The pathophysiology of the dysglycaemia of diabetes: A personalised journey from insulin and glucose sensitivities and beta cell function to the incretins – familial vs acquired?

Frank P Alford
Outline of Talk

• The beginning
  – Insulin sensitivity
  – Beta cell function
  – Glucose-mediated glucose disposal
  – Alpha cell function
  – Hepatic “insulin resistance”

• Insulin sensitivity + glucose sensitivity
  – Metabolic pathways
Outline of talk

• Regulation of HGP
  – Primary vs peripheral (SkM)
• Metabolic impact of AMP-K activation
• Non-diabetic relative and twin studies
  – A glimpse of the future?
• Incretin hormone actions and the beta cell
  – Primary or secondary?
• Conclusions
“Equivocal” glucose tolerance, insulin sensitivity and β cell function
Insulin Secretion in “equivocal” GT

Alford F et al. Diabetologia 7:173, 1971
Kg vs. Acute insulin secretion or $K_{ITT}$

Alford F et al Diabetologia 7:173, 1971
Eu vs Hyperglycaemia in Diabetes


![Graph showing glucose utilisation in euglycaemia and hyperglycaemia for control and diabetic patients with different levels of IRI (50mU/l, 50mU/l, 250mU/l). The graph indicates significant differences (* p<0.005 - <0.001) between groups.]
Changes in Glucose uptake per unit change in plasma glucose in CON and DM subjects

Proietto et al; Metabolism, 32(11): 1022 (1983)
What are the metabolic consequences of hyperinsulinaemia?
20hr Pulsatile vs Continuous Insulin infusion

What is the role of glucagon (alpha cell function) in glucose metabolism?
What is the Metabolic Role of Chronic Hyperglucagonaemia?

**In cirrhosis:**

IRG X 4 fold higher and IRI 2X higher vs Controls

\( \text{HGP}_{\text{BASAL}} \) is decreased \((p<0.003)\) and is suppresses by insulin normally

\( \text{Rd} \) is decreased \((p<0.005)\) and correlates with FG \((r=-0.87)\)

Hepatic response to glucagon bolus is normal

Glucose tolerance: NGT, iIGT/DM2

Alford F et al, Clin Endocrin 11:413, 1979


**In glucagonoma subject:**

IRG X 100 fold higher and IRI equal vs Controls

\( \text{HGP}_{\text{BASAL}} \) not raised

\( \text{Rd} \) is decreased

Hepatic response to glucagon bolus is absent \((\text{no cAMP rise})\)

Glucose tolerance: iIGT

## Glucose Processing During and IVGTT vs Clamp and Minimal Model Analysis

<table>
<thead>
<tr>
<th></th>
<th>IVGTT</th>
<th>Clamp 1</th>
<th>Clamp 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Insulin Level</strong></td>
<td>~ 25</td>
<td>~ 25</td>
<td>~ 60</td>
</tr>
<tr>
<td><strong>Glucose Disposal</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td><strong>Glucose Oxidation</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Glucose Storage</strong></td>
<td>↔</td>
<td>↔</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Glycogen Synthase</strong></td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid Oxidation</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Note*  
$SI_{IVGTT} = $ Transmembrane glucose transport + Glucose phosphorylation (IRI 10 – 100 mU/l)  
$SI_{CLAMP_1} = $ Transmembrane glucose transport + Glucose phosphorylation (IRI 10 – 100 mU/l)  
$SI_{CLAMP_2} = $ Transmembrane glucose transport + Glucose phosphorylation + Glycogen synthase activation (IRI >30 mU/l)  

$SI_{CLAMP_1}$ glucose processing matches $SI_{IVGTT}$ glucose processing.
Comparisons of Sg and Si by Clamp and Minimal Model Analyses

Compounding effect of the defect in glucose sensitivity (Sg) on glucose tolerance in insulin resistant subjects.

