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The effects of illicit drugs on the HIV infected brain

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1. ABSTRACT

Evidence accumulating from clinical observations, neuroimaging and neuropathological studies suggests that illicit drug abuse accentuates the adverse effects of HIV on the central nervous system (CNS). Experimental investigation in cell culture models supports this conclusion. Injecting drug abuse is also a risk factor for the acquisition of HIV infection, the incidence of which continues to rise in intravenous drug users (IVDU) even in countries with access to effective therapy. In order to understand the interactions of drug abuse and HIV infection, it is necessary to examine the effects of each insult in isolation before looking for their combined effects. This review traces progress in understanding the pathogenesis of HIV related CNS disorders before the introduction of effective therapy and compares the state of our knowledge now that effective therapy has significantly modified disease progression. The additional impact of intravenous drug abuse on HIV-associated brain disease, then and now, is also reviewed. Predictions for the future are discussed, based on what is known at present and on recently emerging data.

2. INTRODUCTION

Knowledge regarding the HIV infected brain has progressed considerably since the first years of the AIDS epidemic. HIV is thought to enter the central nervous system (CNS) compartment at or soon after the time of initial HIV infection but whether this happens in all individuals is not known (1, 2). In untreated or partially treated HIV infection, involvement of the brain is revealed symptomatically as cognitive impairment or frank dementia in a significant proportion of individuals with AIDS (3). These individuals frequently show evidence of HIV encephalitis (HIVE) and are found at autopsy to have a high brain viral burden (4). In contrast, infected individuals who have died prior to the onset of AIDS do not display HIVE and their brains show only low or undetectable levels of proviral DNA (5). Whether the virus has been successfully eliminated from the CNS in this latter group, or never entered the brain compartment in the first place, is not known. At the early stages of infection a CD8 lymphocyte response is seen in the brain (6, 7) but later in HIV/AIDS declining numbers of circulating CD8 and CD4 lymphocytes may be a factor in less effective control of

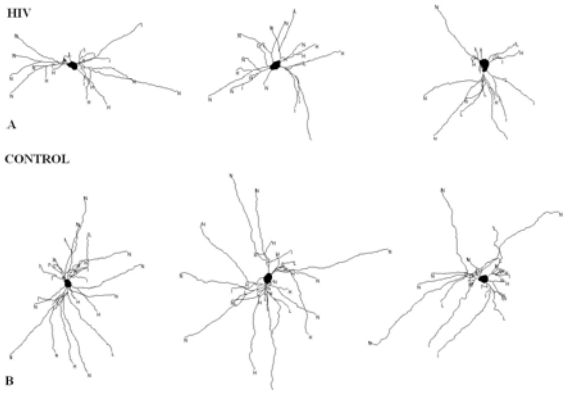

Figure 1 . Tracings of Golgi preparations of basal ganglia neurons from the caudate nucleus of a drug user with HIV encephalitis (1A) compared with similar neurons in an age-matched control subject (1B). A silver nitrate Golgi technique was applied to $5mm^3$ blocks of brain tissue fixed in gluteraldehyde. Vibratome sections were prepared at 100µm, dehydrated, embedded in resin and mounted on slides. The dentritic arbour was traced only for neurons whose cells bodies were located in the middle of the section. Lettering on the dendrites identifies (N) processes traceable right to the end and (H) and (L) processes heading towards the top and bottom of the section. Analysis of 25 dentrites in each of 6 neurons revealed a 38% reduction in the overall length of the dentrites in the HIV subject.

brain infection. There is evidence that once inside the brain compartment, viral populations evolve and become neuroadapted, subsequently interacting with later entrants so that mosaic subspecies emerge in the CNS (8, 9).

The natural history of HIV/AIDS has been significantly modified by the use of highly effective antiretroviral therapy (HAART) that became widespread in 1996. The previous distinctions between the presymptomatic and symptomatic phases of the disease are no longer useful in assessing the progress of the illness and the incidence of severe clinical manifestations of HIV brain infection has fallen. A new definition of the HIV infected brain is required in the present context as compliance with therapy results in sufficient immune competence to withstand the terminal complications of the disease. It is unclear whether HAART protects the brain by restraining progress of the initial infection, or whether, by controlling replication in the periphery and keeping circulating virus at a minimum, it reduces the chance of later viral entrants contributing to re-infection. Most likely HAART acts in both ways.

Person to person spread of HIV occurs through sexual intercourse and exposure to infected blood. Intravenous drug abuse is a major risk factor for acquiring HIV infection since infection may be spread through the sharing of contaminated needles (10). This scenario forms the backdrop for HIV/AIDS in a significant and growing proportion of the infected population worldwide. Illicit drug taking produces both pleasurable and damaging effects on the CNS (11). Evidence is accumulating that drugs of abuse may interact with HIV in a way that promotes or augments the effects of the virus in the brain (12-14). In order to understand this interaction more fully it is necessary to consider separately the damaging effects of each insult in the brain. In addition other factors may further complicate the pathogenesis of HIV related brain damage. These include co-infection with hepatitis C which has come to be viewed recently as potentially neurotropic (15-17). One current and growing concern is that chronic HIV infection, and its associated upregulated neuroinflammatory mechanisms, may predispose to accelerated neuroaging in treated subjects who survive long term (18). There is growing interest in the possible parallels between the effects of chronic HIV infection of the CNS and those of neurodegenerative brain disorders.

