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Expression of Human Immunodeficiency Virus Type 1 in the Nervous System of Transgenic Mice Leads to Neurological Disease

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Patients infected with the human immunodeficiency virus type 1 (HIV-1) frequently develop central and peripheral nervous system complications, some of which may reflect the effect of the virus itself. In order to elucidate the pathogenic mechanisms of HIV in neurological disease in a small animal model, we generated transgenic mice expressing the entire HIV genome under control of the promoter for the human neurofilament NF-L gene. The transgene was predominantly expressed in anterior thalamic and spinal motor neurons. Animals developed a neurological syndrome characterized by hypoactivity and weakness and by axonal degeneration in peripheral nerves. These results provide evidence for a role of HIV in affecting both the central and peripheral nervous systems. This animal model may also facilitate the development of therapeutic agents against the human disease.

Patients with AIDS frequently suffer from diseases of the peripheral nervous system (PNS) and the central nervous system (CNS). While many of these are caused by infectious or neoplastic processes that are secondary to infection with human immunodeficiency virus (HIV), the AIDS dementia complex (ADC) occurs even in the absence of intercurrent conditions and is thought to be caused, directly or indirectly, by HIV itself (8). ADC is characterized clinically by progressive deterioration of both mental and motor functions and pathologically by abnormalities in the white and gray matter, with neuronal loss, myelin changes, vacuolation, gliosis, and infiltration by microglia, macrophages, lymphocytes, and multinucleated cells, termed HIV encephalopathy (8, 30, 31). Some patients with ADC show only minimal pathologic changes (30). In many brains a discrepancy is found between the extensive pathologic changes and the small number of cells harboring the virus (24). Cells of the macrophage/microglial lineage consistently show evidence of infection by HIV (24), while neurons, astrocytes, and oligodendrocytes are only rarely shown to be infected, possibly because of the low sensitivity of the methods used to detect viral gene products and difficulties in precisely identifying cell types (41, 47). However, neuronal and glial cell lines can be infected with HIV (6, 18). In addition to ADC, a large proportion of patients with AIDS develop peripheral neuropathies (reviewed in reference 39) characterized pathologically by axonal and myelin abnormalities; mononuclear infiltrations are prominent in some cases. The occasional identification of HIV in nerve biopsies by microscopy or by culture has suggested a direct role for HIV in the pathogenesis of some forms of PNS involvement, namely distal symmetric polyneuropathy and mononeuropathy multiplex (13, 19, 39).

The mechanisms through which neurological disease develops in AIDS are still unclear, but experimental data suggest both a direct and an indirect role for HIV: in vitro and in vivo studies have suggested neurotoxic properties for several viral gene products, including Tat and gp120 (5, 9, 15, 28, 36, 44, 46), and HIV-infected macrophages secrete factors, including cytokines, that may be toxic to primary neuronal cultures, an effect that might be dependent on interaction with astrocytes (12, 14).

On the basis of in vitro evidence suggesting a direct effect of HIV gene products on neurons and the possibility of infection of neurons by HIV followed by low and undetectable expression of the viral gene products and in order to facilitate the study of the pathogenic mechanisms of HIV in neurological disease in a small animal model, we generated transgenic mice that express the HIV genome in neurons under the transcriptional control of a neurofilament promoter.

MATERIALS AND METHODS

Construction of transgenic mice. The DNA construct used to generate the transgenic mice consisted of three fragments: the 5′ upstream regulatory sequences of the gene for the human neurofilament subunit NF-L, which has been previously used to direct specific expression into cells of neuronal lineage (21); the entire open reading frame of the HIV genome, from which the 5′ long terminal repeat, part of the 3′ long terminal repeat, and part of the untranslated leader sequences were deleted; and the simian virus 40 polyadenylation signal (Fig. 1). The 2.3-kbp *Eco*RI-*Hin*dIII 5′ sequences of the NF-L gene were subcloned into the *Sma*I site of pUC18 and excised with *Hin*dIII and *Sac*I. The 8.9-kbp *Sac*I HIV fragment was obtained from the BH10R3 plasmid (35). The simian virus 40

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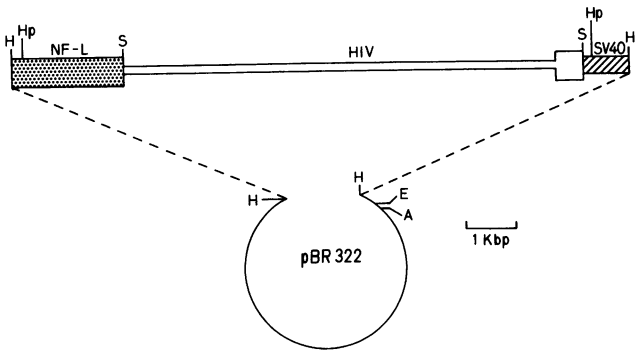

FIG. 1. Schematic representation of the NF-L-HIV fusion gene. The restriction sites are A, *Aat*II; E, *Eco*RI; H, *Hin*dIII; Hp, *Hpa*I; and S, *Sac*I.

