Short report

Tyrosine hydroxylase and levodopa responsive dystonia

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SUMMARY It has been suggested that a form of inherited dystonia responsive to levodopa might be due to an abnormality of the tyrosine hydroxylase gene. This hypothesis has been tested using a cDNA tyrosine hydroxylase gene probe in three families with this disorder. No evidence for genetic linkage between the disease and tyrosine hydroxylase loci was found; it is possible that the disorder results from a post-transcriptional defect confined to the brain.

Tyrosine hydroxylase (TH) is the rate limiting enzyme in the catecholamine synthetic pathway and therefore plays a central role in the function of adrenergic neurons. The TH gene has been cloned and localised to the short arm of chromosome 11, closely linked to the loci for the beta-globin-like genes, insulin and the cellular proto-oncogene H-ras-1.

Altered catecholamine neurotransmission is thought to be important in a number of neurological and psychiatric disorders and abnormal TH function could be the basis of some of these conditions. Of interest in relation to this is the recent finding that the gene locus for one form of bipolar affective disorder is linked to that for H-ras-1, which is very close to the TH locus.

Dopa responsive dystonia (DRD) is an extrapyramidal disorder consisting of dystonia and Parkinsonism, usually developing in childhood and often inherited as an autosomal dominant trait. Frequent diurnal fluctuation of symptoms and a dramatic and prolonged response to small doses of levodopa serve to differentiate DRD from other extrapyramidal disorders of children and young adults, particularly idiopathic torsion dystonia. These features also suggest an abnormality of dopaminergic pathways with preserved dopa decarboxylase activity and dopamine receptor function. Necropsy studies of one case of DRD showed a reduced level of TH in the striatum with minimal cell loss and hypopigmentation in the substantia nigra. On the basis of these findings, along with the clinical and pharmacological features, it has been proposed that DRD may be due to a reduced level of TH in the nigrostriatal projection. A similar clinical syndrome has been described in association with deficiency of biopterin which is a cofactor for TH.

We have investigated the possibility that DRD is due to a defect of the TH gene by attempting to demonstrate linkage between the disease and restriction fragment length polymorphisms (RFLPs) detected by a TH cDNA probe, and a probe for H-Ras-1 which also maps to 11p15.5.

Subjects and methods

Three families (A, B and C) containing 17 individuals affected by DRD were studied. All showed autosomal dominant inheritance. Twenty-six blood samples from 16 affected and 10 normal subjects were obtained.

DNA was extracted from peripheral blood leucocytes by standard methods and digested with the restriction enzymes Taq I and Bgl II under conditions recommended by the manufacturers (Northumbria Biologicals Ltd). The resulting fragments were separated by agarose gel electrophoresis and transferred to nylon membranes (Genescreen, New England Nuclear) by Southern blotting. Probes (H-Ras-1 and TH) were labelled with 32P to high specific activity by the random primer method. Hybridisations were carried out as recommended for Genescreen except for TH which required more stringent conditions (hybridisation with 5% dextran sulphate, 2% sodium dodecyl sulphate, 1M sodium chloride, filters washed in 0·1 × sodium chloride/sodium citrate at 65°C for 1 hour). Autoradiography was at −70°C for 1–10 days.

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Discussion

Our results demonstrate that DRD is not due to an alteration of the TH gene itself; nor have we been able to show conclusively that the disease locus is closely linked to it. Systemic TH deficiency would be expected to have more widespread deleterious effects than the syndrome of DRD. The possibility remains that the disease could result from an abnormality of transcription or translation of the TH gene confined to the striatum, or the presence of brain specific isozymes. The TH gene encodes at least three TH isozymes by variable splicing of mRNA transcripts, and there is evidence that the expression of these different mRNAs varies in different parts of the brain. Other complex mechanisms also affect TH gene expression and enzyme activity. The underlying defect in DRD may therefore be a tissue specific defect of TH synthesis or regulation.

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