3. THE HIV INFECTED BRAIN

3.1. In the absence of therapy

Clinical observation and neuropathological studies of individuals with AIDS suggested quite early in the epidemic that the CNS was a direct target of the virus. The recognition of cognitive disorders and motor symptoms in around 40% of AIDS patients led to the discovery of giant cells in the brain of many affected individuals (4, 19). The appearance of these cells, together with the demonstration of HIV proteins within microglia, gave rise to the new entity of HIV encephalitis (HIVE) as described in a number of US and European centres. Consensus on the definition of HIVE was achieved in 1991 (20), leading to clearer separation of the neuropathological findings directly attributable to HIV from the confounding effects of CNS opportunistic infections. HIVE is accompanied by a variable degree of CNS parenchymal inflammation and damage (21). In addition to giant cells and infected microglial cells, generalised microglial activation and focal microglial nodules may be present. Brain atrophy is usually manifested by ventricular dilatation. This is likely due to neuronal loss and damage (22-24) and a number of studies have documented neuronal and glial apoptosis in HIVE (25, 26). Some neuronal populations may be more vulnerable to HIV than others and selective loss of parvalbumin, calbindin and somatostatin positive neurons has been described in separate studies (27-30). At a more subtle level there is evidence of dendritic (24), synaptic (23) and axonal (31) injury, all of which may contribute significantly to the CNS symptomatology (Figure 1). White matter pallor and frank demyelination may result from primary HIV-related damage to oligodendrocytes and myelin (32), or may be secondary to axonal damage. Astrocytic hyperplasia is a striking feature also present in many cases of HIVE (21).

With growing knowledge of HIV in the systemic compartment, it became clear that cells that support productive HIV infection are characterised by the possession of surface CD4 and chemokine receptors, usually CCR5 and CXCR4. These characteristics explain the vulnerability of microglia for direct HIV infection since these are the only brain cells to carry both types of receptor (33). CD4 receptors serve as sites of attachment for HIV to host cells and one or other chemokine receptor facilitates viral entry through the host cell membrane. In addition to microglia, astrocytes may also be infected *in vivo,* albeit in a restricted form (34). These cells are quite readily infectable *in vitro* and sometimes display immunopositivity for HIV Nef *in vivo*. The mechanism of

astrocytic infection remains uncertain since these cells are CD4 negative although in common with all other cells of the CNS they do possess chemokine receptors. Occasional reports of oligodendrocytic, endothelial and neuronal infection have been published over the years. More recently, the use of *in situ* PCR and laser cell microdissection techniques have led to claims for infection of neurons but there is no evidence that these cells are productively infected (35, 36). Overall, productive CNS HIV infection is confined to microglia and infiltrating macrophages in the brain.

HIV is an RNA virus belonging to the *Lentivirus* genus in the family *Retroviridae*, viruses characterised by a replication cycle in which viral RNA is reverse transcribed into a DNA proviral form that is integrated into the host cell genome. Both integrated and unintegrated forms of viral DNA as well as viral RNA have been found within brain tissue samples from subjects with AIDS, particularly those with HIV-associated dementia (HAD) (37). HIV is thought to enter brain parenchyma at, or shortly after, the primary infection. Entry is most likely to occur across the blood brain barrier (BBB), possibly as free virus, or by carriage in the nucleated blood cells which traffic normally in low numbers into the brain compartment. The choroid plexus and cerebrospinal fluid also represent a possible source of brain infection although viral populations found in the brain and CSF compartments are frequently genetically distinct. Breakdown of the BBB (38) may facilitate viral entry to the brain. Perivascular microglia/macrophages, as a result of their proximity to blood vessels, are the first brain cells to be exposed to incoming virus. They represent a cellular pathway through which the long lived parenchymal microglia may become infected. Both cell types are likely to be a repository for HIV sequestered in the brain from the early stages of infection (39). The turnover of infected cells within the brain is poorly understood. While it seems that viral variants within the brain undergo a process of neuroadaptation in terms of optimising their ability to infect cells expressing low levels of CD4 receptors (9), it is unclear where and how this adaptation takes place. The CNS viral load remains low to undetectable throughout the presymptomatic stages of HIV/AIDS and is probably held in check partly by the influx of CD8 positive lymphocytes (40). Thus it is unusual for productive viral infection to occur in the brain before the onset of significant systemic immunosuppression. Whether the virus is ever eliminated from brain tissue or whether indeed it enters this compartment in every case, is not known. However, with the onset of AIDS, viral subspecies detected in the brain are invariably found to have diverged genotypically in the env gene from those present in lymphoid tissue in the same individual, providing evidence for their adaption for replication in different cell types in the CNS (8, 41).

