



## Guest Editorial

# FIV and neuroAIDS

Howard S Fox<sup>1</sup> and Tom R Phillips<sup>2</sup>

<sup>1</sup>Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California, USA; and <sup>2</sup>Vaccine Research Institute of San Diego, San Diego, California, USA

The feline immunodeficiency virus (FIV) is a lentivirus related to the human immunodeficiency virus (HIV-1). Although clearly evolutionarily divergent at the genetic level, similarities between HIV and FIV are present at structural, molecular, and biochemical levels of the virus. FIV infection of cats shares many clinical features with HIV-1 infection of humans, including a chronic course of infection, the development of immunodeficiency, and occurrence of peripheral and central nervous system (CNS) abnormalities.

Examination of brain-derived cells *in vitro* has revealed that FIV predominantly infects microglia/macrophages and astrocytes. *In vivo*, it appears that both cells of the macrophage lineage and astrocytes are infected (Poli *et al*, 1999; Hein *et al*, 2001) but detailed studies, such as those in simian immunodeficiency virus (SIV)-infected monkeys revealing predominate infection of perivascular macrophages in the brain (Williams *et al*, 2001) and the studies of astrocytes in pediatric AIDS encephalopathy revealing restricted HIV-1 infection of astrocytes (Saito *et al*, 1994), are lacking. Both astrogliosis (Hurtrel *et al*, 1992) and microglia activation (Podell *et al*, 1997) are present in the brains of infected cats, but multinucleate giant cells, found in the encephalitis induced by SIV in monkeys and HIV-1 in humans, are only rarely found in FIV-infected cats.

FIV has an expanded lymphocyte cellular tropism relative to HIV and SIV, infecting CD8+ as well as CD4+ T cells, and B cells. FIV does not use the CD4 molecule as a receptor, but interestingly at least some FIV strains and clones can use the chemokine receptor CXCR4 for cell entry (Poeschla and Looney, 1998; Richardson *et al*, 1999; Frey *et al*, 2001). CXCR4 has been shown to be the primary receptor for astrocyte infection with the CrFK strain of FIV (Nakagaki *et al*, 2001). In contrast to HIV, where CCR5-utilizing (R5) strains are commonly found in brain, no use of CCR5

has been demonstrated for FIV. However interest in CXCR4-utilizing (X4) HIV-1 strains in the neurological complications of AIDS has grown recently with the demonstration of the CXCR4 molecule on neurons (Lavi *et al*, 1997), and that X4 viruses or envelope proteins can induce neuronal apoptosis (Hesseltger *et al*, 1998; Kaul and Lipton, 1999; Ohagen *et al*, 1999; Zheng *et al*, 1999). The ability of FIV to use CXCR4 is a distinction from the SIV system, in which only rare viruses can utilize CXCR4.

Given the inaccessibility of the brain for invasive study in humans, the SIV/monkey and FIV/cat systems have a great utility for neuroAIDS studies. Although the primate virus and host in SIV/monkey more closely resemble that of humans, the cost, housing, and safety issues make the FIV/cat model ideal for many studies. This especially applies to ones in which large numbers of animals are required.

The three studies reported in the current issue of the *Journal of Neurovirology* add to our knowledge about the brain in FIV infection and illustrate ways in which the FIV/cat system can be used to address important questions in HIV pathogenesis. Two of the reports concern the role of the choroid plexus in brain infection and neurotoxicity. HIV is found in the choroid plexus, and it has been proposed that the choroid plexus may be a site in which blood-borne virus can access the CNS (Chen *et al*, 2000). In the first report (Bragg *et al*, 2002) inoculation of cultured choroid plexus macrophages with FIV was found to induce macrophage proliferation. Interestingly, separate experiments in which a trimer of CD40 ligand (CD40L) was added to the cultures, mimicking one form of T cell-macrophage interaction, led to robust proliferation of the macrophages. Although not studied here, such treatment has recently been found to stimulate the replication of X4 strains of HIV-1 in macrophages (Bakri *et al*, 2002). Examination of early changes in the brain following infection revealed a decrease of cortical N-acetylaspartyl glutamate (NAA) content, thought to represent neuronal loss, as early as 6 weeks postinoculation. Although virus in the brain was not examined, a population of macrophages

---

Address correspondence to Howard Fox, Department of Neuropharmacology, TSRI, 10550 North Torrey Pines Road, CVN8, La Jolla, CA 92037, USA. E-mail: hsfox@scripps.edu

Received 5 March 2002; accepted 8 March 2002.

identified by the MAC387 antibody, recognizing the MRP14 protein implicated in monocyte entry into tissues and present in newly immigrated inflammatory macrophages, was studied in the CNS. A marked increase in immunoreactivity was found in animals with feline AIDS. This was most pronounced in the perivascular region, revealing parallels to studies with HIV and SIV, in which increased numbers of monocytic cells are found in the brain.

The second report (Bragg *et al*, 2002) found that inoculation of choroid plexus macrophage indeed led to infection, based on the finding of proviral DNA and production of low, but detectable amounts, of FIV gag antigen. Addition of a cat CD4+ T cell line to the cultures resulted in recovery of appreciable amounts of virus. This is similar to recent findings on viral recovery from microglia isolated from FIV-infected cats, in which coculture with activated PBMC was found to greatly increase cell-free viral yields (Hein *et al*, 2001). These two studies on choroid plexus macrophages point to a mechanism by which these cells can act as a reservoir for virus, as well as increase its transmission into the brain. Signals provided by trafficking cells, such as T cells, may greatly increase viral replication in the choroid plexus, leading to increased virus, perhaps of neuropathogenic subtypes, in the CNS. *In vivo* studies can now address such hypotheses in the cat/FIV system.

A third report (Gavrillin *et al*, 2002) addresses methamphetamine's effects on FIV replication in primary feline astrocytes and a feline astrocyte cell line, G-355-5. The FIV-Maryland strain was used in this report. Contrary to previously reports for FIV-34TF10 (Phillips *et al*, 1990) and FIV-PPR (Billaud and Phillips, 1998; Billaud *et al*, 2000), cell-free virus infection of astrocytes did not occur with FIV-Maryland strain. However, cell-free virus recovered from the infected astrocyte cultures was then able to infect both cell types. The recovered virus was demonstrated to contain four amino acid changes that localized to the Env region of the virus, furthering earlier studies revealing the Env-dependence of viral replication in astrocytes (Billaud *et al*, 2000). As with the CrFK strain, the CXCR4 receptor was found to be required

for FIV-Maryland astrocyte infection. In addition to methamphetamine increasing FIV replication in the astrocyte cell line G-355-5 (Phillips *et al*, 2000), the present study found similar effects in primary astrocyte cultures. Additionally, it was demonstrated that the methamphetamine effect was limited to only the cell-associated infection and did not occur in PBMC cultures.

However a limitation of any *in vitro* study is that the results may not reflect the *in vivo* condition. For example, it was shown that the application of opiates to a cell culture system enhanced FIV replication (Billaud and Phillips, 1998). Yet, when the effects of opiates were later examined in FIV-infected cats, the *in vitro* results did not predict the *in vivo* findings, in that disease progression was significantly delayed and a trend toward decreased virus load was demonstrated (Barr *et al*, 2000). Thus, with any *in vitro* experimentation, extrapolation into the whole animal system and the human condition must be cautious, for *in vitro* systems can not effectively reproduce the complexities of an intact animal. This is one of the main advantages of FIV/cat model, in that results obtained *in vitro* can be examined for their *in vivo* relevance.

The precise interaction of methamphetamine with HIV is not known. Methamphetamine use is often greatest in those individuals that have a higher risk of acquiring HIV-1. Therefore, in certain populations, there is a convergence of methamphetamine and HIV-1; yet our understanding of the potential effects that simultaneous exposure to these two agents might have on disease progression is extremely limited. The CNS abnormalities induced by HIV may synergize with those caused by methamphetamine and other drugs of abuse (Nath *et al*, 2001). Determining if methamphetamine can act as a cofactor in AIDS is both important and timely, as numerous individuals may be unknowingly altering the course of their disease. To thoroughly understand methamphetamine's effects on lentivirus disease progression, an animal model, such as FIV, that is both clinically relevant and easily manipulated is essential.

## References

- Bakri Y, Mannioui A, Ylisastigui L, Sanchez F, Gluckman JC, Benjouad A (2002). CD40-activated macrophages become highly susceptible to X4 strains of human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses* **18**: 103–113.
- Barr MC, Billaud JN, Selway DR, Huitron-Resendiz S, Osborn KG, Henriksen SJ, Phillips TR (2000). Effects of multiple acute morphine exposures on feline immunodeficiency virus disease progression. *J Infect Dis* **182**: 725–732.
- Billaud JN, Phillips TR (1998). FIV. A lentivirus model for opiate effects on disease. *Adv Exp Med Biol* **437**: 101–116.
- Billaud JN, Selway D, Yu N, Phillips TR (2000). Replication rate of feline immunodeficiency virus in astrocytes is envelope dependent: implications for glutamate uptake. *Virology* **266**: 180–188.
- Bragg DC, Childers TA, Tompkins MB, Tompkins WA, Meeker RB (2002). Infection of the choroid plexus by feline immunodeficiency virus. *J NeuroVirol* **8**: 213–226.
- Bragg DC, Hudson LC, Liang YH, Tompkins MB, Fernandes, Meeker RB (2002). Choroid plexus macrophages proliferate and release toxic factors in response to feline immunodeficiency virus. *J NeuroVirol* **8**: 227–241.

