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The MFN2 gene is responsible for mitochondrial DNA instability and optic atrophy ‘plus’ phenotype

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Summary

MFN2 and OPA1 genes encode two dynamin-like GTPase proteins involved in the fusion of the mitochondrial membrane. They have been associated with Charcot-Marie-Tooth disease type 2A and autosomal dominant optic atrophy, respectively. We report a large family with optic atrophy beginning in early childhood, associated with axonal neuropathy and mitochondrial myopathy in adulthood. The clinical presentation looks like the autosomal dominant optic atrophy ‘plus’ phenotype linked to OPA1 mutations but is associated with a novel MFN2 missense mutation (c.629A>T, p.D210V). Multiple mitochondrial DNA deletions were found in skeletal muscle and this observation makes MFN2 a novel gene associated with ‘mitochondrial DNA breakage’ syndrome. Contrary to previous studies in patients with Charcot-Marie-Tooth disease type 2A, fibroblasts carrying the MFN2 mutation present with a respiratory chain deficiency, a fragmentation of the mitochondrial network and a significant reduction of MFN2 protein expression. Furthermore, we show for the first time that impaired mitochondrial fusion is responsible for a deficiency to repair stress-induced mitochondrial DNA damage. It is likely that defect in mitochondrial DNA repair is due to variability in repair protein content across the mitochondrial population and is at least partially responsible for mitochondrial DNA Instability.

Key words: MFN2 • mitochondrial DNA instability • dominant optic atrophy
There is a lack of consensus about the effects of the type of menopause (surgical or natural) and of oestrogen replacement therapy on Parkinson’s disease. The effects of the timing of replacement therapy and the female’s age may explain the observed differences in such effects. However, the mechanisms involved are poorly understood. The renin-angiotensin system mediates the beneficial effects of oestrogen in several tissues, and we have previously shown that dopaminergic cell loss is enhanced by angiotensin via type 1 receptors, which is activated by ageing. In rats, we compared the effects of oestrogen replacement therapy on 6-hydroxydopamine-induced dopaminergic degeneration, nigral renin-angiotensin system activity, activation of the nicotinamide adenine dinucleotide phosphate oxidase complex and levels of the proinflammatory cytokine interleukin-1β in young (surgical) menopausal rats and aged menopausal rats. In young surgically menopausal rats, the renin-angiotensin system activity was higher (i.e. higher angiotensin converting enzyme activity, higher angiotensin type-1 receptor expression and lower angiotensin type-2 receptor expression) than in surgically menopausal rats treated with oestrogen; the nicotinamide adenine dinucleotide phosphate oxidase activity and interleukin-1β expression were also higher in the first group than in the second group. In aged menopausal rats, the levels of nigral renin-angiotensin and nicotinamide adenine dinucleotide phosphate oxidase activity were similar to those observed in surgically menopausal rats. However, oestrogen replacement therapy significantly reduced 6-hydroxydopamine-induced dopaminergic cell loss in young menopausal rats but not in aged rats. Treatment with oestrogen also led to a more marked reduction in nigral renin-angiotensin and nicotinamide adenine dinucleotide phosphate oxidase activity in young surgically menopausal rats (treated either immediately or after a period of hypo-oestrogenicity) than in aged menopausal rats. Interestingly, treatment with the angiotensin type-1 receptor antagonist candesartan led to remarkable reduction in renin-angiotensin system activity and dopaminergic neuron loss in both groups of menopausal rats. This suggests that manipulation of the brain renin-angiotensin system may be an efficient approach for the prevention or treatment of Parkinson’s disease in oestrogen-deficient females, together with or instead of oestrogen replacement therapy.
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Key words: ageing, angiotensin, oestrogen, menopause, Parkinson's disease

Introduction

Sex steroids have been shown to have a neuroprotective role in several models of neurological diseases, although the effects of the loss of ovarian function and
Article

This Article

First published online: December 20, 2011

Abstract

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