The clinical effects of HIV infection of the brain and of related brain damage include neurological, psychological and psychiatric abnormalities, the most significant of which is HAD (42). The exact substrate for HAD is not entirely understood and while there is undoubtedly a general association with productive HIV infection (37) the correlation is not exact. Early studies seeking to establishing the mechanisms of brain damage demonstrated the neurotoxic effects of viral proteins on brain cells *in vitro* (43). However no simple relationship exists between the presence of HIV in the brain and the degree of associated brain damage and a range of pathogenetic mechanisms has been invoked, similar to those which have been implicated in other neurodegenerative diseases. The agents under suspicion include excitotoxins, free radicals, nitric oxide, cytokines and chemokines. Reviews devoted to the pathogenesis of HAD continue to explore these issues (44-47). Surprisingly the amount of neuronal loss and damage within the brain does not correlate precisely with the degree of cognitive impairment (22) and a number of studies have suggested that the closest correlate for dementia is the degree to which the brain microglia and macrophages are activated. This proposal was first put forward unambiguously by Glass *et al* (48) and the finding has been replicated elsewere. Activated microglia and macrophages are known to secrete a wide variety of the neurotoxic agents referred to earlier, including pro-inflammatory cytokines (44).

Until 1996, the effects of HIV in the brain were self-limiting because of the inevitably fatal outcome resulting from severe immunosuppression. Early drug treatment with Zidovudine and Didanosine did little to affect this situation although some slight beneficial effects were reported with respect to dementia (49). That position has changed completely with the advent of therapeutic regimes (HAART) which are capable of sustaining or partially restoring the immune function of HIV infected individuals, thereby converting HIV infection to a much more chronic disease.

3.2. Changes resulting from effective therapy

The outlook for HIV infected individuals improved dramatically when it was found that viral production could be efficiently suppressed, and immune decline slowed or halted, by using two or three classes of antiretroviral drugs together, a combination known as HAART. While HAART is not able to completely eliminate HIV from the body because of viral persistence in sanctuary sites including lymphoid tissue, the maintenance of at least partial immune competence protects against the emergence of previously fatal opportunistic infections. The incidence of HAD and of HIVE has declined markedly (50). However as the total number of infected individuals rises, the overall prevalence of these conditions is increasing. Careful examination of treated individuals who undergo neurocognitive testing suggests that minor cognitive disorder is increasing in prevalence (51-53). It also appears that the characteristics of HAD are changing and that the predominantly subcortical pattern which was characteristic of HAD in former times is shifting to a pattern of cognitive decline with more cortical deficit (42, 54). The question of whether the brain may represent a sanctuary site for HIV in HAART treated individuals is still under investigation (52). Although the component drugs used in HAART, particularly protease inhibitors, do not transfer efficiently across an intact BBB, it is likely that breakdown of the barrier occurs periodically in HIV/AIDS (55). Whether this facilitates penetration of therapeutic drugs into the brain *in vivo* is not known.

The prospect of prolonged survival brings with it the likelihood that a significant proportion of older people will be living with HIV infection and will present with HIV

Table 1. Major drugs of addiction and their modes of action in the brain[1]

Drug (s)	Mode of Action	Effects
Opiates eg heroin (diamorphine)[2], methadone[2]	Act mainly at μ as well as other opiate receptors, mimicking endogenous opiates and activating adenylate cyclase intracellular signalling.	CNS depressants
Cocaine	Acts at dopamine receptors to prevent reuptake of dopamine. Also prevents reuptake of noradrenaline and serotonin.	CNS stimulant. Leads to dopamine surges.
Amphetamines[3] e.g .methylenedioxymethamphetamine MDMA (Ecstasy)	Act at receptors for dopamine, noradrenaline and adrenaline or facilitates these endogenous transmitters	CNS stimulants. Ecstasy is a hallucinogen
Cannabis [4]	Acts on G protein coupled cannabinoid receptors inhibiting adenylate cyclase.	CNS depressant.
Benzodiazapines eg diazepam (Valium)[4]	Bind to GABA receptors, increasing GABA binding, can also decrease serotonergic activity	CNS depressants. Sedative, anxiolytic and hypnotic effects reducing arousal.
Barbiturates	Bind to GABA receptors.	CNS depressants.
Alcohol[4]	Enhances GABA mediated inhibitory receptors but also enhances serotonin binding at 5HT receptors.	Complex; CNS stimulant or CNS depressant.
Others eg solvents	Similar to alcohol.	CNS stimulants or depressants Cardiac arythmias