Bergman et al, Endocrinol Rev 6: 45, 1985

<table>
<thead>
<tr>
<th>FG</th>
<th>&lt;5.5</th>
<th>&lt;6.0</th>
<th>&lt;6.5</th>
<th>≤8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h OGGT G</td>
<td>&lt;8.0</td>
<td>&lt;10.0</td>
<td>&gt;11.0</td>
<td>&gt;&gt;11.0</td>
</tr>
<tr>
<td>↓ Ins Secr.</td>
<td>0</td>
<td>↑↑</td>
<td>25 %</td>
<td>&gt;50 %</td>
</tr>
<tr>
<td>Gluc Toler.</td>
<td>NGT</td>
<td>IGT</td>
<td>DM</td>
<td>DM++</td>
</tr>
</tbody>
</table>

Reaven et al, Diabetes:
Parallel increases in GF and GS occur during matched normo-hyperinsulaemic clamps, with euglycaemia and hyperglycaemia, but greater ΔGS is reflected in SkM by matched increases of glycogen and glycogen synthase activation at higher insulin.

At matched Rd values (i.e. high glucose/low insulin vs. normal glucose/raised insulin): GS and GS are similar i.e. hyperglycaemia alone can stimulate both GS and GF pathways in SkM.

At normo-physiologic hyperinsulinaemia (<25mU/l): GS contributes ~15% and GF ~85% to Sg.

HGP is suppressed more with combined hyperglycaemia/normoinsulinaemia vs. euglycaemia/normoinsulinaemia, and is therefore a major contributor to Sg.

HGP in Type 2 DM and Control Subjects – What Regulates HGP?
Hepatic “Insulin Resistance” in Diabetes

A = Pre-treatment
B = Post-treatment

Nankervis A et al, Diabetologia 23:320, 1982
DR Curves for Rd and HGP in Con vs DM2: Hepatic Resistance vs. Hepatic Sensitivity

Controls

Diabetes

Staehr P et al, Diabetes 50:1363, 2001
Regulation of HGP – Autonomy of the Liver VS Peripheral metabolic needs?

Metabolic Responses to:

Normal Dog
- Prolonged 20h fast
- Low (30% of HGP) GINF vs High dose GINF (at basal Insulinaemia)
- Exercise

Alloxan Diabetic Dog
- Hyperglycaemia (at basal insulinaemia) vs Phlorizin-induced “Normoglycaemia”
- Exercise
Prolonged 20hr fast – Normal Dog  
[Glucose Deprivation]

<table>
<thead>
<tr>
<th></th>
<th>15h</th>
<th>20h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGP (umol.kg⁻¹.min⁻¹)</td>
<td>13.6 ± 1.2</td>
<td>12.3 ± 1.1 *</td>
</tr>
<tr>
<td>Rd (umol.kg⁻¹.min⁻¹)</td>
<td>13.6 ± 1.2</td>
<td>12.3 ± 1.1 *</td>
</tr>
<tr>
<td>MCRg (ml.min⁻¹)</td>
<td>2.6 ± 0.3</td>
<td>2.4 ± 0.2 **</td>
</tr>
<tr>
<td>GF (umol.kg⁻¹.min⁻¹)</td>
<td>11.4 ± 1.6</td>
<td>9.3 ± 0.8 **</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01

Note: matching of HGP to MCRg and GF
Impact of GINF on Glucose Metabolism in Dog: [Glucose sufficiency]
Impact of Phlorizin Infusion on Glucose Metabolism in Diabetic Dog [Glucopaenia]

Note: HGP vs UGL; $r = 0.89 \ p < 0.001$; $\Delta\text{HGP}_{\text{Phlor}} = \Delta\text{UGL}_{\text{Phlor}}$

* $p < 0.05$ vs Prephlorizin

Note:
SkM intracellular [G] ↓

Christopher M et al
Diabetes Metab Res Rev
22: 155, 2006
Impact of Phlorizin and Exercise on Glucose Metabolism in Diabetic Dog

[Glucopaenia-Exercise]

Stepwise regression analysis:

$\text{Rd}_{\text{EXER}} \propto \text{p[G]}_B + \text{GF}_{\text{EXER}}$

$r^2_{\text{adj}} = 0.88$

Christopher M et al J Appl Physiol 98: 930, 2005
Conclusions

- HGP appears to be set by the peripheral tissues’ metabolic needs.

- During exercise in diabetes, an adequate supply of glucose through hyperglycaemia is critical for the maintenance of normal muscle glucose metabolism ($R_{\text{Tissue}}^d$ and GF) in working muscle.

