of femtosecond sources was the need to measure the dynamics of molecules and solids, the goal that will drive attosecond science will be control over electronic processes. Electrons are much lighter than atoms and can move much faster, so attosecond pulses will give us a tool for studying the motion of electrons. We can imagine experiments in which attosecond pulses are used to directly excite electrons, and then the electrons are precisely directed within the molecule by the field oscillations of an intense femtosecond pulse. ■

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Neurobiology

# Neurofibromin progress on the fly

Ronald L. Davis

One in every 3,500 individuals suffers from the genetic disease neurofibromatosis type 1 (NF1). The many symptoms of the disease, including tumours of the nervous system[1,2], result from a deficiency in the protein neurofibromin. Neurofibromin belongs to the family of GTPase-activating proteins (GAPs), which turn off the growth-promoting function of the Ras family of proteins by stimulating the hydrolysis of GTP bound to Ras. Without enough neurofibromin, Ras remains unchecked, resulting in cellular overgrowth and tumours. About half of NF1 patients also suffer from learning disabilities, which have been assumed to result from abnormal brain development due to aberrant neurofibromin control of Ras and cell division. On page 895 of this issue, Guo *et al.*[3] offer an alternative explanation. They show that neurofibromin deficiency in the fruitfly *Drosophila* also causes a learning disability, but that it arises from a requirement for neurofibromin in activating adenylyl cyclase in the mature brain.

The cognitive impairments associated with NF1 are variable. Around 4–8% of NF1 patients are mentally retarded, but the average IQ for NF1 patients (92) is only slightly lower than the population norm. Yet about half of the affected patients have learning disabilities severe enough to require educational assistance[1,2]. Learning disabilities occur in language-based skills, such as reading, spelling and vocabulary development, and in visuospatial skills, such as face recognition, spatial memory and the judgement of line orientation[1,2]. In addition, NF1 patients often have problems with the execution of goal-directed behaviours, including planning, attention and organization (executive function)[2].

Support for the view[1,2] that the learning disability arises from a problem in brain development comes from brain scans using magnetic resonance imaging, which in many NF1 patients show between one and five unusual bright spots[1,2,4]. Although the presence of spots correlates poorly with learning disabilities[2,5], they do indicate a physical difference in the brains of some NF1 patients. Reported changes in the number and size of cells called astrocytes in the brain, and the size of certain compartments in the NF1 brain[4], could also disrupt learning.

Alternatively, neurofibromin might mediate learning through the physiology of the mature brain. The work of Guo *et al.*[3] supports this idea. *Drosophila* neurofibromin mutants were tested for their ability to learn an odour paired with an electric shock. The mutants showed impaired learning, like their human counterparts, perhaps because neurofibromin has a similar role in the development or function of insect and mammalian brains.

To test whether the learning deficiency was due to lack of neurofibromin during development or during adulthood, Guo *et al.* created transgenic flies carrying a neurofibromin gene linked to a heat-inducible promoter[6,7]. This allowed them to turn the gene on in adult mutants, after development was complete. When they did this, the mutants could learn normally. So *Drosophila*

Volcanology

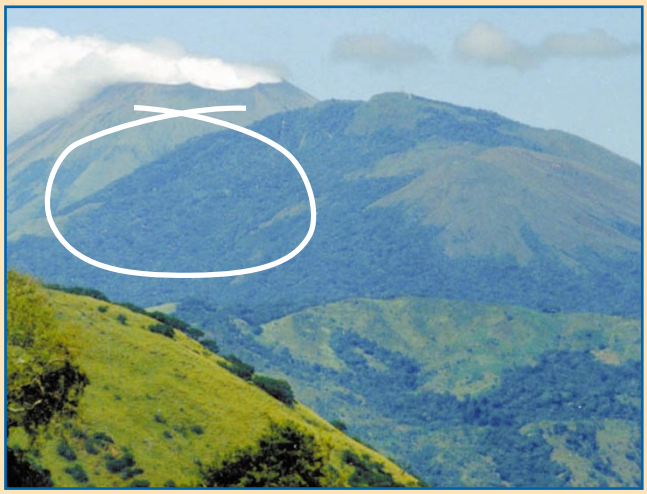
## The bulge of Casita

Volcanoes can be dangerous even when dormant. The centre of attention in this photograph lies not in the smoking cone of San Cristobal volcano in the background but in the less-obvious bulge on the nearer slope (circled). The bulge lies on the flanks of Casita, a dormant 1,400-m-high volcano in Nicaragua, some 100 km northwest of the capital, Managua.