[1] Mode of action of the major classes of illicit drugs is reviewed in Drummer OH and Odell M 2001; 2 main drugs of choice in the Edinburgh cohort. 3amphetamines are used in addition to opiates in 30% if the Edinburgh cohort, 4all drug abusers in Edinburgh are exposed to alcohol (spirits), benzodiazepines and cannabis from time to time as well as nicotine through smoking cigarettes. Illicit drug taking in humans is virtually always a problem of polydrug abuse although many cohorts have a predominant drug of choice. While this complicates the study of the effects of drug abuse, observations in human addicts are necessary to understanding the problem and are well complemented by laboratory studies in cell culture and animal models.

related disease. Comparisons of older and younger HIV infected subjects who have been treated with HAART shows that HAD is more common in the older group and that this finding is not related to the duration of infection (18). These findings suggest that the older brain may be more vulnerable to HIV related damage. Elevated levels of hyperphosphorylated Tau protein have been found in the CSF of HIV infected subjects, with a corresponding fall in beta amyloid levels, a pattern reminiscent of the results in Alzheimer's disease (56).

The pattern of neuropathology in HAART treated individuals is also changing compared with that observed in previous times. It seems clear that the prevalence of opportunistic infections has declined markedly with the possible exception of progressive multifocal leucoencephalopathy (PML) (50, 57, 58). CNS lymphoma continues to pose problems and it is unclear whether the incidence is actually rising or whether the numbers of cases are simply rising in an enlarging cohort of HIV infected individuals in the late stages of infection. The evidence with respect to HIVE is variable with some studies claiming a lower incidence and some a maintained level of productive infection, compared with the pre-HAART era (59, 60). Recent studies have also highlighted that the viral load in HAART treated brains is generally low but not always so despite compliance with HAART, confirming the ability for the virus to persist in sanctuary sites such as the CNS (61).

One pathological phenomenon that has emerged in the wake of the HAART epidemic is the so-called immune reconstitution syndrome (IRIS). In these cases, extensive demyelination and white matter damage is found in HIV infected individuals following the institution of HAART (62, 63). The myelin damage is accompanied by marked lymphocytic infiltrate of brain parenchyma suggesting that the pathogenesis of the white matter damage may be immunologic following a HAART-induced upturn in the numbers of circulating CD4 and CD8 lymphocytes and sudden massive influx of these cells into the brain. No information is available with regard to the viral load in brain tissue in these cases. Although the explanation is plausible, it should be noted that lymphocytic infiltrate of the brain is also prominent in some presymptomatic individuals without obvious myelin damage.

One current focus of interest is the neuropathological status of subjects who are growing older with HIV infection. Two separate questions arise in this context. The first concerns whether HIV accelerates the ageing process such that premature neurodegeneration occurs in young individuals who would not otherwise display such changes. The second question is whether HIV infection and its attendant therapy facilitate the development of other recognised neurodegenerative conditions such as Alzheimer's disease. Evidence regarding hyperphosphorylated Tau and beta amyloid levels in the CSF of infected individuals (56) together with the cognitive impairment noted clinically (51) suggest the presence of an underlying pathological process in the brain. Apart from the dramatic cases of immune-mediated demyelination described above, brains from HAART-compliant subjects which are deemed normal or near normal on routine examination may on further investigation show a significant degree of neuroinflammation in the form of microglial activation (64). This is accompanied by a greater degree of hyperphosphorylated Tau deposition within neurites and neuronal cell bodies compared with the amount present in age-matched controls (65). Other reports have suggested that Beta amyloid is deposited to an excess degree in HIV infected individuals (66). Ubiquitin immunopositivity is also enhanced in the white matter of HIV infected individuals (67). All these factors suggest that for their age HIV positive brains have a higher prevalence of neurodegenerative changes, but it is currently unclear whether this signals the onset of premature and ongoing neurodegeneration. These subtle forms of brain injury may be clinically silent in young people with sufficient brain reserve to sustain apparently normal function.

4. EFFECTS OF DRUG ABUSE

4.1. In the absence of HIV

Drugs that are commonly misused include the opiates, cocaine, amphetamines, benzodiazepines and cannabis (68, 69). The major classes of drugs which lead to dependence or addiction are listed in Table 1 together

Table 2. Selected study groups of subjects with various combinations of HIV infection and illicit drug abuse

