Insulin Resistance in Muscle
Pump it up or Walk it out?
6/15/12

Conflict of Interest

• I have no financial disclosures.

• This presentation involves comments or discussion of unapproved or off-label experimental or investigational use of medications.

Objectives

1. To review how insulin resistance develops in skeletal muscle

2. Examine the role of exercise in the treatment of obesity and T2DM

3. Discuss some potential therapeutic options for T2DM based on knowledge gained from exercise studies

Obesity and Severe Obesity Forecasts Through 2030

Prevalence of Cardiovascular Disease Risk Factors Among US Adolescents, 1999-2008

Type 2 diabetes

• The percentage of T2DM in cases of new-onset diabetes in adolescence has increased from 3% a few decades ago to approximately 50% today

• Diagnosis of T2DM in children is made on average between 12 and 16 years of age
  – Children as young as 4yo have been diagnosed

• Insulin resistance is highly complex and no yet fully understood
  – Insulin resistance can be present without obesity
Intake vs Output

1. Decrease food intake
2. Increase physical activity
3. Increase basal metabolic rate
4. Increase adaptive thermogenesis

Calories burned vs Calories consumed

<table>
<thead>
<tr>
<th>Activity</th>
<th>230 lbs</th>
<th>330 lbs</th>
<th>730 lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycling (cycling, exercise)</td>
<td>296</td>
<td>281</td>
<td>365</td>
</tr>
<tr>
<td>Swimming</td>
<td>265</td>
<td>139</td>
<td>1380</td>
</tr>
<tr>
<td>Jumping Rope (fast)</td>
<td>704</td>
<td>883</td>
<td>1041</td>
</tr>
<tr>
<td>Swimming (slow, moderate)</td>
<td>366</td>
<td>132</td>
<td>1270</td>
</tr>
<tr>
<td>Walking (slow, moderate)</td>
<td>188</td>
<td>176</td>
<td>216</td>
</tr>
<tr>
<td>Walking (fast)</td>
<td>207</td>
<td>281</td>
<td>852</td>
</tr>
</tbody>
</table>

FDA approved Diabetes Medication

**Injectable medications**
- Insulin
  - Long-acting
    - Insulin glargine (Lantus), Insulin detemir (Levemir)
  - Intermediate-acting
    - NPH (Humulin N, Novolin R)
  - Short-acting
    - Regular (Humulin R, Novolin R)
  - Rapid-acting
    - Insulin aspart (NovoLog), Insulin lispro (Humalog), Insulin glulisine (Apidra)

**Amylin mimetics**
- Pramlintide (Symlin)

**Incretin mimetics**
- Exenatide (Byetta, Bydureon), Linagliptide (Tradjenta)

**Oral medications**
- Meglitinides
  - Repaglinide (Prandin), Nateglinide (Starlix)
- Sulfonylureas
  - Glipizide (Glucotrol), Glimepiride (Amaryl), Glyburide (Diabeta, Glynase)
- Dipeptidyl peptide-4 (DPP-4) inhibitors
  - Saxagliptin (Onglyza), Sitagliptin (Januvia), Linagliptin (Tradjenta)
- Biguanides
  - Metformin (Fortamet, Glucophage)
- Thiazolidinediones
  - Pioglitazone (Actos), Rosiglitazone (Avandia)
- Alpha-glucosidase inhibitors
  - Acarbose (Precose), Miglitol (Glyset)

Food Intake

We eat too much
We eat bad things
We eat too fast

Diabetes Prevention Program (DPP)

- 3,234 overweight adults at risk for diabetes
- Randomized to one of three arms
- Followed for a mean of 2.8yrs

Treatment Options for T2DM
- Diet
- Exercise
- Medications
Type 2 Diabetes in Children and Adolescents: Lessons from the TODAY Study

- 699 subjects with recently diagnosed T2DM
- 10-17yo with BMI>85%
- Randomized to one of three arms
- Primary outcome was loss of glycemic control
  - HbA1c ≥ 8.0%

TODAY Study

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Failure rate</th>
<th>Median time to failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met + rosi</td>
<td>90 of 230</td>
<td>38.6%</td>
</tr>
<tr>
<td>Met + lifestyle</td>
<td>109 of 234</td>
<td>46.6%</td>
</tr>
<tr>
<td>Met alone</td>
<td>120 of 232</td>
<td>51.7%</td>
</tr>
</tbody>
</table>


