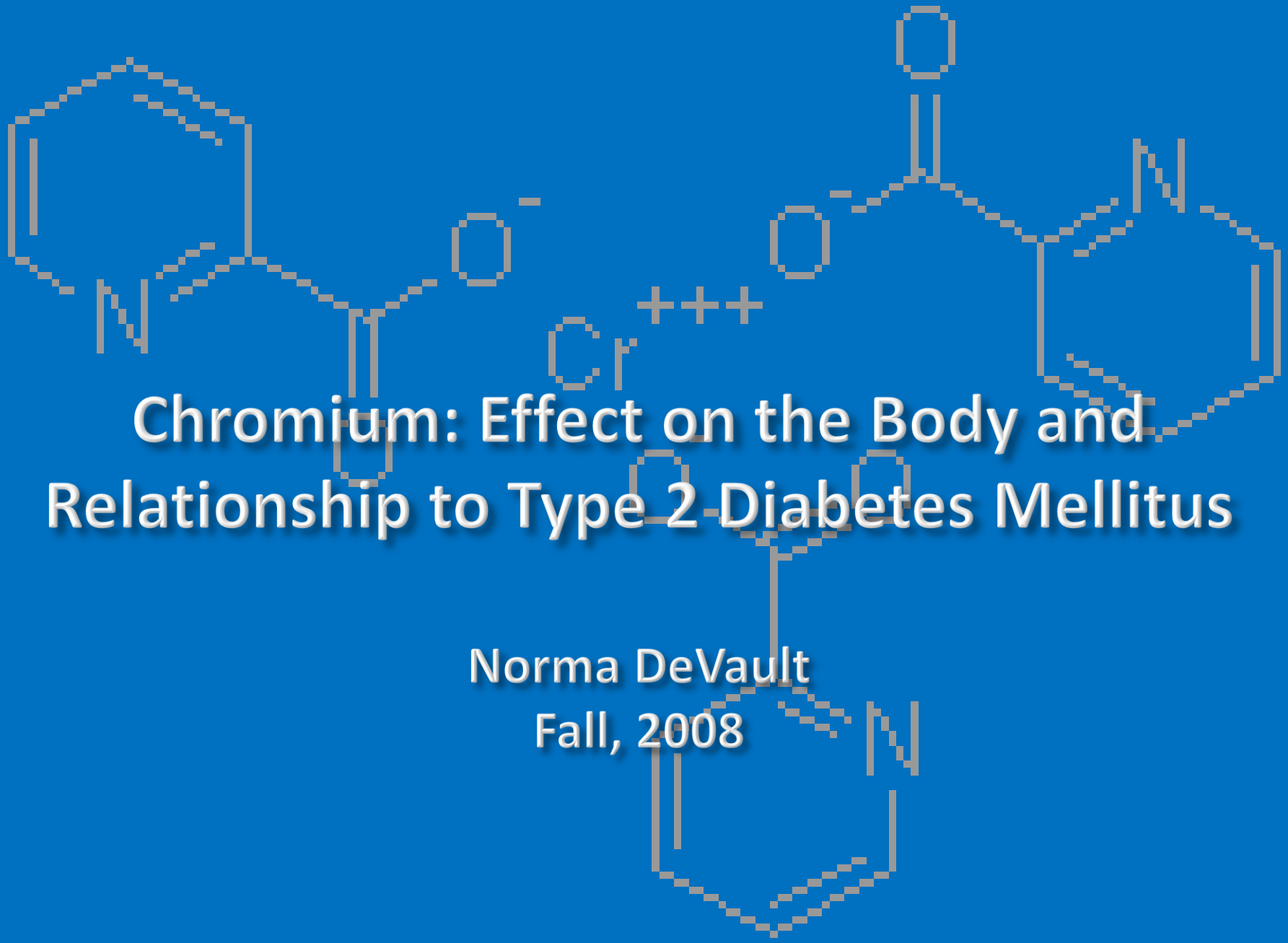


Chromium: Effect on the Body and Relationship to Type 2 Diabetes Mellitus

Norma DeVault

Fall, 2008

Chromium: Effect on the Body and Relationship to Type 2 Diabetes Mellitus

- Background
- Absorption, transport, storage, excretion
- Biochemistry and metabolism
  - Proposed role and mechanisms
- Chromium status, deficiency, toxicity
- Chromium supplementation and Type 2 Diabetes
- Chromium supplementation controversy
- Implications
- Future Research

