The effect of high-dose sodium salicylate on chronically elevated plasma nonesterified fatty acid-induced insulin resistance and β-cell dysfunction in overweight and obese nondiabetic men

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Xiao C, Giacca A, Lewis GF. The effect of high-dose sodium salicylate on chronically elevated plasma nonesterified fatty acids is not well understood. We have shown previously in humans and rats that β-cell functional impairment induced by chronic elevation of NEFA is ameliorated by antioxidant therapy (41, 54). Recent studies in animal models suggest a role of inflammation in development of insulin resistance; thus pharmacological or genetic activation of the NF-κB pathway may also play a role in chronic elevation of NEFA-β-cell dysfunction in overweight and obese nondiabetic men.

Insulin secretion; insulin sensitivity; lipid; human

Type 2 diabetes is characterized by defects in both insulin action and insulin secretion (26). The underlying cause of β-cell dysfunction is not clear, but chronically elevated plasma nonesterified fatty acids (NEFA) may play a role, an effect referred to as “lipotoxicity” (51). It is generally accepted that plasma NEFA are essential for maintaining basal insulin secretion in the fasted state (48) and that an acute increase in plasma NEFA potentiates glucose-stimulated insulin secretion (5, 45). On the other hand, most in vitro studies and studies in rodent models have demonstrated impairing effects of prolonged elevation of plasma NEFA on glucose-stimulated insulin secretion (24, 39). In contrast, the in vivo effects of prolonged elevation of plasma NEFA on insulin secretion in humans are more controversial (2, 9, 33). Since chronic elevation of NEFA induces insulin resistance (4, 6, 10, 47, 54), it is more appropriate to assess β-cell function using an index of secretion that accounts for the whole body insulin sensitivity, the disposition index (a product of insulin sensitivity and secretion) (27, 34). In previous studies, we and others have shown in humans that chronic elevation of plasma NEFA through lipid infusion or fat ingestion induces insulin resistance that is not appropriately compensated by insulin secretion, demonstrating the detrimental effects to β-cells, particularly in obese individuals and in offspring of parents with type 2 diabetes (9–11, 13, 28, 32, 54).

The mechanisms by which chronically elevated NEFA impair β-cell function are not well understood. We have shown previously in humans and rats that the β-cell functional impairment induced by chronic elevation of NEFA is ameliorated by antioxidant therapy (41, 54). Recent studies in animal models suggest a role of inflammation in development of insulin resistance; thus pharmacological or genetic activation of the NF-κB pathway may also play a role in chronic elevation of NEFA-β-cell dysfunction in overweight and obese nondiabetic men.

Materials and Methods

Subjects. Six overweight or obese but otherwise healthy Caucasian men participated in the study (Table 1). To exclude the influences of family history of type 2 diabetes and impaired glucose tolerance on the response to lipotoxicity (12), no subjects with family history of type 2 diabetes or impaired oral glucose tolerance tests were included in the study. None of the participants was taking any medication or had any known systemic illness. Informed, written consent was obtained from all participants in accordance with the guidelines of the

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Table 1. Characteristics of the subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Means ± SE</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>48.7±3.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>91.9±4.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.2±1.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.3±1.4</td>
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<tr>
<td>Fasting plasma levels</td>
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</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.1±0.2</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>87.4±19.7</td>
</tr>
<tr>
<td>C-peptide, pmol/l</td>
<td>0.74±0.13</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.42±0.29</td>
</tr>
<tr>
<td>NEFA, pmol/l</td>
<td>0.45±0.04</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 6. BMI, body mass index; TG, triglycerides; NEFA, nonesterified fatty acids. All subjects are male.

Human Subjects Review Committee of the University Health Network, University of Toronto, which approved the study.

