IN THE NEWS

Hungry neurons

Obesity has fast become one of the world's most serious health problems, and a study of the brain's involvement in feeding may help in the quest for effective treatments.

Feelings of hunger and satiety are regulated by cells of the arcuate nucleus in response to hormones such as insulin, ghrelin and leptin. Two types of neuron seem to be involved in this process — pro-opiomelanocortin (POMC) neurons, which reduce appetite, and neurons that release neuropeptide Y and agouti-related protein (NPY/AgRP), which have been thought to have the opposite effect.

Researchers led by Richard Palmiter (Howard Hughes Medical Institute, Maryland, USA) and Serge Luquet (University of Washington, Seattle, USA) questioned whether NPY/AgRP neurons are vital for feeding in mice.

Their results indicated that NPY/AgRP neurons are essential in adult animals, in which elimination of their activity led to starvation. However, ablation of NPY/AgRP neurons in neonates appeared to have no effect.

Palmiter suggests that "Killing these neurons before they're functionally engaged gives the developing mouse brain a way to compensate. But it's still a tall challenge. You're asking some other neuron, presumably, to either increase what it normally does, or to do something that it never did before" (*The Guardian*, 28 October 2005).

But how do these results relate to humans? "Everybody in the field believes that NPY/AgRP neurons and POMC neurons are undoubtedly doing the same in humans as they do in rodents" says Palmiter, "So I would predict that if you could do the experiment in humans, the results would be the same" (*BBC News Online*, 28 October 2005).

If this is the case, the next step will be to find a way to modulate the activity of these neurons to reduce obesity.

Sarah Archibald

DEVELOPMENT

The mystery of *Maths*

The cerebellar rhombic lip is a germinal zone that is located between the fourth ventricle and the roof plate, and has traditionally been thought to generate only precursor cells that give rise to granule cells, the most common type of cerebellar neuron. Two fate-mapping studies, published in *Neuron*, challenge this view of cerebellar and pre-cerebellar development, and, for the first time, characterize several distinct cell populations that emerge from the cerebellar rhombic lip. Importantly, they reveal that the basic helix–loop–helix transcription factor *Math1* is pivotal for establishing this neuronal diversity, and that timing is a crucial determinant for cell type.

Machold and Fishell used an innovative molecular mapping technique (developed by their colleagues in the Joyner laboratory) in embryonic mice to specifically label

and track over time *Math1*-positive neural progenitor cells that originated in the cerebellar rhombic lip. Unexpectedly, they found that early in embryogenesis (before embryonic day (E)12.5) *Math1*-positive cells generated not only deep cerebellar nuclei, but also specific migratory non-granule cell types of the rostral hindbrain, including cholinergic neurons of the mesopontine tegmental nuclei, all of which contribute to the cerebellar/vestibular/auditory network. *Math1* seems to be only transiently expressed in these cells, but is crucial for generating the diversity of neuronal types, as absence of this transcription factor prevented their development.

After E12.5, however, *Math1* was persistently expressed in precursor cells, which principally developed into granule cells. Of these, the most distal extracerebellar nuclei were the first to emerge, whereas

those that populate more posterior regions, and therefore have a shorter migration distance, arose later in development.

In a contrasting approach, Wang and colleagues tracked derivatives of the rhombic lip by monitoring *Math1*-driven β -galactosidase expression. They too reported diverse *Math1*-expressing cell types in the cerebellum, pons and isthmus

NEURODEGENERATIVE DISORDERS

Silencing neurodegeneration

The aberrant processing of amyloid precursor protein (APP), leading to a build-up of amyloid- β peptide ($A\beta_{1-42}$), is a key molecular event in the pathogenesis of Alzheimer's disease. An increase in the activity of the proteolytic enzyme β -secretase (BACE1), which contributes to this abnormal processing, is associated with neurodegeneration, accumulation of APP products and Alzheimer's disease. Consequently, the inactivation of BACE1 might represent a viable therapeutic strategy for the treatment of this disease. Using the relatively new technique of RNA interference (RNAi) to reduce BACE1 activity in APP transgenic mice, the groups of Masliah and Verma

recently demonstrated the efficacy of such an approach.

Lentiviral vectors, chosen for their ability to transduce non-dividing cells such as neurons, were engineered to carry selected 'short hairpin' RNA (shRNA) molecules complementary to target sequences in the open reading frame of human BACE1. Transcription of these results in the expression of small interfering RNA (siRNA) molecules capable of inhibiting the translation of complementary mRNA species, thereby silencing the target gene BACE1.

Following validation of lenti-siBACE1 constructs in cell culture, where these were tested for their ability to knockdown the BACE1 protein and reduce levels of $A\beta_{1-42}$,

the most promising construct was selected for trial in a mouse model of Alzheimer's disease.

Mice expressing high levels of double-mutant human APP received lenti-siBACE1 constructs through intracranial injection to the susceptible neuronal populations in the hippocampus. These mice were chosen as they recapitulate many of the features of Alzheimer's disease, including neurodegeneration, memory impairment and amyloid plaques.

As in the cell culture assays, there was a significant reduction in the expression of BACE1 in the hippocampus, which contributed to a significant reduction in APP proteolysis and $A\beta$ plaque formation in the same region.