Chromium Profile

- Elemental Chromium: Cr^0
  - First row transition metal (1798)

24: Chromium 2,8,13,1

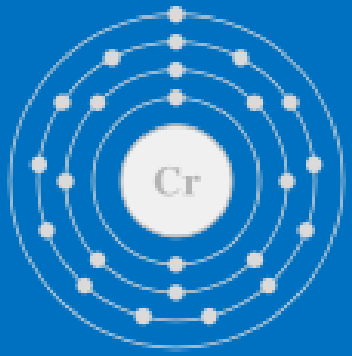
- Hexavalent form : Cr^{+6}
  - Carcinogenic
  - Industrial origin
  - Damages genetic material

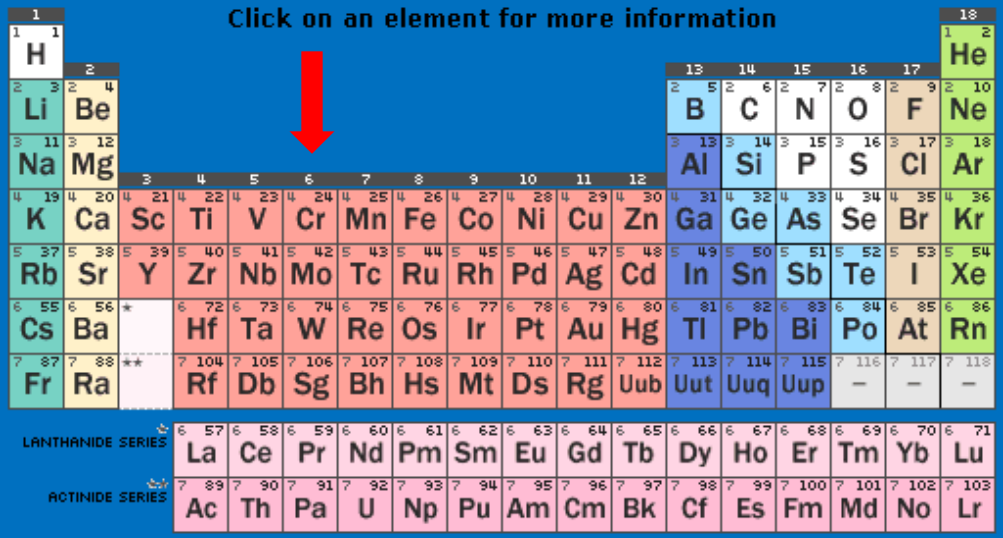
    [Erin Brockovich litigation:

    Industrial water contamination

    with hexavalent chromium]

- Trivalent form: Cr^{+3}
  - Essential nutrient (1977)
  - Naturally occurring
  - Involved in action of insulin





Chromium Sources

- Eating, drinking, skin contact, food processing, preparation and storage
- Found in many fruits and vegetables, grains, meats, spices, yeast
- Usual diets contain 20-40 µg/day
- FNB: AI is 25 µg/day (women) 35 µg/day (men)
- FNB: TL not established
- EPA: RfD is 1 mg/kg/day
- FDA: RDI is 125 µg/day for food labels % /serving

Food Source	Chromium (µg)
Broccoli, 1cup	22
Turkey, leg, 3 oz.	10
Grape juice, 1 cup	8
Waffle, egg, 1	7
Ham, 3 oz.	4
English muffin, whole wheat, 1	4
Potatoes, mashed, 1 cup	3
Garlic, dried, 1 teaspoon	3
Cookies, chocolate chip, 1 large	3
Basil, dried, 1 tablespoon	2
Beef cubes, 3 ounces	2
Orange juice, 1 cup	2
Turkey breast, 3 ounces	2
Whole wheat bread, 2 slices	2
Green beans, 1 cup	2
Red wine, 5 ounces	1-13
Apple, unpeeled, 1 medium	1
Banana, 1 medium	1

FNB (Food and Nutrition Board), EPA (Environmental Protection Agency), FDA (Federal Drug Administration)