- HIV negative drug users (**DU+HIV-**)
- Presymptomatic HIV positive drug users (**DU+HIV+**)
- Drug users progressing to AIDS without HIV encephalitis (HIVE) or central nervous system (CNS) opportunistic infections (**DU+AIDS+HIVE-**)
- Non drug users in AIDS with no evidence of CNS pathology (**DU-AIDS+HIVE-**)
- Drug users in AIDS with evidence of HIVE and no CNS opportunistic infections (**DU+AIDS+HIVE+**)
- Non-drug users in AIDS with HIVE and no CNS opportunistic infections (**DU-AIDS+HIVE+**)
- HAART treated HIV positive drug users (**DU+ HIV+HAART+**)
- Controls (**DU-HIV-**)

with their modes of action in the CNS. Drugs of addiction commonly act at receptors for neurotransmitters thereby mimicking their effects, or at G protein coupled receptors, including opiate receptors, which activate second messenger systems (69, 70). The site of action of these drugs is maximal where such receptors are enriched. For instance opiates, cocaine and amphetamines are active in the mesolimbic dopaminergic pathways between the ventral tegmental area of the brain stem and the ventral striatum. The nucleus accumbens of the ventral striatum is sometimes viewed as the reward centre of the brain and has connections with both the frontal cortex and the limbic system. Other brain stem nuclei, including the noradrenergic locus coeruleus and the serotonergic dorsal raphe nucleus, also form direct targets for illicit drugs. These drugs are capable not only of causing surges of neurotransmitters, particularly dopamine (71), but are also potentially neurotoxic in these pathways. Acute psychoses and episodes of aggression and violent behaviour are all linked to changes in neurotransmitter level in the brain, reviewed in (70). Although opiates are not usually linked to psychotic behaviour, heroin withdrawal is known to induce such episodes which are also potentiated by a chaotic lifestyle and erratic access to supplies of illicit drugs. In any one individual, the pattern of drug abuse is usually complex and polydrug use is the norm together with excess alcohol intake and smoking. Additionally, such individuals may have an impoverished lifestyle and poor nutrition. Subjects who have a serious drug habit are at risk of sudden death, not just from accidental or intentional drug overdose but also because of a heightened risk of cerebrovascular accidents (72-74). This may be the result of atherogenic effects of some illicit drugs. Other side effects include a general suppression of immune function and increased susceptibility to infection (75), attributed to central effects in the brain, notably in the periaqueductal grey matter (76).

On superficial examination, the brains of IVDUs may show little in the way of pathology. The brain is often swollen when compared with those of non-drug using age matched individuals who die suddenly. Cerebral oedema is present in these cases. The most consistent visible change is focal thickening and sclerosis of the small vessels of the white matter which are frequently associated with a small number of perivascular pigmented macrophages (77, 78). Some of these abnormal small vessels show microvascular proliferation and a decrease in collagen content of the vascular basal lamina has been reported (79). It is generally assumed that these changes represent damage to the blood brain barrier (5, 80). Disturbances in the circulation to the brain may well be intermittent in the context of a drug habit and are likely to lead to neuronal hypoxic damage. Opiate misuse also leads to respiratory depression and episodes of hypoxia (Table 2). Such a mechanism may be the basis for the finding of increased levels of Beta amyloid precursor protein expression in the white matter in drug abuse (81, 82). Hypoxic/ischaemic changes may be confined to acute terminal hypoxia affecting vulnerable neuronal subsets particularly in the hippocampus, or may include evidence of preceding injury including infarcts and neuronal loss. A recent careful study of 50 drug abusers compared with 30 controls revealed widespread cortical neuronal loss (78). This is borne out by the results of studies using the TUNEL (TdT-mediated-dUTP nick end labelling) technique which has shown that TUNEL positive neurons are more frequent in the cortex of drug abusers than they are in controls (83). Whether this neuronal DNA damage and neuronal loss is a direct result of drug abuse or mediated indirectly through drug induced hypoxia is not yet clear. Another possible causative factor may be the microglial upregulation consistently present in the brains of drug abusers (6, 7, 84). Recent studies have shown upregulation of hyperphosphorylated Tau expression in neuronal cell bodies and neurites in young drug abusers (81). Damage to dopaminergic systems has been reported in drug abuse and it is generally supposed that dopaminergic neurons are a key target for illicit drugs, as noted above, both in terms of producing the desired effect and of being vulnerable to drug associated damage and loss (85). Drug abuse can also lead to neurocognitive deficits (86, 87). Documented atrophy of the CNS, particularly in the temporal lobe, may underlie these neurocognitive problems (88)

Effects of illicit drugs on astrocytes have not attracted much attention. Our own previous investigations suggested that there was no conspicuous activation of astrocytes in drug abusers (7) and Buttner and Weis (78) have reported an actual fall in the number of GFAP positive astrocytes associated with drug abuse. In this context, it is pertinent to separate the direct effects of drugs on the brain from those of co-morbid factors such as hepatitis B and C infection. Disorders of liver function, particularly those present in cirrhosis caused by the hepatitis viruses, can lead to the onset of hepatic encephalopathy (89). The pathological substrate of this condition is a change in astrocytic morphology, known as Alzheimer type II astrocytosis, which is most prominent in the basal ganglia and the brain stem nuclei. Alzheimer type II astrocytes are not strongly positive for the glial marker, glial fibrillary acidic protein, but display enlargement and clearing of the nuclear morphology with distortion of the nuclear outline. The changes seen in astrocytes attributable to hepatic encephalopathy may be associated with manganese deposition in the brain (89). The resulting disturbance of glutamate homeostasis and other metabolic changes including the accumulation of ammonia results in cognitive and motor dysfunction. This is a not insignificant problem

