Effect of Salsalate on Insulin Action, Secretion, and Clearance in Nondiabetic, Insulin-Resistant Individuals: A Randomized, Placebo-Controlled Study

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OBJECTIVE

Salsalate treatment has been shown to improve glucose homeostasis, but the mechanism remains unclear. The aim of this study was to evaluate the effect of salsalate treatment on insulin action, secretion, and clearance rate in nondiabetic individuals with insulin resistance.

RESEARCH DESIGN AND METHODS

This was a randomized (2:1), single-blind, placebo-controlled study of salsalate (3.5 g daily for 4 weeks) in nondiabetic individuals with insulin resistance. All individuals had measurement of glucose tolerance (75-g oral glucose tolerance test), steady-state plasma glucose (SSPG; insulin suppression test), and insulin secretion and clearance rate (graded-glucose infusion test) before and after treatment.

RESULTS

Forty-one individuals were randomized to salsalate (n = 27) and placebo (n = 14). One individual from each group discontinued the study. Salsalate improved fasting (% mean change −7% [95% CI −10 to −14] vs. 1% [−3 to 5], P = 0.005) but not postprandial glucose concentration compared with placebo. Salsalate also lowered fasting triglyceride concentration (−25% [−34 to −15] vs. −6% [−26 to 14], P = 0.04). Salsalate had no effect on SSPG concentration or insulin secretion rate but significantly decreased insulin clearance rate compared with placebo (−23% [−30 to −16] vs. 3% [−10 to 15], P < 0.001). Salsalate was well tolerated, but four individuals needed a dose reduction due to symptoms.

CONCLUSIONS

Salsalate treatment in nondiabetic, insulin-resistant individuals improved fasting, but not postprandial, glucose and triglyceride concentration. These improvements were associated with a decrease in insulin clearance rate without change in insulin action or insulin secretion.

PATHOPHYSIOLOGY/COMPLICATIONS

Although the ability of salicylates to improve glycemic control in patients with type 2 diabetes has been appreciated for over a century (1), their potential use as therapeutic agents has gained recent traction in light of evidence that inflammation may underlie the development of insulin resistance (2,3). However, despite general agreement that salicylates can lower glucose concentrations, the mechanisms

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for this effect remain unclear. Thus, whereas the results of some studies have suggested that salicylates can enhance insulin sensitivity (4–6), others have found either no effect on insulin action (7–9) or an actual worsening (10,11). The discrepancies in these studies may relate to differing methodologies, including participant characteristics, sample size, and treatment duration. In addition, although all of the studies evaluated the effect of salicylates on insulin action, none of them specifically enrolled participants with insulin resistance.

The current study was initiated in an effort to provide experimental information that might help clarify the impact of salicylates on several aspects of glucose homeostasis. For this purpose, we conducted a placebo-controlled study of salsalate, a nonacetylated salicylate, in nondiabetic individuals screened to be insulin resistant. Measurements were made of several facets of glucose metabolism, with the aim of quantifying insulin-mediated glucose disposal (insulin suppression test [IST]) and insulin secretion and clearance rates (graded-glucose infusion test [GGIT]).

RESEARCH DESIGN AND METHODS

Study Design

This was a single-blind, randomized, placebo-controlled, parallel-group study to evaluate the mechanism of salsalate in nondiabetic individuals with insulin resistance. Participants were blinded to treatment assignment and randomized 2:1 to receive salsalate 3.5 g/day or placebo in two divided doses. The protocol was approved by the Stanford Institutional Review Board, and informed consent was obtained from all participants.

Participants

Participants were recruited through online and print advertisements from a single academic center from October 2010 to September 2013. Eligible individuals were aged 30–75 years, overweight/obese (BMI 25–40 kg/m^2), and insulin resistant based on results of the IST. In addition, they were nondiabetic (fasting glucose $<$7 mmol/L and on no antidiabetic drugs) and had no known cardiac, liver, or kidney disease.

Intervention

Participants were block randomized 2:1 (salsalate:placebo) by sex and BMI ($<$30 and $\geq$30 kg/m^2). Salsalate was started at 3.5 g (0.5 g/pill), divided into two daily doses, and continued for 4 weeks. Participants assigned to placebo took the same number of pills. Participants were blinded to treatment assignment for the duration of the study. Study investigators were aware of treatment assignment, but nurses conducting the baseline and end-of-study testing were blinded. Participants were seen weekly to monitor for symptoms and instructed to maintain medication and activity regimen. During these weekly visits, adherence to salsalate or placebo was assessed by participant report and pill count. Dose of salsalate or placebo was titrated down by 0.5 g for persistent symptoms related to salsalate (e.g., tinnitus). Four individuals assigned to salsalate required a dose titration down to 3 g/day.

Metabolic Studies

All study visits were conducted in the Stanford Clinical and Translational Research Unit. All blood samples were collected after 12 h of fasting.

Oral Glucose Tolerance Test

A 75-g oral glucose tolerance test (OGTT) was performed at baseline and after 4 weeks of intervention. Glucose and insulin concentrations were measured at baseline and at 30, 60, 120, and 180 min after glucose challenge. The area under the curve (AUC) for glucose and insulin was calculated using the trapezoidal method. The Matsuda/DeFronzo Index, a surrogate of insulin sensitivity, was also calculated as follows:

$$10,000/\sqrt{(\text{fasting glucose} \times \text{fasting insulin} \times \text{mean glucose} \times \text{mean insulin})}$$

(12,13).

Mean glucose and insulin were calculated using all available time points during the OGTT (30, 60, 120, and 180 min).

IST

Peripheral insulin resistance was directly measured with the modified version (14) of the IST at baseline and after 4 weeks of intervention. The values for insulin sensitivity obtained with this approach are highly correlated ($r \geq 0.87$) with the euglycemic clamp technique (14,15). In brief, after an overnight fast, an intravenous catheter was placed in each of the participant's arms. One arm was used for the administration of a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min); the other arm was used for collecting blood samples. Blood was drawn at 10-min intervals from 150 to 180 min of the infusion to determine the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations. The SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, higher SSPG concentration indicates greater degree of peripheral insulin resistance. All participants were required to have an SSPG concentration $\geq$8.3 mmol/L; this cut point was chosen as this degree of insulin resistance has been predictive of incident type 2 diabetes (16).

GGIT

To measure insulin secretory function, participants received graded intravenous infusions of glucose at progressively increasing rates (1, 2, 3, 4, 6, and 8 mg/kg/min) as previously described (17,18). Each glucose infusion rate was administered for a total of 40 min. Glucose, insulin, and C-peptide concentrations were measured at fasting and then 30 and 40 min into each glucose infusion period. The last two values at the end of each infusion period were averaged and used as the mean for that infusion. AUC for glucose, insulin, and C-peptide were calculated using the trapezoidal method.

Insulin secretion rates (ISRs) were derived by deconvolution of peripheral plasma C-peptide concentrations, using a two-compartment model of C-peptide kinetics and standard parameters for C-peptide clearance estimated for each participant based on body surface area and age (19). For each participant, the mean ISR before and during the six glucose infusion periods was plotted against the corresponding mean glucose to construct a dose-response relationship.

Calculations

Metabolic clearance rate of insulin (MCR-I) was estimated during the IST and GGIT. During the IST, MCR-I was estimated by dividing insulin infusion rate by SSPI, which provides an estimate of

clearance rate of exogenous insulin. During the GGIT, MCR-I was calculated by dividing ISR AUC by insulin AUC, which provides an estimate of endogenous insulin clearance rate (17). Both MCR-Is were adjusted for body surface area.

Glucose was determined by the oxidase method (Analyzer 2; Beckman, Brea, CA). Insulin and C-peptide concentrations were measured at Washington University (St. Louis, MO) using radioimmunoassay (Millipore, St. Charles, MO). The inter- and intra-assay coefficient of variation ranged between 4.7 and 9.7% for insulin and between 5.2 and 10.9% for C-peptide. Lipid profile, creatinine, and alanine aminotransferase (ALT) were measured in the clinical laboratory at Stanford University Medical Center.

Statistical Methods

The primary outcome of the study was change in insulin resistance (SSPG). With 26 participants assigned to salsalate and 13 to placebo, we had 83% power to detect a 2.2 mmol/L difference in SSPG concentration (~20%). This degree of change in SSPG concentration is comparable to that observed after weight loss of 7% of body weight (20).

All statistical analyses were performed using SPSS (version 21 for Windows; SPSS, Chicago, IL). Data are reported as mean ± SD or median [interquartile range]. The percent mean change represents change in a variable relative to baseline value; for example, the percent mean change of fasting glucose was calculated as follows: ($glucose_{after\ treatment}$ − $glucose_{before\ treatment}$) divided by $glucose_{before\ treatment}$. Mean differences within groups were assessed using paired Student *t* tests. Differences between salsalate and placebo groups were assessed using an independent Student *t* test.

RESULTS

Originally, 41 participants were randomized (27 salsalate and 14 placebo). One participant assigned to salsalate dropped from the study due to tinnitus and heartburn. A participant assigned to placebo dropped from the study for personal reasons. Therefore, a total of 39 participants (26 salsalate and 13 placebo) were analyzed (see Supplementary Fig. 1).

Table 1 shows the baseline characteristics of participants assigned to salsalate and placebo. The two groups were not different in age, sex, ethnicity, estimates of adiposity, or plasma glucose concentrations. SSPG concentrations were elevated to a similar degree in both groups. Not surprisingly in these insulin-resistant individuals, the majority of participants in both groups had prediabetes.

A comparison of all metabolic measurements made in the salsalate versus placebo groups is presented in Table 2. Focusing initially on the more general comparisons, it can be seen that weight remained stable in both groups. Triglyceride concentration significantly decreased in participants receiving salsalate, but not in placebo-treated individuals. There were no changes in other lipid, creatinine, or ALT concentrations.

Figure 1 shows the changes in glucose and insulin concentrations after oral glucose ingestion during the OGTT, and the quantitative data are provided in Table 2. Fasting glucose concentrations, prior to the oral glucose load, were lower in participants given salsalate (% mean change −7% [95% CI −10 to −4] vs. 1% [−3 to 5], $P = 0.005$). However, the response to the glucose challenge (glucose AUC) did not change in salsalate-treated participants (Fig. 1*A*), whereas placebo treatment was associated with a 9% decline in glucose AUC (Fig. 1*B*). In contrast, insulin AUC significantly increased after salsalate treatment (Fig. 1*C*), but there was no significant change in participants receiving placebo (Fig. 1*D*). However, when the treatment-associated increases in insulin AUC were directly compared, the values in the two groups were not significantly different (36% [17–54] vs. 16% [−5 to 37], $P = 0.18$). The Matsuda/DeFronzo Index decreased in both groups but only significantly in the placebo group; the difference between the two groups was not significant (−9% [−24 to 7] vs. −14% [−25 to −3], $P = 0.64$).

Results of the IST are summarized in Table 2. As before, fasting plasma glucose concentration was significantly lower in the salsalate-treated participants on the morning of the IST (−8% [95% CI −11 to −5] vs. 0% [−9 to 12], $P = 0.004$). However, this improvement in fasting glucose concentration was not associated with any change in SSPG concentration, and the values before and after intervention were essentially similar in both experimental groups. However, it should be noted that SSPI concentrations were significantly higher after salsalate treatment (20% [10–30] vs. −5% [−17 to 7], $P = 0.003$), associated with a decreased MCR-I (−13% [−20 to −6] vs. 10% [−6 to 26], $P = 0.002$) (Fig. 2*A*). The fact that SSPG concentrations were not lower in those receiving salsalate, despite higher SSPI concentrations, provides further evidence that insulin sensitivity had not improved in response to treatment with salsalate. For completeness sake, we also adjusted change in SSPG by change in SSPI, and there was still no significant difference in SSPG concentration between salsalate and placebo groups ($P = 0.83$). Thus, it is clear that salsalate treatment decreased insulin catabolism and was without effect on insulin action.

The changes observed during the GGIT are shown in Supplementary Fig. 2, and the findings are summarized in Table 2. Fasting plasma glucose concentration was again lower in salsalate-treated

Table 1—Baseline characteristics

	Salsalate ($n = 26$)	Placebo ($n = 13$)	*P*
Age (years)	54 ± 10	54 ± 10	0.96
Female, *n* (%)	12 (46%)	4 (31%)	0.49
Non-Hispanic white, *n* (%)	16 (62%)	7 (54%)	0.73
BMI (kg/m^2)	32.9 ± 3.8	33.2 ± 3.0	0.84
Waist circumference (cm)	108 ± 11	108 ± 8	0.90
OGTT			
Fasting glucose (mmol/L)	6.0 ± 0.5	5.7 ± 0.6	0.07
2-h glucose (mmol/L)	7.9 ± 2.0	8.4 ± 2.2	0.52
Prediabetes, *n* (%)	23 (89%)	9 (69%)	0.19
SSPG (mmol/L)	11.9 ± 2.5	11.6 ± 1.6	0.63

Data are mean ± SD unless otherwise specified.