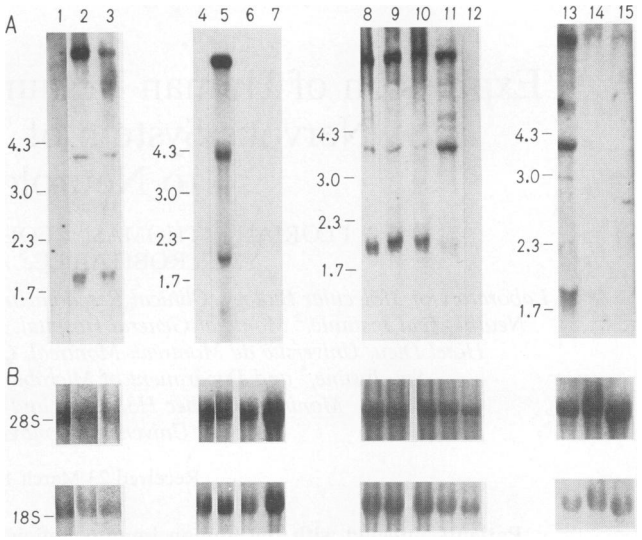

FIG. 2. (A) Northern blot analysis of NF-L-HIV expression in tissues of transgenic mice. Hybridization was performed with a ^{32}P-labelled 8.9-kbp *Sac*I fragment from the BH10R3 plasmid; 20 μg of RNA was used. Lane 1, transgene-negative thalamus. Lanes 2 to 4 from NF-HIV 6202: 2, thalamus; 3, spinal cord; 4, sciatic nerve. Lane 5, HIV-infected lymphocytes. Lane 6, transgene-negative sciatic nerve. Lanes 7 to 15 from NF-HIV 29: 7, sciatic nerve; 8, brain; 9, thalamus; 10, spinal cord; 11, thymus; 12, liver; 13, spleen; 14, salivary gland; 15, kidney. (B) Ethidium bromide-stained 28S and 18S rRNA bands indicate that similar amounts of RNA were applied on gels.

poly(A) addition signal was obtained from the pSV2neo vector. The 885-bp *Bam*HI-*Pst*I fragment was first subcloned in pUC18 and then released by digestion with *Sac*I and *Hin*dIII. The three fragments were ligated in *Hin*dIII-digested vector pBR322. The 11.3-kbp fragment used for microinjection was obtained by cleaving the plasmid DNA with *Hpa*I. The fragment was isolated by preparative agarose gel electrophoresis before further purification on a CsCl gradient as described previously (4). Pronuclei of one-cell (C57BL/6 × C3H)F_2 embryos were microinjected as previously described (4). Offspring were analyzed by Southern hybridization analysis of tail DNA with a HIV-1-specific probe (8.9-kbp *Sac*I fragment). Transgene-positive mice were then bred to C3H mice (Charles River Laboratories, St. Constant, Quebec, Canada).

Northern (RNA) blot analysis of transgene expression. RNA was isolated and separated on formaldehyde-agarose gels, transferred onto nylon membranes (Hybond), and hybridized as described previously (7, 40).

In situ hybridization and immunohistochemistry. Hybridization of paraffin-embedded tissue was done with a ^{35}S-labelled HIV *gag* RNA probe, consisting of the 627-bp *Hin*dIII fragment cloned in GEM4 as the DNA template, as previously described (33). Double-label in situ hybridization-immunohistochemistry with antibodies to nonphosphorylated neurofilaments (SMI 32; Sternberger Monoclonals Inc., Baltimore, Md.) to identify neurons was performed as previously described (16).

Analysis of protein expression. After homogenizing 50 mg of spinal cord or brain tissue that consisted mostly of thalamic tissue in phosphate-buffered saline, expression of HIV protein was quantitated by using an enzyme immunoassay which detects predominantly Gag proteins (Abbott Laboratories, Abbott Park, Ill.), according to the manufacturer's instructions. Protein expression was also tested by Western immunoblot (20) and immunohistochemistry (33) with monoclonal and polyclonal antibodies to p24, p17, and gp120. Mammary gland tissues in which MMTV/HIV transgenic mice express viral proteins (20) were used as positive controls. Thalamic and spinal cord tissues from transgene-negative littermates and from mice of the NF-HIV 6207 founder line, which does not express the transgene, were used as negative controls in all assays.