- HPG response to phlorizin during exercise is finite and fails to meet peripheral metabolic needs ($R_{\text{Tissue}}^d$ and GF).
Metabolic Actions of AMPK Activation

**Metabolic Responses to:**

- **AMPK SkM Activation (by AICAR):**
  - Glucose uptake and oxidation $\uparrow$
  - Fatty acid oxidation $\uparrow$
  - Glycogenolysis $\uparrow$
  - Glycogen synthase activation $\downarrow$

- **AMPK Liver Activation:**
  - Glycogenolysis $\uparrow\uparrow$
  - Gluconeogenesis $\downarrow$
  - Lypogensis $\downarrow$ and FA oxidation $\uparrow$
  - Insulin action on HGP $\downarrow$

Note: AICAR’s metabolic impact in vivo on the liver is due to the direct allosteric effect of ZMP (Camacho R et al, Amer J Physiol 89: 289, E1039, 2005)
AMPK_α_1+2 and ACCβ Activation in Dog with Exercise

## In Vivo Effects of AICAR Activation on AMPK in Normal Dog

<table>
<thead>
<tr>
<th>In normal dogs infused with AICAR infusion for 3h:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose response</td>
</tr>
<tr>
<td>Insulin response</td>
</tr>
<tr>
<td>FFA response</td>
</tr>
<tr>
<td>Lactate response</td>
</tr>
<tr>
<td>HGP</td>
</tr>
<tr>
<td>Rd&lt;sub&gt;TISSUE&lt;/sub&gt;</td>
</tr>
<tr>
<td>GF&lt;sub&gt;EXOG&lt;/sub&gt;</td>
</tr>
<tr>
<td>SkM AMPKα1+2</td>
</tr>
<tr>
<td>SkM ACC-β</td>
</tr>
</tbody>
</table>

** p<0.05  
*** p<0.001

Note: In diabetic dog: NO impact of AICAR on HGP, Rd<sub>TISSUE</sub> and GF<sub>EXOG</sub> in the presence of raised basal AMPK and ACCβ activities.

Comparison of the Effect of Exercise and AICAR on Metabolism and Plasma Metabolites

Conclusions

In normal dog:

- AMP pathway activated by Exercise and AICAR but with different responses

In sub-optimally controlled diabetic dog:

- Chronically elevated basal SkM AMPKα1+2 and ACCβ activities contribute to the ongoing normal supply of glucose (and fatty acid metabolism);
- Whether these raised basal AMPK and ACC activities of the diabetic state play a permissive metabolic role to exercise remains uncertain;
- The acute in vivo metabolic responses seen in normal dog to activation of AMPK and ACCβ by AICAR do not occur in diabetic dog.

Christopher M et al, J Appl Physiol 95: 2003
Glucose metabolism depends on:
- Insulin sensitivity
- Glucose sensitivity
- β-cell function
- Eu- vs. hyperglycaemia impact on partitioning of GS vs. GF
- Both basal insulin and glucagon regulate fasting glucose, BUT
- Glucagon’s chronic metabolic action on liver in diabetes is uncertain
- Hyperglucagonaemia of DM reflects intra-islet insulinopaenia

HGP regulation appears to be secondary to the metabolic needs of peripheral glucose metabolism.

The potential therapeutic use of “rescue” metabolic “stress” pathways (eg. AMPK activation agonists) is complex.
Studies in Normo-glycaemic Relatives of Type 2 DM

- Young subjects <35y of age (i.e. ~10-20y before onset of DM2)
- Carefully age, BMI and sex matched controls
- Studied by Minimal Model IVGTT analysis and classical clamp studies with SkM biopsies
- Followed prospectively for 10y.

