Research Update

Investigating insulin

Researchers in Montreal and Ottawa have uncovered a clue to the metabolic processes that lead to obesity and non-insulin-dependent diabetes mellitus — and their finding could lead to new treatments (*Science* 1999;283:1544-8).

The researchers have modified mice genetically so that they lack the gene for a recently discovered enzyme, protein tyrosine phosphatase-1B (PTP-1B). Mice without the enzyme resist weight gain and remain insulin sensitive, even when eating a high-fat diet, whereas mice with the enzyme rapidly gain weight and become insulin resistant. This proves the importance of the enzyme in insulin sensitivity and metabolism. If the enzyme has the same function in humans as in mice, it could be a target for the treatment of obesity and non-insulin-dependent diabetes.

The researchers did not begin by looking at obesity but at immunity, explains coauthor Dr. Brian Kennedy of the Merck Frosst Centre for Therapeutic Research in Montreal. "We were looking at a whole family of enzymes, called protein tyrosine phosphatases, that is large and growing." Interest first centred on another enzyme found in T and B cells and involved in immunosuppression. This led to development of inhibitors of enzymes in this family. As it happened, the researchers identified inhibitors that were "very, very specific for PTP-1B."

To discover what they were inhibiting, the researchers needed to know the function of the enzyme. Based on previous research, "we had a pretty good gut feeling that it was involved in insulin," says Kennedy.

Scientists at Merck Frosst teamed up with researchers at McGill University and the University of Ottawa to develop the "knock-out" mice lacking the gene. Now that the role of PTP-1B in mice is established, the next task is to investigate the enzyme's role in humans. "We have to prove that this connection [between PTP-1B and obesity] also holds true in humans. I have a hunch that it will."

The researchers are also working on therapies to try in animal models. These experiments are still a long way from therapies for humans, but Kennedy believes that the outlook is promising.

Discoveries like this one involving the key processes of metabolism could also change our understanding of obesity and non-insulin-dependent diabetes. "What comes first?" asks Kennedy. "The type 2 diabetes or the obesity? I don't think we know. It's a chicken-and-egg thing." — *C.J. Brown*

Research news . . .

Screening hair for breast cancer

Hair from patients with breast cancer or with the most common genetic mutation causing breast cancer is actually different on a molecular level than hair from people without the disease (*Nature* 1999;398:33-4). The discovery was made by researchers who used x-ray diffraction studies with synchrotron radiation to examine hair. The finding is so clear and consistent that the researchers suggest that hair analysis can be used as a simple way to screen women for breast cancer.

Creatine to treat ALS

Creatine improves muscle coordination and extends life in mice genetically engineered to have amyotrophic lateral sclerosis (ALS), a new study has determined (*Nat Med* 1999;5:347-50). Creatine is important in the function of mitochondria, dysfunction of which is one of the earliest pathologic features of ALS. Giving mice with ALS creatine by mouth protected them from the loss of motor neurons and substantia nigra characteristic of the disease, and offered greater protection in higher doses. The researchers suggest that creatine may be used as therapy for ALS in humans.

Cisplatin helps stop cervical cancer

Treating cervical cancer with the drug cisplatin, in combination with radiotherapy, cuts the risk of disease progression or death almost in half, according to 3 studies to be published in the *New England Journal of Medicine* and released early on the Internet. The first study compared radiotherapy with 3 possible chemotherapy regimens — cisplatin alone; cisplatin plus fluorouracil and hydroxyurea; and hydroxyurea alone — to treat locally advanced cervical cancer. The 2 regimens containing cisplatin achieved much better progression-free survival than hydroxyurea alone. The second study compared radiotherapy, alone or in combination with cisplatin, followed in all cases by hysterectomy, to treat bulky stage IB cervical cancer. The risk of disease progression and death was twice as high in patients who did not receive cisplatin. The third study compared pelvic radiotherapy alone with pelvic radiotherapy plus fluorouracil and cisplatin in advanced cervical cancer, finding that disease-free survival was much higher in patients who received the chemotherapy.