Table 2—Summary of changes after salsalate or placebo treatment

	Salsalate (n = 26)				Placebo (n = 13)				
	Baseline	4 weeks	% mean change*	P	Baseline	4 weeks	% mean change*	P	Between-group P
Weight (kg)	95 [84–106]	96 [84–16]	0 (0–1)	0.48	92 [85–99]	92 [87–98]	0 (−1 to 1)	0.40	0.62
Triglyceride (mmol/L)	1.4 [0.9–2.3]	1.1 [0.7–1.5]	−25 (−34 to −15)	<0.001	2.1 [1.4–2.7]	1.7 [1.6–2.4]	−6 (−26 to 14)	0.33	0.04
HDL-C (mmol/L)	1.2 [0.9–1.4]	1.2 [1.0–1.5]	2 (−4 to 7)	0.91	1.1 [0.9–1.2]	1.1 [0.9–1.2]	1 (−6 to 9)	0.95	0.93
LDL-C (mmol/L)	3.0 [2.6–3.5]	3.1 [2.6–3.7]	6 (−4 to 15)	0.45	3.9 [3.2–4.6]	3.9 [2.8–4.6]	−3 (−9 to 4)	0.63	0.25
Creatinine (μmol/L)	80 [71–91]	80 [71–97]	2 (−6 to 9)	0.67	80 [71–93]	80 [57–102]	−2 (−18 to 15)	0.99	0.64
ALT (units/L)	44 [34–53]	42 [36–49]	29 (−29 to 88)	0.33	41 [32–56]	42 [37–60]	9.1 (−7.1 to 25)	0.50	0.62
OGTT									
Fasting glucose (mmol/L)	6.0 [5.6–6.5]	5.6 [5.4–5.7]	−7 (−10 to −4)	<0.001	5.5 [5.4–6.2]	5.8 [5.2–6.2]	1 (−3 to 5)	0.77	0.005
Glucose AUC (mmol/L × 3 h)	24 [22–28]	23 [20–28]	−1 (−6 to 5)	0.72	26 [21–29]	24 [19–25]	−9 (−14 to −4)	0.004	0.03
Insulin AUC (pmol/L × 3 h)	1,730 [1,426–3,107]	2,596 [1,568–3,388]	36 (17–54)	0.001	2,096 [1,688–2,971]	2,457 [1,769–3,488]	16 (−5 to 37)	0.23	0.18
Matsuda/DeFronzo Index	1.9 [1.4–2.7]	1.6 [1.2–2.5]	−9 (−24 to 7)	0.12	2.1 [1.4–2.7]	1.7 [1.2–2.3]	−14 (−25 to −3)	0.01	0.64
IST									
Fasting glucose (mmol/L)	6.0 [5.7–6.3]	5.5 [5.2–5.7]	−8 (−11 to −5)	<0.001	5.6 [5.3–6.5]	5.6 [5.3–6.4]	0 (−9 to 12)	0.98	0.004
SSPG (mmol/L)	12.3 [9.6–13.5]	11.9 [10.2–13.8]	−3 (−10 to 5)	0.29	11.1 [10.4–12.7]	11.3 [10.3–13.7]	2 (−9 to 12)	0.91	0.47
SSPI (pmol/L)	516 [403–617]	607 [511–699]	20 (10–30)	<0.001	549 [474–636]	538 [381–637]	−5 (−17 to 7)	0.47	0.003
MCR-I (L/min/m^2)	0.43 [0.36–0.55]	0.37 [0.32–0.43]	−13 (−20 to −6)	0.001	0.40 [0.35–0.47]	0.41 [0.35–0.58]	10 (−6 to 26)	0.17	0.002
GGIT									
Fasting glucose (mmol/L)	6.0 [5.7–6.4]	5.6 [5.2–6.0]	−7 (−11 to −3)	<0.001	5.6 [5.4–5.9]	5.7 [5.4–6.3]	1 (−3 to 5)	0.66	0.008
Glucose AUC (mmol/L × 4 h)	33 [30–35]	32 [30–34]	−2 (−6 to 1)	0.07	31 [29–33]	30 [28–35]	0 (−6 to 6)	0.99	0.35
Insulin AUC (pmol/L × 4 h)	1,185 [782–1,746]	1,274 [1,053–2,070]	29 (14–43)	0.003	1,183 [758–2,036]	1,090 [740–1,633]	2 (−16 to 20)	0.73	0.02
C-peptide AUC (nmol/L × 4 h)	6.8 [4.8–9.6]	6.0 [4.1–8.7]	−7 (−14 to −1)	0.02	7.3 [6.1–9.4]	6.8 [6.2–9.0]	−2 (−11 to 8)	0.16	0.26
ISR AUC (pmol/min × 4 h)	2,172 [1,446–2,962]	1,850 [1,269–2,976]	−6 (−12 to 0)	0.08	2,334 [1,738–2,845]	2,228 [1,734–2,812]	0 (−9 to 9)	0.33	0.21
MCR-I (L/min/m^2)	0.91 [0.80–1.1]	0.67 [0.55–0.81]	−23 (−30 to −16)	<0.001	0.79 [0.66–1.2]	0.86 [0.72–1.3]	3 (−10 to 15)	0.88	<0.001

