA, Cryer PE, Haymond MW, Gerich JE. Adrenergic mechanisms of catecholamine action on glucose homeostasis in man. *Metabolism.* 1980; 29:1155–1163. [PubMed: 7001182]
3. Johnston DG, Pernet A, McCulloch A, Blesa-Malpica G, Burrin JM, Alberti KG. Some hormonal influences on glucose and ketone body metabolism in normal human subjects. *Ciba Found Symp.* 1982; 87:168–191. [PubMed: 6122546]
4. Fagerholm V, Haaparanta M, Scheinin M. Alpha2-adrenoceptor regulation of blood glucose homeostasis. *Basic Clin Pharmacol Toxicol.* 2011; 108:365–370. [PubMed: 21418144]
5. Rosengren AH, Jokubka R, Tojjar D, Granhall C, Hansson O, Li DQ, et al. Overexpression of alpha2a-adrenergic receptors contributes to type 2 diabetes. *Science.* 2010; 327:217–220. [PubMed: 19965390]
6. Fagerholm V, Gronroos T, Marjamaki P, Viljanen T, Scheinin M, Haaparanta M. Altered glucose homeostasis in alpha2a-adrenoceptor knockout mice. *Eur J Pharmacol.* 2004; 505:243–252. [PubMed: 15556159]
7. Walker J, Maccallum M, Fischer C, Kopcha R, Saylor R, McCall J. Sedation using dexmedetomidine in pediatric burn patients. *J Burn Care Res.* 2006; 27:206–210. [PubMed: 16566567]
8. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. *Br J Anaesth.* 2001; 86:650–656. [PubMed: 11575340]
9. Kurnik D, Muszkat M, Sofowora GG, Friedman EA, Dupont WD, Scheinin M, et al. Ethnic and genetic determinants of cardiovascular response to the selective alpha 2-adrenoceptor agonist dexmedetomidine. *Hypertension.* 2008; 51:406–411. [PubMed: 18071056]
10. Kohli U, Muszkat M, Sofowora GG, Harris PA, Friedman EA, Dupont WD, et al. Effects of variation in the human alpha2a- and alpha2c-adrenoceptor genes on cognitive tasks and pain perception. *Eur J Pain.* 2010; 14:154–159. [PubMed: 19423370]
11. Kurnik D, Muszkat M, Li C, Sofowora GG, Friedman EA, Scheinin M, et al. Genetic variations in the alpha(2a)-adrenoreceptor are associated with blood pressure response to the agonist dexmedetomidine. *Circ Cardiovasc Genet.* 2011; 4:179–187. [PubMed: 21325151]

