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EXPRESS COMMUNICATION

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Enhancement of central nervous system pathology in early simian immunodeficiency virus infection by dopaminergic drugs

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Abstract Human immunodeficiency virus infection (HIV) at late stages of the disease is accompanied by neurological complications, including motor, behavioral and cognitive impairment. Using simian immunodeficiency virus (SIV)-infected rhesus monkeys, an animal model of HIV infection, we found that during the asymptomatic SIV infection dopamine (DA) deficits are early components of central nervous system (CNS) dysfunction. To investigate the role of the DA system in SIV infection and to restore the DA deficiency, we administered selegiline, an agent with DAergic and neuroprotective properties, to SIV-infected monkeys. Selegiline increased DA availability but induced CNS vacuolization, SIV encephalitic lesions, and enhanced CNS viral replication during early SIV infection. The pathological changes seem to be mediated by DA, as treatment with L-DOPA, the precursor of DA, had similar effects. We propose that any natural or induced DAergic dysregulation which results in increased DA availability may potentiate HIV-associated neurological disease (ND). Our findings raise new questions regarding the pathogenesis of HIV-ND and generate concerns about the safety of dopaminergic drugs in the clinical management of HIV-infected patients.

Keywords HIV · Simian immunodeficiency virus · Monkeys · Dopamine · Selegiline

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Introduction

Human immunodeficiency virus (HIV) infection is frequently associated with specific neurological symptoms [17]. This syndrome presents predominantly as a subcortical dementia, and HIV-positive cells and pathological changes within the gray matter are found primarily in the basal ganglia [2, 13]. These dopamine (DA)-rich areas exhibit an extensive neuronal loss [15], and neurochemical investigations indicate a significant decrease in DA and its metabolite levels in the CSF and brain of HIV-infected subjects with AIDS [19]. To treat such DA deficits, selegiline can be useful; selegiline prevents the enzymatic catabolism of DA by monoamine oxidase (MAO) and blocks DA re-uptake into the presynaptic terminals, resulting in increased DA availability [7]. Furthermore, selegiline has been used as a neuroprotective agent in HIV-infected patients, resulting in improvement of the cognitive impairment [6]. Therefore, we used selegiline to investigate the role of the DA system in immunodeficiency virus infection, in the well-established simian immunodeficiency virus (SIV)-infected rhesus monkey model.

Materials and methods

Animals

Juvenile (3.7±0.6 years) rhesus monkeys (*Macaca mulatta*) were housed individually in indoor facilities on a 12:12 light:dark schedule at the German Primate Center (Göttingen, Germany). Dry food with fresh fruits as a dietary supplement was provided twice a day and water was available ad lib.

Animal experiments were approved by, and performed according to the guidelines set out by the ethics committee for animal experimentation of the Bezirksregierung Braunschweig (604.42502/08-02.95).

Experimental design

The monkeys were divided into four groups: uninfected/untreated (*n*=4), SIV-infected/untreated (*n*=6), SIV-infected/selegiline-treated (*n*=6) and uninfected/selegiline-treated (*n*=3). To investigate the mechanism of action of selegiline three more groups were added: SIV-infected/low dose selegiline-treated (*n*=2), SIV-infected/L-DOPA-treated (*n*=3) and uninfected/L-DOPA-treated (*n*=3).

Pharmacological schedule

Animals were infected under ketamine anesthesia (10 mg/kg) with SIVmac 251 MPBMC, a virus strain with enhanced neurotropism [21]. Two weeks post infection, at peak vireamia, six animals were treated with selegiline (2 mg/kg i.m.), once a day until euthanasia. Three uninfected animals were also treated with selegiline at this dose. The treatment with L-DOPA started also at 2 weeks post infection. Four SIV-infected and three uninfected animals were treated with 50 mg/kg L-DOPA p.o. in bananas, twice a day. It was administered in combination with 12 mg/kg benserazide to inhibit peripheral metabolism to DA.