Data are median [interquartile range]. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol. *Percent mean change relative to baseline (95% CI).

participants on the day of the GGIT (−7% [95% CI −11 to −3] vs. 1% [−3 to 5], P = 0.008). However, glucose AUC did not change after either salsalate or placebo treatment. Consistent with the increases in SSPI during the IST and insulin AUC during the OGTT, insulin AUC significantly increased during the GGIT after salsalate treatment compared with placebo (29% [14–43] vs. 2% [−16 to 20], P = 0.02). In addition, C-peptide AUC modestly declined after salsalate treatment, but the difference was not significant when compared with placebo treatment. Neither intervention had any effect on the dose-response relationship between glucose and ISR (Supplementary Fig. 2*G* and *H*). Finally, similar to changes during the IST, MCR-I (Fig. 2*B*) decreased after salsalate treatment whereas placebo treatment had no effect (−23% [−30 to −16] vs. 3% [−10 to 15], $P < 0.001$). Therefore, as with the IST, the physiological effect of salsalate was to decrease insulin clearance rate.

Although salsalate treatment was associated with decline in MCR-I during both the IST and GGIT, the degree of decline was greater during the GGIT (−23 vs. −13%). This difference may relate to the fact that the GGIT measures clearance rate of endogenous insulin whereas the IST predominately assesses clearance rate of exogenous insulin. In addition, although both measures of MCR-I declined after salsalate treatment, the degree of decline in MCR-I was not significantly correlated (r = −0.03, P = 0.88) in the individuals treated with salsalate. On the other hand, there was significant correlation between decline in MCR-I measured during the GGIT and increase in insulin AUC during the OGTT, which also provides a surrogate measure of endogenous insulin clearance rate (r = −0.51, P = 0.007).

The majority in both groups took at least 80% of their pills (89% on salsalate vs. 92% on placebo, P = 0.99). The most common side effect of salsalate was tinnitus. However, a similar number of individuals on placebo also reported tinnitus during the study duration (54 vs. 42%, P = 0.52). However, dose reduction for severe tinnitus only occurred in participants (n = 3) taking salsalate. Another participant required a dose reduction for complaints of fatigue and constipation.