Hypothesis:
- If such subjects have detectable metabolic defects present initially, these abnormalities are most likely to be primary, and not secondary phenomena.
Glucose and insulin kinetic parameters derived from the FSIGT in Normoglycaemic Relatives of NIDDM patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kg (10^{-2} \text{.min}^{-1})</td>
<td>1.60 ± 0.14</td>
<td>1.59 ± 0.18</td>
</tr>
<tr>
<td>Sg (10^{-2} \text{.min}^{-1})</td>
<td>1.93 ± 0.14 *</td>
<td>1.52 ± 0.16</td>
</tr>
<tr>
<td>Phi 1 (\text{mU.l}^{-1}.\text{min}^{-1} \text{per mg.dl}^{-1})</td>
<td>3.56 ± 0.53</td>
<td>4.13 ± 0.62</td>
</tr>
<tr>
<td>Phi 2 (\text{mU.l}^{-1}.\text{min}^{-1} \text{per mg.dl}^{-1})</td>
<td>10.27 ± 1.05</td>
<td>9.11 ± 1.71</td>
</tr>
<tr>
<td>Si (10^{-4} \text{.min}^{-1} \text{per mU.l}^{-1})</td>
<td>3.49 ± 0.43 *</td>
<td>4.80 ± 0.61</td>
</tr>
<tr>
<td>Si x Phi 1 (10^{-4} \text{.min}^{-2} \text{per mg.dl}^{-1})</td>
<td>11.5 ± 2.2 *</td>
<td>16.7 ± 2.0</td>
</tr>
</tbody>
</table>

* p < 0.05 vs Con

Henriksen et al, J Clin Invest 94: 1196, 1994
### Clamp Sg

**Table**: Overview of glucose-mediated glucose disposal rates for REL and CON groups, with p-values for comparison.

<table>
<thead>
<tr>
<th></th>
<th>REL</th>
<th>CON</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{g_{HEP}}$ (min$^{-1}.10^{-2}$)</td>
<td>0.8</td>
<td>0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$S_{g_{PERIPH}}$ (min$^{-1}.10^{-2}$)</td>
<td>2.1</td>
<td>1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Diagram**: Bar chart showing glucose-mediated glucose disposal rates for REL and CON groups, with statistical significances indicated.

*Henriksen J et al, Diabetes 49; 1209; 2000*
The contributions of insulin sensitivity, glucose effectiveness, and insulin secretion to glucose restoration rate during an OGTT

<table>
<thead>
<tr>
<th></th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGGT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [G] (mmol.l⁻¹)</td>
<td>6.37 ± 0.20</td>
<td>6.07 ± 0.20</td>
</tr>
<tr>
<td>Mean incremental insulin (mU.l⁻¹)</td>
<td>25.5 ± 2.4</td>
<td>27.5 ± 2.6</td>
</tr>
<tr>
<td>Glucose restoration rate during OGTT*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>due to insulin [AIRg] (10⁻².min⁻¹)</td>
<td>0.78 ± 0.07</td>
<td>1.21 ± 0.14</td>
</tr>
<tr>
<td>percent of total (%)</td>
<td>30 ± 3</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>due to glucose [Sg] (10⁻².min⁻¹)</td>
<td>1.93 ± 0.07</td>
<td>1.52 ± 0.16</td>
</tr>
<tr>
<td>percent of total (%)</td>
<td>70 ± 3</td>
<td>55 ± 4</td>
</tr>
<tr>
<td>Total</td>
<td>2.72 ± 0.13</td>
<td>2.74 ± 0.15</td>
</tr>
</tbody>
</table>

* Glucose restoration_{OGTT} = [Sg_{OGTT}] + [S_{IVGTT} x Δ_{MEAN} Insulin_{OGTT}]

Henriksen et al, J Clin Invest 94: 1196, 1994
Background

– ~40% of normoglycaemic REL of type 2 DM will develop future diabetes

– With aging, insulin sensitivity (SI) generally deteriorates

Questions

– What is the metabolic impact of DEX–induced insulin resistance on β-cell function in REL and CON subjects?

– Do the REL DEX- responses simulate those seen in later in life?
DEX and 10y Study Designs

- 20 normoglycaemic REL and 20 age, sex, and BMI matched Control subjects were studied at:
  - 10y: pre- and post-exposure to DEX (4mg/day for 5 days)
  - 10y followup.

- Glucose tolerance, acute β-cell function and SI were measured.
Impact of DEX on OGTT in REL vs CON

Henriksen K et al Diabetologia, 40: 1349, 1997
DEX-induced changes in glucose metabolism in REL vs CON

** p < 0.01 Pre vs Post DEX

DEX Study in REL and CON

* p < 0.05; ** p < 0.01; *** p < 0.005 vs Hyp-rel

Acute insulin secretion in CON, REL and Twins

Alford F et al, Metabolism 47:522, 1998
In young insulin resistant normoglycaemic Relatives of type 2 DM:
- Sg is increased by 20%
- HGP is the main site of the hyperglycaemic effect
- Glucose storage and glycogen synthase activation in SkM is decreased (ie SI decreased)
- AIRg.SI is reduced

Conclusion:
- At oy, the metabolic characteristics (↓SI, ↑Sg, ↓↓ AIRg) are inherited.