- Chen H, Wood C, Petit CK (2000). Comparisons of HIV-1 viral sequences in brain, choroid plexus and spleen: potential role of choroid plexus in the pathogenesis of HIV encephalitis. *J NeuroVirol* **6**: 498–506.
- Frey SC, Hoover EA, Mullins JI (2001). Feline immunodeficiency virus cell entry. *J Virol* **75**: 5433–5440.
- Gavrilin MA, Mathes LE, Podell M (2002). Methamphetamine enhances cell-associated feline immunodeficiency virus replication in astrocytes. *J NeuroVirol* **8**: 242–251.
- Hein A, Martin JP, Dorries R (2001). *In vitro* activation of feline immunodeficiency virus in ramified microglial cells from asymptotically infected cats. *J Virol* **75**: 8090–8095.
- Hesselgesser J, Taub D, Baskar P, Greenberg M, Hoxie J, Kolson DL, Horuk R (1998). Neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 alpha is mediated by the chemokine receptor CXCR4. *Curr Biol* **8**: 595–598.
- Hurtrel M, Ganiere JP, Guelfi JF, Chakrabarti L, Maire MA, Gray F, Montagnier L, Hurtrel B (1992). Comparison of early and late feline immunodeficiency virus encephalopathies. *AIDS* **6**: 399–406.
- Kaul M, Lipton SA (1999). Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. *Proc Natl Acad Sci USA* **96**: 8212–8216.
- Lavi E, Strizki JM, Ulrich AM, Zhang W, Fu L, Wang Q, O'Connor M, Hoxie JA, Gonzalez-Scarano F (1997). CXCR-4 (Fusin), a co-receptor for the type 1 human immunodeficiency virus (HIV-1), is expressed in the human brain in a variety of cell types, including microglia and neurons. *Am J Pathol* **151**: 1035–1042.
- Nakagaki K, Takahashi K, Schols D, De Clercq E, Tabira T (2001). CXCR4 is the primary receptor for feline immunodeficiency virus in astrocytes. *J NeuroVirol* **7**: 487–492.
- Nath A, Maragos WF, Avison MJ, Schmitt FA, Berger JR (2001). Acceleration of HIV dementia with methamphetamine and cocaine. *J NeuroVirol* **7**: 66–71.
- Ohagen A, Ghosh S, He J, Huang K, Chen Y, Yuan M, Osathanondh R, Gartner S, Shi B, Shaw G, Gabuzda D (1999). Apoptosis induced by infection of primary brain cultures with diverse human immunodeficiency virus type 1 isolates: evidence for a role of the envelope. *J Virol* **73**: 897–906.
- Phillips TR, Billaud JN, Henriksen SJ (2000). Methamphetamine and HIV-1: potential interactions and the use of the FIV/cat model. *J Psychopharmacol* **14**: 244–250.
- Phillips TR, Talbott RL, Lamont C, Muir S, Lovelace K, Elder JH (1990). Comparison of two host cell range variants of feline immunodeficiency virus. *J Virol* **64**: 4605–4613.
- Podell M, Hayes K, Oglesbee M, Mathes L (1997). Progressive encephalopathy associated with CD4/CD8 inversion in adult FIV-infected cats. *J Acquir Immune Defic Syndr Hum Retrovirol* **15**: 332–340.
- Poeschla EM, Looney DJ (1998). CXCR4 is required by a nonprimate lentivirus: heterologous expression of feline immunodeficiency virus in human, rodent, and feline cells. *J Virol* **72**: 6858–6866.
- Poli A, Pistello M, Carli MA, Abramo F, Mancuso G, Nicoletti E, Bendinelli M (1999). Tumor necrosis factor-alpha and virus expression in the central nervous system of cats infected with feline immunodeficiency virus. *J NeuroVirol* **5**: 465–473.
- Richardson J, Pancino G, Merat R, Leste-Lasserre T, Moraillon A, Schneider-Mergener J, Alizon M, Sonigo P, Heveker N (1999). Shared usage of the chemokine receptor CXCR4 by primary and laboratory-adapted strains of feline immunodeficiency virus. *J Virol* **73**: 3661–3671.
- Saito Y, Sharer LR, Epstein LG, Michaels J, Mintz M, Louder M, Golding K, Cvetkovich TA, Blumberg BM (1994). Overexpression of nef as a marker for restricted HIV-1 infection of astrocytes in postmortem pediatric central nervous tissues. *Neurology* **44**: 474–481.
- Williams KC, Corey S, Westmoreland SV, Pauley D, Knight H, deBakker C, Alvarez X, Lackner AA (2001). Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques. Implications for the neuropathogenesis of aids. *J Exp Med* **193**: 905–916.
- Zheng J, Ghorpade A, Niemann D, Cotter RL, Thylin MR, Epstein L, Swartz JM, Shepard RB, Liu X, Nukuna A, Gendelman HE (1999). Lymphotropic virions affect chemokine receptor-mediated neural signaling and apoptosis: implications for human immunodeficiency virus type 1-associated dementia. *J Virol* **73**: 8256–8267.