New approaches for treatment of type 2 diabetes

October 22, 2007

The metabolic glucostat: The body’s need for glucose is constant, food comes in boluses
Insulin signals the well-fed state

Increases:
glucose uptake by muscle and adipose tissue
- glycolysis
- glycogen synthesis
- triacylglycerol synthesis
- synthesis of DNA, RNA, protein

Decreases:
gluconeogenesis
- fatty acid oxidation
- protein degradation

Diabetes mellitus: syndromes characterized by elevated blood glucose

**Type 1** (juvenile-onset diabetes, insulin-dependent diabetes)
Autoimmune destruction of pancreatic β cells resulting in insulin deficiency. Sudden or gradual onset when >90% of β cells are lost.

**Type 2** (adult-onset diabetes, non-insulin-dependent diabetes)
90-95% of diabetes cases, ~5% of adults in industrialized societies. Insulin resistance and/or abnormal insulin secretion.

**Gestational diabetes** - develops in 2-5% of pregnancies. Risk factor for subsequent development of type 2.

**Inherited single-gene defects** (rare) can cause syndromes resembling type 2. Examples: glucokinase deficiency (heterozygous), some dominant negative PPARγ mutations, some K(ATP) channel mutations.
Chronic hyperglycemia causes severe diabetic complications

Glucose excreted in urine, massive increase in urine production, dehydration
Stress on kidneys can result in renal failure
High blood pressure due to increase in blood osmolytes can lead to retinopathy
Frequent fungal infections due to low pH environment
Swelling of tissues that convert glucose into sorbitol, including lens and nerve, and microvascular pathologies resulting in peripheral neuropathies and retinal damage
Non-enzymatic glycosylation of blood vessel lining promotes atherosclerosis, stroke, and cellulitis
Hyperlipidemia
Ketoacidosis (primarily in type 1)

Type 1 diabetes is treated with insulin

1921 - Purified from cow pancreas (Banting and Best)
1922 - First used in human patients
1978 - Recombinant form produced in bacteria (Genentech)
1982 - First recombinant drug approved by FDA

Delivery mechanisms: Frequent injections (problems with compliance, control)
Insulin pumps (programmable)
Limited use in early type 2 diabetes (may be used for later salvage)
Type 2 diabetes is increasing worldwide

Metabolism in human history

50,000 years:
Food was scarce and seasonal, famines were frequent
Metabolic adaptations for efficient storage enabled survival

100 years:
Food is abundant in many societies, year-round
Consequence: WIDESPREAD METABOLIC DISORDERS
...including obesity and type 2 diabetes

An extreme case: The Pima people, southern Arizona
Caucasians in the American Southwest:
6% have type 2 diabetes, average age of onset 60

Pimas in the American Southwest:
60% have type 2 diabetes, average age of onset 36

Ongoing longitudinal studies since 1963:
http://diabetes.niddk.nih.gov/

Gila River Arts Center
“Metabolic syndrome” or “Syndrome X”

At least 1 of + At least 2 of

- Type 2 diabetes
- Impaired glucose tolerance
- Insulin resistance
- Hypertension
- Obesity
- Hypertriglyceridaemia or low HDL
- Microalbuminuria

Not required for definition, but may be part of the syndrome

Prevalence: Up to 25% of US adults

Insulin resistance and increased insulin secretion precede overt diabetes and β cell failure

Diabetes = fasting glucose >126 mg/dL, twice in a row, and/or glucose spikes >200 mg/dL.
Insulin effects on different tissues and whole-body coordination contribute to the complexity of diabetes

**Normal effects of insulin:**

MUSCLE: increase glucose uptake
decrease glycogen breakdown
increase glycogen synthesis

LIVER: decrease gluconeogenesis
decrease glycogen breakdown
increase glycogen synthesis

ADIPOSE: increase glucose uptake
increase fatty acid synthesis
decrease fatty acid breakdown

**β CELLS:** autocrine or paracrine regulation of insulin secretion

**Tissue-specific insulin receptor knockouts in mice:**

MUSCLE: no disease!!!

LIVER: overt diabetes

ADIPOSE: overt diabetes

β CELLS: impaired insulin secretion

BRAIN: increased food intake, obesity
systemic insulin resistance (?!)

β cell mass increases in response to demand/resistance of tissues

Mouse models for insulin resistance
IR = insulin receptor
IRS1 = insulin receptor substrate 1

Kulkarni et al., 2003, Diabetes 52: 1528
Insulin in type 2 diabetes:

Increased demand for insulin causes β cell compensation
β cells secrete more insulin

Chronic hyperinsulinemia causes:
- Narrowing of blood vessels, hypertension
- Risk of congestive heart failure
- Neovascularization, bleeds in the eye

Insulin demand continues to increase
“Glucose toxicity” causes decrease in insulin secretion
Eventually, β cell damage and death

Associated with amyloid formation
Mice overexpressing IAPP (aka amylin)
develop diabetes: cause or consequence?