in HIV infected drug users since it is estimated that up to 90% of HIV positive IVDUs are hepatitis C virus (HCV) positive (90). HIV positivity appears to accelerate HCV-related liver damage and the resulting complications for the CNS (15, 91). Since some of the drugs used in HAART have the potential to be hepatotoxic, their use in HCV positive patients with liver damage may be fraught with difficulty. Recently, interest has focussed on a possible direct role for HCV in neuroinvasion and neurotoxicity (16, 92). HCV-infected individuals may display neuropsychological dysfunction which does not link to the severity of the liver disease nor to hepatic encephalopathy or drug abuse. HCV RNA has been detected in post mortem brain tissue and there is speculation that this virus may be capable of infecting both peripheral monocytes and microglial cells (15, 16, 93) implying that HCV and HIV may potentially co-infect the same cells with possible direct interaction between these two pathogens. Drugs of abuse may also disturb the immune balance in the brain as well as having an effect on systemic immune function (94). Through a mechanism of microglial activation, opiates may upregulate cytokines, chemokines, free radicals and nitric oxide production by these cells and thereby inflict damage on nerve cells. Opiates are known to have general effects on the immune system and in particular increase chemokine receptors, thereby possibly predisposing to HIV infection of the CNS (95). The use of opiates may also disrupt the endogenous opioid system (96). Recreational drug use results in changes in cytotoxic lymphocyte counts and upsets the balance between neuroprotective and pro-inflammatory cytokine levels (97, 98). Opiates lead to a rise in CD4 lymphocytes with a consequent fall in the CD4/CD8 ratio, also affecting the function of natural killer cells (99). The resulting altered immune response may upset the normal CD8 mediated immune surveillance of the brain compartment (100). It has been shown that acute opiate withdrawal results in immunosuppression (101) a finding which has implications for drug users with interrupted access to illicit drug supplies

Thus at a more subtle level, drugs of abuse can induce changes in the brain which resemble those seen more dramatically as a result of HIV infection. The question has arisen as to whether these effects could be additive or synergistic to those induced by HIV, thereby leading to a greater degree of clinical deterioration, with possible accelerated progress and a greater degree of underlying neuropathological abnormality.

4.2. Interacting with HIV

HIV infection transmitted in the context of intravenous drug abuse continues to be a major problem. Both blood borne and heterosexual transmission can occur from infected drug users (30, 102, 103). Participation by drug users in risk taking behaviour is likely to be affected adversely by the cognitive effects of drug misuse (86). On the clinical front, evidence is conflicting as to whether, ~~that~~ in the absence of therapy, HIV positive drug users progress faster than other groups (104). The problem is confounded in that drug using HIV positive cohorts are often younger than those infected in other risk groups and it is known that older subjects with HIV/AIDS progress faster than younger infected individuals. However HIV positive drug users do appear to be ~~are~~ more prone than non-drug users to develop cognitive impairment (13, 105-108).

Investigation of the neuropathological status of HIV infected drug users compared with non-drug users also suggests a higher prevalence of HIV related pathology in the brain (109, 110). Not all comparative studies have observed these differences (111). These different results may be attributable to particular drug habits. European drug users tend to use heroin and opiates as the drug of choice while cocaine and amphetamines, including methamphetamine, are more widespread in the US. A number of studies have suggested that microglial activation is more pronounced in drug users with HIVE than in non-drug users with HIVE (30, 112).

In order to assess pathologically the degree of drug associated damage in the context of HIV infection it is essential to study a number of different groups of subjects as shown in Table 2. Tables 3 and 4 draw together and summarise the results of a number of our studies relating to these groups of individuals. Microglial marker proteins are confirmed to be upregulated in AIDS cases particularly in those with HIVE. The macrophage marker CD14 is upregulated in some but not all cases of HIVE. CD16 and MHCII expression are more consistently upregulated in HIVE and this effect is accentuated by drug abuse. In contrast, drug abuse appears to have no effect on the HIV related influx of CD8 lymphocytes or on the degree of astrocytosis but does increase the level of damage both to the blood brain barrier and to DNA in resident brain cells. The best correlate for cognitive impairment in these subjects proved to be accelerating microglial activation and this is exacerbated by drug abuse. Studies of the BBB in HAART treated individuals are currently underway. It is known that drugs of abuse damage the blood brain barrier in the context of HIV infection (100, 113, 114).

