Out of the inclusion zone

Protein aggregates are a shared feature of a wide range of neurodegenerative disorders. Although aggregates are commonly assumed to be crucial for neuronal dysfunction and subsequent degeneration, the evidence is not always definitive. In the case of Huntington's disease, some reports have raised the possibility that nuclear inclusions of mutant huntingtin might not be directly related to striatal cell death, and two recent studies provide new evidence in support of this dissociation.

Martín-Aparicio *et al.* used a transgenic mouse model of Huntington's disease, in which expression of mutant huntingtin can be switched off with the antibiotic doxycyclin. They had previously shown that switching huntingtin expression off leads to the disappearance of both huntingtin inclusions and motor impairments in these mice. The authors revisited this model to explore the time course of aggregate formation and reversal *in vitro* and *in vivo*. They found that both processes are very quick: inclusions form in culture after 2 days of huntingtin expression, and disappear within 5 days of transgene suppression. Aggregate reversal was also fast *in vivo*, and, importantly, it preceded the disappearance of motor signs by several weeks. Last, the presence of huntingtin inclusions did not com-

promise neuronal viability in culture, and the authors did not find neuronal death in the transgenic mice, despite a significant reduction in striatal volume.

Parker *et al.* took an entirely different approach, expressing wild-type and mutant human huntingtin in mechanosensory neurons of *Caenorhabditis elegans*, an organism that lacks an endogenous version of this protein. Expression of mutant huntingtin led to touch insensitivity and the formation of inclusions (particularly in axons), but not to cell death. The expression of wild-type huntingtin, on the other hand, did not lead to mechanosensory defects, despite the presence of perinuclear protein aggregates.

Both articles converge on the idea that there is no simple relationship between huntingtin accumulation, neuronal dysfunction and cell death. It is instructive to compare these findings with similar insights obtained in models of other neurodegenerative diseases. For example, tauopathy can occur without the formation of neurofibrillary tangles in *Drosophila*, and the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to primates faithfully reproduces many features of Parkinson's disease, despite the absence of Lewy body formation. It might therefore be a good time to re-examine our ideas about the role of protein inclusions in neurodegeneration, hoping that we will emerge better equipped to find effective therapies for these disorders.

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ADDICTION

A depressing habit

There are many different behavioural manifestations of addiction — drug craving, motor signs, mood changes. In experimental animals, one of its most studied expressions is behavioural sensitization, an enhanced locomotor response that follows repeated exposures to a drug of abuse. As we have good leads on the identity of brain regions that change during sensitization, the molecular analysis of this behavioural response could provide us with new insights into the neurobiology of addiction. A paper published recently in *Nature Neuroscience* highlights this fact by showing a correlation between behavioural sensitization and long-term depression of glutamate-mediated synaptic transmission.

Thomas *et al.* sensitized a group of mice by administering repeated doses of cocaine over 5 days and showing that locomotor activity increased in response to a single dose of the drug after a 2-week rest period. The authors then looked for synaptic changes that could account for this long-lasting behavioural effect, focusing on the nucleus accumbens (nAc), a component of the mesolimbic dopamine system that has been implicated in sensitization. They found that it was more difficult to induce long-term depression in the nAc of sensitized mice. In other words, patterns of synaptic activity that are known to depress the efficacy of glutamate-mediated neurotransmission did not have any detectable effect in the nAc of mice that had been repeatedly exposed to cocaine. This observation prompted the authors to suggest that the development of behavioural sensitization might correlate with the onset of long-term depression, and that this depression precludes the possibility of further suppressing transmission.

Although the evidence presented is solely correlative, the data of Thomas *et al.* underscore the potential of this animal model to bridge behavioural, neurophysiological and molecular studies. It will now be crucial to unravel the molecular mechanisms of depression in the nAc, and to obtain direct evidence that the establishment of long-term depression parallels the course of behavioural sensitization.

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