Neurobehavioral examination. Motor strength was evaluated by placing mice on a narrow horizontal suspension bar consisting of a plastic coathanger (25). The number of falls and the time spent on the beam were assessed in five trials per day of 1-min duration (intertrial interval, 10 min) during 3 consecutive days. Motor activity was measured in a plastic T maze (26) and a wooden box containing a 5 by 5 array of squares (25). The number of squares crossed in the T maze and in the peripheral parts of the box was recorded. The activity tests were conducted for 3 consecutive days during 4-min sessions. Mice were also evaluated in two learning tasks, a test of active avoidance of noxious stimuli (11) and the water maze (25). All behavioral evaluations were performed blindly with regard to group assignments. Controls were transgene-negative littermates. Group comparisons were made with the *t* test, except for the latency measures in the horizontal beam test, for which the Mann-Whitney test was used. Animals were cared for in accordance with institutional guidelines.

Electrophysiological examination. Nerve conduction studies were performed blindly as previously described (34, 43). Mice were anesthetized with 0.02 ml of 1.25% *tert*-amyl alcohol–1.25% 2,2,2-tribromoethanol per g of body weight. The sciatic nerve was supramaximally stimulated at the sciatic notch, and the compound muscle action potential (CMAP) was recorded from the intrinsic foot muscles. In most animals, both sciatic nerves were examined. Mice infected with the neurotropic Cas-Br-E murine leukemia virus (MuLV) and exhibiting hind limb paralysis were used as positive controls (33). *P* values were calculated by comparing transgenic animals and transgene-negative littermates.

Neuropathological evaluation. For analysis of the PNS, both sciatic nerves were exposed in the thigh and the field was flooded with 4% glutaraldehyde for 10 min. A 2-cm portion of the nerve was removed and processed for analysis of Epon-embedded semithin and ultrathin sections or teased fibers according to published methods (10). Evaluation was done blindly with regard to group assignment.