Absorption

- Takes place in the mucosal cells of the intestine
  - Mostly in the jejunum
- Absorption is relatively low
  - 0.5 to 2.5% of ingested chromium
  - Dose dependent; lower absorption with higher doses
- Increased Absorption
  - Oxalate, Vitamin C, Niacin, Aspirin
  - Beta-blockers, corticosteroids, insulin, nicotinic acid, nonsteroidal anti-inflammatory drugs (NSAIDS), prostaglandin inhibitors
- Decreased absorption:
  - Phytate
  - Diet high in simple carbohydrates
  - Antacid buffers (magnesium or calcium carbonates) corticosteroids, H2 blockers, proton-pump inhibitors

Transport

Not yet fully identified (Stoecker, 1999)

- Transferrin is primary transport protein
  - Albumin can also be a carrier
  - Some evidence for passive diffusion

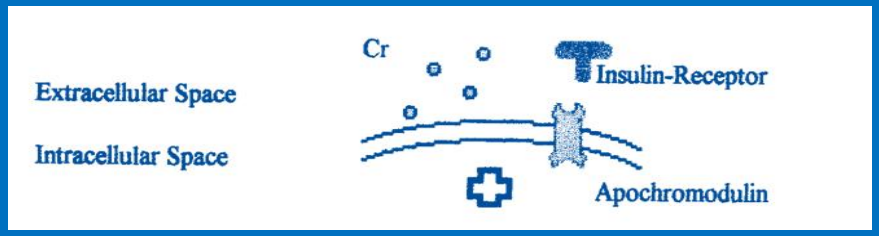
Storage and Excretion

- Chromium circulating in blood picked up by bones, liver, and kidneys and accumulates in the spleen (Stoecker, 1999).
  - Also picked up in the muscle, heart, and pancreas (Pechova, 2007)
- Absorbed chromium
  - excreted in urine by glomerular filtration in the kidneys
- Most unabsorbed chromium
  - excreted in the feces
- Small amounts of chromium
  - excreted through bile, perspiration, and in milk (Pechova, 2007)

PROPOSED ROLE OF CHROMIUM:
ACTIVATION OF THE INSULIN RECEPTOR (DATILLO, 2003)

Phase I

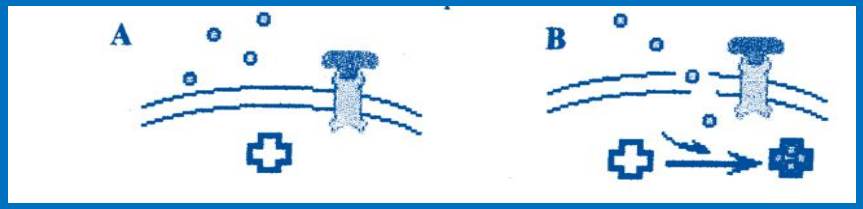
Inactive Insulin-sensitive cell



In response to a glucose load, extracellular insulin concentration increases. Chromium, Also in extracellular space, circulates with transferrin. Intracellularly, chromodulin, a low molecular weight peptide, pictured here prior to binding with chromium is present.

Phase II

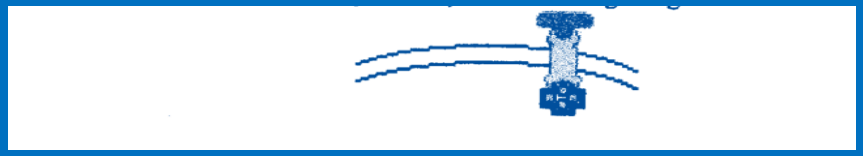
Insulin mediated chromium ion flux



A. Insulin binds to the external alpha subunit of the Insulin Receptor.
B. As a result of the insulin binding, chromium ions move across the cell membrane of insulin dependent cells to intracellular space. Chromodulin sequesters 4 chromium ions to become complete.