Our studies have shown for the first time that B lymphocytes are present in small numbers in the normal adult human brain and that they join the influx of CD8 lymphocytes in the brains of presymptomatic individuals. However the numbers of B lymphocytes in the brain are very scanty in the later stages of HIV CNS disease, suggesting that they play no further role in controlling the infection although their presence may be significant for development of primary CNS lymphoma in the late stages of AIDS. HIV causes direct neuronal damage through a variety of mechanisms including the release of neurotoxic proteins such as Tat (13, 115, 116). Recent *in vitro* studies have suggested that when neuronal cultures are exposed to Tat and methamphetamine together, they show a greater degree of damage than that seen in cells exposed to one or other insult in isolation. Mitochondrial damage was observed in the cultured neurons and there was concomitant decrease in calbindin and microtubule associated protein (MAP2) (117).

It is unlikely that HIV proteins and illicit drugs exert precisely the same effects on cells of the brain and it is not known whether microglia which are activated in the context of illicit drug use release the same profile of pro-inflammatory cytokines as that produced during HIV-

Table 3. Neuroinflammatory responses compared in 8 groups of subjects – composite of data in Refs X, Y and Z

Reactive Cell Type	Marker	Results compared to control subjects						
		DU+ HIV-	DU+ HIV+ (presymptomatic)	DU+ AIDS+ HIVE-	DU- AIDS+ HIVE-	DU+ AIDS+ HIVE+	DU- AIDS+ HIVE+	DU+ HIV+ HAART+
Microglial	CD14	–	–	-	–	↑↑	↑↑	–
	CD16	↑	↑	↑	↑	↑↑↑	↑↑	↑
	CD45	↑	↑	↑↑	↑	↑↑	↑	↑
	CD68	–	↑	↑	↑↑	↑↑↑	↑↑	↑↑
	MHC II	–	↑	↑↑↑	↑↑	↑↑↑	↑↑	↑↑
Lymphocytes	CD3 (T)	–	↑↑	–	–	↑↑	↑↑	-
	CD8 (T)	–	↑↑	–	–	↑↑	↑↑	–
	CD20 (B)	–	↑↑	↓	↓↓	↓	↓	–
	CD45 (B+T)	–	↑↑	↓	↓↓	↓	↓	–
	CD79 alpha (B)	–	↑↑	↓	↓↓	↓	↓	–
Astrocytes	GFAP	–	↑	↑	↑	↑↑	↑↑	↑

↑ increase, ↓ decrease, – no change, T - T lymphocyte, B - B lymphocyte, HIVE – HIV encephalitis, DU – drug user

associated activation. The interactions between HIV, illicit drugs and the cells of the brain are complex, with some neuroprotective mechanisms brought into play (94, 118). Some drugs including benzodiazepines bind to microglia directly and in so doing may inhibit TNF alpha production and down regulate HIV replication. A further complicating factor is the effect of therapeutic drugs on the brain. In essence, the synergy between drugs of abuse and HIV in causing CNS damage arises from their similar targets. Microglial activation is caused not only by HIV (119-121) but also by drug abuse (7, 84). The glial changes induced by both agents are reviewed by Hauser *et al* (122). Both agents can lead to neuronal loss and resulting brain atrophy (22, 123).

Since HAART was introduced the beneficial effects have been observed in all risk groups despite the greater difficulties in achieving compliance in drug users and possible interaction between methadone in particular and therapeutic drugs (104). Dougherty *et al* (124) showed that IVDUs with HIV associated dementia did less well on HAART than non-drug users.

5. LABORATORY STUDIES

Rogers *et al* have reviewed the cell culture model systems in which the effects of drugs of abuse on HIV replication and infectivity have been investigated (125). Here the finding that drugs of abuse upregulate chemokine expression on a variety of cell types has been confirmed. Kanmogne *et al* have conducted blood brain barrier studies *in vitro* and investigated the effects of drugs in this context (113). Turchan-Cholewo *et al* showed that Apolipoprotein E (ApoE) 4 neurons were more vulnerable than ApoE 3 neurons to HIV associated damage indicating the effects of host genotype (126). Currently there is considerable interest in the effects of drugs of abuse and of HIV on neural progenitor cells in culture (127, 128)

Although no animal model exists for HIV infection *per se,* SCID mice have been used effectively when "humanised" (129). The SCID model has been used to study the blood brain barrier (130) as well as for testing the efficacy of antiretroviral drugs (131). Neurodegeneration has been shown to follow the intracerebral injection of infected astrocytes (132). Neuronal plasticity is reduced in this model in the context of HIV infected macrophages (133).

Larger laboratory animals are vulnerable to specific retroviruses including feline immunodeficiency virus (FIV) and the sooty mangabey simian immunodeficiency virus (SIV_{SMM}) in macaques. The FIV model has been used to review compartmentalisation of virus between the CNS and systemic systems as well as the distribution of infection between the CNS and the periphery via the cerebrospinal fluid pathways (134, 135). Other studies have used cats infected with FIV to investigate the effects of the virus in the brain (136, 137). Phillips *et al* have shown behavioural changes and an increase in reverse transcriptase activity with methamphetamine in drug treated animals (138).