For CNS examination, brain and spinal cord tissues were

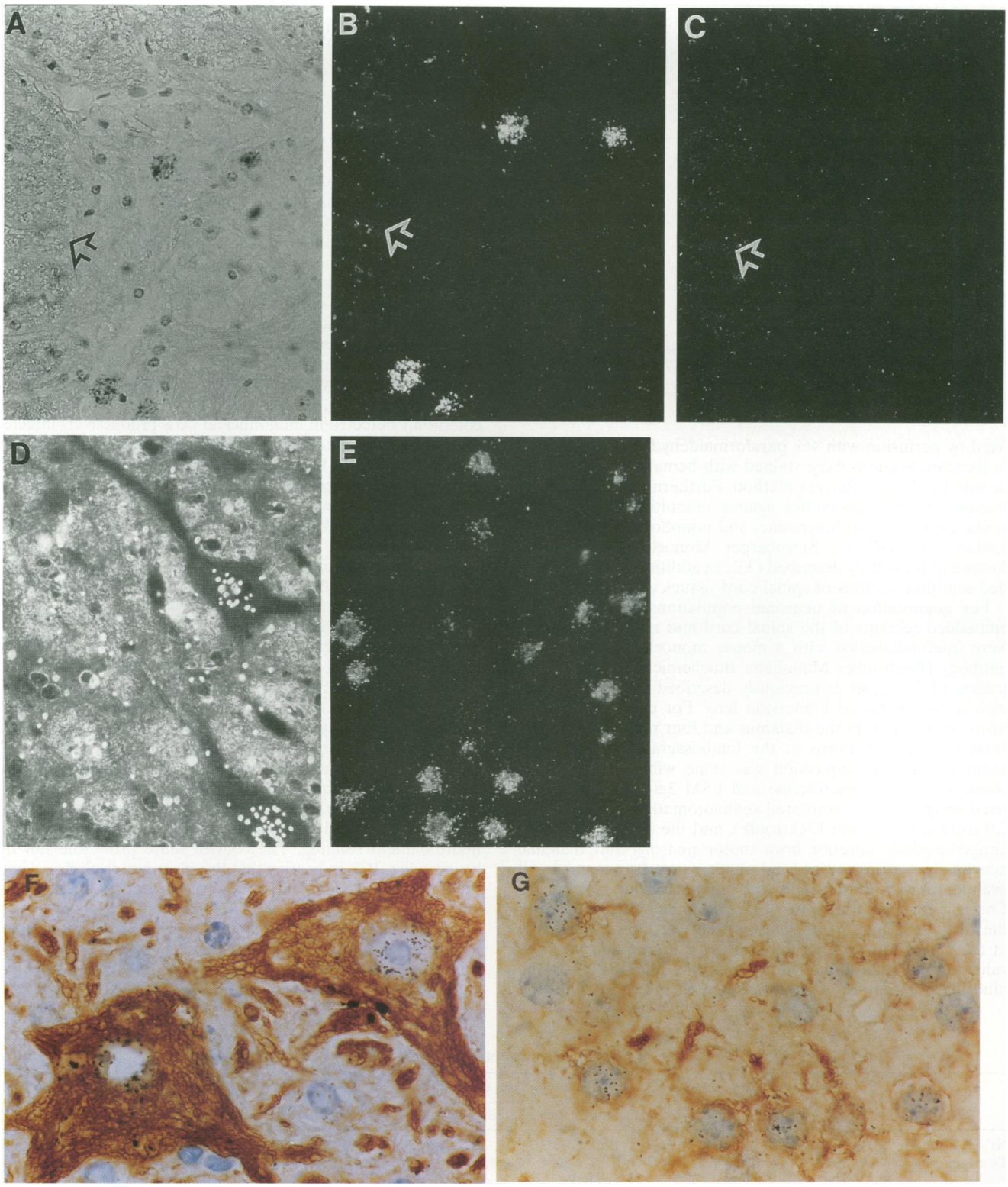

FIG. 3. Regional distribution of neurons expressing the HIV transgene. HIV RNA was detected in large motor neurons in the anterior horn of the spinal cord with the antisense probe (A, D, and F, bright field; B, dark field) but not with the sense probe (C, dark field). The arrows indicate the junction between white and gray matter. HIV RNA was also detected in the anterior thalamic neurons (E, dark field; G, bright field). Cells containing silver grains in the spinal cord and the thalamus were identified as neurons by morphology or immunohistochemistry (F and G) with an antibody to neurofilaments. Original magnification, ×250 (A, B, C, and E); ×400 (D); ×1,000 (F and G).

TABLE 1. Expression of viral protein

Group	Tissue	No. of animals examined	Age (mo)	Cncn of viral antigen in tissue (pg/mg; mean ± SD)
NF-HIV 29	Thalamus	6	7	1.42 ± 0.83
	Thalamus	4	4	1.69 ± 1.22
	Spinal cord	4	7	2.84 ± 0.55
	Spinal cord	4	4	2.57 ± 0.57
NF-HIV 6202	Thalamus	5	7	1.48 ± 0.83
	Thalamus	4	4	1.68 ± 0.87
	Spinal cord	4	7	2.70 ± 0.40
	Spinal cord	4	4	2.39 ± 1.11
NF-HIV 6207[a]	Thalamus	3	6	<0.2
	Spinal cord	3	6	<0.2
Transgene-negative control	Thalamus	4	6	<0.2
	Spinal cord	4	6	<0.2
Positive control[b]	Mammary gland	6		>800

[a] Transgenic mice with no RNA expression in the CNS.
[b] MMTV/HIV transgenic mice (20).

fixed by perfusion with 4% paraformaldehyde and embedded in paraffin. Sections were stained with hematoxylin and eosin or with the Klüver-Barrera method. Furthermore, immunohistochemistry with antibodies against ubiquitin, glial fibrillary acidic protein, phosphotyrosine, and nonphosphorylated neurofilaments (SMI 32; Sternberger Monoclonals) was performed as previously described (33). In addition, Epon-embedded semithin sections of spinal cord tissues were assessed.

For quantitation of neuronal populations, 7-μm paraffin-embedded sections of the spinal cord and anterior thalamus were immunolabelled with a mouse monoclonal anti-Map-2 antibody (Boehringer Mannheim Biochemicals) at a concentration of 20 μg/ml as previously described (42) and viewed with a 40× Zeiss oil immersion lens. For each animal, two microscopic fields in the thalamus and four microscopic fields from the anterior horns in the lumbosacral segments were examined. Image acquisition was done with a Zeiss laser-scanning confocal microscope and LSM 3.54 software. Digitized images were quantitated semiautomatically using IBAS 2.0 software (Kontron Elektronik), and the density of Map-2 antigen-positive anterior horn motor neurons and thalamic neurons was expressed as total number of cells per mm^2. All evaluations were done blindly with regard to group assignment. Comparison with transgene-negative animals was made with the *t* test, the Mann-Whitney test, or the Welch test. The ability of the method to detect differences in neuronal densities was validated by quantitating motor neurons in mice exhibiting hind limb paralysis after experimental infection with the neurotropic Cas-Br-E MuLV, which causes motor neuron death (33): neuronal densities were reduced by 50% in two Cas-Br-E MuLV-infected animals compared with two age-matched uninfected controls.

RESULTS

Construction of transgenic mice. Six founders were obtained. Restriction endonuclease analysis revealed the transgene to be intact and integrated at a unique site in all founders, except for one which showed a truncated transgene (data not shown). Founders NF-HIV 29, 5888, 6202, and 6207 transmitted the transgene to their progeny in an apparently Mendelian fashion and have been bred through several generations by mating with C3H mice. Mice from these founder lines and from founder 38 were analyzed for gene expression and phenotypic manifestations.