**Experimental protocol.** Participants were admitted to the Metabolic Test Centre of the Toronto General Hospital on four occasions in random order, 4–6 wk apart, after a 12-h overnight fast. On each occasion subjects received one of the four following treatments: 1) 1-wk placebo followed by intravenous (iv) infusion of normal saline for 48 h (SAL); 2) 1-wk placebo followed by iv infusion of intralipid plus heparin for 48 h to raise plasma NEFA by approximately twofold, as described previously (IH) (10); 3) 1-wk oral sodium salicylate (4.5 g/day, divided into 3 equal dosages; Stella Pharmaceutical Canada, Don Mills, ON, Canada), followed by 48-h IH infusion as described above (IH + SS); and 4) 1-wk oral sodium salicylate followed by 48-h saline infusion (SS). Salicylate was well tolerated by all subjects, and compliance (>95%) was ascertained by pill counting. Omeprazole (Losec; AstraZeneca Canada) was administered to patients for all four studies at a dose of 20 mg/day for the week prior to the clamp studies to prevent gastrointestinal side effects from the salicylate. In each occasion, on day 3 of the admission to the Metabolic Test Centre, an iv catheter was placed in the superficial vein of one forearm for infusion of glucose and insulin (and ongoing infusion of saline or intralipid plus heparin). A second iv catheter was placed in the opposite forearm, which was maintained in a heating blanket (~65°C) to "arterialize" venous blood for blood sampling. At ~0800, a 30-min baseline sampling period was started, followed by a 2-h, 20 mmol/l hyperglycemic clamp, as described previously (10, 14). Urine glucose loss was assumed to be equal between studies for the same individual because plasma glucose levels were similar. At the end of the 2-h hyperglycemic clamp, the iv dextrose infusion was slowly tapered while avoiding hypoglycemia, allowing the blood glucose to return to basal level. Two hours after the end of the hyperglycemic clamp, a euglycemic hyperinsulinemic clamp was started with a primed infusion of 40 mU·m²·min⁻¹ of insulin and 20% dextrose, as described previously (14). Considering that the subjects are obese/overweight and more insulin resistant following lipid infusion, the current insulin infusion dose likely did not maximally stimulate peripheral glucose uptake or maximally suppress endogenous glucose production. However, insulin infusion at this rate was sufficient to detect further impairment of insulin sensitivity following lipid infusion. In addition, any underestimation of the insulin resistance would be similar for all treatments. The potential interference of the prior hyperglycemic clamp on assessment of insulin sensitivity by the ensuing euglycemic hyperinsulinemic clamp was minimized by inclusion of a 2-h equilibration period between the hyper- and euglycemic clamp studies, and the euglycemic clamp had sufficient sensitivity to detect the lipid infusion-induced insulin resistance. Nevertheless, we cannot exclude some carryover effect of the hyperglycemic clamp on insulin sensitivity as assessed by the subsequent euglycemic clamp. Since each subject, acting as their own control, underwent four identical study protocols of hyperglycemic clamp followed by euglycemic clamp, any carryover effect would have been identical between the four study protocols and would still allow a valid comparison of the lipid and salicylate interventions.

**Calculations of first-phase insulin response, insulin secretion rate, insulin sensitivity index, insulin clearance, and disposition index.** First-phase insulin response was calculated as insulin concentration area under the curve during the first 10 min of the hyperglycemic clamp. insulin secretion rate (ISR) was calculated from deconvolution of plasma C-peptide concentrations during the last 30 min of the hyperglycemic clamp (52). Insulin sensitivity index (SI) was calculated as $SI = Ins_{clamp} / Ins_{basal}$ from the last 30 min of the euglycemic clamp, where $Ins_{clamp}$ is the glucose clearance estimated as glucose infusion rate (GIR) divided by glucose concentration, $Ins_{clamp}$ is the insulin concentration during the clamp, and $Ins_{basal}$ is the basal insulin level. Insulin clearance ($Cl_I$) was calculated as $Cl_I = ISR / (Ins_{clamp} - Ins_{basal})$ during the last 30 min of the hyperglycemic clamp. $Cl_I$ was also calculated as $Cl_I = Ins_{inf} / (Ins_{clamp} - Ins_{basal})$ during the last 30 min of the euglycemic clamp, where $Ins_{inf}$ is insulin infusion rate (40 mU·m²·min⁻¹). Disposition index (DI) was calculated as $DI = ISR \times Cl_I$, using the ISR estimated from the hyperglycemic clamp and $Cl_I$ estimated from the euglycemic clamp as described above.

**Laboratory analysis.** Plasma glucose was assayed at the bedside using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin and C-peptide were measured with radioimmunoassay kits (Linco Research, St. Charles, MO). Plasma triacylglycerides (TG; Roche Diagnostics, Laval, QC, Canada) and NEFA (Wako Industries, Osaka, Japan) were analyzed with enzymatic colorimetric kits. Plasma C-reactive protein (CRP) was measured with ELISA (Helica, Fullerton, CA). Salicylate was measured with an enzyme assay kit (Cambridge Life Sciences, Cambridgeshire, UK).

