

Seizure spray

Leptin, a hormone best known for controlling feeding and energy metabolism, also counteracts seizures, according to findings in two models of epilepsy in rats (*J. Clin. Invest.* **118**, 272–280; 2007).

Leptin originates in fat tissue and operates through the hypothalamus to control feeding and metabolism. The receptor for leptin is also present in other areas of the brain, such as the hippocampus, and preliminary studies have suggested that leptin has anti-convulsant actions and a role in learning and memory.

Lin Xu *et al.* found that nasal administration of leptin delayed chemically induced seizures, whereas delivery to the cortex shortened the duration and frequency of local seizures. Leptin directly suppressed glutamate-induced excitatory transmission in the hippocampus. Such suppression required the leptin receptor and involved JAK and PI3K signalling.

The findings help explain why a high-fat, low-carbohydrate diet that elevates leptin suppresses seizures. The results also suggest new types of treatment for epilepsy, such as a quick-acting leptin nasal spray. Unlike the related neuropeptides neuropeptide Y (NPY) and galanin, leptin can cross the blood-brain barrier and so is suitable for peripheral administration.—KJ

Controlling pain control

A new approach to pain relief may lead to drugs that kill chronic pain without side effects such as sedation. The approach involves selectively targeting GABA_A receptors that contain specific subunits (*Nature* **451**, 330–334; 2008).

A role for GABA-mediated neurotransmission in analgesia has long been established, but drugs that activate GABA receptors, such as benzodiazepines, tend to cause sedation and motor impairment and even have the potential to become addictive.

In the new study, Julia Knabl *et al.* used mice carrying point mutations in different α subunits, mutations that abolished the subunit's response to benzodiazepines. They found that the analgesic action of diazepam disappeared in mice carrying mutant $\alpha 2$ or $\alpha 3$ subunits. Moreover, the administration of L-838,417, a benzodiazepine that activated the $\alpha 2$ and $\alpha 3$ subunits but spared $\alpha 1$, reduced pain without any benzodiazepine-induced side effects.

Targeting specific GABA receptor subunits to dissociate the analgesic role of this transmitter from its other neural functions could be a promising strategy to treat pain.—JCL

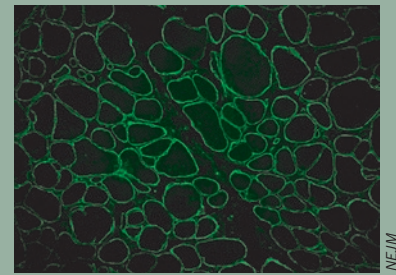
Shot for muscular dystrophy

An antisense oligonucleotide partially restores expression of the protein missing in Duchenne muscular dystrophy, according to findings from a clinical trial in four boys (*N. Engl. J. Med.* **357**, 2677–2686; 2007).

Individuals with DMD commonly die of this muscle wasting disease by age 30. Such individuals have mutations in the *DMD* gene that result in a truncated, nonfunctional form of dystrophin, an essential muscle protein.

To restore expression of dystrophin, Judith van Deutekom *et al.* used an antisense oligonucleotide chemically modified to enhance stability and affinity. The oligonucleotide is designed to prompt specific exon skipping during RNA splicing, thereby correcting the open reading frame of the *DMD* gene. After a single injection of the oligonucleotide, the researchers observed partial restoration of dystrophin expression near the site of administration.

Testing whether such an approach can restore full-body muscle function will require delivery of the oligonucleotide beyond a single injection site. Experiments in the MDX mouse model have shown that systemic delivery of an antisense oligonucleotide can restore dystrophin expression throughout the animal and improve muscle function.—CS



Dystrophin expression restored.

Numb to treatment

NUMB, a protein best known for controlling asymmetric stem cell divisions, has now been tied to the regulation of the tumor suppressor p53 (*Nature* **451**, 76–80; 2008). The findings raise the possibility that p53 might help set up stem cell divisions.