Expression of transgenic RNA. Transgene expression was examined by Northern blot analysis and in situ hybridization. Northern blot analysis was performed with total RNA from various organs (Fig. 2). The three main species of HIV RNA commonly detected in mononuclear cells productively infected with HIV were detected in brain and spinal cord tissues of mice from founder lines 29 and 6202, indicating expression of appropriately spliced RNA species. Viral RNA was also detected in thymus and spleen tissues of these mice but not in peripheral nerve, kidney, liver, and salivary gland tissues. Transcription from the NF-L promoter outside the nervous system has also been observed in other transgenic mice (21). No expression was detected in brain and spinal cord tissues of mice from founder lines 5888 and 6207.

In situ hybridization with a ^{35}S-labelled antisense HIV *gag* probe revealed high levels of viral RNA in anterior thalamic (Fig. 3E) and spinal and brain stem motor neurons (Fig. 3A, B, and D) in founder 38 and in mice from founder lines 29 and 6202. The identity of cells containing silver grains was confirmed by in situ hybridization combined with immunohistochemistry using a neurofilament antibody (Fig. 3F and G). Silver grains were absent from glial cells not stained by the neurofilament antibody and from white matter tracts. Silver grains were present in ~80% of anterior thalamic neurons and ~50% of spinal and brain stem motor neurons as identified by neurofilament staining. The control sense probe did not hybridize (Fig. 3C), indicating that the silver grains observed with the antisense probe resulted from the detection of viral RNA and not viral DNA. No viral RNA was detected by in situ hybridization in dorsal root ganglia, peripheral nerve, striated muscle, liver, kidney, spleen, or thymus tissue. No expression was detected in mice from founder lines 5888 and 6207.

Expression of viral proteins. HIV antigens were detected in

TABLE 2. Neurobehavioral examination

Group	No. of animals examined	T maze (squares crossed)		Hole box (squares crossed)	Horizontal suspension test	
		First 2 min	Second 2 min		No. of falls[a]	Time spent (s)[b]
NF-HIV 29	12	112.9 ± 64.7	78.6 ± 34.5	198 ± 91.5	7.25 ± 6.2	672 ± 225.5
Transgene-negative control	9	161.5 ± 51.4	134.1 ± 38.2	256 ± 40.4	1.8 ± 1.5	865 ± 35.3
P value		<0.05	<0.01	<0.05	<0.01	<0.05
NF-HIV 6202	13	78.5 ± 20.8	80.2 ± 22.9	ND[c]	8.6 ± 3.7	613 ± 160.6
Transgene-negative control	11	153.7 ± 35.7	155.5 ± 13.0	ND	1.6 ± 1.5	872 ± 30.8
P value		<0.001	<0.001		<0.01	<0.01

[a] Maximum number of falls was 15 (one per trial in 15 trials).
[b] Maximum time spent on bar was 900 s (60 s in 15 trials).
[c] ND, not done.

TABLE 3. Electrophysiological examination of sciatic nerves

Group	No. of animals examined	Avg age (mo)	CMAP (mV, mean ± SD)	*P* value
NF-HIV 29	11	9.8	6.48 ± 2.2	0.009
NF-HIV 6202	13	7.4	7.2 ± 1.5	0.04
Transgene-negative control	11	7.26	9.8 ± 2.2	
Positive control[a]	6	9	4.0 (2.6–4.8)	

[a] Mice infected with the neurotropic Cas-Br-E MuLV and exhibiting hind limb paralysis (33).

TABLE 4. Neuropathology of sciatic nerve

Group	Age (mo)	No. of animals	No. of abnormal nerves/no. of nerves examined	No. of abnormal nerves showing different degrees of pathological changes			
				Mild	Mild/moderate	Moderate	Severe
NF-HIV 29	4	10	0/20				
	7–12	12	14/23	7	3	3	1
NF-HIV 6202	4	10	0/20				
	7–12	11	13/22	4	3	6	
NF-HIV 6207[a]	7–12	7	0/13				
MMTV/HIV[a]	7	5	0/10				
Transgene-negative control	7	11	0/21				

[a] Transgenic mice with no expression in the CNS.

thalamic and spinal cord extracts from mice of founder lines 6202 and 29 at a concentration of ~1.5 and 2.5 pg/mg, respectively (Table 1). Protein levels were similar in animals aged 4 months and 7 months. Viral protein was not detectable in the serum. No viral proteins could be detected by Western blot or immunohistochemistry with monoclonal or polyclonal antibodies to gp120, gp160, p24, or p17, presumably because of the lack of sensitivity of these techniques.

Neurobehavioral examination. No differences in longevity, appearance, or size were found among transgenic mice from founders 29 and 6202 and transgene-negative littermates kept in the same cage. However, the evaluation of motor strength and motor activity with more sensitive neurobehavioral tests revealed significant group differences (Table 2). During examination on the narrow suspension bar, transgenic animals from founder line 29 fell more often and more quickly than controls. They also showed less spontaneous activity in the T maze and the wooden box. No group differences were found in the water maze and the test of active avoidance of noxious stimuli (data not shown), suggesting that the motor weakness and hypoactivity were deficits specific to the task and not indicative of a generalized neurological dysfunction. Examinations with the T maze and the suspension bar of mice from founder line 6202 revealed similar deficits.