**Statistics.** Plasma glucose, insulin, C-peptide, triglycerides and NEFA were analyzed by two-way ANOVA for repeated measurements with Tukey's t-test to detect differences between treatments at each time and between times within treatment during the 48-h infusion period and differences between treatments during the last 30 min of the clamp. A P value of <0.05 was considered significant. All statistical analyses were performed with Statistical Analysis System software (Version 8.0; SAS, Cary, NC).

**RESULTS**

**Preclamp data.** Lipid infusion for 48 h resulted in an approximately twofold increase in plasma TG and NEFA ($P < 0.05$). No significant effects of 1-wk prior treatment with oral sodium salicylate (4.5 g/day) on TG and NEFA were observed when compared with placebo. However, fasting insulin concentrations were higher ($P < 0.05$) in SS and IH + SS than in SAL and IH, respectively, at the end of the 1-wk treatment period and immediately prior to the 48-h infusion of saline or intralipid plus heparin (Table 2). Salicylate concentrations measured on samples prior to the start of the clamp were 1.59 ± 0.30 mmol/l in SS and 1.80 ± 0.28 mmol/l in IH + SS, all within the established therapeutic range for rheumatoid arthritis (0.7–2.2 mmol/l). Salicylate levels were undetectable in placebo-treated groups. CRP levels were not significantly different between groups (1.10 ± 0.41, 1.28 ± 0.44, 1.24 ± 0.38, and 0.99 ± 0.34 μg/ml in SAL, IH, IH + SS, and SS, respectively).

**Hyperglycemic clamp: acute insulin response.** During the first 10 min of the hyperglycemic clamp, plasma insulin levels were similar between IH and SAL but were higher in SS and IH + SS than in SAL and IH, respectively (Fig. 1A). As a result, first-phase insulin response (insulin area under curve during the first 10 min of the hyperglycemic clamp) in SS and
Table 2. Fasting levels of plasma glucose, insulin, C-peptide, TG, and NEFA before and after 48-h infusion of saline or intralipid plus heparin

<table>
<thead>
<tr>
<th></th>
<th>SAL</th>
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<th>SS</th>
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<tr>
<td>Glucose, mmol/l</td>
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</tr>
<tr>
<td>Preinfusion</td>
<td>5.2±0.2</td>
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<tr>
<td>Preclamp</td>
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<td>5.6±0.2</td>
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<td>5.1±0.1</td>
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<td>Insulin, pmol/l</td>
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<tr>
<td>Preinfusion</td>
<td>85.6±15.7</td>
<td>76.5±11.3</td>
<td>119.6±29.1†‡</td>
<td>103.0±24.8*</td>
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<tr>
<td>Preclamp</td>
<td>67.5±9.5</td>
<td>82.2±8.3</td>
<td>127.8±28.5†‡‡</td>
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<tr>
<td>C-peptide, nmol/l</td>
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<td>Preinfusion</td>
<td>0.78±0.14</td>
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<tr>
<td>Preclamp</td>
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<td>0.88±0.13†‡‡</td>
<td>0.72±0.14†‡§</td>
<td>0.43±0.07</td>
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Data are means ± SE; n = 6. SAL, saline infusion; IH, intralipid plus heparin infusion; IH + SS, 1-wk oral sodium salicylate followed by intralipid plus heparin infusion; SS, 1-wk oral sodium salicylate followed by saline infusion. Insulin concentrations in the SS treatment group were likely due to decreased insulin clearance (Fig. 2B). As a result, the calculated insulin secretion rates did not differ among treatments (Fig. 2C). Higher insulin levels in the IH and SS treatment groups combined with similar insulin secretion rates suggests decreased insulin clearance. This was confirmed by the significantly lower calculated insulin clearance rates in IH, IH + SS, and SS studies compared with SAL (P < 0.05; Fig. 2D). Decreased insulin clearance was shown in our previous studies after 24-h oral fat ingestion (53) or 48-h IH infusion (10, 11).

**Euglycemic hyperinsulinemic clamp.** During the last 30 min of the euglycemic hyperinsulinemic clamp, to maintain plasma glucose at the clamped level (~5.6 mmol/l), lower glucose infusion rates were required in the lipid infusion treatment groups (P < 0.05, IH and IH + SS vs. SAL) (Fig. 3A). IH was associated with higher plasma insulin concentration during the euglycemic hyperinsulinemic clamp study compared with SAL (P < 0.05). IH + SS was associated with a further elevation of insulin compared with IH infusion alone (P < 0.05). Insulin in the SS treatment group was also higher than SAL (P < 0.05; Fig. 3B). Since endogenous insulin secretion is completely or almost completely suppressed at the fixed and identical insulin infusion rate used in all four studies (40 mU·m²·min⁻¹), the higher insulin levels in the lipid infusion and/or SS treatment groups were likely due to decreased insulin clearance (P < 0.05), as shown in Fig. 3C.