- Lifestyle Interventions focused on diet and activity
- Utilized trained interventionists call PALs
- Implemented strategies such as self-monitoring, goal setting, social support, and motivational techniques

Physical Activity is Declining

- Physical Activity in children is low and sedentary behavior is high
- Basterfield et al followed children (age 7 to 9) for 2 years and found a significant decrease in time spent in moderate to vigorous physical activity
- Only 9 out of 405 (2.2%) achieved the recommended average of 60min of activity per day

Type 2 Diabetes

- Decreased Insulin Secretion
- Increased HGP
- Decreased Glucose Uptake

Skeletal Muscle Insulin Resistance

- Fatty Acyl-CoA
- Lipid Accumulation
- AMPK
- GLUT4
- Exercise
- Metformin
- Decreases fatty acid oxidation
- Improves carbohydrate metabolism

Inflammatory Pathway

- LPS
- TNF-α
- IL-1, IL-6

Exercise and Metformin

- Increases fatty acid oxidation
- Improves carbohydrate metabolism
**VO₂max**

- Low VO₂max is associated with increased IL-6 and other inflammatory markers
- Lower VO₂max correlated with higher body fat in 222 children aged 8-11yo
- It can be improved through training, but there is genetic variability in the response
- Exercising at different VO₂ percentiles will have different results

**Respiratory Exchange Ratio (RER)**

- \( RER = \frac{CO₂}{O₂} \)
- It depends on the substrate used to produce energy
  - Fat = 0.7
  - Carbohydrate = 1.0
- As exercise intensity increases and the VO₂max is approached, more carbohydrate is burned
- RER of > 1.1 often signals VO₂max has been reached

**Optimal VO₂max for fat metabolism**

1. Romijn et al. (1993, 2000) arrived at the conclusion that 65% of VO₂max was associated with maximal fat oxidation
2. van Loon et al. (2000) determined this maximum at 57% of VO₂max, on average
3. Bergman and Brooks (1999) found maximal fat oxidation at 40% VO₂max in trained subjects, but at 59% in untrained ones.

**VO₂max may be a better predictor of insulin sensitivity than percent body fat**


- 106 middle school children with BMI > 95th percentile
- In obese middle school children, the relationship between VO₂max and fasting insulin levels was significant in both sexes but was particularly profound and stronger than percent body fat in males.
- Efforts to reduce risk of type 2 diabetes mellitus in an increasingly obese child population should include exercise intervention sustained enough to improve CVF.
Aerobic Exercise

- Improves VO2max and level of fitness
- Increases fat metabolism leading to weight loss
- Reduces insulin resistance
- Reduces systolic and diastolic blood pressure
- Reduces hepatomegaly and LFT elevation
- Strengthens bone
- Improved sense of well being

Resistance Exercise

- Decreases body fat
- Increases muscle mass and BMR
- Increases insulin sensitivity
- Strengthens bone
- Improve mental health and well being
- Enjoyed more by obese youth?
- Risk associated with weight lifting is less than previous thought, if performed correctly

The Effect of Resistance and Aerobic Exercise on Insulin Resistance

![Graph showing the change in insulin resistance with different exercises](image)

Skeletal Muscle Insulin Resistance

![Diagram illustrating skeletal muscle insulin resistance](image)

European Journal of Pharmacology

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TAK-242 selectively suppresses Toll-like receptor 4-signaling mediated by the intracellular domain

Tomohiro Kawamoto, Masayuki li, Tomoyuki Kitazaki, Yuji Iizawa, Hitoshi Kimura

Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Osaka 532-8860, Japan


Abstract

TAK-242, a new Toll-like receptor 4 (TLR4) antisepsis agent, has shown to suppress Toll-like receptor 4 (TLR4) signaling. In this study, we examined whether TAK-242 selectively modulates the intracellular domain (TIR) of human TLR4 in different cell lines. TAK-242 dose dependently suppressed intracellular TLR4-mediated responses in mouse Raw264.7 macrophages and HEK293 cells, but not in human monocytes, primary CD4 T cells, THP-1 cells, or HEK293 cells expressing human TLR1/2, TLR2/6, TLR3, TLR5, TLR7, TLR8, and TLR9. However, TAK-242 did not affect TLR1/2 signaling in mouse Raw264.7 macrophages. Therefore, TAK-242 selectively inhibited intracellular signaling of human TLR4 without influencing other TLR signaling. TAK-242 provides a new avenue for the design of Toll-like receptor 4-targeted therapeutics.