12. Morgan CR, Lazarow A. Immunoassay of insulin: Two antibody system, plasma insulin levels of normal, subdiabetic and diabetic rats. *Diabetes*. 1963; 12:115–126.
13. He HB, Deegan RJ, Wood M, Wood AJ. Optimization of high-performance liquid chromatographic assay for catecholamines. Determination of optimal mobile phase composition and elimination of species-dependent differences in extraction recovery of 3,4-dihydroxybenzylamine. *J Chromatogr*. 1992; 574:213–218. [PubMed: 1618952]
14. Ji QC, Zhou JY, Gonzales RJ, Gage EM, El-Shourbagy TA. Simultaneous quantitation of dexmedetomidine and glucuronide metabolites (g-dex-1 and g-dex-2) in human plasma utilizing liquid chromatography with tandem mass spectrometric detection. *Rapid Commun Mass Spectrom*. 2004; 18:1753–1760. [PubMed: 15282775]
15. Snapir A, Posti J, Kentala E, Koskenvuo J, Sundell J, Tuunanen H, et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. *Anesthesiology*. 2006; 105:902–910. [PubMed: 17065883]
16. Talmud PJ, Cooper JA, Gaunt T, Holmes MV, Shah S, Palmen J, et al. Variants of adra2a are associated with fasting glucose, blood pressure, body mass index and type 2 diabetes risk: Meta-analysis of four prospective studies. *Diabetologia*. 2011; 54:1710–1719. [PubMed: 21455730]
17. Kurnik D, Muszkat M, Li C, Sofowora GG, Solus J, Xie HG, et al. Variations in the alpha2a-adrenergic receptor gene and their functional effects. *Clin Pharmacol Ther*. 2006; 79:173–185. [PubMed: 16513442]
18. Devedjian JC, Pujol A, Cayla C, George M, Casellas A, Paris H, et al. Transgenic mice overexpressing alpha2a-adrenoceptors in pancreatic beta-cells show altered regulation of glucose homeostasis. *Diabetologia*. 2000; 43:899–906. [PubMed: 10952463]
19. Lattermann R, Schrickler T, Georgieff M, Schreiber M. Low dose clonidine premedication accentuates the hyperglycemic response to surgery. *Can J Anaesth*. 2001; 48:755–759. [PubMed: 11546715]
20. Klein C, Morton N, Kelley S, Metz S. Transdermal clonidine therapy in elderly mild hypertensives: Effects on blood pressure, plasma norepinephrine and fasting plasma glucose. *J Hypertens Suppl*. 1985; 3:S81–84. [PubMed: 3868715]
21. Uyar AS, Yagmurdu H, Fidan Y, Topkaya C, Basar H. Dexmedetomidine attenuates the hemodynamic and neuroendocrinal responses to skull-pin head-holder application during craniotomy. *J Neurosurg Anesthesiol*. 2008; 20:174–179. [PubMed: 18580347]
22. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: An a priori-designed analysis of the mends randomized controlled trial. *Crit Care*. 2010; 14:R38. [PubMed: 20233428]
23. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: A meta-analysis. *Intensive Care Med*. 2010; 36:926–939. [PubMed: 20376429]
24. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA*. 2009; 301:489–499. [PubMed: 19188334]
25. Li T, Zhu X, Wu X, Li J, Pan L, Li P, et al. Evaluation of the association between the adra2a genetic polymorphisms and type 2 diabetes in a chinese han population. *Genet Test Mol Biomarkers*. 2012; 16:1424–1427. [PubMed: 23153004]
26. Chen X, Liu L, He W, Lu Y, Ma D, Du T, et al. Association of the adra2a polymorphisms with the risk of type 2 diabetes: A meta-analysis. *Clin Biochem*. 2013; 46:722–726. [PubMed: 23462695]

Figure 1. Plasma insulin concentrations at baseline, after placebo, and after dexmedetomidine Insulin concentrations after dexmedetomidine were significantly lower than after placebo ($P<0.001$) and at baseline ($P<0.001$). Medians are represented by the bold horizontal lines, the interquartile range by error bars.

Figure 2. Baseline plasma insulin concentrations (left panel) and change in plasma insulin after dexmedetomidine (right panel) in rs2484516 genotypes

Genotype differences in baseline insulin were significant (adjusted $P=0.014$), while differences in insulin (unadjusted $P=0.016$) were no longer significant after adjustment for covariates ($P=0.58$). Horizontal lines in the boxes represent the medians, the boxes the interquartile ranges, and the whiskers the ranges.

Table 1

Demographic and baseline characteristics (n= 64)

Parameter	N (%) or Mean±SD				
Female sex	27 (42%)				
Age (years)	25.3±4.7				
Race					
Caucasian-American	31 (48%)				
African-American	33 (52%)				
Body Mass Index (kg/m ²)	25.5±3.7				
Plasma Insulin (μU/mL), median (IQR) *	6.8 (4.8 to 9.3)				
Blood Glucose (mg/dL)	77±7				
Systolic Blood Pressure (mmHg)	114±9				
Diastolic Blood Pressure (mmHg)	69±7				
Heart Rate (bpm)	65±8				
Plasma norepinephrine (pg/mL), median (IQR) *	216 (158 to 291)				
Plasma epinephrine (pg/mL), median (IQR) *	18 (10–30)				
rs553668 genotype	variant alleles			MAF [†]	
	0	1	2		
	24	5	2	14.5%	
Whites, n	24	5	2	14.5%	
Blacks, n	20	12	1	21.2%	
rs2484516 genotype					
Whites **	27	0	0	0%	
Blacks	28	4	1	9.1%	

* Data presented as median and interquartile range (IQR)

^{**} In 4 subjects, the rs2484516 genotype was undetermined.[†] MAF=minor allele frequency