Question:
- What about the future?
Sg_{0y} vs 10y Glycaemia Outcomes in REL

<table>
<thead>
<tr>
<th></th>
<th>DM_{REL}</th>
<th>iIFG_{REL}</th>
<th>NGT_{REL}</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sg_{0y}</td>
<td>1.35 ± 0.10</td>
<td>2.00 ± 0.19*</td>
<td>2.15 ± 0.23*</td>
<td>1.53 ± 0.18(^t)</td>
</tr>
</tbody>
</table>

\* P < 0.05 vs DM_{REL}; \(^t\) p < 0.05 vs NGT_{REL}

<table>
<thead>
<tr>
<th></th>
<th>FG_{10y}</th>
<th>FG_{0y}</th>
<th>r = 0.71</th>
<th>p &lt; 0.005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs</td>
<td>\sqrt{Sg}_{0y}</td>
<td>r = -0.044</td>
<td>p = 0.06</td>
</tr>
<tr>
<td></td>
<td>vs</td>
<td>BMI_{0y}</td>
<td>r = 0.52</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2h.G_{10y}</th>
<th>FG_{0y}</th>
<th>r = 0.48</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs</td>
<td>\sqrt{Sg}_{0y}</td>
<td>r = -0.043</td>
<td>p = 0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>logAIR_{g10y}</th>
<th>FG_{0y}</th>
<th>r = 0.48</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
</table>

**Multiple Regression:**

\[ FG_{10y} = FG_{0y} - \sqrt{Sg}_{0y} \]
\[ r^2_{adj} = 53\%, \ p < 0.001 \]

\[ 2h.G_{10y} = FG_{0y} \text{ alone}; \ r^2_{adj} = 29\%, \ p < 0.03 \]
Acute DEX vs 10y Responses

**2h OGTT.G**

- DEX Response
- 10y Response

**ΔI_{30}/ΔG_{30} \times SI_{HOMA}**

- p<0.0005
- p<0.0005
- p<0.0005
- p<0.0005

- p=0.006
- p=0.01
- p=0.04
- p=0.01

**SI_{HOMA}**

- p=0.05
- p=0.05

Alford, F et al submitted (2011)
DEX- and 10y-induced relative changes in REL and CON of insulin secretion and insulin sensitivity.

\[ \Delta I_{30}/\Delta G_{30} \text{ (pmol/mmol)} \]

\[ SI_{HOMA} \text{ (mmol/l.pmol/l)}^{-1} \]

Alford, F et al submitted (2011)
Conclusion of the Dex vs. 10 y Study

- The metabolic responses to DEX mirror those seen in REL after 10y, particularly the $DM_{DEX}$ subgroup, who had the most profound abnormalities at 10y.
- Diabetes emerged at 10y in 4/7 subjects only from the $DM_{DEX}$ subgroup of the REL.
- iIFG emerged in 5 REL at 10y, unrelated to their DEX responses, (but related to their $Sg_{oy}$).
β cell function deteriorates over time with progression to glucose intolerance –

What happens to the Incretin Effect in Relatives and Controls over 10y?
Background to the Incretin Effect Study

1. The Incretin Effect is due to the release of the gut incretin hormones GLP-1 and GIP, which together augment nutrient stimulated insulin release from the β cell;

2. The magnitude of the GLP-1 and GIP release depends on
   a. the size of the oral/intraduodenal glucose load;
   b. the magnitude and biological efficacy of GLP-1 and GIP determine the β-cell response;
   c. GLP-1 and GIP secretions during an OGTT are biphasic;

3. Oral glucose tolerance is critically dependent on the magnitude of the acute phase insulin release ($AIR_{OGTT}/AIR_{IVGTT}$);

4. It is estimated that 60% of $AIR_{g}$ is due to the GLP-1 and GIP augmentation of the β cell function;
5. Traditionally, the measurement of the Incretin Effect is based on an OGTT induced insulin release matched to an identical IV glucose infusion glycaemic profile over 0-120 minutes;

6. The insulinogenic index \( \frac{\Delta I_{\text{AREA}}}{\Delta G_{\text{AREA}}} \) is the most “physiological measure of AIRg;

7. Incretin hormones increase Sg (as well as \( \beta \)-cell secretion);

8. Genetic factors are linked to decreased incretin hormone action on the \( \beta \) cell e.g. TCF7L2 allele in Type 2 DM).

