Focusing on the Cerebral Cortex in Huntington’s Disease: Experience-Dependent Plasticity Deficits as the Cellular Basis of Dementia

Huntington’s disease (HD) belongs to an expanding family of devastating neurological disorders caused by abnormally elongated CAG trinucleotide repeats which encode extended polyglutamine tracts in the disease proteins.1-6 HD is characterised by extensive neurodegeneration in the striatum and the cortex.7,8 The disease is classically known for its choreic and dystonic motor symptoms. However, cognitive deficits (dementia) and psychiatric manifestations (the most common of which is depression) represent major symptoms in HD, which usually precede the onset of motor abnormalities.9-11

This observation has led to an increased research effort concentrating in the examination of abnormal neurotransmission in areas involved in higher cognitive functions.12-14 More recently, impaired synaptic transmission has been reported in HD mouse neocortical neurons even before the onset of motor symptoms.15 Evidence of cortical neuronal dysfunction has also been reported in HD patients, for example using transcranial magnetic stimulation of the motor cortex.16

Long-term changes in synaptic efficacy (synaptic plasticity) are thought to underlie higher cognitive functions such as learning and memory.17 If cognitive function in HD is compromised before the onset of the motor symptoms then one could hypothesise that synaptic plasticity deficits may be the cellular basis of early symptomatology. Moreover, if higher cognitive functions are dependent on cortical functioning then a plausible hypothesis is that alterations in synaptic plasticity should be evident in the cerebral cortex of HD brains and correlate with the onset of dementia.

Initial evidence of abnormal synaptic plasticity in the hippocampus of R6/2 HD transgenic mice showed abnormalities in the form of long-term potentiation (LTP) and long-term depression (LTD) in the CA1 region of the hippocampus.18 Interestingly, these synaptic plasticity deficits correlated with poor performance in a spatial memory task even before the onset of clear motor deficits. Similar impairment in hippocampal synaptic plasticity has also been reported in other HD mouse models.19,20 A key regulator of synaptic plasticity, brain-derived neurotrophic factor (BDNF), has been shown to be decreased in the hippocampus of R6/1 HD mice (a transgenic line with a shorter CAG repeat length and later onset of symptoms than R6/2 mice) and correlated with the onset of cognitive deficits.21,22

Furthermore, deficits of BDNF in the hippocampus and striatum are rescued by environmental enrichment, a form of cognitive and motor stimulation which has been found to delay the onset and progression of HD in transgenic mice.23-25 Interestingly, Cybulskaja-Klosowicz and colleagues showed that R6/1 HD mice show impaired functional cortical reorganisation – a form of experience-dependent plasticity - following a simple form of passive associative learning.26 In normal rodents, a short period of classical conditioning causes cortical enlargement of the functional representation of the sensory modality (e.g. row of whiskers) that has been conditioned. However, in this study R6/1 HD mice showed a clear impairment to display an increase in the functional representation of the conditioned row of whiskers. Similarly, following a period of sensory deprivation, such as trimming a row of whiskers, the cortex displays a remarkable ability to reorganise the functional representations of neighbouring intact whiskers take over the cortical region of those that have been deprived.27 In this context, we showed, using 2-deoxyglucose metabolic labelling, that R6/1 HD mice which were sensory deprived failed to show cortical plasticity, in the form of map reorganisation, and that this cortical impairment correlated with a severe deficit to learn a sensory discrimination task.28 It is interesting to note that the R6/1 mice used in the study were not yet displaying any motor symptoms, suggesting that cortical plasticity deficits and cognitive symptoms occur relatively early. More recently, Cummings and colleagues showed that cortical slices from R6/1 HD mice displayed abnormal short-term plasticity (exhibited as altered paired-pulse facilitation) and LTD.29 Moreover, they showed a decrease in the cortical levels of both D1 and D2 dopamine receptors and found that in vitro administration of the D2 agonist, quinpirole, dramatically reversed the impairment in both short-term plasticity and LTD in the perirhinal cortex of R6/1 HD mice.

The above studies using transgenic mice that express the HD gene mutation suggest a functional impairment in cortical activity. Deficits in synaptic and structural plasticity could underlie the cognitive and psychiatric deficits observed in patients with HD. An interesting question is whether these cortical abnormalities are aetiologically involved in the striatal degeneration associated with the devastating motor symptoms characterising HD. One hypothesis is that cortical abnormalities, involving abnormal glutamatergic neurotransmission, might cause excitotoxic damage to striatal neurons via corticostriatal pathways. In other words, rather than medium spiny neurons dying via cell-autonomous ‘suicide’ they may be ‘murdered’ by corticostriatal afferents.30 In this scenario, therapeutic interventions targeting the cortex could not only delay or ameliorate the cognitive and psychiatric abnormalities, but also the motor symptoms. Further evidence for the primary role of cortical pathology has been provided by the effect of environmental enrichment in salvaging cortical degeneration in HD mice,31 as well as cortical transplantation experiments32 and cortex-specific HD transgene expression in mice.33

In any case, the observation of early cortical dysfunction and neural plasticity deficits could provide a very useful biological marker that would be particularly useful in terms of monitoring both the progress of the dis-
References


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