Preparation of samples

Untreated and treated animals were euthanized in pairs at different time points during the asymptomatic phase of SIV infection (8–20 weeks post infection). Due to experimental reasons (virological and neurochemical investigations), the anesthetized animals were killed by exsanguination and perfused with RPMI 1640. The brains were quickly removed, dissected and partly immersion-fixed (5% neutral buffered formaldehyde for light microscopy, or 2.5% glutaraldehyde for electron microscopy) and partly frozen at –70°C (for neurochemical and virological analysis).

Measurement of DA, homovanillic acid, and 3,4-dihydroxyphenylacetic acid

Regions for neurochemical analysis were dissected according to a stereotactic atlas using standardized procedures on a Teflon plate at –20°C. Brain tissue was prepared according to [8] The filtrates (25–50 µl) were injected into a Rheodyne injector (type 8,125 Eppelheim, Germany) and analyzed for DA, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) by reverse-phase HPLC with electrochemical detection [12]. Qualitative and quantitative analysis was performed by comparing retention times and peak heights with those of commercially available standards (Sigma).

Histopathological examination and in situ hybridization

Neuropathological assessment was performed on 3-µm H&E-stained paraffin sections of the whole brain. In situ hybridization analysis of paraffin-embedded tissue sections was performed as described previously [5]. Briefly, each tissue was analyzed in triplicate, and numbers of SIV-infected cells were counted on complete sections. Transcription vectors (pGEM-4, Stratagene) containing env-, gag- or nef-specific sequences were used to generate ^{35}S-labeled antisense and sense RNA probes. A cocktail of the three riboprobes (1×10^6 cpm/µl for each probe) was applied to the slides and incubated overnight at 45°C. Slides were then dipped into "Ilford K2" (Ilford, UK) photo emulsion and exposed for 10–20 days.

Results

All SIV-infected animals developed a course of infection characteristic for slow disease progression [21]. Selegiline treatment did not alter the peripheral course of the SIV infection or the intrathecal immune response. None of our animals developed any signs of immunodeficiency or overt clinical neurological signs.

DA metabolism is changed during SIV infection

DA levels were reduced in putamen, hippocampus and frontal cortex of SIV-infected/untreated compared with uninfected/untreated animals but remained unchanged in the substantia nigra (Fig. 1), a region with high density of DAergic cell bodies. It is interesting to note that the loss of DA observed in the above regions was accompanied by an increase in DA turnover as indicated by the ratio of HVA/DA and DOPAC/DA (Fig. 1, right panels). Selegiline inhibited MAO-B activity (data not shown) in all brain areas and reversed the SIV-induced changes in DA metabolism (Fig. 1).

Selegiline induces vacuolization and accelerates SIV encephalitis

Although the increase in DA concentration following treatment with selegiline initially appeared beneficial since the loss of DA caused by SIV was restored by treatment with selegiline, histological examination unexpectedly revealed extensive pathological changes in the CNS; specifically, SIV-infected/selegiline-treated animals presented two main histological features: (a) diffuse vacuolar degeneration (Fig. 2), and (b) SIV encephalitic lesions (SIVEL) without indications of AIDS (Table 1).

The vacuolization consisted of numerous small round-oval vacuoles with sharp borders disseminated within the neuropil. The vacuoles were not associated with the neuronal perikarya (Fig. 2d, e) but originated in swollen dendrites (Fig. 2g, h) some with characteristic spines (Fig. 2h, k). The observed vacuolization was restricted to the neocortical layers II–IV and subcortical gray matter. The vacuoles were particularly apparent in the basal ganglia (putamen, caudate nucleus and globus pallidus), frontal cortex and hippocampus and were absent in the substantia nigra, raphe nuclei and cerebellum. No vacuoles were observed in uninfected/selegiline-treated or SIV-infected/untreated animals. Moreover, such widespread vacuolization with such a distribution restricted to only gray matter areas has never been detected in our previously investigated cohort of SIV-infected animals [5].