Electrophysiological examination. In order to corroborate the clinical finding of weakness, mice were examined electrophysiologically. Compared with negative controls, transgenic animals of founder lines 29 and 6202 showed a 30% reduction in the amplitude of the negative phase of the CMAP, consistent with a reduction in the number of functioning motor axons and indicating an impairment of nerve conduction (Table 3).

Pathological examination. To confirm the neurobehavioral and electrophysiological data, brain, spinal cord, and sciatic nerve tissues were examined histologically and immunohistochemically. Abnormalities were found in nerves of ~50% of all transgenic animals from founder lines 29 and 6202 (Table 4). In semithin sections, abnormal nerves showed a mild to moderate reduction in nerve fiber density and evidence of axonal degeneration (Fig. 4A and C). Fibers with thin myelin sheaths relative to axon caliber occurred in increased numbers. Some of these fibers were surrounded by circumferentially directed Schwann cell processes. Findings were identical or similar in both sciatic nerves from individual animals. The finding of axonal degeneration was confirmed by electron microscopy (Fig. 4D) and by teased fiber analysis (Fig. 4E and F). These abnormalities were seen in 7- to 12-month-old animals but not in younger (4-month-old) animals. Nerves from transgene-negative controls (Fig. 4B and G), from mice of the nonexpressor founder line 6207, and from MMTV/HIV transgenic mice (expressing HIV proteins in several organs but not the brain [20]) were normal (Table 4).

There was no evidence of inflammatory infiltrates, gliosis, vacuolation, or myelin abnormalities in brain or spinal cord tissue of any of the transgenic or control animals as assessed by semithin sections, the hematoxylin and eosin stain, and the Klüver-Barrera method. No differences between transgenic and control animals were detected in brain and spinal cord tissues by immunohistochemistry with antibodies to glial fibrillary acidic protein, neurofilaments, tyrosine-phosphorylated proteins, or ubiquitin (data not shown). Dorsal root ganglia were normal. There were no statistically significant differences between transgenic and control animals in the densities of spinal motor neurons and thalamic neurons (Table 5). Sections from spleen, kidney, liver, striated muscle, salivary gland, and thymus tissues from five animals from founder lines 29 and 6202 were normal, with the exception of one thymus specimen which showed evidence of a thymoma (data not shown).

DISCUSSION

Our findings in NF-L-HIV transgenic mice indicate that expression of the HIV genome in neurons is capable of triggering degenerative changes in the nervous system. As the findings were very similar in mice from two founder lines, it is likely that high expression of the transgene in the CNS, and not insertional mutagenesis, was responsible for the phenotype. The absence of pathological changes in the sciatic nerves of young animals suggests that the deleterious effect of the transgene does not occur during developmental stages. Pathological changes were observed in ~50% of the animals. Similar moderate penetrance has also been reported for other transgenic mice exhibiting a neurodegenerative phenotype (22, 23, 45). This phenotypic variation may be due to differences in the genetic background of the mice. The NF-L-HIV transgenic mice originated from (C57BL/6 × C3H)F_2 founders that were subsequently mated to C3H mice. A gene(s) potentially conveying resistance to the effects of the transgene may still be segregating in these mice. Alternatively, the moderate penetrance of the observed phenotype may result from the low level of expression of the transgene, which may be at a threshold level. The difficulty in detecting HIV proteins in these mice suggests that small amounts are sufficient to cause the neurological syndrome. Similarly, in other transgenic systems low-level or undetectable transgene expression was also sufficient to cause a biological effect (2, 23, 32, 44). The level of Gag protein expression in the CNS of the NF-L-HIV transgenic mice was within an order of magnitude of the concentration found in the brains of patients with AIDS (1). As the transgenic mice express all three species of HIV RNA in the