Phase III

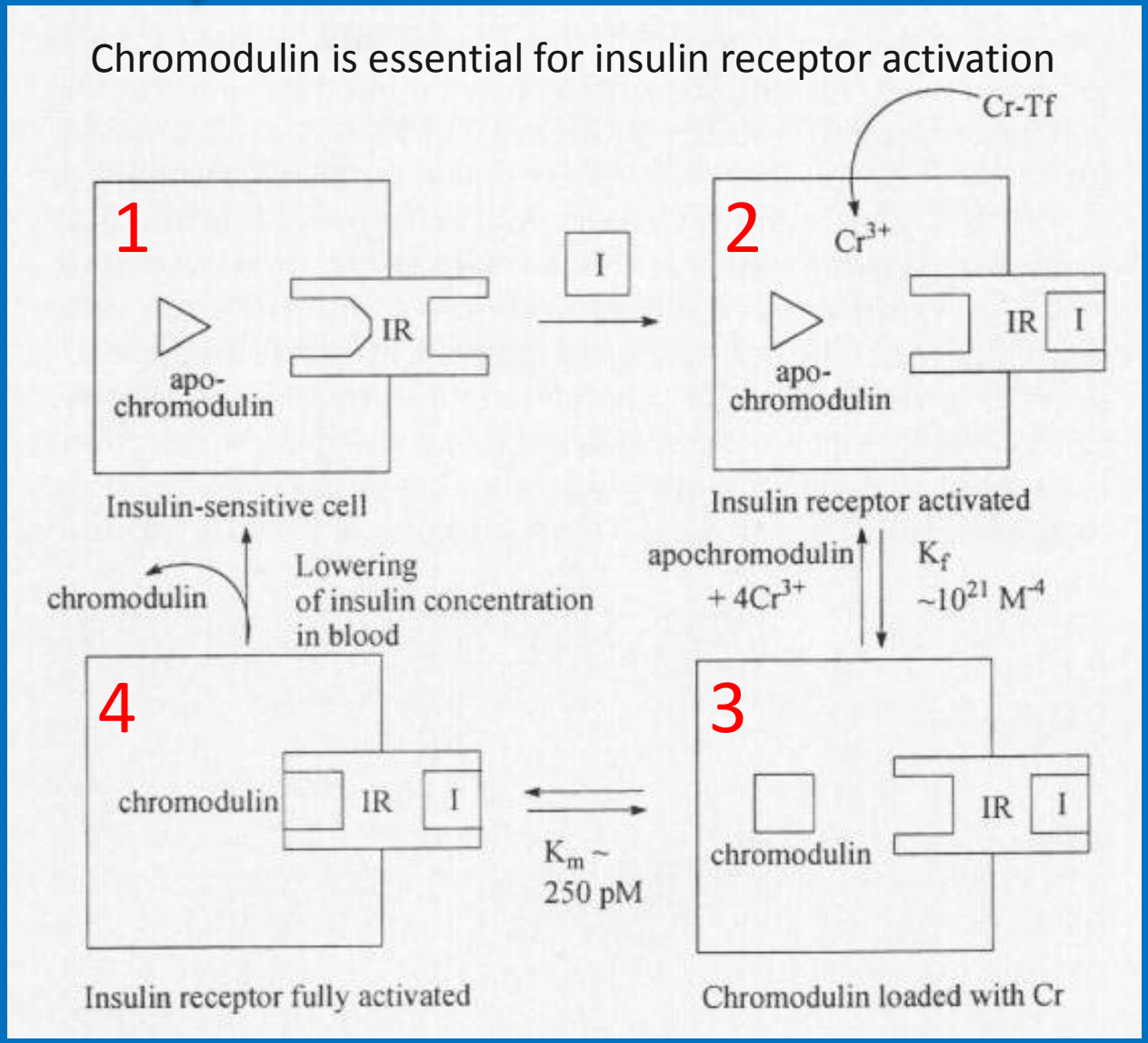
Activated insulin receptor



Complete chronodulin binds to insulin-stimulated Insulin-Receptor, which further activates receptor kinase activity and amplifies insulin signaling.

Proposed Mechanism:
Activation of Insulin Receptor Kinase Activity by Chromodulin in Response to Insulin

1. Inactive form of insulin Receptor (IR) is
2. converted to active form by binding insulin. This triggers movement of Cr-tf from blood to insulin-dependent cells.
3. That, in turn, results in the binding of chromium to Apochromodulin (triangle). Finally, Holochromodulin (square)
4. binds to insulin receptor and further activates the kinase activity. (Apochromodulin unable to bind to insulin receptor and activate kinase activity.) When insulin concentration drops, holochromodulin is released from the cell to relieve its effects.



Vincent, J.B., The Biochemistry of Chromium. J Nutr, 2000. 130:p.715-718.