SIV encephalitis consisting of massive perivascular cuffs and inflammatory microglia nodules was most pronounced in the basal ganglia (Table 1). Contrary to the SIV encephalitis in animals with AIDS and to the HIV encephalitis as defined in the consensus report [3], en-

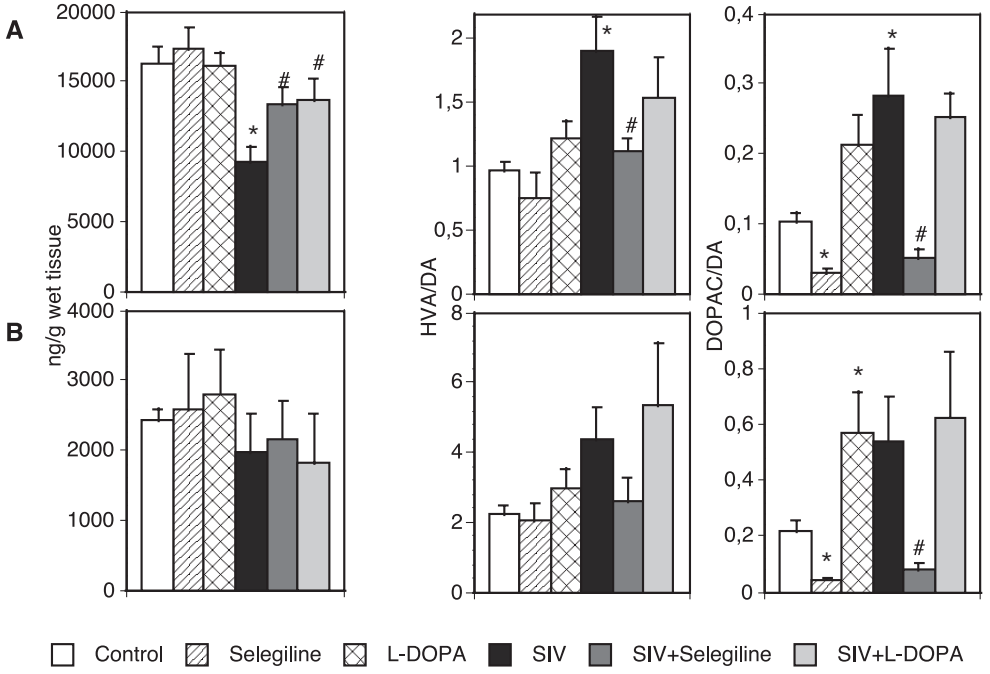

Fig. 1 DA metabolism in brain regions of SIV-infected and uninfected rhesus monkeys: **A** putamen (as representative of the DA metabolism in basal ganglia, hippocampus and frontal cortex); **B** substantia nigra; *left* and *right panels* depict the same regions. *Left panels* DA in ng/g wet tissue, *right panels* HVA/DA and DOPAC/DA ratios. Animals were divided into six groups: controls (uninfected/untreated), selegiline (uninfected/selegiline-treated), L-DOPA (uninfected/L-DOPA-treated), SIV (SIV-infected/untreated), SIV+selegiline (SIV-infected/selegiline-treated), and SIV+L-DOPA (SIV-infected/L-DOPA-treated). Selegiline (2 mg/kg, i.m) and L-DOPA (50 mg/kg, p.o.) were administered daily until euthanasia. Data represent mean values ± SEM from three to six animals per experimental condition. **P*<0.05 significantly different from controls; #*P*<0.05 from SIV-infected group. The Mann-Whitney *U* test for nonparametrically distributed values was used for statistical analysis (*DA* dopamine, *SIV* simian immunodeficiency virus, *HVA* homovanillic acid, *DOPAC* 3,4-dihydroxyphenylacetic acid)