Study Design

- 20 REL and 20 CON subjects were followed for 10y, with measurements for:
  
  - Glucose tolerance: OGGTT and IVGTT
  
  - Acute insulin secretion:
    - OGGTT: \( \frac{\Delta I_{\text{AREA 0-30'}}}{\Delta G_{\text{AREA 0-30'}}} = IGI_{\text{OGTT 0-30'}} \)
    - IVGTT: \( \frac{\Delta I_{\text{AREA 0-5'}}}{\Delta G_{\text{AREA 0-5'}}} = IGI_{\text{IVGTT 0-5'}} \)
  
  - Insulin Sensitivity (SI\text{HOMA})
  
  - Incretin Effect:
    - \( \% = (IGI_{\text{OGTT}} - IGI_{\text{IVGTT}} / IGI_{\text{OGTT}}) \times 100 \)
Cremental (Δ) Changes Induced by DEX

ΔFG

Δ2h OGTT G

ΔInc Effect

ΔIGI

OGTT

ΔIGI

IVGTT

ProI/I Ratio

p<0.01

p<0.001

p=0.07

p<0.05

p<0.02

p<0.02

p<0.05

p<0.04

p=0.02

p=0.04

DMT

DEX

NGT

DEX

CON

DM

DEX

NGT

DEX

CON

Alford et al, submitted (2011)
Cremental (Δ) Changes Over 10y

ΔFG

Δ2h OGTT G

ΔInc Effect

(ΔIGI

OGTT

ΔIGI

IVGTT

ProI/I Ratio

(%) (%)

(mmol/l)

(pmol/mmol)

p<0.006

p=0.01

p=0.02

p<0.003

p<0.005

p=0.07

p=0.03

p<0.003

p<0.005

p=0.06

p<0.01

p<0.006

p<0.005

p=0.07

p<0.01

p<0.01

p=0.06

p=0.01

p=0.06

DM<sub>REL</sub> iIFG<sub>REL</sub> NGT<sub>REL</sub> CON

DM<sub>REL</sub> iIFG<sub>REL</sub> NGT<sub>REL</sub> CON

DM<sub>REL</sub> iIFG<sub>REL</sub> NGT<sub>REL</sub> CON

DM<sub>REL</sub> iIFG<sub>REL</sub> NGT<sub>REL</sub> CON

Alford et al submitted (2011)
Summary

• The DEX-induced changes of AIR$_{OGTT}$ and Glucose tolerance in mildly insulin resistant normoglycaemic REL are secondary to a marked inhibition of the acute incretin effect on the β-cell.

• A preserved or even raised acute incretin effect (i.e. compensatory) is present at 0y in normoglycaemic REL who have the most severe initial defect of AIRg$_{OGTT}$ (data not shown).

• The acute incretin effect does not deteriorate over time in CON subjects nor in normoglycaemic REL who develop iIFG or those REL who do not develop diabetes.

• The time (10y) induced deterioration of AIR$_{OGTT}$ in diabetic subjects is primarily due to β-cell dysfunction and not a failing incretin effect.
General Conclusions

• Insulin resistance has a relatively mild “genetic” metabolic impact (i.e. ↓glycogen synthase activity) and becomes important in those subjects who have a low-normal or normal Sg, and/or in those who have declining β cell function; and/or develop progressive ↑ intracellular SkM lipid.

• “Abnormal” HGP seems to be a secondary phenomenon in the pathogenesis of dysglycaemia of diabetes.

• The metabolic role of the chronic hyperglucagonaemia on increasing hepatic insulin resistance and the development of the dysglycaemia of diabetes remains to be determined.
General Conclusions

• Over time, β-cell dysfunction remains the primary “genetic” factor (together with declining Sg) in the development of type 2 diabetes.

• Incretin agonist therapy needs to be commenced early whilst sufficient β-cell reserve is present.