Proposed Mechanism:
Movement of chromium from blood to chromodulin

1 In response to increases in plasma insulin concentrations, transferrin-receptor (Tr-R) in insensitive cells migrates from vesicles

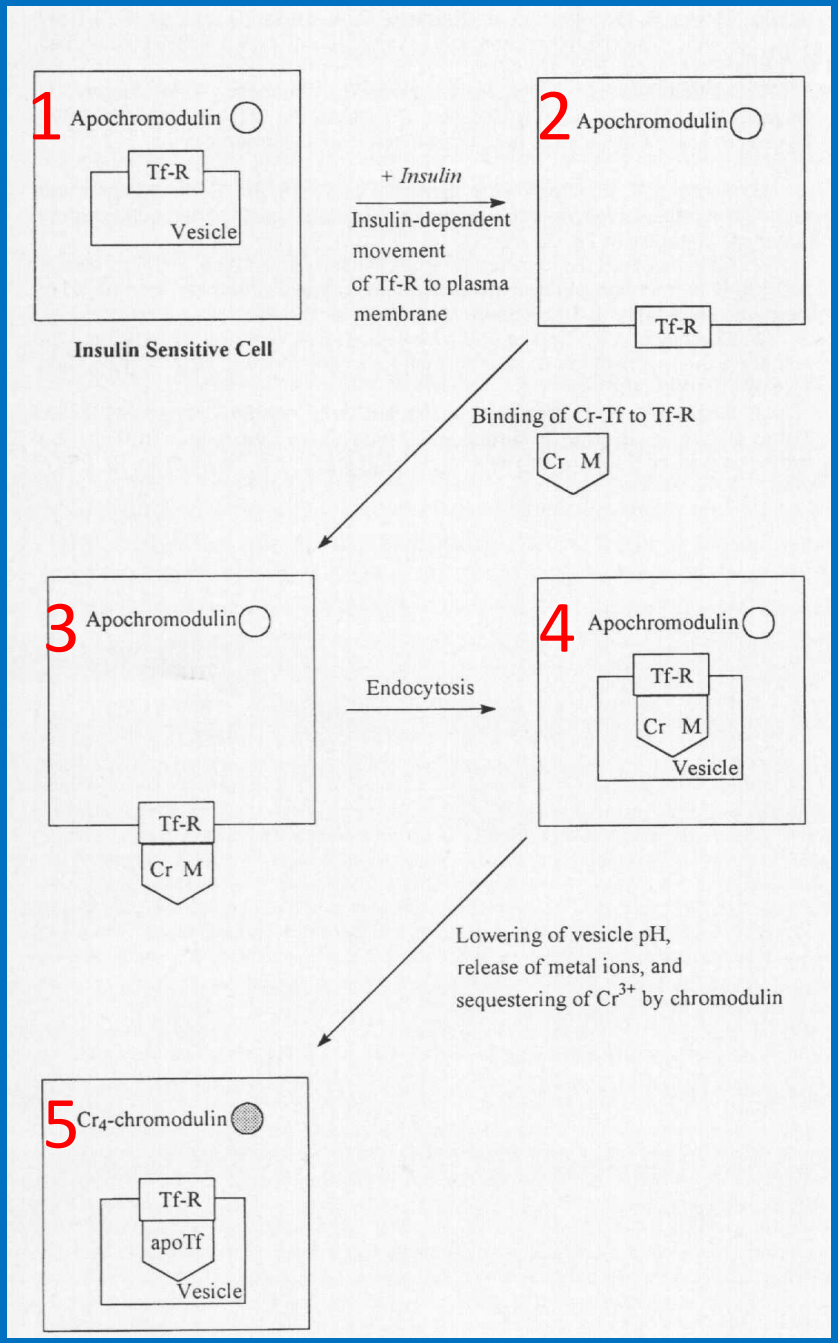
2 to the plasma membrane.

3 Transferrin (pentagon), which contains two bound Metal ions [in this case one chromic ion and one Other metal cation (M)], binds to the receptor

4 and Is internalized by endocytosis.

5 The pH of the resulting vesicle is reduced by ATP-driven proton pumps, resulting in the release of the metal ions from transferrin.