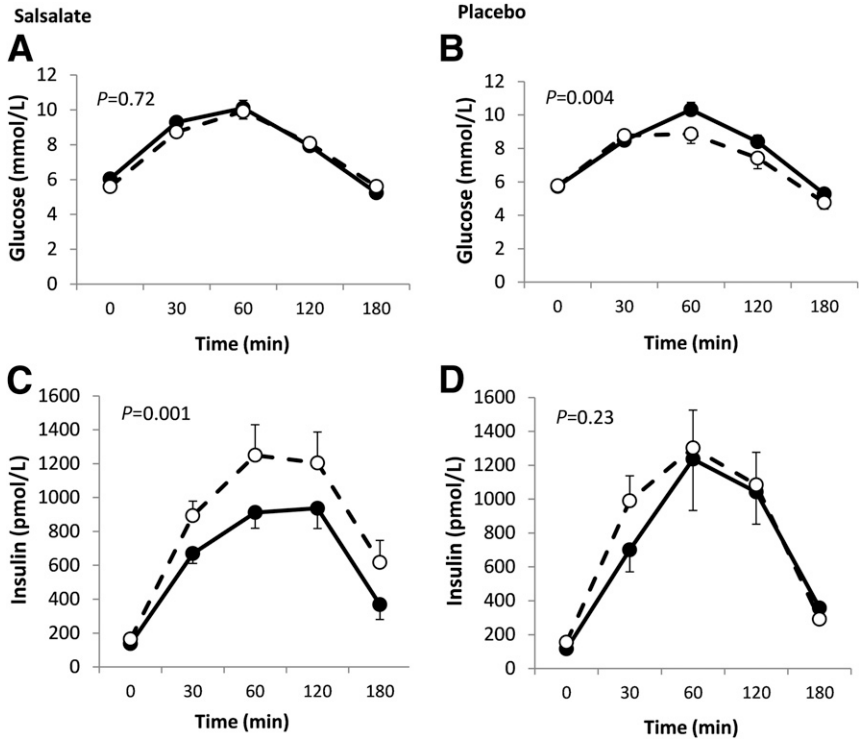

Figure 1—Changes during the OGTT in glucose (*A* and *B*) and insulin (*C* and *D*) profile following salsalate (*A* and *C*) and placebo (*B* and *D*) treatment. Curves at baseline (closed circles) and 4 weeks (open circles) after treatment are shown. Glucose AUC was significantly lower after placebo (P = 0.004), and insulin AUC was significantly higher after salsalate (P = 0.001). P values represent within-group difference in AUC.

CONCLUSIONS

Perhaps the most useful approach to placing our results in the context of what is known of the relationship between salicylates and carbohydrate metabolism would be to begin by focusing on the central findings, followed by consideration of the implications of our observations. At the simplest level, we could not discern any evidence that salicylate administration improved insulin-mediated glucose disposal in nondiabetic, insulin-resistant participants. This conclusion differs with findings from previous studies that salicylate treatment enhanced insulin sensitivity (4–6). However, it should be noted that the experimental protocols were quite different. Thus, in one instance (4), it was shown that acute administration of salicylates to healthy individuals decreased the magnitude of the increase in degree of insulin resistance induced by an acute lipid infusion. The other two studies (5,6) reporting that salicylates improved insulin sensitivity did not measure insulin action directly but used a surrogate estimate (homeostasis model assessment of insulin resistance), and the potential limitations of that measurement have recently been emphasized (21). Recent studies, focusing on individuals at increased risk of type 2 diabetes in an effort to evaluate the effects of salicylates in insulin-resistant individuals, have found no effect on insulin action using either the frequently sampled intravenous glucose tolerance test (7) or the euglycemic clamp (8,9) after 1–4 weeks of salicylate administration.

Our second major finding was the salicylate-associated decrease in insulin catabolism as evidenced by significantly lower MCR-I during both the IST and GGIT. Therefore, salsalate treatment affected the catabolism of both exogenous (IST) and endogenous (GGIT) insulin. Surprisingly, few past studies have evaluated changes in MCR-I after salicylates. However, when evaluated, MCR-I has been found to be decreased (8,9,11). Although the exact mechanism for the decrease in MCR-I is unknown, this effect is possibly the major reason why salicylates lower plasma glucose concentrations.

Our third major finding was the absence of any effect of salsalate treatment on ISR or pancreatic β-cell sensitivity to glucose. As seen in Supplementary Fig. 2*G*, the dose-response relationship between glucose and ISR was identical after salsalate treatment. Two past studies suggested that salicylates may increase the ISR based on increased insulin concentrations during the frequently sampled intravenous glucose tolerance test (7) or the hyperglycemic clamp (10). Since these studies only measured plasma insulin concentration, not ISR, it is quite likely that the described increase in plasma insulin concentration was secondary to a salicylate-induced decrease in insulin removal rate, not an increase in insulin secretion.

Although our results provide measurements of the effects of salicylates on insulin action, secretion, and clearance in an insulin-resistant population, questions as to the metabolic effects of salicylates remain. For example, our findings do not rule out the possibility that the magnitude of the anti-inflammatory effect of salsalate was insufficient to improve insulin action in our study. Thus, in a study similar to ours (9), a somewhat greater dose of salsalate (4 g/day) did not significantly improve C-reactive protein, interleukin 6, or soluble vascular adhesion molecule 1 in subjects with abnormal

