(Anti-) Inflammation in T2D and CVD: Pathogenic Mediator and Clinical Outcomes

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In dieser Woche (Jahrg. 1873 No. 49, und 1875 No. 5) haben Julius Müller und ich den Nachweis geliefert, dass die Carbolösure in einer Reihe von Fällen beim Diabetes mellitus die diabetischen Symptome zum Verschwinden bringt. Der Kreis unserer Beobachtungen hat sich in dieser Beziehung seit unserer letzten Publikation bedeutend erweitert, und wir gedenken auf diesen Gegenstand in nächster Zeit wieder zurückzukommen, bei welcher Gelegenheit wir auch eine Reihe einschlägiger fremder positiver und negativer Erfahrungen mitteilen werden.

Ich schicke diese Bemerkung voraus, damit es nicht den Anschein habe, als solle durch die nachfolgenden Mitteilungen die günstige Wirksamkeit der Carbolösure bei gewissen leiden, leider zur
ON THE TREATMENT OF GLYCOSURIA AND DIABETES MELLITUS WITH SODIUM SALICYLATE.

By R. T. WILLIAMSON, M.D.Lond., F.R.C.P.
Physician to the Ancoats Hospital, Manchester, and Assistant Lecturer on Medicine, Owens College.

It is somewhat difficult to form a correct estimate of the action of drugs on the sugar excretion in cases of glycosuria and diabetes for many reasons. The occurrence of complications, such as phthisis for example, in the course of the disease may cause a diminution of the sugar excretion, which at first sight appears to be the result of medical treatment. Also in the treatment of diabetes the diet is restricted, more or less, at the same time that various drugs are prescribed; hence it is often impossible to say how much of the improvement which follows is due to the action of the restricted diet and how much to the drug. In the most severe form of diabetes it is usually easy to demonstrate that no drug has much influence on the sugar excretion. But in the milder forms of diabetes or persistent glycosuria, considerable care is necessary in

“The results just recorded appear to me to prove conclusively that in this case sodium salicylate had a definite influence in greatly diminishing the sugar excretion.”
High-Dose Salicylate in Zucker Fatty Rats

OGTT

Glucose (mg/dl)

Time (min)

Vehicle

3 wk salicylate

Insulin (ng/ml)

Time (min)

Vehicle

3 wk salicylate

Yuan...Shoelson (2001) Science 293, 1673
Do salicylates lower blood glucose and thus thus thus provide:

1) Clues to better understand molecular pathogenesis in insulin resistance, T2D and CVD?

2) Leads for pharmacological target identification and validation?

3) Potential new treatment strategies for patients with diabetes and CVD?
What is the Molecular Target of High-Dose Salicylate?

Inhibit Platelet Aggregation
- 81-100 mg COX1
- 650 mg COX1/2
- 3-5 g NF-κB

Fever, Headache, Aches & Pains
- Fever
- Headache
- Aches & Pains

Rheumatic Fever, Arthritis
- Rheumatic Fever
- Arthritis


TNFRs

IL-1R / TLRs

PKCs

ROS

Ceramides

ER stress

NF-κB

IKKβ

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What are the Primary Sites of IKKβ/NF-κB Mediated Insulin Resistance?

IKKβ → IκBα/ NF-κB → NF-κB

Activated
IKKβ SS/EE
Muscle, MCK MIKK
Liver, Alb LIKK
Fat, aP2 FIKK
β Cell, Ins2 βIKK

Inhibited
IκBα SR
MISR MIKK-KO
LISR
FISR FIKK-KO
βISR βIKK-KO

Salicylate Reverses Muscle Wasting

Tumor-induced muscle wasting

Cancer Cachexia

IKKβ/NF-κB Activation Causes Severe Muscle Wasting in Mice

Dongsheng Cai,1,6 J. Daniel Frantz,1,6,10
Nicholas E. Tawa, Jr.,2,7 Peter A. Melendez,1,6,11
Byung-Chul Oh,1,6 Hart G.W. Lidov,3,8
Per-Olof Hasselgren,2,7 Walter R. Frontera,4,9
Jongsoon Lee,1,6 David J. Glass,5
and Steven E. Shoelson1,6,*

1Research Division

Growth Factors  →  Akt1  →  Foxo  →  MAFbx/atroglin-1  →  Proteasome  →  Muscle Atrophy

Cachexia Factors

IKK

NF-κB

MuRF1

Proteasome

Muscle Atrophy

Salicylates

IκB Super Repressor
NF-kB inhibition in Adipocytes Protects Against Weight Gain
Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters

Markus Feuerer\textsuperscript{1,5}, Laura Herrero\textsuperscript{2,5}, Daniela Cipolletta\textsuperscript{1,4,5}, Afia Naaz\textsuperscript{2}, Jamie Wong\textsuperscript{1,5}, Ali Nayer\textsuperscript{2}, Jongsoo Lee\textsuperscript{2}, Allison B Goldfine\textsuperscript{3}, Christophe Benoist\textsuperscript{1,5}, Steven Shoelson\textsuperscript{2} & Diane Mathis\textsuperscript{1,5}

Obesity is accompanied by chronic, low-grade inflammation of adipose tissue, which promotes insulin resistance and type-2 diabetes. These findings raise the question of how fat inflammation can escape the powerful armamentarium of cells and molecules normally responsible for guarding against a runaway immune response. CD4\textsuperscript{+} Foxp3\textsuperscript{+} T regulatory (T\textsubscript{reg}) cells with a unique phenotype were highly enriched in the abdominal fat of normal mice, but their numbers were strikingly and specifically reduced at this site in insulin-resistant models of obesity. Loss-of-function and gain-of-function experiments revealed that these T\textsubscript{reg} cells influenced the inflammatory state of adipose tissue and, thus, insulin resistance. Cytokines differentially synthesized by fat-resident regulatory and conventional T cells directly affected the synthesis of inflammatory mediators and glucose uptake by cultured adipocytes. These observations suggest that harnessing the anti-inflammatory properties of T\textsubscript{reg} cells to inhibit elements of the metabolic syndrome may have therapeutic potential.
NF\textsubscript{\textkappa}B-GFP Transgenic Mice

Obesity

NF\textsubscript{\textkappa}B Dimers

3 NF\textsubscript{\textkappa}B promoter binding sites

GFP Gene

GFP
Obesity Activates NFκB+ and Salicylate Inhibits NFκB+ in Circulating Monocytes

Yasuhiko Yamamoto & Jongsoon Lee
Obesity Activates NF-κB and Salicylate Inhibits NF-κB in Circulating Monocytes

15 week HFD / 4 week Salicylate

Goldfine...Shoelson, CTS, 2008;1;36
Human Trials?

Is inflammation a practical therapeutic target in type 2 diabetes?

Do anti-inflammatory strategies prevent diabetes and decrease risk of CVD?
4.0 g/d salsalate in T2D: 4 weeks duration/placebo controlled

Mixed meal tolerance test

Goldfine…Shoelson, CTS, 2008;1;36
TINSAL-T2D Stage 1

Targeting Inflammation with Salsalate in Type 2 Diabetes, a NIDDK-Sponsored Trial

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Kathleen Jablonski, DCC/GWU    Myrlene Staten, NIDDK

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New Orleans, LA
TINSAL-T2D Trial Design

Stage I: 14-week multicenter, double-masked, placebo-controlled dose ranging study in inadequately controlled T2D (7.0 < HbA1c ≤ 9.5)

Screen n=240, Randomize n=108

- Placebo n=27
- 3.0g n=27
- 3.5g n=27
- 4.0g n=27

Stage II: 26-week multicenter, double-masked, placebo-controlled phase III trial

Screen n=564, Randomize n=282

- Placebo n=141 randomized
  - Placebo n=113 complete
- Optimal Salsalate Dose n=141 randomized
  - Salsalate n=113 complete
TINSAL-T2D* Stage 1 Trial Design

*TINSAL-T2D is an NIH/NIDDK sponsored multi-center, randomized, double-masked, placebo-controlled, dose ranging parallel-group clinical trial.
# TINSAL-T2D Stage 1: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (27)</th>
<th>3.0 g/d (27)</th>
<th>3.5 g/d (27)</th>
<th>4.0 g/d (27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>55.9 ± 8.2</td>
<td>55.4 ± 9.4</td>
<td>56.7 ± 9.8</td>
<td>55.0 ± 10.2</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Male / Female (%)</strong></td>
<td>56 / 44</td>
<td>52 / 48</td>
<td>67 / 33</td>
<td>59 / 41</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>White / Black / Other (%)</strong></td>
<td>56 / 33 / 11</td>
<td>44 / 46 / 7</td>
<td>52 / 37 / 11</td>
<td>56 / 40 / 4</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>99.1 ± 22.1</td>
<td>92.9 ± 22.2</td>
<td>97.7 ± 18.8</td>
<td>102 ± 20.7</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>34.0 ± 6.1</td>
<td>32.3 ± 6.8</td>
<td>32.9 ± 6.5</td>
<td>35.0 ± 6.5</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>104 ± 22.7</td>
<td>103 ± 15.6</td>
<td>106 ± 18.7</td>
<td>109 ± 23.0</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Years since T2D diagnosed</strong></td>
<td>5.1 ± 3.7</td>
<td>6.4 ± 5.2</td>
<td>6.9 ± 6.0</td>
<td>6.4 ± 4.4</td>
<td>0.58</td>
</tr>
</tbody>
</table>
# TINSAL-T2D Stage 1: Baseline Patient Characteristics