**S̄ and DI.** S̄ was derived from the last 30 min of the euglycemic hyperinsulinemic clamp. In accord with the reduced glucose infusion rates and/or higher insulin levels, S̄ in IH, IH + SS, and SS were lower than in SAL (IH = 67% of IH + SS, IH, and SS studies compared with SAL (Fig. 3B). Since endogenous insulin secretion is completely or almost completely suppressed at the fixed and identical insulin infusion rate used in all four studies (40 mU·m²·min⁻¹), the higher insulin levels in the lipid infusion and/or SS treatment groups were likely due to decreased insulin clearance (P < 0.05), as shown in Fig. 3C.

**Fig. 1.** Plasma concentrations of insulin (A) and C-peptide (B) during the first 10 min of the hyperglycemic clamp. A, inset: first-phase insulin response (FPR). B, inset: C-peptide area under the curve (AUC). Hyperglycemic clamps were performed on subjects in 4 randomized visits after 48-h saline infusion (SAL), 48-h intralipid plus heparin infusion (IH), 1-wk oral sodium salicylate (4.5 g/day) followed by 48-h intralipid plus heparin infusion (IH + SS), or 1-wk oral sodium salicylate followed by 48-h saline infusion (SS).

*P < 0.05 vs. SAL; †P < 0.05 vs. IH.
SAL, IH + SS = 56% of SAL, and SS = 69% of SAL, P < 0.05, no difference between these 3 treatment groups; Fig. 4A). Since the absolute insulin secretion rates were not significantly affected by IH infusion or oral SS, DI in IH, IH + SS, and SS were similar and all lower than in SAL (P < 0.05; Fig. 4B).

DISCUSSION

In the present study we examined the effects of oral high-dose (4.5 g/day, 1 wk) sodium salicylate treatment, with and without prolonged lipid infusion, on insulin sensitivity and pancreatic β-cell function in obese and overweight nondiabetic men. Since prolonged elevation of plasma NEFA induces insulin resistance (3), we assessed β-cell function by reporting the disposition index, a product of insulin secretion and insulin sensitivity that is well accepted as an accurate measure of insulin secretion (1, 27). Sodium salicylate markedly decreased insulin clearance but did not prevent lipid-induced insulin resistance, nor did it ameliorate the lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54). The similar patterns of insulin sensitivity, secretion, and disposition index in the lipid infusion groups (with and without pretreatment with high-dose oral sodium salicylate) do not support a role for sodium salicylate in ameliorating lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54). The similar patterns of insulin sensitivity, secretion, and disposition index in the lipid infusion groups (with and without pretreatment with high-dose oral sodium salicylate) do not support a role for sodium salicylate in ameliorating lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54). The similar patterns of insulin sensitivity, secretion, and disposition index in the lipid infusion groups (with and without pretreatment with high-dose oral sodium salicylate) do not support a role for sodium salicylate in ameliorating lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54). The similar patterns of insulin sensitivity, secretion, and disposition index in the lipid infusion groups (with and without pretreatment with high-dose oral sodium salicylate) do not support a role for sodium salicylate in ameliorating lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54). The similar patterns of insulin sensitivity, secretion, and disposition index in the lipid infusion groups (with and without pretreatment with high-dose oral sodium salicylate) do not support a role for sodium salicylate in ameliorating lipid-induced impairment in β-cell function that we have described consistently in previous studies in humans (10, 11, 13, 28, 32, 54).

SAL, IH + SS = 56% of SAL, and SS = 69% of SAL, P < 0.05, no difference between these 3 treatment groups; Fig. 4A). Since the absolute insulin secretion rates were not significantly affected by IH infusion or oral SS, DI in IH, IH + SS, and SS were similar and all lower than in SAL (P < 0.05; Fig. 4B).
1–4 wk. In these latter studies, β-cell function was not directly assessed. In the study by Fleischman et al. (17), insulin sensitivity was not directly assessed by euglycemic hyperinsulinemic clamp. Most studies reporting increased insulin secretion examined the acute or first-phase insulin response, which may not be indicative of the β-cell’s maximal capability to secrete insulin and was not interpreted in relation to the associated changes in insulin sensitivity.