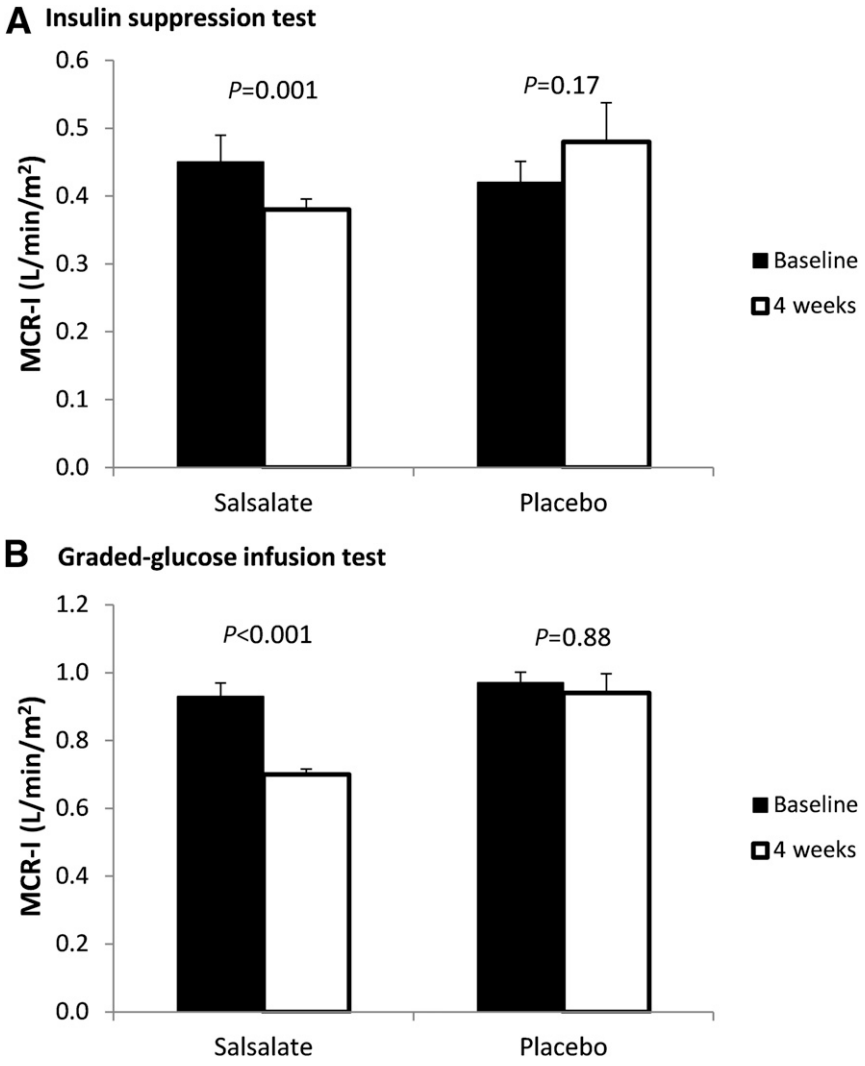

Figure 2—Change in MCR-I during the IST (*A*) and GGIT (*B*). Salsalate significantly decreased MCR-I during both the IST and GGIT.

glucose tolerance. Consequently, it is possible that a greater salicylate-induced anti-inflammatory effect could enhance insulin sensitivity. In addition, the glucose-lowering effect of salsalate was confined to the fasting state, and we did not observe any improvement in post-glucose challenge hyperglycemia. Thus, despite a significantly higher insulin AUC during the OGTT, the glucose AUC was almost identical in salicylate-treated individuals (the glucose AUC was actually somewhat lower in the placebo-treated participants, which we believe is likely due to type I error). Furthermore, a recent study has shown in patients with type 2 diabetes that salsalate significantly lowered fasting glucose concentration without any change in postprandial glucose (22). One possible explanation for the apparent predominant effect on fasting versus postprandial glucose might be an action of salicylate on the liver, and there is evidence that hepatic glucose production is inhibited by salicylates in patients with type 2 diabetes (11,23). Finally, more information is needed concerning the effect of salicylates on lipoprotein metabolism. Although we did not observe a salsalate-induced increase in LDL cholesterol concentration as described by Goldfine et al. (9), both studies noted a significant decline in fasting triglyceride concentration. Recently, salicylates have been shown to activate adenosine monophosphate-activated protein kinase (AMPK) in human cell lines (24,25). AMPK has numerous effects on metabolism (e.g., fatty acid oxidation) and inflammation (26), and it remains to be seen if AMPK activation explains the effects of salicylates on lipid and carbohydrate metabolism.