cephalitic lesions in SIV-infected /selegiline-treated animals were characterized by multiple disseminated foci composed of lymphocytes and some microglia cells at the side. These foci were most pronounced in the basal ganglia (Table 1). Additionally, in all animals, significant infiltrates of lymphocytes often involved leptomeninges and perivascular spaces. Scarce perivascular infiltrates and isolated foci of spongiform change in the white matter, specific for the early phase of SIV infection, were detected in the SIV-infected animals. Such a combination of lesions distinctive for the terminal stage of disease (inflammatory nodules, however, with an atypical cellular composition) with lesions characteristic for the early stage of disease (meningitis, perivascular cuffing) has never been found before in our cohort of SIV-infected monkeys. These pathological changes were absent in SIV-infected/selegiline-untreated animals and in uninfected/selegiline-treated animals, indicating that selegiline induced CNS pathology only in SIV-infected animals.

Selegiline acts through dopaminergic mechanisms

Consequently, we had to address the question, whether selegiline induced CNS changes via a selegiline-specific pharmacological action or via its effects on the DAergic system. Selegiline at a low dose has been shown to induce transcription independent of MAO-B inhibition [22] and thus, independent of DA mechanisms. Therefore, we treated two SIV-infected monkeys with a low dose of selegiline (0.01 mg/kg) known from animal experiments not to inhibit MAO-B. Low dose of selegiline caused pathological changes similar to those seen using 2 mg/kg selegiline (data not shown), indicating that it was not the high concentration of selegiline responsible for the induced pathology. However, the low dose of selegiline also caused inhibition of MAO-B (data not shown), so that we could not reach a conclusion about specific pharmacological action of selegiline. To address this further, we then treated seven monkeys with L-DOPA, the DA precursor capable of passing the blood-brain barrier and forming DA in respective cells. The pathology detected in SIV-infected/L-DOPA-treated animals was similar but less pronounced to that in SIV-infected/selegiline-treated animals (Fig. 2, Table 1), suggesting that this pathology may indeed be a result of a synergism between increased DA availability and immunodeficiency virus infection.

Selegiline enhances viral replication

To further investigate whether increased viral replication is associated with the pathology following treatment with DAergic substances, we determined the viral load in brain tissue by radioactive in situ hybridization. In the early phase of SIV infection, only a few infected cells can be detected by in situ hybridization [5]. Selegiline treatment,