Writing in *Geology* (28, 167–170; 2000), Benjamin van Wyk de Vries and colleagues describe their survey of Casita and experimental simulations of how such bulges grow and collapse. The cause of the deformation is hydrothermal activity which, over the course of decades or centuries, can weaken the core edifice of a dormant volcano by turning solid rock into much weaker clays. The resulting structures on the flanks are unstable, and earthquake activity or heavy rainfall can trigger an avalanche. Indeed, a secondary consequence of bulge formation on Casita was a comparatively small-scale landslide in 1998, which was triggered by Hurricane Mitch and caused widespread devastation.

The experiments of van Wyk de Vries *et al.* involved building 10-cm-high cones of sand and plaster to simulate solid rock, with silicone to simulate hydrothermally altered, deformable clays. If the silicone was offset from the central axis, the result was 'slump-like' structures on one side, and eventual collapse of those structures. The process of bulge formation took about 15 minutes. The authors estimate that the bulge on Casita has taken at least 500 years to develop; taking scaling into account, the experimental result is in broad agreement with that figure.

van Wyk de Vries *et al.* point out that monitoring of dormant volcanoes does not have high priority. But identifying and keeping tabs on unstable structures such as that on Casita would pay dividends in hazard assessment, especially when large populations are potentially under threat. **Tim Lincoln**



B. VAN WYK DE VRIES

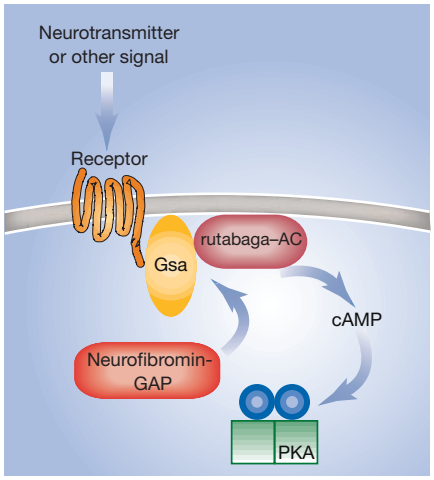



Figure 1 **Neurofibromin signalling in learning. G-protein-coupled receptors are linked to adenylyl cyclase (AC) through the α-subunit of the stimulatory G protein, Gs. Receptor activation stimulates adenylyl cyclase to synthesize cyclic AMP (cAMP) and activates the downstream effector, protein kinase A (PKA). Guo *et al.*[3] show that the neurofibromin protein is required in this pathway for normal odour learning in *Drosophila*, perhaps by direct interaction with the G protein or with the adenylyl cyclase encoded by the *rutabaga* gene.**

neurofibromin is needed in the mature brain for normal odour learning to occur.

But does neurofibromin involvement in learning depend on Ras? In *Drosophila*, the answer seems to be no. It was previously shown that a neuropeptide known as PACAP increases the activity of voltage-gated potassium channels[8]. This response involves the combined activation of the Ras pathway and the cyclic AMP pathway through adenylyl cyclase. Neurofibromin is required for this biological response to the neuropeptide but, surprisingly, the requirement lies not in the Ras pathway but in the cyclic AMP pathway, as application of cyclic AMP itself can restore the response in NF1 mutants[9]. So, in flies, neurofibromin is involved in the activation of adenylyl cyclase (Fig. 1).