There were limitations to the current study. The sample size was relatively small and the duration of treatment was short. In addition, we cannot exclude that effects of salsalate may differ in individuals with type 2 diabetes compared with our population of nondiabetic individuals with insulin resistance. On the other hand, our study is also the first one to simultaneously evaluate the effect of salsalate on insulin action, secretion, and catabolism in insulin-resistant individuals. More specifically, we have shown in insulin-resistant individuals that salsalate administration significantly impairs insulin catabolism, without any effect on insulin secretion or insulin-mediated glucose disposal. Although no methodology is perfect, the same findings were observed with three different experimental approaches, the OGTT, IST, and GGIT. Finally, we believe

it is important to initiate further studies in an effort to understand why fasting glucose and triglyceride concentrations decreased in association with salsalate administration in nondiabetic individuals with insulin resistance and/or abnormal glucose tolerance (9).

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.H.K. helped design and conducted the research, analyzed the data, and wrote and edited the manuscript. A.L., D.A., F.A., C.L., K.G., V.T., and H.O. conducted the research. G.R. designed the study and edited the manuscript. S.H.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Williamson RT. On the treatment of glycosuria and diabetes mellitus with sodium salicylate. Br Med J 1901;1:760–762
2. Yuan M, Konstantopoulos N, Lee J, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science 2001;293:1673–1677
3. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793–1801
4. Möhlig M, Freudenberg M, Bobbert T, et al. Acetylsalicylic acid improves lipid-induced insulin resistance in healthy men. J Clin Endocrinol Metab 2006;91:964–967
5. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. Diabetes Care 2008;31:289–294
6. Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. Reduction of insulin resistance and plasma glucose level by salsalate treatment in persons with prediabetes. Endocr Pract 2012;18:826–833
7. Fernández-Real JM, López-Bermejo A, Ropero AB, et al. Salicylates increase insulin secretion in healthy obese subjects. J Clin Endocrinol Metab 2008;93:2523–2530
8. Koska J, Ortega E, Bunt JC, et al. The effect of salsalate on insulin action and glucose tolerance in obese non-diabetic patients: results of a randomised double-blind placebo-controlled study. Diabetologia 2009;52:385–393
9. Goldfine AB, Conlin PR, Halperin F, et al. A randomised trial of salsalate for insulin resistance and cardiovascular risk factors in persons with abnormal glucose tolerance. Diabetologia 2013;56:714–723
10. Newman WP, Brodows RG. Aspirin causes tissue insensitivity to insulin in normal man. J Clin Endocrinol Metab 1983;57:1102–1106
11. Bratusch-Marrain PR, Vierhapper H, Komjati M, Waldhäusl WK. Acetyl-salicylic acid impairs insulin-mediated glucose utilization and reduces insulin clearance in healthy and non-insulin-dependent diabetic man. Diabetologia 1985;28:671–676
12. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
13. DeFronzo RA, Matsuda M. Reduced time points to calculate the composite index. Diabetes Care 2010;33:e93
14. Greenfield MS, Doberne L, Kraemer F, Tobey T, Reaven G. Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. Diabetes 1981;30:387–392
15. Knowles JW, Assimes TL, Tsao PS, et al. Measurement of insulin-mediated glucose uptake: direct comparison of the modified insulin suppression test and the euglycemic, hyperinsulinemic clamp. Metabolism 2013;62:548–553
16. Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. J Clin Endocrinol Metab 2001;86:3574–3578
17. Kim SH, Abbasi F, Chu JW, et al. Rosiglitazone reduces glucose-stimulated insulin secretion rate and increases insulin clearance in nondiabetic, insulin-resistant individuals. Diabetes 2005;54:2447–2452
18. Jones CN, Pei D, Staris P, Polonsky KS, Chen YD, Reaven GM. Alterations in the glucose-stimulated insulin secretory dose-response curve and in insulin clearance in nondiabetic insulin-resistant individuals. J Clin Endocrinol Metab 1997;82:1834–1838
19. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 1992;41:368–377
20. McLaughlin T, Carter S, Lamendola C, et al. Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. Am J Clin Nutr 2006;84:813–821
21. Reaven GM. What do we learn from measurements of HOMA-IR? Diabetologia 2013;56:1867–1868
22. Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. Acta Diabetol 2013;50:537–543
23. Hundal RS, Petersen KF, Mayerson AB, et al. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. J Clin Invest 2002;109:1321–1326
24. Hawley SA, Fullerton MD, Ross FA, et al. The ancient drug salicylate directly activates AMP-activated protein kinase. Science 2012;336:918–922
25. Din FV, Valanciute A, Houde VP, et al. Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. Gastroenterology 2012;142:1504–1515.e3
26. Steinberg GR, Dandapani M, Hardie DG. AMPK: mediating the metabolic effects of salicylate-based drugs? Trends Endocrinol Metab 2013;24:481–487