Chromium released from multiple transferrin Molecules is sequestered by apochromodulin (open circle) to produce chromium-loaded chromodulin (dark circle).



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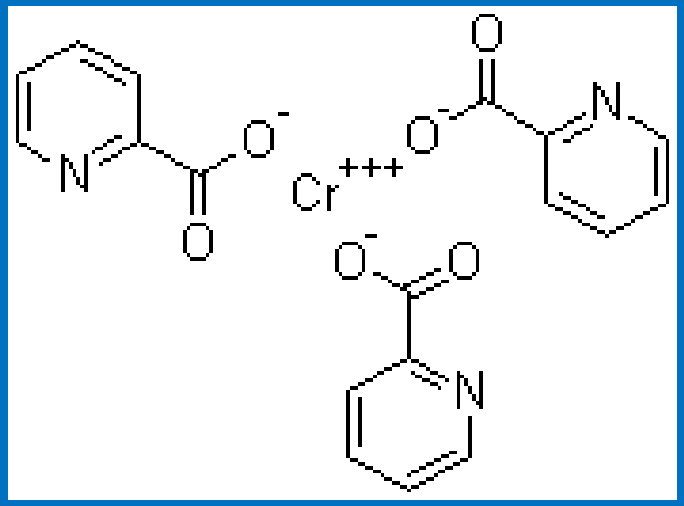
Chromium Deficiency as a Risk Factor for Type 2 Diabetes

- Insufficient chromium intake has been implicated as a risk factor for the development of diabetes (Kazi, 2008)
  - Chromium concentrations in scalp-hair and blood were significantly lower ($p<0.001$) in diabetes patients compared to controls
- Chromium deficiency associated with impaired glucose tolerance, fasting hyperglycemia, glucosuria, elevated percent body fat, decreased lean body mass, and Type 2 diabetes mellitus (Lau, 2008)
- Glucose intolerance, weight loss, and neuropathy symptoms in women maintained on total parenteral nutrition for five years was reversed by supplementation of 250 µg of chromium (Jeejebhow, 1977). As a result, chromium is now included in TPN solutions.

Dietary Supplement: Chromium Picolinate



Name	Chromium Picolinate
Synonyms	Picolinic acid chromium(III) salt
	2-Pyridinecarboxylic acid chromium salt

Molecular Formula $Cr(C_6H_4NO_2)_3$

http://www.chemblink.com/products/14639-25-9.htm

Dietary Supplement: Chromium Picolinate

Reduced food intake in both humans and Sprague Dawley rats (Anton, et al., 2008)

- Human trial, 8 weeks
  - Random, double-blind placebo-controlled trial
  - 42 overweight adult women with CHO cravings
  - 1000 µg of chromium picolinate or placebo
  - Significantly ($p<0.0001$) reduced calorie intake with no increased hunger
- Animal model
  - Chromium picolinate in increasing doses: 1, 10, 50 µg/kg.
  - Significant ($p<0.03$) decrease in 24-hour food intake at highest dose.

Dietary Supplement: Chromium Picolinate

Beneficial effects against microvascular complications (Sahin, et al., 2007)

- Sprague-Dawley rats (n=45, 8 weeks old), 3 groups
  - Group 1 (Controls): standard diet
  - Group 2: high fat diet (40% of calories from fat) and then injected with streptozotocin on day 14 to induce diabetes
  - Group 3: group 2 diet and injection plus 8 µg/kg chromium picolinate/day (equivalent to 560 µg/d for a 70 kg person)
- Group 3 treatment lowered glucose by an average of 63% ($p<.01$), lowered cholesterol by 9.7% ($p<.001$), and lowered triglycerides by 6.6% ($p<.001$) compared with group 2 treatment
- Further treatment for 10 weeks significantly attenuated changes in metabolic risk factors associated with the liver, kidney, and pancreas
- Similar observations in human Type 2 Diabetes clinical trials (Cefalu and Hu, 2004, Rabinovitz, et al., 2004)

Dietary Supplement: Chromium Picolinate

Proposed mechanisms of action (Cefalu, et al., 2002, Wang, et. al, 2006)

- Possible decrease in hepatic glucose production
- Increase in peripheral glucose disposal
- Reduction of intestinal glucose absorption
- Chromium supplementation may improve insulin action by enhancing intracellular signaling in obese, insulin-resistant rats

Dietary Supplement in Human Nutrition: Uses of Chromium Picolinate

- Impaired carbohydrate metabolism
- Prevention for the formation of atherosclerotic plaques
- Improved glycemic control in patients with Type 2 Diabetes Mellitus

Concerns Raised About Possible Toxic Effects of Chromium Picolinate

- Tolerable upper limit unknown
  - Large dosages in many studies
  - Are other forms of chromium supplementation effective?
- Study of alternate chromium treatment in the form of chromium yeast (Kleefstra, et al., 2007)
  - 6 month randomized, double-blind, placebo-controlled trial
  - 400 µg Cr^{3+}yeast
  - Found no difference for change in HbA_{1c}
  - No evidence that chromium yeast is effective in improving glycemic control in a Western population with T2 diabetes and oral hypoglycemic agents

Safety and Efficacy of Chromium Picolinate with Biotin on Glycemic Control

Study of chromium picolinate, combined with biotin, 90 day trial with patients currently on oral therapy (Albarracin, et al., 2008)

- Randomized, double-blind, placebo-controlled study of treated, uncontrolled, overweight to obese patients (n=447)
- Findings: the combination of 600 µg chromium and 2 mg biotin provided a significant (p=0.03) improvement of long-term glycemic control (HbA_{1c})

Chromium Supplementation Controversy

- Nutritional supplements containing chromium picolinate are a multi-million dollar industry in the U.S.
  - $85 million in 2002 , according to National Institute of Health
  - Dietary Supplement Fact Sheet: Chromium http://ods.od.nih.gov/factsheets/chromium.asp
  - The extreme popularity of chromium picolinate as a dietary supplement is not commensurate with the current level of understanding of how chromium works in the body
- Most, but not all, studies report benefits
- Differences in study design, subjects included, dose administered, and statistical power may explain outcome differences

Chromium Supplementation Controversy

- Chromium picolinate appears to be absorbed in a manner different from that of dietary chromium
  - Chromium picolinate is very stable
  - It remains intact for hours in synthetic gastric juice and appears to pass intact through the jejunum (Gammelgaard, et al., 1999)
  - The picolinate ligands shift the redox potential such that it can be reduced by ascorbate and thiols
  - The resulting complex can interact with oxygen to generate the hydroxyl radical
- Release of chromium from chromium picolinate for use in cells can potentially have harmful effects
- Institute of Medicine and other regulatory agencies reviewed a dozen clinical trials and found no safety concerns or toxic effects

Chromium Supplementation Controversy

- Chromium is generally accepted as an essential nutrient for normal CHO, FAT, and PRO metabolism
- Many unanswered questions about supplementation
- Study (Wang, et al., 2007) to predict clinical response to chromium picolinate
  - Randomized, double-blinded, placebo-controlled, (n=73) subjects with Type 2 diabetes
  - 63% of diabetes patients responded to chromium treatment (1000 µg/day) compared to 30% with placebo
  - Baseline insulin sensitivity was significantly (p=0.0004) associated with the clinical response to chromium.

Chromium Supplementation Controversy

- Challenges
  - No reliable method for diagnosing chromium deficiency
  - There are no chromium markers
  - Cannot accurately determine the chromium status of a healthy or chronically ill individual
  - Measurement tools and methods need improvement
- Studies of healthy people or diabetic patients with chromium supplementation not conclusive; results widely disparate

Chromium Supplementation Implications

- Chromium supplements are widely used as alternative therapy for Type 2 Diabetes Mellitus
- Public demand for chromium growing due to reports that chromium is associated with
  - Reducing body fat, lowering cholesterol, stabilizing blood sugar, managing diabetes
- Chromium picolinate has shown promise , but mechanisms of action are somewhat obscure and study results inconsistent
- No diagnostic markers for chromium status and more accurate diagnostic tools only recently available
- Benefits vague but encouraging; Long term effects not known

Future Research Needed

- Role of chromium in the body
- Accurate measures of marginal chromium deficiency
- Valid, reliable measures of chromium status
- Controlled human studies to identify subjects most likely to benefit
- Randomized controlled clinical trials in well-defined at risk populations with known dietary intakes to determine effects of chromium on diabetes markers
- Monitor chromium supplementation, especially by diabetic patients, for long term safety issues
  - Diabetic patients typically present with renal damage; chromium accumulates in kidneys
- Nutrigenomics to identify genes regulated by chromium and suggest strategies to attenuate insulin-resistance