• Given the complexities of the metabolic responses to activation of the rescue stress AMPK pathways in different tissues, its future as an effective therapeutic agent is guarded.

• Future therapies should be aimed at (i) preserving β-cell function and (ii) minimising the impact of reduced SI and Sg.
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Hypothesis: Pathophysiology of Dysglycaemia and Type 2 DM

- Genetic Defect of glycogenesis in skeletal muscle
  - $\rightarrow \uparrow S_g$
  - $\downarrow S_I$

- Genetic Defect of $\beta$ cell function
  - $\downarrow$ acute $\beta$ cell response (vs SI)
  - $\uparrow$ Atherogenesis
  - $\uparrow$ Lypogenesis
  - $\uparrow$ NEFA

- Hyperinsulinaemia (compensated)
  - $\uparrow$ Atherogenesis
  - $\uparrow$ Lypogenesis

- HGP Normal
  - $R_{d,tissue}$ Normal

- Decompensation of $\beta$ cell function
  - $\uparrow$ Obesity
  - $\uparrow$ “metabolic” Insulin resistance

- Stress hormones

- Hyperglucagonaemia
  - $\downarrow S_g$

- iIFG

- $\downarrow S_I$

- $\uparrow$ HGP

- IGT/DM2

- Stress hormones
  - $\uparrow$ “metabolic” Stress
Extras
What is measured in a Clamp Study

ED50 Dose Response Curves

Nankervis A et al Diabetologia 28:427, 1985
Glucagon kinetics in cirrhosis

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal IRG (pg/ml)</th>
<th>MCR (ml/kg/min)</th>
<th>t½ (min)</th>
<th>BSDR (pg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>53 ± 13</td>
<td>13.0 ± 1.3</td>
<td>3.8 ± 0.4</td>
<td>750 ± 244</td>
</tr>
<tr>
<td>Cirrhotics Pre-op</td>
<td>213 ± 27***</td>
<td>13.3 ± 1.7</td>
<td>4.0 ± 0.3</td>
<td>3042 ± 454***</td>
</tr>
<tr>
<td>Cirrhotics Post-op</td>
<td>382 ± 73***†</td>
<td>7.6 ± 1.3*†</td>
<td>3.5 ± 0.5</td>
<td>2518 ± 535**</td>
</tr>
</tbody>
</table>

Alford F et al Clinical Endocrinology 11: 413, 1979
Twin Study

Metabolic Parameters in REL and CON at 0y and 10y

Fasting glucose

2h OGTT glucose

AIRg

Note: 4 REL: DM2 at 10y; 5 REL: iIFG at 10y

Alford, F et al submitted (2011)
Glucose Kinetic Parameters Before and After DEX Exposure

Kg

Sg

SI

* p< 0.05 vs CON

P. Glucose, Kg and AIRg at 10y, grouped by Sg tertiles

- **FG\textsubscript{10y}**
- **Kg\textsubscript{10y}**
- **2h G OGTT\textsubscript{10y}**
- **log AIRg\textsubscript{10y}**

Alford, F et al submitted (2011)
Determinants of FG and 2hOGTT glucose at 10y

\[ \text{FG}_{10y} \propto \text{FG}_{0y} + 2\text{hOGTT.G}_{0y} + \log \text{SI}_{\text{HOMA}} \]
\[ (r^2_{\text{adj}} 66\%; p<0.0005) \]

\[ 2\text{hOGTT.G}_{10y} \]
\[ \propto \text{FG}_{\text{postDEX}} + 2\text{hOGTT.G}_{\text{postDEX}} + \log \text{SI}_{\text{HOMA post-DEX}} \]
\[ (r^2_{\text{adj}} 56\%; p<0.001) \]

**Note:** No oy pre-or post-DEX insulin secretion parameters entered into the models.

Alford, F et al submitted (2011)
Conclusions

• “The postulate is that active treatment of a ‘potential’ diabetic might delay the onset of islet cell failure;

• The testing of such a hypothesis must depend on the ability to diagnose with absolute certainty an ‘early’ diabetic abnormality of glucose tolerance;

• A confident diagnosis of diabetes mellitus in patients with mild abnormalities of oral glucose tolerance alone cannot be made readily.”

Alford F et al Diabetologia 7:173, 1971