phagic. Hypothalamic NPY inhibits growth hormone release, but it is unlikely that dysregulated secretion of this anabolic hormone causes increased body weight in both Y1 and Y5 receptor deficient mice because these animals accumulate fat rather than increasing lean body mass.

The development of obesity in Y1 and Y5 deficient mice displayed sex-dependent variations. Thus obesity was most pronounced in Y1 deficient females and in Y5 deficient males. Y1 receptors have been implicated in anxiolytic effects of NPY (ref.15); consequently, Y1 knockout mice might be expected to be more anxious than wild-type controls. This might, in part, explain why Y1 deficient mice display reduced locomotor activity. Indeed, it will be interesting to see what future studies with knockout mice will tell us about the role of Y1 and Y5 receptors in various other behaviors and physiological events such as, anxiety, epilepsy, and temperature regulation.

NPY is a well established vasoconstrictor and also potentiates vasoconstriction induced by noradrenaline. Another interesting finding in Y1 deficient mice is the complete absence of NPY-mediated vasoconstriction. This indicates that Y1 receptors are essential for the vasoconstrictory effects of NPY, suggesting that Y1 antagonists might prove of therapeutic value in hypertension. However, if long-term treatment with Y1 antagonists results in obesity, as suggested by the Y1 knockout data, this is likely to limit the usefulness of Y1 antagonists in the treatment of hypertension. Obviously, the development of obesity as a side effect of Y1 and Y5 receptor antagonism will definitely put many of the current Y1 and Y5 anti-obesity drug development programs to rest.

1. Turton, M.D., O'Shea, D. & Bloom, S.R. Central effects of neuropeptide Y with emphasis on its role in obesity and diabetes. In *Neuropeptide Y and drug development* (eds. Grundemar, L. & Bloom, S.R.) 15–39 (Academic Press, London, 1997).
2. Kalra, S.P. Appetite and body weight regulation: is it all in the brain. *Neuron* **19**, 227–230 (1997).
3. Rohner-Jeanrenaud, F., Cusin, I., Sainsbury, A., Zakrzewska, E. & Jeanrenaud, B. The loop system between neuropeptide Y and leptin in normal and obese rodents. *Horm. Metab. Res.* **28**, 642–648 (1996).
4. O'Shea, D. *et al.* Neuropeptide Y induced feeding in the rat is mediated by a novel receptor. *Endocrinology* **138**, 196–202 (1997).
5. Gerald, C. *et al.* A receptor subtype involved in neuropeptide Y-induced food intake. *Nature* **382**, 168–171 (1996).
6. Larsen, P.J., Sheikh, S.P., Schwartz, T.W., Rehfeld-Jacobsen, C. & Mikkelsen, J.D. Regional distribution of putative NPY Y1 receptors in forebrain areas of the rat central nervous system. *Eur. J. Neurosci.* **5**, 1622–1637 (1993).
7. Schaffhauser, A.O. *et al.* Inhibition of food intake by neuropeptide Y Y5 receptor antisense oligodeoxynucleotides. *Diabetes* **46**, 1792–1798 (1997).
8. Pedrazzini, T. *et al.* Cardiovascular response, feeding behaviour, and locomotor activity in mice lacking the NPY Y1 receptor. *Nature Med.* **4**, 722–726 (1998).
9. Marsh, D.J., Hollopeter, G., Kafer, K.E. & Palmiter, R.D. Role of the Y5 neuropeptide Y receptor in feeding and obesity. *Nature Med.* **4**, 718–721 (1998).
10. Erickson, J.C., Clegg, K.E. & Palmiter, R.D. Sensitivity to leptin and susceptibility to seizures in mice lacking neuropeptide Y. *Nature* **381**, 415–418 (1996).
11. Broberger, C., Landry, M., Wong, H., Walsh, J.N. & Hökfelt, T. Subtypes of Y1 and Y2 of the neuropeptide Y receptor are respectively expressed in pro-opiomelanocortin- and neuropeptide Y-containing neurons of the rat hypothalamic arcuate nucleus. *Neuroendocrinology* **66**, 393–408 (1997).
12. Erickson, J.C., Hollopeter, G. & Palmiter, R.D. Attenuation of the obesity syndrome of *ob/ob* mice by the loss of neuropeptide Y. *Science* **274**, 1704–1707 (1996).
13. Stephens, T.W. *et al.* The role of neuropeptide Y in the antiobesity action of the *obese* gene product. *Nature* **377**, 530–532 (1995).
14. Herzog, H. *et al.* Overlapping gene structure of the human neuropeptide Y receptor subtypes Y1 and Y5 suggests coordinate transcriptional regulation. *Genomics* **41**, 315–319 (1997).
15. Wahlestedt, C. *et al.* Modulation of anxiety and neuropeptide Y–Y1 receptors by antisense oligodeoxynucleotides. *Science* **259**, 528–531 (1993).

[1]*Department of Pharmacology*
University of Copenhagen
2200 Copenhagen, Denmark
[2]*Neuroendocrine Pharmacology*
Novo Nordisk A/S
2760 Måløv, Denmark

Vaccination: Only skin deep

Alternatives to injected vaccines have been vigorously sought not only to allay the fears of the many who wince at a needleprick but to remove the threat of injecting patients using contaminated needles (a particular problem in the Third World). Now Glenn and colleagues from the Walter Reed Army Institute of Research report that applying a vaccine solution containing cholera toxin (CT) to the surface of the skin elicits antigen-specific immune responses in mice (*Nature* **391**, 851, 1998).

Courtesy of Gregory M. Glenn and Carl R. Alving

Cholera toxin, the cause of the symptoms of cholera, is a powerful adjuvant that is often combined with other antigens because it enhances the immune response against the other vaccine components. Glenn and his team put this characteristic to good use in their skin vaccine experiments. First, they used a vaccine composed of CT alone in a saline solution and applied this to the shaved skin of mice, which were anesthetized so that they would not lick the shaved area thus inadvertently orally immunizing themselves. A booster solution was topically administered three weeks later. To show that this vaccination effect was not caused by puncturing the skin during shaving, another group of mice received two applications of the CT solution on an unshaved ear. The investigators found that the mice developed strong IgG antibodies to CT, which could still be detected several months after the booster application.

Now the crucial experiment was to see if CT's adjuvant properties could be exploited to boost the immune response to other vaccine antigens. Glenn's group found that skin immunization of mice with CT combined with either diphtheria toxoid or tetanus toxoid elicited marked IgG responses against the antigen combination. Antigen-specific IgG antibodies could be detected for up to eight months after skin immunization in the case of diphtheria toxoid. In the absence of CT, no immune response to either toxoid antigen was elicited.

A survey of skin vaccines composed of common pediatric antigens (combined with CT) in mice is yielding excellent mucosal antibody responses for many of the antigens. Furthermore, phase I trials in human volunteers receiving topical application of CT and a common bacterial enterotoxin are underway.

Glenn postulates that Langerhans cells—phagocytic antigen presenting cells that live in the skin (see photograph)—engulf the vaccine antigen and, after migrating to nearby lymph nodes, present the antigen to lymphocytes, prompting a strong immune response. The next step, says Glenn, is to see if skin immunization with a combination vaccine will protect against toxin-mediated diseases.

As for the future, Glenn predicts that vaccinating your child could be as simple as attaching a small vaccine-soaked patch to the skin on the back (well out of reach!) and removing it, like a band aid, a day later.

Orla Smith