It is perhaps the SIV model that most closely resembles the human disease of HIV/AIDS. The clinical course of presymptomatic and symptomatic infection of SIV_{SMM} in macaques represents an accelerated form of HIV/AIDS in humans and the model has been used in a variety of ways to study the evolving neuropathology as well as brain viral load (139). Infection of the microglial population including perivascular and parenchymal microglia/macrophages, was described by Williams *et al* (140) and axonal injury was detected in SIV_{SMM} infected macaques by the presence of βamyloid precursor protein positivity (141). Infection of astrocytes by SIV_{SMM} has been demonstrated (142). Czub *et al* discovered that increased availability of dopamine following the administration of dopaminergic drugs potentiated SIV_{SMM} dementia (143, 144), the early control of which was modulated by CD8 lymphocytes (145). Donahoe *et al* showed that opiates actually retarded AIDS progression in the SIV_{SMM} macaque model (146). In contrast cocaine and opiates have been found to potentiate the expression of HIV in systemic cells of the immune system including lymphocytes and macrophages (147).

These and other aspects of laboratory model systems are reviewed by Rogers *et al* (125).

6. CONCLUSIONS AND PREDICTIONS FOR THE FUTURE

The CNS has come to be viewed as a sanctuary site where HIV can evade the action of HAART and where

Table 4. Neuronal, glial and blood brain barrier damage compared in 8 groups of subjects

Type of damage		Marker	Results compared to control subjects						
			DU+ HIV-	DU+ HIV+ (pre-symptomatic)	DU+ AIDS+ HIVE-	DU- AIDS+ HIVE-	DU+ AIDS+ HIVE+	DU- AIDS+ HIVE+	DU+ HIV+ HAART+
Axonal		BetaAPP	↑	↑	↑	↑	↑	↑	−
Neuronal DNA		TUNEL	−	−	↑	↑	↑↑	↑↑	−
Neuro-degeneration	Beta amyloid deposition	BetaA-4	−	−/↑	−/↑	−/↑	−/↑	−/↑	−/↑
	Hyper-phosphorylated Tau deposition	AT8	↑↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑↑
Glia	DNA	TUNEL	−	−	↑	↑	↑↑	↑↑	−
	apoptosis	BAX	↓	−	↑↑	↑	↑↑	↑	↑↑
Blood Brain Barrier integrity (loss of ZO-1 tight junction immuno reactivity indicates damage)		ZO-1	↓	↓↓↓	↓↓	↓	↓↓↓	↓↓	NA

↑ increased, ↓ decreased, − no change, NA Not available, HIVE – HIV encephalitis, DU – drug user

the virus is controlled only indirectly. Consequently there is a risk that cessation of therapy or emerging resistance to therapy will be followed by the emergence of HIVE. It is also possible that infection might spread from the brain to the systemic compartment (148). Recent studies have shown that the brain viral load in HAART compliant patients is generally low but not so in all cases. The rigorous use of HAART has not succeeded in eliminating cognitive disturbance and this problem may be compounded in IVDUs. Reports are accumulating which suggest that even in HAART compliant subjects there is a greater burden of neurodegenerative proteins in HIV positive individuals than in age matched controls. Neuroinflammation in the form of activated microglia and macrophages is also present to a level resembling that seen in HIVE and this raises further concerns for the future. One caveat attached to autopsy studies relates to whether the findings are relevant to survivors or merely confined to those who died. However more generalised clinical and neuroimaging data are in keeping with the neuropathological findings suggesting that the latter are valid for survivors. Neuroinflammation has been implicated as a major pathogenetic factor in the onset of AIDS dementia and is common in other dementing illnesses such as Alzheimer's disease (149).

Analysis of the pathogenesis of HIV related brain disease suggests that while brain damage may be initiated by viral infection, other factors are also important. These include oxidative and nitrative stress, excitotoxicity, inflammatory chemokines and cytokines, neuronal and glial apoptosis, mitochondrial dysfunction and altered proteolosis. It is possible that these combined factors will accelerate ageing and predispose to early onset of one of the recognised neurodegenerative disorders or may result in a previously unrecognised ageing-associated cognitive disorder. Some of these have been invoked in the development of other conditions such as Alzheimer's disease, multiple sclerosis and Parkinson's disease (150-152). Neuroinflammation as a basis for dementia is an interesting concept which may well have contributed in the context of neurosyphilis, another major infective ~~ed~~ dementia. However the end result of these disorders is very different and comparisons with them may not shed light on the likely future state of HIV infected, HAART treated individuals as they grow older. Evidence from clinical, *in vitro* and neuropathological studies shows that drug abuse causes HIV related brain damage to be worse than that seen in drug free individuals. Other confounding factors including HCV infections that may lead to hepatic encephalopathy, or directly infect the brain (15), as well as host genotypic variations, will require further study. The requirement for ongoing pathological investigation of neuroAIDS to complement clinical cohort studies remains paramount in the context of HAART therapy.

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