Therapeutic agents for type 2 - 2000

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecular target</th>
<th>Site(s) of action</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin receptor</td>
<td>Liver, muscle, fat</td>
<td>Hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Sulphonylureas (e.g. glibenclamide) plus nateglinide and repaglinide</td>
<td>SU receptor/ K+ ATP channel</td>
<td>Pancreatic β-cell</td>
<td>Hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Metformin — biguanides</td>
<td>Unknown</td>
<td>Liver (muscle)</td>
<td>inhibits gluconeogenesis</td>
</tr>
<tr>
<td>Acarbose</td>
<td>α-glucosidase</td>
<td>Intestine</td>
<td>Gastrointestinal disturbances, lactic acidosis</td>
</tr>
<tr>
<td>Pioglitazone, rosiglitazone (thiazolidinediones)</td>
<td>PPARγ</td>
<td>Fat, muscle, liver</td>
<td>Weight gain, oedema, anaemia</td>
</tr>
</tbody>
</table>

Note range of target tissues…
Treatment recommendations, 2007

A1C = glycated hemoglobin measured by HPLC

American Diabetes Association

Thiazolidinediones

Discovered serendipitously; under investigation for hyperlipidemia and found to have stronger effects on hyperglycemia in animal models

Target of action is PPAR_\gamma_ (peroxisome proliferator activated receptor type \gamma)

Drugs act as agonists (activators)

Troglitazone approved 1997 withdrawn 2000 (hepatic failure)

Rosiglitazone approved 1999

Pioglitazone approved 1999

American Diabetes Association
Nuclear hormone receptors

“Nature’s little drug targets”

**Often there are several distinct active conformations**
Humans have about 50 NHR

Natural ligands are small hydrophobic molecules

PPARγ

Expressed in adipocytes, liver, bone (osteoblasts) spleen, heart, skeletal muscle, blood vessel walls (endothelium, smooth muscle, monocytes)

Forms heterodimer with retinoic acid receptor (RXR)
Natural ligands are probably fatty acids and prostaglandins derived from arachidonic acid (originally an “orphan”)
Overexpression or activation (e.g. with an agonist) causes fibroblasts and myoblasts to differentiate into adipocytes

Human heterozygotes with P12A in adipose-specific isoform (PPARγ2) have decreased body mass index and improved insulin sensitivity
Humans with a dominant negative destabilizing mutation in the ligand-binding domain have severe insulin resistance, hypertension, early type 2 diabetes
PPARγ activation in rats increases the number of adipocytes and decreases average adipocyte size

Larsen et al., 2003, Int. J. Obes. 27:147

Treatment with PPARγ agonists causes weight gain

Larsen et al., 2003, Int. J. Obes. 27:147
Why does increasing the number of fat cells by PPARγ activation improve insulin sensitivity?

Primary effect: Adipose cells have the highest level of insulin receptor expression; more fat cells deplete insulin in the blood

Secondary effects: Adipose cells secrete leptin, resistin, TNF-α, adipsin, etc., which can affect insulin utilization in other tissues...any of these might be better points of intervention

Complications…

All glitazones cause weight gain; counterproductive for patients with type 2 diabetes

Thioglitzazone was withdrawn from the market due to severe hepatotoxicity

Rosiglitazone causes congestive heart failure in a subset of patients

Drug class induces bone loss via PPARγ signaling:
- decrease in osteoblast number, increase in osteoclast number, etc.

Clinical trials are usually SHORT (~months)
Chronic treatment for chronic conditions last for years
**Therapeutic agents for type 2 - 2007**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of Introduction or FDA Approval</th>
<th>Efficacy as Monotherapy, Measured as a Reduction in the Glycated Hemoglobin Concentration (percentage points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>Pulmonary</td>
<td>2006</td>
<td>1.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.3</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Oral</td>
<td>1957</td>
<td>0.5</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>1995</td>
<td>0.3</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5–0.8</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Oral</td>
<td>1999</td>
<td>0.8–1.0</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Oral</td>
<td>1997</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Oral</td>
<td>1999</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Oral</td>
<td>1999</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>1997</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>GLP analogues</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>Amylin analogues</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5–0.9</td>
</tr>
</tbody>
</table>

* GLP denotes glucagon-like peptide, and DPP-IV dipeptidyl peptidase IV.
† Metformin has been available in other countries since 1957 but was approved in the United States in 1995.
‡ Troglitazone was approved in 1997 but was withdrawn from the market in 2000 because of hepatotoxicity.

**New pathway: Incretin effect**

First postulated in 1902
Oral/GI glucose induces insulin secretion more effectively than blood glucose
Several gut peptide hormones implicated in insulin regulation:
GLP-1 made from proglucagon
Effects on liver, pancreas, muscle, adipose tissue, brain, also stomach emptying rate

Keiffer & Habener, 1999, Endocr. Rev. 20: 876

McIntyre et al., 1964, Lancet 2:20
GLP-1 analogs from Gila monster venom: exendin-3 and exendin-4

GLP-1 rapidly degraded by protease DPP-IV (dipeptidyl peptidase), recognizes Ala at position 2

Gila monster venom (Heloderma horridum, Heloderma suspectum) has GLP-1-like bioactive peptides with Ser at position 2 (Why???)

Recombinant form sold as “Byetta”

Drawback: has to be injected

Moderate beneficial effects on glycemic control when combined with other drugs, no weight gain

DPP-IV inhibitors also available (sitagliptin, Januvia)

Other pathways?

Interleukin-1 receptor antagonist (anakinra) improves beta cell function (Larsen et al., 2007, NEJM 356:1517)

Retinol Binding Protein 4 levels in serum strongly correlated with insulin resistance (Graham et al., 2006, NEJM 354:2552)

ER stress reduction with chemical chaperones for beta cell preservation (Ozcan et al., 2006, Science 131:1137)

Liver glucose production, multiple possible targets (Link, 2003, Curr. Opin. Invest. Drugs, 4:421)

Why are some people more susceptible?

Unbiased genetic screens of large patient samples (Paper #1)
On the horizon: β-cell regeneration?

Possibilities:
- Replication of preexisting β-cells
- Differentiation of stem/progenitors in the ductal epithelium
- Acinar transdifferentiation to β-cells

The only mode of β-cell regeneration that is known to occur normally in adult animals is replication of preexisting β-cells

Note: β-cell preservation will not improve underlying insulin resistance

Papers for Wednesday:
