DDT Vol. 8, No. 21 November 2003

Harnessing chromium in the fight against diabetes

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A new chapter has opened up in the controversial story of a chromium dietary supplement. Recent clinical trials have reinforced the case for using chromium picolinate as an adjunctive treatment for type 2 diabetes. Similar trials have addressed this issue before. However, the new study differs by proposing a molecular mechanism that could account for the ability of the chromium supplement to increase insulin sensitivity in diabetics.

Type 2 diabetes

Diabetes affects around 194 million people worldwide. Type 2 diabetes represents ~90% of cases and is caused by either insufficient secretion or action of insulin, a hormone that helps glucose enter cells. The condition leads to an accumulation of extracellular glucose, and a dearth of this energy source where it is most needed: within the cells of skeletal muscles. The resulting symptoms are diverse and can include blindness and heart disease. Type 2 diabetes has a complex etiology, involving both genetic and environmental factors. The disease can often be controlled by careful diet and exercise management, but insulin injections or medication often become necessary. Unfortunately, such treatments are of low efficacy as monotherapy and can cause side-effects. To augment drug treatment, sufferers often take dietary supplements containing chromium, which plays an ill-defined role in glucose metabolism. The safety of this practice has been called into question, however, and until a more detailed picture emerges of how

chromium supplements might work at the molecular level, there will always be voices of caution.

Controversial chromium

Chromium is an essential trace element for humans, necessary for regulation of lipid and carbohydrate metabolism. It also has an important, if poorly understood, role in insulin metabolism, acting as a cofactor for the hormone. Details of its molecular biology are somewhat sketchy. Indeed, the quantities required by the body are so small that dieticians are unsure of the doses to recommend for good health. The effects of chromium on the human body get a mixed press. In its hexavalent form, chromium is a recognized carcinogen and a significant occupational hazard. Fortunately, the trivalent form of chromium is safer, being poorly absorbed by the body. Prompted by the known role of chromium in insulin signalling, various chromium dietary supplements are available and extremely popular with diabetics in the USA; chief among these supplements is chromium picolinate. Clinical trials have consistently shown that chromium picolinate can increase insulin sensitivity and improve the health of diabetics (see, for example, Refs [1,2]). However, such supplements are not without safety concerns. Studies have found that chromium picolinate could damage genetic material in animal cells, suggesting carcinogenic properties. The controversy continues, with the UK's Food Standards Agency (http://www.foodstandards.gov.uk) advising against taking the supplement, whereas in the USA, it is deemed to be generally safe.

Towards a mechanism

Clearly, more information is required about the molecular biology of chromium picolinate if such differences of opinion are to be resolved. Studies have provided some clues, suggesting that the supplement increases insulin binding, the number of insulin receptors and also the phosphorylation of these receptors [3]. Now, a series of clinical trials have provided more hints into the mechanism and pointed to a phosphorylation event as the root cause.

The results of a human clinical trial headed by William Cefalu at the University of Vermont College of Medicine (http://www.med.uvm.edu/) were recently presented at the *18th International Diabetics Federation Congress* [4]. Two cohorts of subjects with type 2 diabetes were treated with sulfonylureas (which increase insulin secretion) or a diet program. The cohorts were then randomized to receive daily doses of either 1000 μg chromium picolinate or a placebo.

 PII: S1359-6446(03)02892-7

Glucose uptake was measured in all subjects at the beginning and end of the study. Those randomized to the chromium supplement had a mean increase in insulin sensitivity of 8.9%, whereas the placebo group showed a mean decrease of 3.6%.

Importance of the findings

The researchers tied in their results to recent findings about the molecular biology of chromium picolinate. Previously, it had been suggested that the supplement increases the phosphorylation of the protein Akt. This intracellular enzyme is activated by insulin and facilitates the uptake of insulin into cells. The researchers found that insulin-stimulated Akt activation was significantly increased at the end of the study compared with placebo measurements. No adverse side effects were observed. Cefalu commented on the relevance of this finding. 'As this intracellular pathway is implicated in contributing to insulin resistance, this represents a possible mechanism to explain chromium picolinate's beneficial effect on insulin sensitivity as observed in several clinical studies,' he said.

Despite the small number of patients in the study, the findings could be important. John Vincent, an expert on chromium biology from the University of Alabama (http://www.ua.edu) and not connected with this study, commented on the significance. 'Any information on the mechanism by which chromium may positively affect metabolism is potentially quite valuable, both in terms of the scientific community in understanding the role of this poorly understood potential nutrient and in attempting to develop therapeutic agents for the treatment of type 2 diabetes.' However, he called attention to the fact that the study did not address whether the effects are unique to chromium picolinate, or whether other chromium supplements, for example, chromium chloride, might also be effective.

References

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4 Cefalu, W.T. *et al.* (2003) Chromium picolinate supplementation increases insulin-stimulated Akt phosphorylation *in vivo* in skeletal muscle from subjects with Type 2 diabetes. *18th International Diabetes Federation Congress* 24–29 August, Paris, France (Abstract No. 154)

News in brief

Targets and Mechanisms

Survival tactics

Two cell types have been found to adapt in the absence of oxygen, enabling them not only to survive but also to become 'tougher' [1,2]. Researchers at the Medical College of Georgia (http://www.mcg.edu/) removed the oxygen supply from tubular cells of the kidney (through which the body's entire fluid volumes flows) and found that some of these cells appear to adapt by up-regulating two genes, IAP-2 and Bcl-xL. When the genes are knocked out, the sensitivity of the cells to injury returns.

Zheng Dong, co-author of the reports, believes that this response enables the cells to survive ischaemic stress, giving them a chance to repair the injured kidney. He explains that some cancer cells show similar adaptation, as a tumour grows too big for its oxygen supply, although probably not via the same route; as Dong explains, 'they simply become stronger, tougher and more resistant to injury, and for those in tumours, more resistant to cancer therapies'.

The work details how a poorly understood protein, Bax – which is usually found in the cytosol – moves into mitochondria in a hypoxic cell, where it perforates the membrane and, thus, acts pro-apoptically. However, in resistant cells, membrane accumulation of this molecule is suppressed and IAP-2 was induced in the cytosol.

The work could ultimately lead to gene therapy, where survival genes, such as IAP-2 and Bcl-xL, can be up-regulated in ailing cells (e.g. in cardiovascular disease or diabetes) and down-regulated in proliferating cells, such as cancer cells. Dong is optimistic; 'hopefully, we can identify some therapeutic tool that is either genetic or pharmaceutical, to switch these as needed'.

1 Dong, Z. *et al.* (2003) Apoptoisis-resistance of hypoxic cells. *Am. J. Pathol.* 163, 663–671

2 Yi, X. *et al.* (2003) Inhibition of Bid-induced Apoptosis by Bcl-2. tBid insertion, Bax translocation and Bax/Bak oligomerization suppressed. *J. Biol. Chem.* 278, 16992–16999

New turn-ons for T-cells

A newly developed retroviral gene-delivery system has been implemented in the discovery of novel immunoregulators [3]. Researchers from Rigel Pharmaceuticals (http://www.rigel.com/) observed that, when transfected with certain lymphoid-derived genes, T-cells failed to activate. This could aid in the development of drugs that target the immune response.

  PII: S1359-6446(03)02871-X