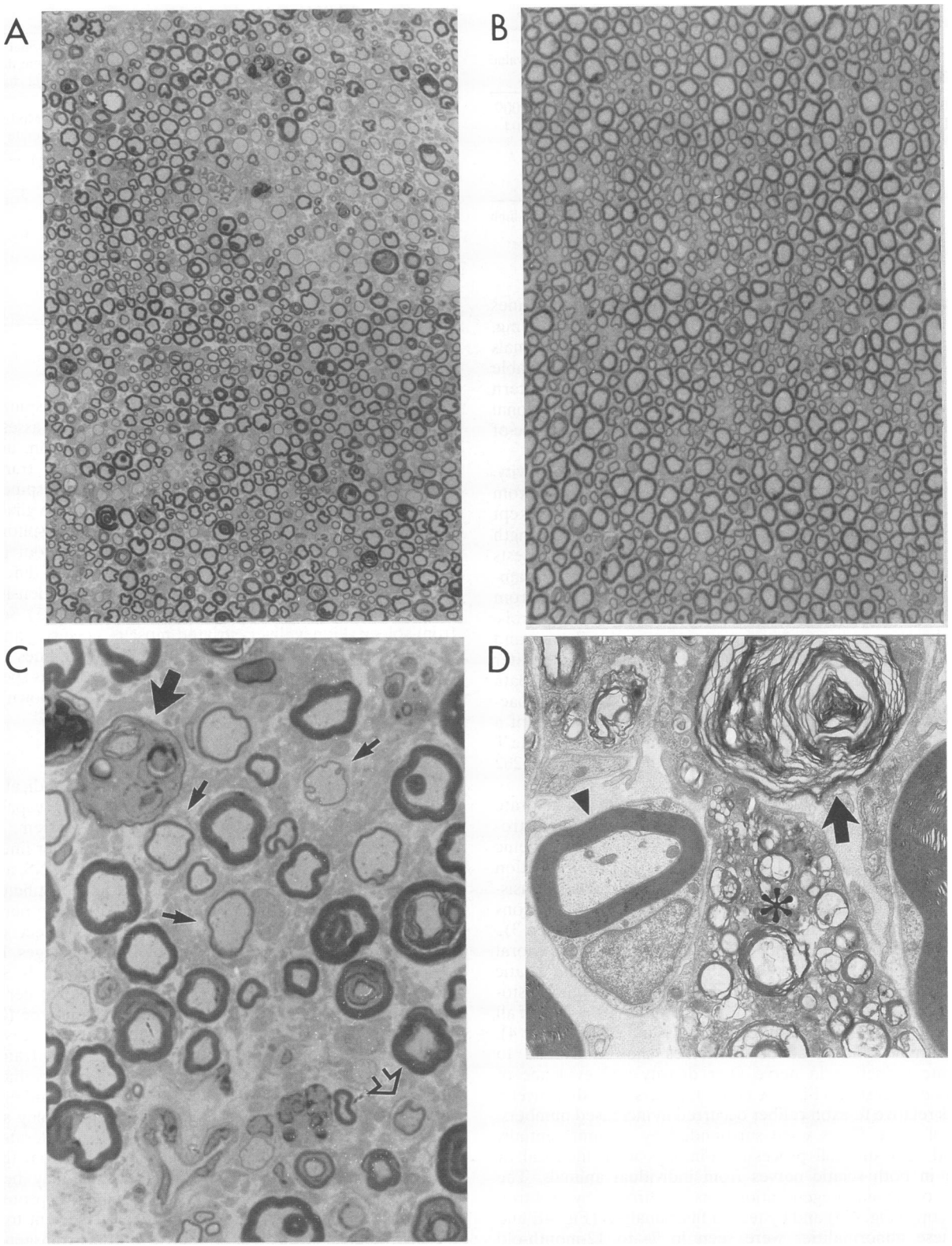

FIG. 4. Sciatic nerve from an NF-L-HIV transgenic mouse of line 29 (A, C, and D) and a nontransgenic littermate control (B). Note the reduction in myelinated fiber density in panel A. Panel C shows degenerating fibers (large arrow), thinly myelinated fibers (small arrows), and a circumferentially directed Schwann cell process (open arrow). The electron micrograph (D) shows a degenerating nerve fiber (large arrow), a phagocyte containing cellular debris (asterisk), and a normal myelinated fiber (arrowhead). In the teased fiber preparations (E to G), two fibers undergoing axonal degeneration (E and F) (arrowheads on myelin ovoids) are contrasted with a normal large myelinated fiber (G). Magnification, ×250 (A and B); ×1,000 (C); ×2,650 (D); ×300 (E, F, and G).