## Physical Findings

<table>
<thead>
<tr>
<th></th>
<th>Placebo (27)</th>
<th>3.0 g/d (27)</th>
<th>3.5 g/d (27)</th>
<th>4.0 g/d (27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125 ± 14.4</td>
<td>125 ± 12.8</td>
<td>124 ± 13.2</td>
<td>128 ± 11.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>76 ± 8.2</td>
<td>79 ± 7.4</td>
<td>77 ± 9.5</td>
<td>76 ± 9.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74.0 ± 10.9</td>
<td>72.4 ± 8.6</td>
<td>73.5 ± 13.2</td>
<td>71.8 ± 7.1</td>
<td>0.85</td>
</tr>
</tbody>
</table>

## Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>Placebo (27)</th>
<th>3.0 g/d (27)</th>
<th>3.5 g/d (27)</th>
<th>4.0 g/d (27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>180 ± 48.6</td>
<td>164 ± 50.0</td>
<td>186 ± 54.4</td>
<td>170 ± 26.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>183 ± 92.8</td>
<td>184 ± 178</td>
<td>151 ± 75.6</td>
<td>160 ± 80.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>153 ± 39.8</td>
<td>154 ± 41.5</td>
<td>149 ± 38.5</td>
<td>144 ± 36.2</td>
<td>0.76</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.8 ± 0.8</td>
<td>7.9 ± 1.1</td>
<td>7.4 ± 0.7</td>
<td>7.6 ± 0.9</td>
<td>0.25</td>
</tr>
</tbody>
</table>
### TINSAL-T2D Stage 1: Baseline Patient Characteristics

#### Ongoing diabetes therapies (%)

<table>
<thead>
<tr>
<th>Treatment Arm (n)</th>
<th>Placebo (27)</th>
<th>3.0 g/d (27)</th>
<th>3.5 g/d (27)</th>
<th>4.0 g/d (27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle only</td>
<td>14.8</td>
<td>14.8</td>
<td>18.5</td>
<td>11.1</td>
<td>0.98</td>
</tr>
<tr>
<td>Metformin</td>
<td>81.5</td>
<td>81.5</td>
<td>66.7</td>
<td>85.6</td>
<td>0.35</td>
</tr>
<tr>
<td>Insulin secretagogue</td>
<td>48.1</td>
<td>37.0</td>
<td>44.4</td>
<td>44.4</td>
<td>0.94</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>3.7</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Two or more DM drugs</td>
<td>37.4</td>
<td>28.7</td>
<td>17.9</td>
<td>34.7</td>
<td>0.76</td>
</tr>
</tbody>
</table>
TINSAL-T2D Stage 1: HbA1c (primary endpoint)

*Holm’s procedure

<table>
<thead>
<tr>
<th>Placebo</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 g</td>
<td>0.02</td>
</tr>
<tr>
<td>3.0 g</td>
<td>0.02</td>
</tr>
<tr>
<td>4.0 g</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*P vs. placebo

Trial week: 0, 4, 8, 14

Percent HbA1c (change from baseline)
### TINSAL-T2D Stage 1: HbA1c (primary endpoint)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.5 g</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>3.0 g</td>
<td>8</td>
<td>75</td>
</tr>
<tr>
<td>4.0 g</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

**Graph Description:**
- **Y-axis:** Percent HbA1c (change from baseline)
- **X-axis:** Trial week
- **Legend:**
  - Placebo (black line)
  - 3.5 g (blue line)
  - 3.0 g (green line)
  - 4.0 g (red line)
- **Mild Hypoglycemia:**
  - Patients: 2
  - Events: 3
TINSAL-T2D Stage 1: HbA1c (primary endpoint)

Percent HbA1c (change from baseline)

Trial week

Placebo

Con Meds

3.5 g

3.0 g

4.0 g
TINSAL-T2D Stage 1: Fasting Blood Glucose

FBG (mg/dl, change from baseline)

Trial week

*Holm’s procedure

*P vs. placebo

- 4.0 g  *<0.001
- 3.5 g  *<0.001
- 3.0 g  *<0.001
TINSAL-T2D Stage 1: Fasting Blood Glucose

Glycated Albumin (%) vs. Trial week

*Holm’s procedure

*P vs. placebo

3.0 g  <0.001
4.0 g  <0.001
3.5 g  <0.001
TINSAL-T2D Stage 1: Triglycerides

The F-test for the overall effect of treatment group was significant (p=0.005)
The F-test for the overall effect of treatment was not significant (p=0.5542).
TINSAL-T2D Stage 1: Adiponectin

*P vs. placebo

- 3.0 g: *<0.001
- 4.0 g: * 0.003
- 3.5 g: *<0.001

*T-test adjusted for multiple comparisons using Holm’s procedure
TINSAL-T2D, Placebo Adjusted Change from Baseline