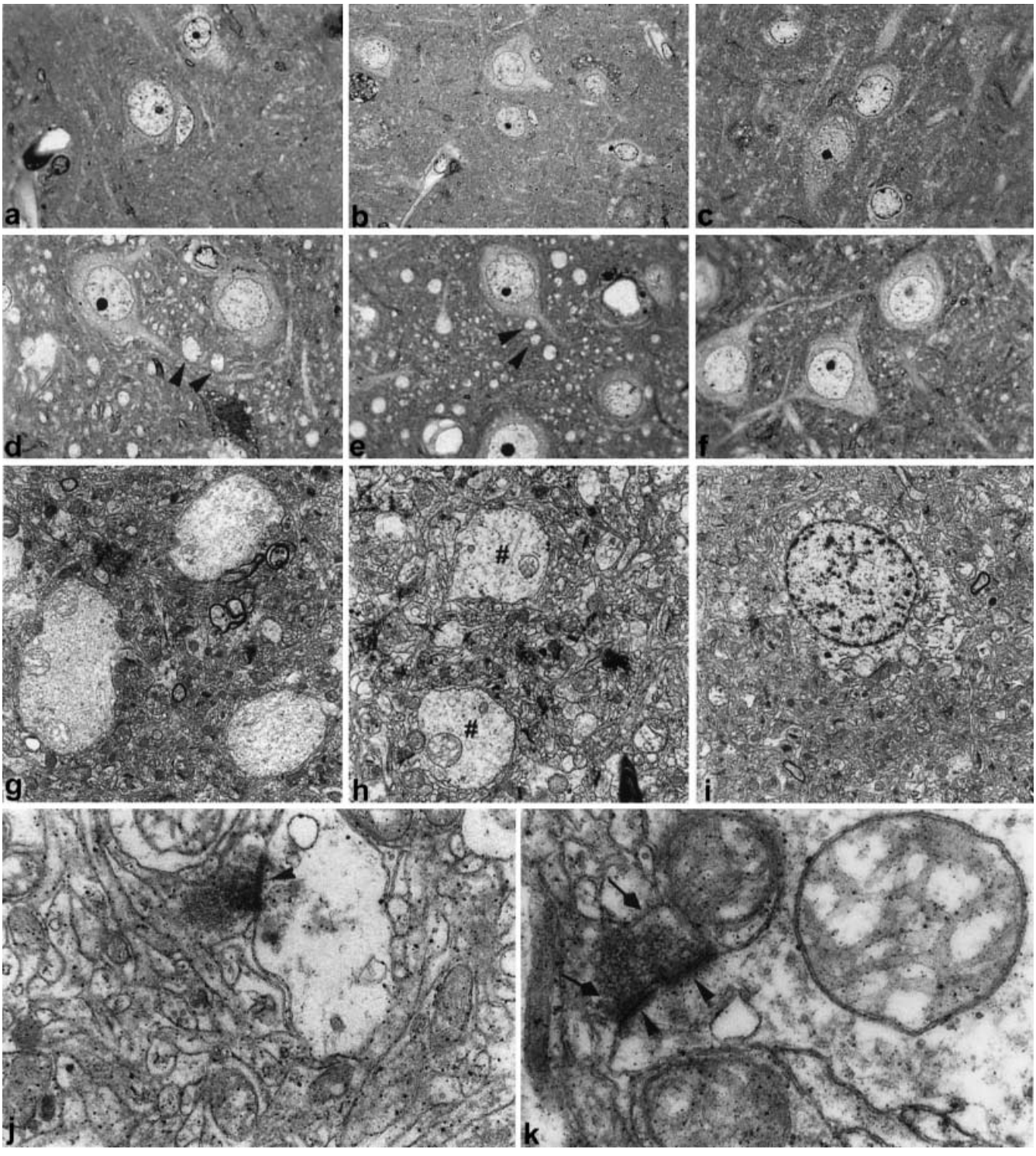

Fig. 2 Treatment of SIV-infected monkeys with selegiline or L-DOPA was associated with vacuolization that was not evident in SIV-infected animals not treated with these drugs or in uninfected/treated animals. Representative picture of the vacuolization in frontal cortex: **a** uninfected/selegiline-treated; **b** uninfected/L-DOPA-treated; **c** uninfected/untreated; **d** SIV-infected/selegiline-treated; **e** SIV-infected/L-DOPA-treated; **f** SIV-infected/untreated animals; **g** SIV-infected/selegiline-treated; **h** SIV-infected/L-DOPA-treated; **i** SIV-infected/untreated **j**:SIV-infected/selegiline-treated animals at higher magnification. *Arrowhead* in the distended dendrite points towards an asymmetrical synapse; **k** depicts the lower vacuole seen in **h** at higher magnification. *Two arrowheads* are placed in a dendritic spine forming an asymmetrical synapse with an axon terminal containing spherical synaptic vesicles (*two arrows*). # indicates vacuole. **a–f** Semithin, Giemsa-stained sections; **g–k** electron micrographs; **a–f** ×1,700; **g** ×3,600; **h** ×5,720; **i** ×3,300; **j** ×18,000; **k** ×35,600

