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Estrogen, neuroinflammation and neuroprotection in Parkinson's disease: glia dictates resistance versus vulnerability to neurodegeneration.

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Post-menopausal estrogen deficiency is recognized to play a pivotal role in the pathogenesis of a number of age-related diseases in women, such as osteoporosis, coronary heart disease and Alzheimer's disease. There are also sexual differences in the progression of diseases associated with the nigrostriatal dopaminergic system, such as Parkinson's disease, a chronic progressive degenerative disorder characterized by the selective degeneration of mesencephalic dopaminergic neurons in the substancia nigra pars compacta. The mechanism(s) responsible for dopaminergic neuron degeneration in Parkinson's disease are still unknown, but oxidative stress and neuroinflammation are believed to play a key role in nigrostriatal dopaminergic neuron demise. Estrogen neuroprotective effects have been widely reported in a number of neuronal cell systems including the nigrostriatal dopaminergic neurons, via both genomic and non-genomic effects, however, little is known on estrogen modulation of astrocyte and microglia function in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. We here highlight estrogen modulation of glial neuroinflammatory reaction in the protection of mesencephalic dopaminergic neurons and emphasize the cardinal role of glia-neuron crosstalk in directing neuroprotection vs neurodegeneration. In particular, the specific role of astroglia and its pro-/anti-inflammatory mechanisms in estrogen neuroprotection are presented. This study shows that astrocyte and microglia response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine injury vary according to the estrogenic status with direct consequences for dopaminergic neuron survival, recovery and repair. These findings provide a new insight into the protective action of estrogen that may possibly contribute to the development of novel therapeutic treatment strategies for Parkinson's disease.

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Estrogen counteracts ozone-induced oxidative stress and nigral neuronal death.

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Oxidative stress is implicated in the premature death of dopamine neurons in substantia nigra in Parkinson's disease. The incidence of Parkinson's disease is higher in men than in women, and estrogen may provide neuroprotection against oxidative damage. We examined the protective effects of estrogen on rat nigral death after chronic ozone inhalation. Ozone inhalation produced impaired nigral cell morphology and loss of dopamine neurons in ovariectomized rats. This was counteracted after 60 days of 17beta-estradiol treatment, when blood levels were highest. These results indicate that ozone exposure may be a useful Parkinson's disease model and neuroprotection afforded by 17beta-estradiol is dependent on the high levels achieved after its prolonged administration.

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Full text
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Influence of oestrogenic compounds on monoamine transporters in rat striatum.

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Oestrogens have been reported to modulate rat membrane (DAT) and vesicular (VMAT(2)) dopamine transporters. A recent pilot study of postmenopausal women showed that chronic oestrogen replacement therapy increases striatal DAT. In the present study, we first investigated whether the oestrogen receptors alpha and beta mediate the effects of oestradiol on DAT and VMAT(2). Two days after ovariectomy, Sprague-Dawley rats were treated for 2 weeks with oestradiol or specific ligands for oestrogen receptor alpha, 4,4',4''-(4-propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol (PPT) or oestrogen receptor beta, 2,3-bis(4-hydroxyphenyl)-propionitrile (DPN). Ovariectomy caused a decrease in [(125)I]-3beta-(4-iodophenyl)-tropane-2beta-carboxylic acid isopropyl ester ([(125)I] RTI-121) specific binding to DAT transporters in the middle striatum compared to values for intact rats, and this was reversed by oestradiol replacement therapy. DPN, but not PPT, mimicked the effect of oestradiol. [(125)I] RTI-121 specific binding in the anterior and posterior striatum was not affected by ovariectomy or any of the drug treatments. Second, we investigated whether oestradiol increased DAT specific binding after a longer period of hormonal withdrawal (a model of hormonal withdrawal at menopause) and whether the selective oestrogen receptor modulators (SERMs), tamoxifen and raloxifene, could reproduce the oestradiol-induced increase of [(125)I] RTI-121 specific binding in long-term ovariectomised rats. Four months after ovariectomy, Sprague-Dawley rats were treated for 2 weeks with oestradiol, tamoxifen or raloxifene, and then killed. Ovariectomy decreased [(3)H] RTI-121 specific binding to DAT transporters in the middle striatum compared to values for intact rats. Treatment with oestradiol, tamoxifen and raloxifene reversed this effect. [(125)I] RTI-121 specific binding in anterior and posterior striatum was not affected by ovariectomy or treatment with oestrogen receptor ligands. In both experiments, neither ovariectomy nor the oestrogenic treatments modulated striatal [(3)H] tetrahydrobenazine specific binding to VMAT(2). Overall, these results suggest that oestrogen receptor beta mediates the oestradiol-induced increase of striatal DAT and that oestradiol can increase DAT density even after long-term steroid withdrawal. The results also support the premise that the SERMs tamoxifen and raloxifene exert oestrogenic agonist effects in the brain.
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