NUMB is asymmetrically partitioned at mitosis, and it helps determine cell fate by counteracting the activity of NOTCH family members. Ivan Colaluca *et al.* found that NUMB also complexes with p53, resulting in p53 stabilization.

NUMB is frequently underexpressed in breast cancers. To explore the effect of NUMB underexpression, the researchers examined a cohort of 443 individuals with breast cancer. They found that NUMB-defective breast tumors were particularly aggressive and that NUMB status is a predictor of poor prognosis. The researchers provide evidence that NUMB underexpression results not only in misregulation of the oncogene NOTCH but also in misregulation of p53.

The researchers speculate that NUMB and p53 might be involved in cell fate decisions in mammary stem cells. Previous studies have hinted that p53 may be involved in stem cell divisions, for instance in helping to mediate DNA segregation so that the 'older' strand remains in the mother cell.—CS

Transmitting fat

If you want to raise lean, healthy children, it's best to shed those extra pounds before becoming pregnant. That's the implication of a study

in rats examining how the environment of the womb can influence the weight of offspring, independent of genetics (*Am. J. Physiol. Regul. Integr. Comp. Physiol.*, doi:10.1152/ajpregu.00316.2007).

It's well documented that overweight mothers tend to raise overweight children. Although much of this correlation may relate to genetic factors and household eating habits, researchers have long suspected a role for the environment of the womb. For instance, children's weight correlates more closely with the mother's than with the father's, and overweight women are more likely to give birth to fat babies.

To exclude the effects of genes, Kartik Shankar *et al.* examined rat pups born to genetically identical mothers. The mothers were fed either a control 'healthy' diet or a high-fat diet, which made them obese. Pups from obese moms and lean moms weighed about the same at birth, and when fed the control diet their body weights remained similar. But the offspring from obese mothers had more subcutaneous fat.

Things deteriorated when the pups from obese mothers were raised on a high-fat diet. These pups gained much more weight than pups from lean mothers, and had higher serum levels of insulin and leptin—indicating a predisposition to type 2 diabetes.

The findings dovetail with other experiments implicating a role for the womb environment in obesity, including a recent study showing metabolic and cardiovascular defects in mice from obese mothers (Anne-Maj Samuelsson *et al. Hypertension* doi: 10.1161/hypertensionaha.107.101477).—CS

Sick stroma

Mutations in the tumor suppressor p53 in cells surrounding a tumor—and not in the cancer cells themselves—is predictive of metastasis status, according to a study of individuals with breast cancer.

Tumor-associated cells in the stroma are thought to benefit a nearby tumor by secreting factors that help in its motility and invasive potential. The genetic makeup of these stromal cells, however, was presumed to be normal and without mutations.

Attila Patocs *et al.* used laser-capture microdissection to isolate the surrounding stroma or the cancer epithelium from 43 individuals with hereditary breast cancer and 175 with sporadic breast cancer (*N. Engl. J. Med.* 357, 2543–2551; 2007). They performed a genome-wide analysis of both compartments and found that in more than one-quarter of the tumors, the stromal cells harbored mutations in the p53 gene in the absence of any changes in that gene in the cancer epithelial cells. These mutations were associated with increased lymph node metastases in individuals with sporadic cancer. No such association was found in those with hereditary breast cancer.

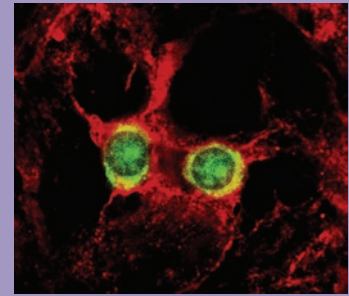
Exactly why and how stromal cells develop cancer mutations remains unclear. One possibility is that stromal and epithelial cells originate from different progenitors and that the tumor microenvironment induces mutations in the stroma.—KJ

Breaking the blood-brain barrier

Immune cells can sneak across the blood-brain barrier (BBB) by tethering onto the adhesion molecule CD166, according to a report in *Nature Immunology* (9, 137–145; 2007). The findings have implications for multiple sclerosis (MS) and related diseases.