The one finding that is consistent across studies (e.g., Refs. 7, 23, and 30), including the present study, is that salicylates decrease insulin clearance. The reduction in insulin clearance is manifest during both basal and glucose-infused conditions, as indicated by increased insulin levels before and during both the hyper- and euglycemic clamps in our study and in studies by others (23, 30). It is not known whether sodium salicylate affects C-peptide clearance. Therefore, insulin clearance in the hyperglycemic clamp, which is calculated using a measurement of prehepatic insulin secretion derived by deconvolution of plasma C-peptide levels, might not be 100% accurate were salicylate to affect C-peptide clearance. However, insulin clearance assessed in the euglycemic hyperinsulinemic clamp was independent of C-peptide concentrations and was clearly reduced by salicylate. The effects of salicylates on insulin clearance may contribute to the controversy with regard to their reported effects on insulin secretion and action. The reduction in insulin clearance contributes to peripheral hyperinsulinemia, which can erroneously be interpreted as an increase in insulin secretion unless accompanied by an increase in plasma C-peptide concentrations or calculated insulin secretion rate, as we have done in the present study. As can be seen from our results, the increase in first-phase insulin response with salicylate treatment was not accompanied by an increase in insulin secretion and therefore likely occurred as a result of decreased insulin clearance. In addition, measurements of glucose disposal must be assessed in relation to circulating insulin concentration. If this calculation is not performed, as we have done in the present study, the increased glucose disposal associated with higher circulating insulin concentrations may be misinterpreted as improved insulin sensitivity. Not all previous studies have taken these important factors into account. Indeed, in a recent study in obese nondiabetic subjects, salsalate increased glucose disposal along with increased insulin levels as a result of decreased insulin clearance. The effect of salicylate on glucose disposal was abolished after normalizing for...
the increased insulin levels (30). In our study, the glucose infusion rates might have been even lower had the insulin levels not increased due to the impaired insulin clearance. Insulin clearance is mediated by similar and partly overlapping pathways affecting insulin sensitivity, and indeed salicylate also decreased insulin action. This may be due to a decrease in cyclooxygenase-1- and cyclooxygenase-2-mediated production of prostaglandin E2, which increases insulin actions (35, 37, 50). Prostaglandin E2 instead decreases insulin secretion (49), which is one of the reasons why salicylate alone might affect insulin secretion. The mechanism by which salicylates reduce insulin clearance warrants further study.

In the present study, we found that the anti-inflammatory agent sodium salicylate did not ameliorate or prevent lipid-induced impairment of insulin secretion and insulin sensitivity in humans. One recent study in healthy men reported that acetylsalicylic acid (a total of 4 g given in 48 h) attenuated lipid-induced insulin resistance (38). In that study, insulin concentrations during a clamp were not reported, and potential effects of salicylates on insulin secretion were not assessed. In a study in rats, 24-h treatment with iv salicylate prevented whole body and skeletal muscle insulin resistance induced by 5-h iv lipid infusion (29). In our recent studies in rats, iv coinfusion of sodium salicylate prevented short-term (7-h) lipid-induced hepatic and peripheral insulin resistance (43). However, we have recently observed reduced effectiveness of sodium salicylate in preventing hepatic insulin resistance induced by prolonged (48-h) lipid infusion in rats (44). However, in the same model, salicylate prevented lipid-induced β-cell dysfunction (42). We do not have an adequate explanation for the different effects of salicylates in humans vs. rodents. Although blood salicylate levels were comparable with those reported that had similar doses of various salicylate products, CRP levels were at the lower end of the normal range, indicating low inflammation. Lipid infusion did not increase circulating CRP, and salicylate at the current dose did not suppress CRP beyond basal level. We cannot rule out the possibility that amelioration of lipid-induced impairment in β-cell function may be observed with a higher oral dose and/or different route of administration. However, higher oral doses of salicylates, including sodium salicylate, are poorly tolerated because of tinnitus, thus limiting their use in practice (23).

In conclusion, the current study does not show that the anti-inflammatory agent sodium salicylate, administered orally at this dose and for this duration, ameliorates or reverses lipid-induced impairment of insulin secretion or insulin sensitivity in nondiabetic, overweight, and obese men. However, on the basis of these data, we cannot exclude a role for inflammation in mediating these lipid effects. Antagonism of interleukin-1β receptor has recently been shown to improve both insulin sensitivity and β-cell function in type 2 diabetic patients (31), and thus more specific and potent anti-inflammatory agents should be examined in future studies.

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GRANTS

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