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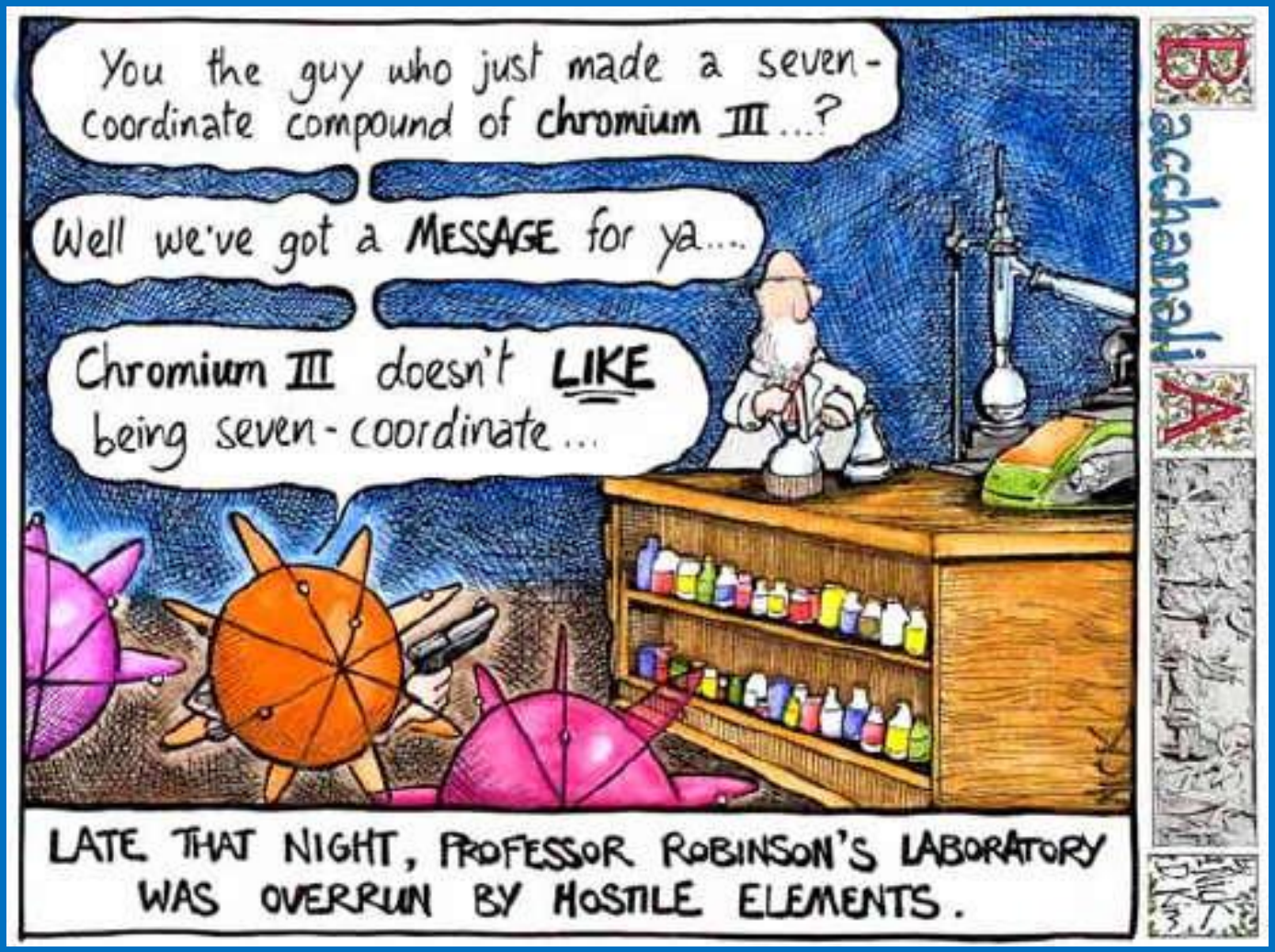

Hexavalent Chromium may be a "hostile element," but trivalent Chromium is an <u>essential nutrient</u> in human metabolism!