Numb no more

Researchers have harnessed capsaicin, the molecule that makes chili peppers 'hot', to cool down pain (*Nature* **449**, 607–620).

Local anesthetics such as lidocaine, used by dentists before filling a cavity, diffuse freely across cell membranes. As a result, such drugs block neuronal activity in all neurons, not just the ones that sense and signal pain—leading to a generalized 'numbness'.

The receptor for capsaicin is expressed primarily on pain neurons and, when bound to capsaicin, allows positively charged molecules to cross into the neuron. Alexander Binshtok *et al.* reasoned that if they applied capsaicin along with a positively charged anesthetic, capsaicin would open the channel and let the anesthetic cross into pain neurons but not into other cells. The researchers co-injected capsaicin with QX-314, a positively charged anesthetic that normally has to be injected into cells. The rats showed less pain in response to noxious stimuli, but normal tactile and motor responses.

The findings open the door to new treatments for chronic pain—and they may one day allow you to leave the dentist's office without a numb tongue. —*EC*

Bird flu almighty

H5N1 'bird flu' virus has infected more than 250 people since 2003 and killed more than 150—prompting widespread interest in what makes the virus so deadly and how it would need to mutate to spark a pandemic. Three new studies tackle these issues and offer insight into the virulence of the virus, its potential for human-to-human transmission and its ability to infect select immune cells.

Masato Hatta *et al.* reported that the H5N1 virus possesses a single amino acid mutation that provides it with a strong growth advantage in the upper and lower respiratory tracts of mammals. This location may provide an efficient route for human-to-human virus transmission by facilitating virus excretion through coughing and sneezing, and it may underlie the tendency of the infection to lead to severe pneumonia (*PLoS Pathog.* **3**, e133).

Gina Conenello *et al.* found a single amino acid mutation in the cell death–associated protein PB1-F2 that is produced by H5N1. The presence of the mutation correlated with the pathogenicity of the virus in mice. Alarmingly, this same mutation was found in the 1918 pandemic virus, and mutating this amino acid in nonpathogenic viruses induced disease in mice (*PLoS Pathog.* **3**, e141).

Arunee Thitithanyanont *et al.* showed that H5N1 preferentially infects and kills myeloid dendritic cells (mDCs) but not other immune cells. Infection resulted in rapid killing, with the presence of only one virus particle per 250 cells resulting in 60% cell death. Pretreating the mDCs with interferon-α or Toll-like receptor agonists protected from infection and death, revealing a potential new treatment strategy (*J. Immunol.* **179**, 5220–5227). The infection of DCs may also explain why H5N1, unlike other influenza A viruses, is detected outside the respiratory tract in blood and damaged organs.—*KJ*

Dampening diabetes

The histone deacetylase SIRT1 can reverse insulin resistance through its ability to directly silence a major negative regulator of insulin, protein tyrosine phosphatase-1B (PTP1B; *Cell Metab.* 6, 307–319).

Resistance to the actions of insulin is the hallmark of type 2 diabetes. Alleviating this resistance is one of the key avenues to treating the disease, which currently affects 170 million people worldwide.

Janice Zabolotny *et al.* show that increasing the expression of SIRT1, which is lowered in insulin-resistant cells, can restore insulin sensitivity. To activate SIRT1, the researchers used resveratrol, the compound in red wine known for its antiaging and weight loss effects. Resveratrol—at doses much higher than those found in wine—ameliorated insulin resistance in mice fed a high-fat diet and reestablished normal glucose uptake. The effect of SIRT1 on insulin resistance was achieved through its ability to directly silence PTP1b transcription.

PTP1b is a hot drug target for diabetes that promotes resistance to insulin. PTP1b does so by acting directly on the insulin receptor and by increasing appetite and decreasing metabolism through its inhibition of leptin. These new findings suggest that drugs that enhance SIRT activity, including resveratrol, might prove valuable for targeting PTP1b and treating insulin resistance and type 2 diabetes.—*KJ*

Parsing pot

Subscribers to *High Times* magazine might regard marijuana as a universal salve, but to most researchers in the field, cannabinoids have both positive and negative attributes. To tease out the neural circuits underlying the various effects of cannabinoids, Krisztina Monory and her colleagues examined mice lacking cannabinoid receptor-1 (CB1) in specific neuronal populations (*PLoS Biol.* **5**, e269).

Removing CB1 from inhibitory neurons had no effect on any action of cannabinoids, whereas knocking it out in the forebrain dampened all of its effects. Moreover, removing CB1 solely from forebrain excitatory neurons abolished only the motor and hypothermic effects of cannabinoids, whereas knocking it out in forebrain neurons that express the D1 dopamine receptor prevented the cataleptic action of the drug exclusively.

The results begin to separate the psychotropic and analgesic effects of cannabinoids—a goal that may have clinical ramifications. —*JCL*

Microtwist in metastasis

MicroRNAs have recently been implicated as tumor suppressors and oncogenes. Now, Li Ma and colleagues provide evidence that miRNAs also affect metastasis (*Nature* 449, 682–689). The researchers found that a specific miRNA, miR-10b, is overexpressed in metastatic breast cancer and regulates cell invasion. Although metastasis is a complex process, expression of miR-10b alone could transform a nonmetastatic cell line into an aggressively metastatic version.

The researchers asked how this RNA operates and found that the transcription factor Twist controls its expression. miR-10b in turn affects expression of the transcriptional regulator HOXD10. By inhibiting the translation of HOXD10, miR-10b enables the upregulation of one of its targets, RhoC, which in turn increases cell migration and invasion.

Identifying additional targets of miR-10b will further clarify how it regulates metastasis and may suggest fresh avenues for therapeutic intervention.—*AF*

Written by Eva Chmielnicki, Alison Farrell, Kate Jeffrey & Juan Carlos López