Table 1 Effects of selegiline and L-DOPA on CNS pathology and viral load in SIV-infected monkeys. Treatment of SIV-infected monkeys with selegiline (2 mg/kg i.m) or L-DOPA (50 mg/kg p.o.) daily until euthanasia resulted in the induction of vacuolization in cortical and subcortical areas and in the occurrence of SIVEL during the asymptomatic phase of infection. SIV-RNA was quantified in selected brain regions of each animal (frontal cortex, hippocampus, basal ganglia, substantia nigra, brain stem and cerebellum) (*SIV* simian immunodeficiency virus, *SIVEL* SIV encephalitic lesions, *wpi* weeks post infection, +/- presence/absence of pathological changes). **P*<0.05, Student's *t*-test

Treatment	wpi	Vacuolization			SIVEL	SIV-RNA infected cells/cm^2
		Basal ganglia	Frontal cortex	Hippo-campus	Basal ganglia	CNS
SIV	8	–	–	–	–	4.8
	12	–	–	–	–	4.1
	15	–	–	–	–	7.9
	16	–	–	–	–	5.3
	19	–	+	–	+	12.5
	20	–	–	–	–	2.2
						6.13±1.46
SIV+selegiline	8	+	+	–	+	22.5
	12	+	+	+	+	24.9
	12	–	+	+	+	7.7
	15	+	+	+	+	20.5
	16	+	+	–	+	6
	20	+	+	+	+	22
						17.26±3.3*
SIV+L-DOPA	12	+	+	–	+	10.3
	15	+	+	+	+	11.7
	15	–	+	+	+	7.2
	15	–	–	+	–	4
						8.3±1.7

however, resulted in a significant increase in SIVmRNA-expressing cells compared with the number in SIV-infected /untreated animals (Table 1).

Discussion

The pathophysiological process that causes neurological complications in HIV infection is unclear because there is no apparent indication of direct neuronal infection by HIV. Current data suggest, however, that basal ganglia dysfunction plays a critical role in the neuropsychiatric manifestation of HIV infection [13]. To explore the possible involvement of the dopaminergic system in the pathogenesis of HIV infection, we used the SIV/macaque animal model. Our results provide the first direct evidence for a decrease in DA levels already 2–3 months post infection, in the early asymptomatic phase. DA reduction was apparent at target areas of dopaminergic projections. The substantia nigra, a region rich in dopaminergic cell bodies showed no DA loss, indicating the influence of virus on dopaminergic terminals in the postsynaptic DA areas. Whether a further retrograde degeneration of the dopaminergic projections accompanies late stages of SIV infection remains to be elucidated. To treat the observed DA deficiency of SIV-infected monkeys we used the dopaminergic and neuroprotective substance selegiline in SIV-infected rhesus monkeys. The concentration of selegiline we used has been shown to inhibit MAO-B and MAO-A [14]. This ensures that DA can not be further enzymatically metabolized and, thus, DA availability is increased. Moreover, at high doses selegiline inhibits DA uptake and acts as an anti-oxidative substance [7]. We found, however, that even a low dose (0.01 mg/kg) of selegiline caused similar effects on SIV infection. The action seems to involve MAO inhibition since both doses inhibited MAO-B and -A activity (data not shown), and thus increased DA availability. Treatment with L-DOPA, at a concentration used as a monotherapy for Parkinson's disease, resulted in similar effects. The enhanced availability of DA effected by dopaminergic drugs such as selegiline and L-DOPA accounts for the symptomatic benefit of these drugs in Parkinson's disease, a disease characterized by a regional reduction in DA levels. However, increased DA availability in the presence of a retroviral infection of the CNS was associated in the current study with the induction of neuropathology rather than neuroprotection.