Even though the brain has been regarded as an immunologically privileged organ, immune-cell invasion of the nervous system is critical in diseases such as MS. In fact, the therapeutic agent natalizumab treats MS by blocking the entry of monocytes mediated by vascular cell adhesion molecule-1 expressed in endothelial cells of the BBB.

In the new study, Romain Cayrol *et al.* discovered that the BBB expresses CD166 (also known as activated leukocyte cell adhesion molecule), an adhesion molecule known to interact with CD6 on leukocytes. Expression of CD6 was increased in the nervous system of people with MS, and an antibody against CD166 restricted the migration of lymphocytes and monocytes into the nervous system in a mouse model of this disease. The antibody also had a therapeutic effect on the mice, identifying CD166 as a potential target for the treatment of MS.—JCL



Expression of CD166 (red) on endothelial cell localizes with CD4⁺ T cells (green).

The fate of fat

Eating a lot of fat can promote the development of insulin resistance in muscle, a step toward full-blown type 2 diabetes. New findings on the mitochondria suggest how this resistance develops and challenge previous thinking in the area.

Previous work had hinted that insulin resistance develops in the muscle when too much fat

enters the tissue to be processed by mitochondria. The excess was thought to accumulate in the tissue, leading to the buildup of proinflammatory lipid metabolites such as diacylglycerol and ceramide, which engage in signaling events that impede the insulin pathway.

Instead, Timothy Koves *et al.* found that excess fat in muscle cells instead essentially overloads the mitochondrial pathway that processes fatty acids, β -oxidation, and leads to insulin resistance (*Cell Metab.* 7, 4556; 2008).

The authors found high levels of acylcarnitines—intermediates in the steps of β -oxidation—in the serum of mice fed a high-fat diet. When normal mice are fed standard chow after fasting, they switch from using stored lipids to the incoming glucose, and Koves *et al.* detected a corresponding change in the acylcarnitine profiles of these mice. Mice previously fed a high-fat diet, however, continued to generate high levels of β -oxidation intermediates after switching to standard chow.

Koves *et al.* predicted that this inability to switch from fatty acid metabolism to glucose metabolism led to insulin resistance. To test this, the researchers slowed down the β -oxidation pathway by genetically inhibiting the entry of fatty acids into the mitochondria. These mice maintained insulin sensitivity when on a high-fat diet, suggesting a new approach to limiting the effects of indulging in too much ice cream and cake.—KS

Written by Kate Jeffrey, Juan Carlos López, Charlotte Schubert & Katherine Stevens

Melting away

A dip in the hot tub—“heat therapy”—can improve insulin sensitivity in individuals with diabetes. Jason Chung *et al.* examine the mechanistic basis for this effect and home in on a new drug target (*Proc. Natl. Acad. Sci.*, doi:10.1073/pnas.0705799105).

The researchers found that obese, insulin-resistant humans have low levels of heat-shock protein 72 (HSP72) in skeletal muscle, and that, in mice, heat therapy can induce HSP72. When HSP72 was genetically overexpressed, mice were protected from insulin resistance after consuming a high fat diet.

The researchers next found that HSP72 affected the activation of the serine-threonine kinase c-Jun amino terminal kinase (JNK), which can impair insulin signaling. Mice expressing high levels of HSP72 had reduced JNK activation, which allowed the insulin pathway to continue signaling despite a high-fat diet. The HSP72-overexpressing mice also had increased energy expenditure and reduced fat stores compared to wild-type mice fed a high-fat diet.

Inducing HSP72 expression in obese mice with a small molecule resulted in improved insulin sensitivity throughout the body. The drug is now in clinical trials.—KS



Fighting diabetes.