Table 2

Differences in parameters after placebo and dexmedetomidine infusion

Parameter	Baseline Mean±SD or median (IQR)	Placebo Mean±SD or median (IQR)	Dexmed Mean±SD or median (IQR)	Overall P-value	P-values placebo/dexmed
Plasma insulin * (μU/mL)	6.8 (4.8 to 9.3)	7.9 [†] (6.0 to 12.6)	4.9 (3.5 to 7.9)	<0.001	<0.001
Blood glucose (mg/dL)	77±7	76±6	79±7	<0.001	0.001
Systolic BP (mmHg)	114±9	114±10	100±9	<0.001	<0.001
Diastolic BP (mmHg)	69±7	68±6	58±7	<0.001	<0.001
Heart rate (bpm)	65±8	65±8	61±8	<0.001	<0.001
Norepinephrine * (pg/mL)	216 (158 to 291)	225 (172–299)	95 (66–154)	<0.001	<0.001
Epinephrine * (pg/mL)	18 (10–30)	20 [†] (12–36)	12 (7–23)	<0.001	<0.001

* Data presented as median and interquartile range (IQR), and P-values for nonparametric comparisons.

[†] Compared to baseline measures, there was a small but significant increase in plasma insulin and epinephrine after placebo (both P 0.001), while there were no significant placebo effects for any of the other parameters.

Table 3
Baseline insulin and glucose concentrations stratified by rs553668 and 2484516 genotype groups

Data for plasma insulin are expressed as medians and interquartile ranges (IQR), for blood glucose as mean $\pm$ standard deviation (SD), and for coefficients as means and 95% confidence intervals (CI). Comparisons of insulin concentrations among genotype groups were performed using multiple linear regression analyses after logarithmic transformation of insulin concentrations.

No. of minor alleles	Baseline Insulin				Baseline Glucose			
	Baseline Insulin, μ U/mL median (IQR)	-coeff (95% CI)	Unadj. P-value	Adjust. P-value*	Baseline glucose, mg/dL mean $\pm$ SD	-coeff (95% CI)	Unadj. P-value	Adjust. P-value*
rs553668								
0 (n=44)	6.4 (4.4 to 8.5)				76 $\pm$ 7			
1 (n=17)	8.3 (5.8 to 12.1)	0.08 (−0.03 to 0.19)	0.13	0.46	77 $\pm$ 4	2.6 (−0.3 to 5.5)	0.08	0.31
2 (n=3)	6.0 (2.1 to 6.0)				84 $\pm$ 11			
rs2484516								
0 (n=55)	6.6 (4.7 to 9.1)				76 $\pm$ 7			
1 (n=4)	12.2 (7.7 to 23.7)	0.30 (0.13 to 0.47)	0.001	0.014	79 $\pm$ 2	6.5 (1.7 to 11.2)	0.009	0.055
2 (n=1)	27.5				95			

* Adjusted for age, sex, race, and BMI.

Table 4

Changes in serum insulin and blood glucose concentrations after dexametomidine stratified by rs553668 and 2484516 genotype groups

Data represent the difference between measures obtained after the dexametomidine infusions minus those obtained after placebo infusions. Data for plasma insulin are expressed as medians and interquartile ranges (IQR), for blood glucose as mean $\pm$ standard deviation (SD), and for β -coefficients as means and 95% confidence intervals (CI).

No. of minor alleles	Insulin				Glucose			
	Insulin, μ U/mL median (IQR)	β -coeff (95% CI)	Unadj. P-value	Adjust. P-value *	Glucose, mg/dL mean $\pm$ SD	β -coeff (95% CI)	Unadj. P-value	Adjust. P-value *
rs553668								
0 (n=44)	-2.8 (-4.5 to -1.7)				3 $\pm$ 6			
1 (n=17)	-3.1 (-5.2 to -2.0)	-0.2 (-1.2 to 0.7)	0.37	0.63	2 $\pm$ 5	-0.9 (-3.5 to 1.6)	0.47	0.48
2 (n=3)	-1.7 (-14.8 to -1.7)				0 $\pm$ 3			
rs2484516								
0 (n=55)	-2.9 (-4.6 to -1.9)				2 $\pm$ 6			
1 (n=4)	-3.4 (-9.3 to -2.3)	-0.5 (-2.2 to 1.2)	0.016	0.58	7 $\pm$ 4	1.7 (-2.7 to 6.0)	0.45	0.30
2 (n=1)	-14.8				-1			

* Adjusted for age, sex, race, BMI, insulin or glucose after placebo phase, respectively, and dexametomidine plasma concentrations.