The mechanisms responsible for the formation of the vacuoles are unknown, as is the significance of DA for their generation. However, the ultrastructural localization of the vacuoles in our animals is identical to that observed in spongiform encephalopathies, the pathogenesis of which may be associated with excitotoxic mechanisms [20]. Moreover, DA seems to be involved in the formation of vacuoles when excitotoxicity is apparent [4], and has neurotoxic properties when it participates in the striatal pathophysiology associated with a number of pathological conditions, such as systemic methamphetamine treatment, ischemia and exposure to high levels of excitatory amino acids [9]. Such vacuolar degeneration and encephalitis have not until now been described in the asymptomatic phase of HIV infection, although increased CNS pathology has been reported in AIDS patients who were also intravenous drug abusers [10, 11]. The fact that a common reaction to drug abuse is enhanced DA release, further

supports the hypothesis of an involvement of DA in immunodeficiency virus-induced CNS pathology. Vacuoles were observed in some cases at terminal stages of HIV encephalitis in both gray and white matter, the latter due to secondary axonal degeneration and consecutive myelin destruction [24]. In our animals, however, the vacuoles were present only in the gray matter. Vacuoles in the gray matter have also been described in the brains of transgenic mice; expression of gp120 directed by the glial fibrillary acidic protein promoter [23] induces dendritic vacuolization in the neocortex, which represents pathological distensions of the smooth endoplasmic reticulum in response to excessive intracellular calcium release [15]. Olney et al. [16] reported microvacuoles in the CNS after treatment with *N*-methyl-L-aspartate (NMDA) receptor antagonists; he suggested that DA hyperactivity might result in an excessive suppression of glutamate release, with consequent hypofunction of the NMDA receptor systems. If NMDA receptors in certain circuits are hypofunctional, GABAergic inhibition of excitatory inputs is abolished, leading to excitotoxic damage.

Besides the induction of pathological changes, selegiline treatment also increased virus replication. Selegiline is known to exert trophic-like actions via transcriptional activation, which may explain this observation. HIV gene expression is controlled by a combination of viral and host cell transcriptional factors which interact with the long terminal repeat. One transcription factor shown to be important for an efficient replication of SIV in macrophages is NF-κB [1], and DA has been shown to stimulate the activity of NF-κB [18]. However, although selegiline enhanced SIV replication, treatment with L-DOPA did not, suggesting either a quantitative difference in the effect compared with selegiline treatment or a specific pharmacological action of selegiline on viral replication not mediated by DA. If the latter is true the effects of selegiline on cellular pathology and on SIV replication may be effected by separate mechanisms. We are currently performing further experiments with DA receptor agonists/antagonists to clarify this issue.

The mechanism of the generation of vacuoles in our model, as in other spongiform encephalopathies, is unknown. However, the effects of DA may follow two major directions: either a direct interaction with infected cells leading to increased viral replication and/or production of neurotoxic substances; or changes in the cellular functions of neural cell populations leading to increased susceptibility to detrimental effects of the viral infection. The finding that agents which increase DA availability may induce a specific cellular pathology during the asymptomatic phase of immunodeficiency virus infection is of critical importance, raises questions regarding the pathogenesis of HIV-associated neurological disease and generates concern about the safety of such drugs in the clinical management of HIV-infected patients.