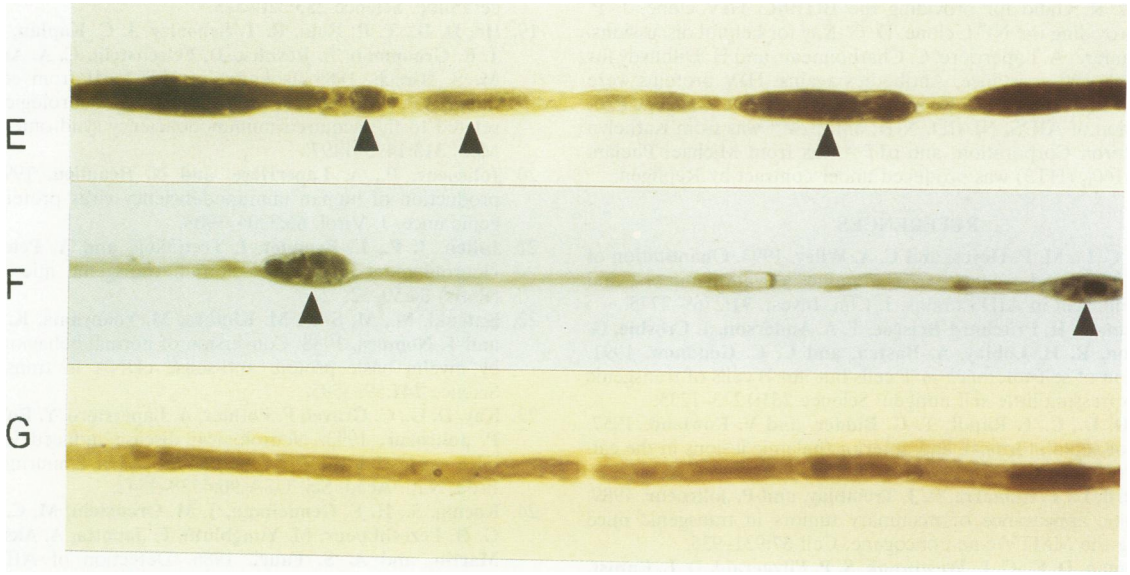

FIG. 4—*Continued.*

CNS, no conclusions can be drawn regarding the gene(s) responsible for the disease. Neurotoxic in vitro and in vivo effects on the CNS have been reported for gp120 (5, 9, 15), Rev (28), Tat (36), and Nef (46); these (including Nef, which is truncated in HIV clone BH10R3 (35)) are therefore candidates for the observed effects. Studies of transgenic mice expressing individual HIV-1 genes should help to elucidate the pathogenic mechanisms further.

In these transgenic mice, HIV was expressed in neurons, which may be directly affected by the viral gene products. In human tissue, neurons are only rarely found to be infected by HIV (41, 47). However, as recent reports indicate that HIV can infect neuronal cell lines (18) and nondividing macrophages (27), postmitotic neurons might also be infected and only express the viral genome at low levels, undetectable by previously used methods. The expression of HIV proteins in neurons might itself affect neuronal function and survival. Alternatively, HIV transgene products might be released from neurons and induce surrounding cells to secrete neurotoxins or to reduce neurotrophin production. It has been suggested that HIV-associated neurological disease in humans results, perhaps indirectly, from the release of factors from HIV-infected microglia or macrophages (12, 14), the cell type most frequently infected in the CNS. Interestingly, NF-L-HIV transgenic mice may be relevant for both models of pathogenesis. A similar mode of disease causation was recently suggested by the detection of neuronal and glial cell pathology in transgenic mice expressing HIV-1 gp120 in astrocytes (44).

TABLE 5. Quantitation of anterior thalamic and spinal motor neurons

Group	Thalamus		Spinal cord	
	No. of animals examined	Neurons/mm^2 (mean ± SD)	No. of animals examined	Neurons/mm^2 (mean ± SD)
NF-HIV 29	6	632.8 ± 217.85	6	207.2 ± 40.48
P value		>0.5		>0.5
NF-HIV 6202	6	567.3 ± 226.78	7	195.6 ± 61.85
P value		>0.5		>0.5
Transgene-negative control	4	618.5 ± 74.02	7	229.2 ± 27.77

Certain parallels between the findings in NF-L-HIV transgenic mice and in human CNS and PNS syndromes associated with AIDS are apparent. Whereas the pathological correlate of the hypoactivity in these mice cannot be established in the absence of detectable morphological changes, it is of interest that it resembles the psychomotor slowing and apathy seen in the early stages of AIDS dementia, which has been described as subcortical dementia (31). While autopsy studies in such cases often show abnormalities in the basal ganglia and thalamus and in the white matter (8, 30), the fact that findings may be mild or minimal, even in the presence of severe clinical findings, has led some to suggest that metabolic disturbances without morphological alterations may contribute to AIDS dementia (30). One could speculate that similar mechanisms might be operative in NF-L-HIV transgenic mice, whose hypoactivity may have been caused by the high level of transgene expression in the thalamus. It is of interest that anterior thalamic lesions in cats and rats also cause hypoactivity (3, 17, 29, 37, 38).

The degenerative changes observed in the sciatic nerves in the NF-L-HIV transgenic mice resemble the pathological findings in the distal sensorimotor polyneuropathy which occurs in about half of all patients with AIDS and is a cause of considerable morbidity (39). In transgenic mice, the neuropathy appears to be the consequence of the high level of expression of the transgene in the cell body of spinal motor neurons, where it may lead to disordered metabolism and impaired trophic support for the axons leading to anterograde degeneration (10).

Our results suggest that NF-L-HIV transgenic mice may further our understanding of the pathogenesis of HIV-1-associated neurological disorders and allow the evaluation of novel therapeutic agents.

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