Guo *et al.*[3] have extended the experimental support for this role in three ways. First, they show that expression in transgenic flies of an active form of protein kinase A, a component of the cyclic AMP pathway, corrects the learning deficiency of NF1 mutants. Second, they find that neurofibromin is required for the normal activation of adenylyl cyclase activity by GTP. Finally, the magnitude of the deficiency in stimulation of adenylyl cyclase by GTP in NF1 mutants is similar to that in learning mutants of the *rutabaga* gene. As *rutabaga* is the structural gene for one type of adenylyl cyclase, it appears that *Drosophila* neurofibromin works specifically through this cyclase.

This adds up to suggest that neurofibromin in the fly has a biochemical function not yet discovered in mammals: positive regulation of the activation of adenylyl cyclase by GTP. Furthermore, this regulation takes place in mature neurons, and its failure in adults causes learning disabilities. But how might these findings apply to mammalian neurofibromin, NF1 patients and mammalian cognition?

It is now imperative to test whether mammalian neurofibromin can interact with and activate adenylyl cyclase/G-protein complexes. There is plenty of room on the protein for direct interactions, as the GAP domain occupies only 10% of the sequence[10]. Furthermore, some alternatively spliced variants of mammalian neurofibromin are expressed only in mature neurons[11], offering the potential for isoform-specific functions such as cyclase activation. Nevertheless, even though *Drosophila* neurofibromin is highly homologous to mammalian neurofibromin and has Ras-GAP activity *in vitro*[12], it may be that the fly neurofibromin simply functions differently. Genetic attempts to show that *Drosophila* neurofibromin also negatively regulates Ras have failed[12], perhaps owing to compensation by other GAPs, or perhaps because neurofibromin has nothing to do with Ras signalling in flies.

But can we really learn about human learning disabilities from the fly? After all, the fly has a small brain, limited intellectual capacity, and no higher cognitive traits such as executive function. It seems so, as the conservation between mammalian and *Drosophila* genes observed to date, even for those involved in behaviour, is remarkable. Several genes that are required for *Drosophila* learning, including *dunce*, *rutabaga*, *DCO*, *CREB*, *Volado*[7,13] and *NF1* (ref. 14), are all involved in mammalian learning or other behaviours. Thus, if the parallels remain true and the learning disabilities of NF1 patients stem from signalling rather than developmental defects, then patient treatment with cognitive enhancers could be approached with optimism. ■

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**Daedalus**

## Grinding waste away

**How to get rid of domestic and urban rubbish? Recycling is troublesome, incineration unpopular, and composting impeded by the presence of plastic and metal. Landfill merely entombs the trash archivally for future archaeologists. One answer might be to feed the stuff to pet goats; they eat anything, and would generate useful metabolic heat from its digestion. Unlike a passive compost heap or landfill, an animal gut is ceaselessly churning. Some animals swallow stones or grit to aid their digestion; these must help the process mechanically or chemically. In this connection, Daedalus recalls that halocarbons can be decomposed by ball-milling them with lime. Mechanical impact and abrasion actually break up the molecules and encourage their reaction.**

**So Daedalus is designing a mechanically agitated composter for all our rubbish. Its steady churning and pounding, shearing the molecules at the point of impact whenever two chunks of rubbish come together, will degrade its contents at an unprecedented rate. Even plastics will be rapidly oxidized to products edible by the resident bacteria. Chemical, mechanical, thermal and biological decomposition will all proceed in parallel. Too violent an agitation might squash the bacteria faster than they could multiply, but slower rates should be entirely effective. Adding domestic sewage to the mix would solve another disposal problem at the same time.**

**A large-scale rubbish composter would be a long inclined cylinder rotating on its axis. Rubbish added continuously at the elevated end would work its way slowly down; the cans and bottles in it would act as grinders for the organics. Its inlet zone would be kept anaerobic, to generate useful methane. Downstream, injected air would switch it to aerobic decomposition. Toxins and pollutants would be totally mineralized by this steady mechano-chemical battering. Only rust, glass and ceramic grit would emerge at the far end.**

**But Daedalus wants to abolish rubbish collection as well. So he plans a simpler domestic composting dustbin, to degrade the rubbish and sewage of one household. It will grind away outside the house, but will be plumbed into the heating system to contribute useful warmth to the domestic interior.** **David Jones**