- **HbA1c**: Decrease over trial weeks with 3.5 g/d, 3.0 g/d, and 4.0 g/d.
- **FBG**: Decrease over trial weeks.
- **Glycated albumin**: Decrease over trial weeks.
- **Adiponectin**: Increase over trial weeks.
Other pertinent negatives

- No change in body weight
- No change in LFTs (AST, ALT, GGT, etc.)
- No change in electrolytes or anion gap
- No change in thyroid function (TSH)
- No significant GI toxicity or evidence of GI bleeding
Other pertinent positives

- Salsalate was well tolerated, with high compliance and low rates of dropout
- Lower than expected rates of tinnitus
- Subjects reported improvements in sense of health and well being (SF36), including improvements in both physical and social functioning
**TINSAL-T2D Trial Design**

**Stage I**: 14-week multicenter, double-masked, placebo-controlled dose ranging study in inadequately controlled T2D (7.0 ≤ HbA1c ≤ 9.5)

- Screen n=240, Randomize n=108
- Placebo n=27
- 3.0g n=27
- 3.5g n=27
- 4.0g n=27

**Stage II**: 26-week multicenter, double-masked, placebo-controlled phase III trial

- Screen n=564, Randomize n=282
- Placebo n=141 randomized
- Salsalate 3.5 g/d n=141 randomized
- Placebo n=113 complete
- Salsalate n=113 complete
TINSAL-T2D Stage 2
An NIDDK funded clinical trial
Common Soil: Metabolic Syndrome

Western Diet

Obesity

Sedentary Lifestyle

Inflammation

Insulin Resistance

Dyslipidemia

Type 2 Diabetes

Hypertension

Atherosclerosis

Salicylate
Quantitation of Atherosclerotic Lesions
(Aortic Root, 16 weeks on WD±S)

Lesion area (mm²)

WD        WD+S

0.0 0.1 0.2 0.3 0.4 0.5

Tatjana Ignjatovic
Ldlr/- mice on diet for 6 months

Chow

Western Diet

Western Diet + Salicylate

Ignjatovic and Shoelson, unpublished
Quantitation of Atherosclerotic Lesions
(En face, 16 weeks on WD±S)

Western Diet
Western Diet + Salicylate

Whole aorta en face (n=7)

Lesion area (% total)

Tatjana Ignjatovic
TINSAL-CVD Trial Design (NHLBI funded)

Screening: Metabolic Syndrome and Stable Coronary Disease
n=1000

Baseline Visit (MDCTA)
n=800 (720 Eligible)

- Lifestyle
  n=240
  Final Visit (MDCTA)
  n=192

- Salsalate
  n=240
  Final Visit (MDCTA)
  n=192

- Placebo
  n=240
  Final Visit (MDCTA)
  n=192

30 months
Calcified plaque

Soft non-calcified plaque
Why Salicylic Acid (SA) is an Attractive Therapeutic Approach in Man

In plants

• SA is present in every plant higher than moss
• SA controls ‘systemic acquired resistance’ in plants, the defensive response to biotic (infectious) as well as abiotic (e.g. thermal, oxidative, osmotic, heavy metal) insults and challenges.
• During a stress response its operative concentration range is 0.1 – 0.5 mM
• Transcription factors (NPR1) and genomic responses are well characterized
Why Salicylic Acid (SA) is an Attractive Therapeutic Approach in Man

**In humans**
- SA has been in clinical use many decades to treat joint pain, and has a long and established safety profile.
- Effective therapeutic concentration range is 0.5 - 2.0 mM.
- Transcription factors including NF-κB and genomic responses can be characterized.

**Hypothesis:** Salicylate activates a systemic antistress response in animals as it does in plants.
Why Salicylic Acid (SA) is an Attractive Therapeutic Approach in Man

Hypothesis: Salicylate upregulates the body’s natural defense mechanisms

Potential conditions
• Insulin resistance and T2D
• Cardiovascular disease
• Neurodegenerative diseases (Alzheimer’s, ALS)
• Sarcopenia, cardiac and skeletal muscle wasting
• Aging
## Colleagues and Collaborators

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- Hagit Shapiro
- Elaine Yi Huang
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- Diane Mathis
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<th>TINSAL trials</th>
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<tr>
<td><strong>TINSAL-T2D</strong></td>
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<tr>
<td>Steve Shoelson, MD, PhD  Chair</td>
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<td>Allison Goldfine, MD</td>
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<td>Vivian Fonseca, MD</td>
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<td>Kathleen Jablonski, PhD</td>
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<td>Myrlene Staten, MD</td>
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<td><strong>TINSAL-FMD</strong> (NHLBI)</td>
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<td>Mark Creager, BWH</td>
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<td>Warren Manning, BIDMC</td>
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