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Guest editorial

Quinolinic acid and neurodegeneration in AIDS

AIDS is associated with a variety of focal neurologic diseases caused by opportunistic infections in addition to a global dementing disease termed HIV associated dementia complex (ADC) (Anonymous, 1991). How HIV infection leads to ADC remains a hotly debated issue. HIV can be recovered from the cerebrospinal fluid soon after infection (Carne *et al*, 1985; Ho *et al*, 1985), however, HIV infection of the central nervous system (CNS) parenchyma appears to be a late manifestation, seen only after significant immune compromise. Some investigators have concluded that ADC can appear in the absence of HIV encephalitis (Glass *et al*, 1993), while others found a tighter association between the clinical and pathologic entities (Wiley *et al*, 1994). Even if one accepts a close link between HIV encephalitis and CNS damage (and thus the clinical syndrome ADC), the pathogenesis remains an enigma. In classical viral encephalitides (eg herpes simplex encephalitis) clinical symptomatology and CNS damage are readily explained by abundant neuroglial infection and lysis. While some have claimed significant HIV infection of neuronal elements (Nuovo *et al*, 1994; Saito *et al*, 1994), the majority of evidence would suggest that CNS damage in HIV encephalitis somehow results from macrophage/microglia infection (Budka *et al*, 1991). Theories abound regarding how CNS damage results from this macrophage infection.

In this issue of the *Journal of NeuroVirology*, two articles address the potential role of quinolinic acid in mediating CNS damage associated with HIV encephalitis. Past work has clearly shown a strong association between inflammatory CNS disease and neurotoxic concentrations of quinolinic acid (Heyes *et al*, 1992). While quinolinic acid can be produced by a variety of cell types, its tight association with inflammatory diseases rather than non-inflammatory neurodegenerative disease, suggests that something associated with the inflammatory response triggers quinolinic acid production. This is well documented in poliomyelitis where there are markedly elevated levels in CNS tissue (Heyes *et al*, 1992). Whether quinolinic acid augments neuronal damage above that mediated by lytic polio infection is unknown.

The two current papers take different tacks to examine the association of HIV and quinolinic acid related to neuronal damage. In the first paper (Brew *et al*, 1995), Brew *et al* show that macrophage production of quinolinic acid is strongly dependent upon the extent of HIV infection. This association is even more striking since it was found 24–60 h after infection which precedes substantial viral production by at least a week, and was found with a low multiplicity of infection when few macrophages were infected. The investigators next examined the relationship between HIV strains isolated from subjects with or without ADC and production of quinolinic acid. Given the quasispecies nature of HIV infection and the difficulty predicting what viral strains can be grown from clinical isolates, it is not surprising that there was not significant association between dementia status of the subject and infectability of macrophages. This does not diminish the importance of macrophage tropic strains in mediating neurologic disease, but rather reflects the difficulty of culturing macrophage tropic virus from clinical specimens.

In the second paper by Kerr *et al* (Kerr *et al*, 1995), neurotoxicity of quinolinic acid is assessed in second trimester human embryonic brain cultures. Previously quinolinic acid toxicity has been demonstrated for a variety of non-human CNS cultures. The current study employs the rather insensitive lactate dehydrogenase (LDH) release assay of cytotoxicity in mixed human CNS cultures containing serum. The investigators found significant LDH release after exposure to 5–10 mM quinolinic acid. Comparable concentrations have been observed *in vivo* and may mediate neuronal death or may mediate more subtle perturbations of CNS physiology (eg synaptic interactions).

These findings provide additional pieces to a very elaborate puzzle of neuronal damage in HIV encephalitis. Without question we can anticipate quinolinic acid production by HIV infected macrophages during HIV encephalitis. Is it an important mediator of CNS damage or an epiphenomenon? Unfortunately this is still unknown. Whether it is the primary mediator of neuronal damage in HIV encephalitis or produced independently, HIV infection of macrophages clearly produces quinolinic acid, a toxin better left out of the brain.

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