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Selegiline completely restores choline acetyltransferase activity deficits in simian immunodeficiency infection

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Abstract

Human immunodeficiency virus (HIV) infection is associated with a progressive dementia, in addition to motor and behavioural deficits. Cognitive deterioration and motor impairments have been observed also in simian immunodeficiency virus (SIV)-infected monkeys, an animal model for HIV infection. We found recently that choline acetyltransferase activity is markedly reduced in brains of SIV-infected monkeys. We report now that selegiline, completely restores the reduced choline acetyltransferase activity which encourages for a meaningful anti-dementia therapeutic strategy.

Keywords: Selegiline; Human immunodeficiency virus (HIV); Dementia

Choline acetyltransferase, the enzyme responsible for the biosynthesis of acetylcholine, is presently the most specific indicator to monitor the functional state of cholinergic neurons in the central nervous system and one of the most used estimates of cognitive dysfunction. We found recently that choline acetyltransferase activity is markedly reduced in putamen and hippocampus of rhesus monkeys infected with simian immunodeficiency virus (SIV) (Koutsilieri et al., 2000). SIV is closely related to human immunodeficiency virus (HIV) and results in abnormalities that are pathologically and clinically similar to those of HIV-induced dementia complex. The symptoms, cognitive deterioration and motor impairments, develop both in humans and monkeys (Murray et al., 1992) and have been associated with the generation of reactive oxygen species and excitotoxicity in brains of the infected subjects (Lipton et al., 1994). We treated SIV-infected rhesus monkeys with selegiline, an irreversible monoamine oxidase inhibitor, reported to act also as an anti-oxidant (Gerlach et al., 1992) and to protect against glutamate-receptor-mediated toxicity (Mytilineou et al., 1997). Selegiline completely restored the diminished activity of choline acetyltransferase in the brains of SIV-infected monkeys.

We infected rhesus monkeys (*Macaca mulatta*) with the SIVmac251MPBMC (monkey peripheral blood mononuclear cells). Two weeks after infection, we administered selegiline, at a dose (2 mg/kg, i.m., once daily, for 8–20 weeks until euthanasia) inhibiting monoamine oxidase-B and -A (data not shown) and conferring anti-oxidative properties (Gerlach et al., 1992). Brains were prepared and choline acetyltransferase was assayed as previously described (Koutsilieri et al., 2000). Animal experiments were performed according to the guidelines of the Bezirksregierung Braunschweig ethics committee (604.42502/08-02.95). Selegiline treatment increased the reduced choline acetyltransferase in the putamen of SIV-infected animals to control levels (Fig. 1) but it had no significant effect in uninfected monkeys (Fig. 1). Selegiline at a low dose (0.01 mg/kg) did not increase choline acetyltransferase activity in putamen of SIV-infected animals (Fig. 1; $n = 2$, 16.53 and 19.34 μmol/h g, respectively), although monoamine oxidase-B and partially monoamine oxidase-A activities were inhibited (data not shown). The difference in action at high doses may be due to the anti-oxidative potential of selegiline or to a blockade of dopamine uptake and inhibition of acetylcholine release (Knoll, 1978).

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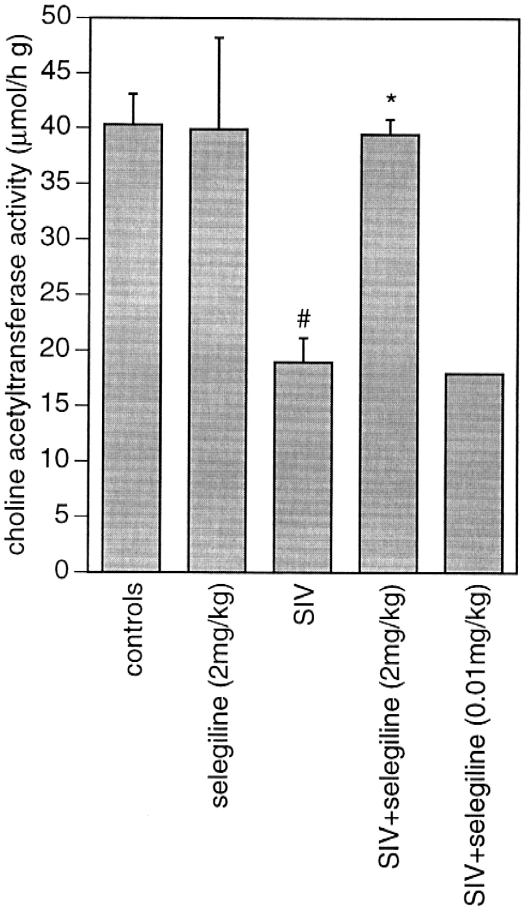

Fig. 1. Effect of selegiline on choline acetyltransferase activity in putamen of SIV-infected monkeys. Animals were divided in five groups: uninfected/untreated (controls, $n = 3$); uninfected/selegiline-treated (selegiline 2 mg/kg, $n = 3$); SIV-infected/untreated (SIV, $n = 3$); SIV-infected/high-dose-selegiline-treated (SIV + selegiline 2 mg/kg, $n = 4$); SIV-infected/low-dose-selegiline-treated (SIV + selegiline 0.01 mg/kg, $n = 2$). Selegiline was administered i.m. once daily until euthanasia. Choline acetyltransferase activity is expressed in µmol/h g protein. Data represent values ± S.E.M. $\#P < 0.05$ significantly different from controls, $^{*}P < 0.05$ significantly different from SIV group. The Mann–Whitney *U*-test for nonparametrically distributed values was used for statistical analysis. Data from the SIV group (SIV-infected/untreated) have been partly published by our group in Koutsilieri et al., 2000.

The restoration of choline acetyltransferase activity by high-dose selegiline treatment in putamen of SIV-infected monkeys was observed also in the hippocampus of the same animals (2.6-fold increased choline acetyltransferase activity in high-dose selegiline-treated group vs. SIV-infected untreated animals). It is known that the putamen is a region with cholinergic interneurons while the hippocampus is the projection area of the long-ascending cholinergic cells originating from the basal forebrain. Selegiline (2 mg/kg) restored choline acetyltransferase deficits in SIV infection in brain regions containing both types of cholinergic neurons. Selegiline at both doses accelerated SIV-induced pathology, but that was independent of the action on choline acetyltransferase activity (unpublished data), indicating that selegiline acts with a different mode in cognitive functions and viral-induced pathology.

Selegiline is currently used as an anti-dementia substance in acquired immunodeficiency syndrome dementia complex (Dana Consortium, 1998) as well as in other types of dementias such as in Alzheimer's and Parkinson's disease (Thomas, 2000). The involvement in therapeutical trials has been attributed so far to its general neuroprotective features. We report in the current study that selegiline acts on the cholinergic system by modulating choline acetyltransferase activity, suggesting this mechanism to be responsible for the anti-dementia effects on humans. It is unclear whether selegiline acted directly or through increased dopamine availability on the expression of choline acetyltransferase and thereby increase of protein synthesis, on specific regulatory sites of the enzyme, or as a neuroprotective agent on cholinergic neurons. Nevertheless, restoration of central cholinergic deficiency provides encouraging data and should be sufficient for a meaningful therapeutic strategy, which would ameliorate impaired cognitive functions.

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