Press Release

February 20, 2009

Takeda Pharmaceutical Company Limited

Discontinuation of Development of TAK-242 for Severe Sepsis

Osaka, Japan, February 20, 2009 - Takeda Pharmaceutical Company Limited ("Takeda") today announced the discontinuation of clinical development for its investigational compound TAK-242, a treatment for severe sepsis.

A Phase 3 clinical study of the compound was being conducted in Japan, the U.S., and Europe. However, following a thorough review of development strategy, Takeda has concluded that TAK-242's profile does not meet the criteria to support continuation of further development activities. This decision has not been influenced by any concerns over the safety or efficacy of the compound.

In the U.S., Takeda recently received FDA marketing approval for both KAPIDEX in the treatment of STER (January) and ULORIC in the treatment of chronic management of hyperuricemia in patients with gout (February). The company will continue to enhance its established R&D pipeline through a mix of accelerating development projects in all major therapeutic areas; in-house R&D activities; LCM (Life Cycle Management); in-licensing and alliances activities.
Obesity induced insulin resistance and T2DM are associated with low grade inflammation

- IL-6 and TNFα are higher in people with obesity related insulin resistance
- Can inhibiting TLR-4 receptors decrease the inflammation associated with insulin resistance? — Do obese patient have higher levels of LPS?

Link between gut flora and obesity

- Studies have demonstrated that LPS plasma concentrations increase significantly (2-3 fold) after the intake of high-fat, high-carbohydrate meals.
- LPS is fat soluble and a high fat diet leads to an increase in LPS permeability
- A high fat diet appears to alter gut flora and increase the proportion of LPS containing organisms in the gut.

Free Fatty Acids have been shown to activate TLR-4 directly

- Data courtesy of Dr. Hussey, UTHSCSA, 2012

TAK-242 improves glucose uptake

- TAK-242 blocks LPS mediated insulin resistance
- TAK-242 does not completely block fatty acid induced insulin resistance

Data courtesy of Dr. Hussey, UTHSCSA, 2012

TLR-4 and LPS reduced by exercise

- Brown Adipose Tissue
- Concentration decreases with age
  - 2-5% of weight in infants
  - 0.05% of weight in adults
Brown Adipose Tissue

- **White adipose tissue**
  - Stores fat
- **Brown adipose tissue**
  - Thermogenesis
  - Contains UCP-1

**PET/CT Registration of FDG-Glucose Uptake Regions**


Lean subjects have more brown adipose tissue activity than obese subjects

Studies by van Marken Lichtenbelt

- 24 men ages 18-32
  - 10 had BMI <25
  - 14 had BMI >25
  - Brown adipose tissue activity was 4 fold higher in the lean (p<0.007)

- 10 morbidly obese subjects before (BMI 41.7) and after bariatric surgery (BMI 29.3)
  - Brown adipose tissue activity
    - 2/10 before surgery
    - 5/10 a year after surgery
  - First evidence that brown adipose tissue can be recruited in adults

**N Engl J Med, 2009.**

Brown fat UCP-1 and exercise

- Exercise in mice and humans increases the expression of PGC-1α.
- PGC-1α is the “master of mitochondrial biogenesis” and over-expression of PGC-1α in skeletal muscle of mice leads to
  - Improved exercise endurance
  - Improved vascularity
  - Relative resistance to age-related obesity, insulin resistance, and diabetes.
- The surprising observation was that white fat in the PGC-1α overexpressing mice exhibited “browning”
  - This suggests that muscle activity during exercise triggers remodeling of distant subcutaneous adipose tissue depots.

So... how is muscle turning white fat into brown fat?

Irisin

A Newly Discovered Hormone

Discovered by Böström et al. earlier this year

- Exercise induced gene expression in muscle caused an increase in circulating plasma irisin
- Irisin activated thermogenesis in white fat cells in culture
- Injection of an adenoviral vector expressing irisin into mice caused browning of white fat and increased total body energy expenditure

**Irisin**

First Line Treatment for obesity and T2DM

Diet and Exercise

Exercise Is Great If You Do It.

- Both aerobic and resistance exercise are beneficial in different ways
- Moderate intensity and longer duration promote fatty acid oxidation and weight loss
- There are metabolic benefits to exercise independent of weight loss
- Muscles will only adapt if they have to
- Needs to be combined with dietary changes
- Incredibly hard to implement

Exercise and video games

Make Exercise Fun

References

University of Texas Health Science Center at San Antonio

Pediatrics Grand Rounds
15 June 2012

References