Reply from W. F. Maragos and colleagues

SIR:

We are pleased that our Viewpoint article[1] has provoked a response. Our article was intentionally speculative and intended to stimulate experimental work in this area. Hardy and Cowburn contend that our hypothesis that some of the damage in dementia of the Alzheimer type (DAT) is due to glutamate excitotoxicity is not warranted. They argue that experimental evidence suggests that glutamatergic function (as well as that of several other neurotransmitters) is underactive not overactive in DAT and therefore that glutamate neurotoxicity is unlikely. They suggest further that the NMDA receptor losses seen by Greenamyre *et al.*[2,3] reflect loss of uptake sites rather than receptors.

Contrary to the statements by Hardy and Cowburn, a decrease in glutamatergic neurons does not imply that excitotoxic mechanisms play no role in the pathogenesis of DAT nor does it imply that the glutamatergic system is 'underactive'. It simply suggests that as the disease progresses, glutamatergic neurons are themselves damaged. Post-mortem studies in DAT reflect end-stage rather than early disease. Biopsy studies during mid-stage disease have shown normal levels of glutamate release[4]. There may be relative glutamatergic overactivity in early disease.

We believe there is no reason to hypothesize that some of the damage in DAT may be related to excitotoxicity. Anatomical evidence suggests that the damage in DAT (plaques and tangles) propagates along putative glutamatergic pathways such as corticocortical association pathways[5,6], and the pathway connecting the amygdala and nucleus basalis of Meynert[7]. Glutamate toxicity provides a potential explanation for this anatomical correlation.

We do not contend that glutamate toxicity is the underlying cause of Alzheimer's disease, only that it may be an agent in the destructive process. If neurons were rendered unable to maintain normal hyperpolarization by any process, they would be more susceptible to subsequent excitotoxic insults because the NMDA subtype of receptor is gated by magnesium in a voltage-dependent fashion[8]. Excess activation of NMDA receptors is neurotoxic and any partially depolarized neuron is thus more susceptible to neurotoxicity.

Cotman's laboratory has found decreases in NMDA receptors in advanced DAT[9] and has reported an average loss of 40% TCP binding[10], similar to our own findings using a well-defined assay[11]. In a large group of early and late DAT brains analysed blindly, we have recently repeated our original experiments and found results similar to Cotman's, i.e. NMDA receptors were decreased by 40–50% as were TCP receptors. Furthermore, receptor losses correlated with the numbers of plaques and tangles (Maragos, W. F. *et al.*, unpublished observations).

Hardy and Cowburn's concern that NMDA-sensitive binding in the presence of chloride may, in part, represent binding to uptake sites is not substantiated experimentally. We have been unable to find any loss of NMDA binding after lesions of several glutamatergic pathways, and NMDA sites are decreased by >90% after lesion of postsynaptic neurons (Maragos, W. F., PhD Dissertation, University of Michigan). Furthermore, there is evidence that NMDA receptor binding actually increases in the presence of chloride (Ref. 12 and Honoré, T., pers. commun.).

There is substantial evidence implicating the glutamatergic system in learning and memory[13–16]. Therefore, we have hypothesized that disruption of the glutamatergic system accounts for some of the clinical manifestations in DAT. We agree with Hardy and Cowburn that the functional changes of DAT likely reflect severe circuitry damage. However, rather than simply ascribe the signs and symptoms of DAT to 'circuitry damage', it seems prudent to attempt to define which neurochemical systems are primarily responsible for the clinical manifestations of DAT. Only by making hypotheses and testing them experimentally will effective, rational therapies be developed.

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ERRATUM

In the article 'Galanin: a newly isolated biologically active neuropeptide' by Åke Rökaeus (April 1987, Vol. 10, pp. 158–164), footnote d was misplaced in Table I. It should refer to *guinea-pig* immunohistochemistry in the gastrointestinal tract, not mouse.

We apologize for this error.