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References

1. Bellas RE, Hopkins N, Li Y (1993) The NF-kappaB binding site is necessary for efficient replication of simian immunodeficiency virus of macaques in primary macrophages but not in T cells in vitro. J Virol 67: 2908–2913
2. Berger JR, Nath A (1997) HIV dementia and the basal ganglia. Intervirology 40: 122–131
3. Budka H, Wiley CA, Kleihues P, et al (1991) HIV-associated disease of the nervous system: review of nomenclature and proposal for neuropathology-based terminology. Brain Pathol 1: 143–152
4. Cubells JF, Rayport S, Rajendran G, Sulzer D (1994) Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. J Neurosci 14: 2260–2271
5. Czub S, Muller JG, Czub M, Muller-Hermelink HK (1996) Nature and sequence of simian immunodeficiency virus-induced central nervous system lesions: a kinetic study. Acta Neuropathol 92: 487–498
6. Dana Consortium (1998) A randomized, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment. Dana Consortium on the therapy of HIV dementia and related cognitive disorders. Neurology 50: 645–651
7. Gerlach M, Youdim MB, Riederer P (1994) Is selegiline neuroprotective in Parkinson's disease? J Neural Transm Suppl 41: 177–188
8. Gerlach M, Götz M, Dirr A, Kupsch A, Janetzky B, Oertel W, Sautter J, Schwarz J, Reichmann H, Riederer P (1996) Acute MPTP treatment produces no changes in mitochondrial complex activities and indices of oxidative damage in the common marmoset ex vivo one week after exposure to the toxin. Neurochem Int 28: 41–49
9. Hastings TG, Lewis DA, Zigmond MJ (1996) Role of oxidation in the neurotoxic effects of intrastriatal dopamine injections. Proc Natl Acad Sci USA 93: 1956–1961
10. Jellinger KA, Setinek U, Drlicek M, Böhm G, Steurer A, Lintner F (2000) Neuropathology and general autopsy findings in AIDS during the last 15 years. Acta Neuropathol 100: 213–220
11. Kibayashi K, Mastri AR, Hirsch CS (1996) Neuropathology of human immunodeficiency virus infection at different disease stages. Hum Pathol 27: 637–642
12. Koutsilieri E, Götz ME, Sopper S, Stahl-Hennig C, Czub M, Meulen V ter, Riederer P (1997) Monoamine metabolite levels in CSF of SIV-infected rhesus monkeys (*Macaca mulatta*). Neuroreport 8: 3833–3836
13. Lopez OL, Smith G, Meltzer CC, Becker JT (1999) Dopamine systems in human immunodeficiency virus-associated dementia. Neuropsychiatry Neuropsychol Behav Neurol 12: 184–192
14. Magyar K (1993) Pharmacology of monoamine oxidase type B inhibitors. In: Szelenyi I (ed) Inhibitors of monoamine oxidase B, pharmacology and clinical use in neurogenerative disorders. Birkhäuser, Basel, pp 125–143
15. Masliah E, Ge N, Mucke L (1996) Pathogenesis of HIV-1 associated neurodegeneration. Crit Rev Neurobiol 10: 57–67
16. Olney JW, Labruyere J, Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 244: 1360–1362
17. Price RW, Brew B, Sidtis J, Rosenblum M, Scheck AC, Cleary P (1988) The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. Science 239: 586–592
18. Rohr O, Sawaya BE, Lecestre D, Aunis D, Schaeffer E (1999) Dopamine stimulates expression of the human immunodeficiency virus type 1 via NF-kappaB in cells of the immune system. Nucleic Acids Res 27: 3291–3299

19. Sardar AM, Czudek C, Reynolds GP (1996) Dopamine deficits in the brain: the neurochemical basis of parkinsonian symptoms in AIDS. Neuroreport 7: 910–912
20. Scallet AC, Ye X (1997) Excitotoxic mechanisms of neurodegeneration in transmissible spongiform encephalopathies. Ann N Y Acad Sci 825: 194–205
21. Sopper S, Sauer U, Hemm S, Demuth M, Muller J, Stahl-Hennig C, Hunsmann G, Meulen V ter, Dorries R (1998) Protective role of the virus-specific immune response for development of severe neurologic signs in simian immunodeficiency virus-infected macaques. J Virol 72: 9940–9947
22. Tatton WG, Ju WY, Holland DP, Tai C, Kwan M (1994) (-)-Deprenyl reduces PC12 cell apoptosis by inducing new protein synthesis. J Neurochem 63: 1572–1575
23. Toggas SM, Masliah E, Rockenstein EM, Rall GF, Abraham CR, Mucke L (1994) Central nervous system damage produced by expression of the HIV-1 coat protein gp120 in transgenic mice. Nature 367: 188–193
24. Wiley CA, Masliah E, Morey M, Lemere C, DeTeresa R, Grafe M, Hansen L, Terry R (1991) Neocortical damage during HIV infection. Ann Neurol 29: 651–657