New drugs for Huntington’s disease

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In this issue of NeuroReport, two articles [1,2] report positive outcomes from small clinical studies of highly unsaturated fatty acids (HUFA) in Huntington’s disease (HD), and a much larger trial of HUFA is reportedly now underway. Given the relentless, progressive nature of this incurable and distressing disease, there is great pressure to take promising potential therapies into the clinical arena as soon as possible. However, given the increasing number of compounds being suggested for consideration in HD and the relatively small pool of patients on which to test them, how should we proceed and should we be aiming for a more concerted approach?

SCIENTIFIC BACKGROUND

Huntington’s disease is a dominantly inherited neurodegenerative disorder in which the primary pathology is neuronal dysfunction and death in the neostriatum (caudate and putamen) [3]. The disease most commonly manifests itself in the third and fourth decades of life with a movement disorder, cognitive decline and psychiatric symptoms. It is relentlessly progressive, currently untreatable, and leads to dependency and death within approximately 20 years. The genetic abnormality was identified in 1993 as an expansion of a CAG repeat length in exon 1 of the IT15 gene on chromosome 4 [4]. In the presence of this mutation, an abnormal form of the gene product, huntingtin, is produced. The mechanisms by which the abnormal protein leads to cell dysfunction and death is not yet understood, although major advances in our understanding have been made over the last few years (for reviews see [5,6]).

Ultimately, the hope must be to interfere with the processes leading to striatal cell dysfunction and death. Despite the hope and excitement generated by the discovery of the gene nearly a decade ago, there is as yet no available drug designed specifically to inhibit such processes. However, candidate drugs with specific modes of action are likely to appear as rapid advances are made in this intensive research area. Indeed, there are medications already established for use in other conditions for which a rational case can be made for testing in HD. For example, sodium valproate has been used successfully in epilepsy for approximately 20 years. The genetic abnormality was identified in 1993 as an expansion of a CAG repeat length in exon 1 of the IT15 gene on chromosome 4 [4]. In the presence of this mutation, an abnormal form of the gene product, huntingtin, is produced. The mechanisms by which the abnormal protein leads to cell dysfunction and death is not yet understood, although major advances in our understanding have been made over the last few years (for reviews see [5,6]).

Perhaps of greater concern is the fact that numbers were so small in both trials: a total of seven patients (and only three on treatment) in the Puri study [1], and 17 (with nine on treatment) in the Vaddadi study [2]. Planned trial lengths were 6 months and two years, respectively. However, the study of Vaddadi et al. was terminated early on the basis that a larger trial had by then been established, and the code was broken prior to scan analysis in the other trial for reasons not explained, suggesting a possible need for more effective design and co-ordination.

HIGHLY UNSATURATED FATTY ACIDS

The present two papers [1,2] consider the potential of HUFA to modify the course of HD, on the basis that they have a role in cell membrane function that may effect the propensity of a cell to undergo apoptosis [11,12], and so may be effective in slowing the rate of neuronal cell death both within and outside the striatum in HD. Both groups have evaluated different HUFA in double-blind, placebo-controlled studies in small numbers of patients. The HUFA used were ethyl-eicosapentaenoic acid for 6 months in the Puri study [1], and a combination treatment of eicosapentaenoic, γ-linolenic and docosahexaenoic acids in the Vaddadi study [2]. Planned trial lengths were 6 months and two years, respectively. However, the study of Vaddadi et al. was terminated early on the basis that a larger trial had by then been established, and the code was broken prior to scan analysis in the other trial for reasons not explained, suggesting a possible need for more effective design and co-ordination.

Thus, whilst HUFA are certainly interesting novel drug candidates for neuroprotection in HD and are clearly deserving of attention, small studies like these should be considered as pilot studies only, providing initial safety data. What they do not provide, in the absence of proper systematic large scale drug trials, is an adequate basis for guiding treatment decisions. At the same time, as more and
more potential drug candidates become identified, a number of dangers arise from a proliferation of small studies. Hopes for an imminent effective treatment can be unduly raised within the patient community; there will be pressure for doctors to prescribe (or indeed for self-administration of) drugs of dubious efficacy; and the relatively small population of suitable subjects available for trial participation will soon be saturated, making it impossible to undertake proper multi-centre controlled trials as and when they are warranted.

**HOW SHOULD DRUG TRIALS PROGRESS?**

Given the relative rarity of HD, and thus the relative paucity of available patients to test, does it make sense for individual groups to test a few patients here and a few there? Rather, there is a need for co-operation between centres and research teams to participate in more systematic planning of clinical trials, with an emphasis on scientific rationale and statistical validity. There is already a model for this in North America, where the Huntington’s Study Group (HSG) has been founded to co-ordinate multicentre collaborations which undertake systematic evaluation of novel therapies in HD. An essential starting point has been the development and validation of the UHDRS, the most widely used and best validated rating scale of clinical progression in HD [14]. This tool has facilitated analysis of the natural history of the early stages of HD, and has been used as the core assessment tool in several large multicentre drug trials using full double-blind, placebo controlled design. The power calculation typically requires several hundred patients in the trials for detecting a significant magnitude of neuroprotection over a 2-year follow-up (n = 347 in the case of the Remacemide/CoQ10 trial cited above [10]). The UHDRS has also been adopted by other groups; for example it forms part of the assessment protocol for neural transplantation in HD coordinated as a multicentre European collaboration [15]. Other groups are only now seeking to establish a parallel organisation for co-operation in HD drug trials within Europe.

Apart from the logistic issues, there are two main questions to address which compounds to target, and how best to design the trials, in particular with regard to sample size? The first issue must be a matter for debate seeking consensus from a broad critical appraisal of the experimental literature. To date, we have been constrained by a limited number of potential neuroprotective compounds. However, this is due to change with a number of initiatives from both the commercial and public/charity-supported arenas for high throughput screening based on modern genetic technologies [16], which can be expected to generate far more compounds than can be properly evaluated in valid animal models let alone within clinical trials. Consequently, reaching a consensus will not be easy. The second issue, the size and design of valid trials, is also crucial. The remacemide/ CoQ10 trial involved a very large number of patients by previous standards in HD clinical research, but was still only powered to detect a 40% slowing of progression over 2 years [10]. A trend to a 13% slowing was seen which did not reach significance. This raises the question as to how large an effect we should be looking at; 13% slowing per year over the course of the disease may well be worth having, but trials to detect such a slowing of the time course would involve very large numbers of patients, increasing the danger of exhausting the patient population before we have sufficiently potent potential drugs to test.

So where does this leave us? There is overwhelming pressure both from the scientific and medical community, and from patients, to explore other avenues and to investigate all possible ways of modifying the course of this distressing condition. Whilst this sentiment deserves great sympathy, it may be that we best serve the patient community by taking the long view, sinking our desire to act individually in a fragmented way, and design a concerted and co-ordinated programme of attack to develop truly effective therapies for the future.

**REFERENCES**

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