Methamphetamine: A molecular and pathological exacerbate of HIV neurocognitive disorder

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ABSTRACT – The use of the recreational drug methamphetamine is becoming more widespread, and it is accompanied by unsafe sexual behaviours that increase the transmission of the human immunodeficiency virus (HIV). This article reviews the available literature of the effect of methamphetamine on the HIV infected brain, and in particular the molecular disturbances and neuropathology associated within this cohort. Our molecular research indicates that methamphetamine and HIV have a synergistic pathological impact on neuronal cell injury and death, which may be mediated by an upregulation of interferon inducible genes observed within this group, thereby contributing to the neurocognitive deficits observed in clinical populations of HIV infected methamphetamine abusers.

Epidemiology of HIV infection and AIDS

Since its initial description amongst a few previously healthy young homosexual men in Los Angeles in 1981, acquired immunodeficiency syndrome (AIDS) has evolved to become a global pandemic, with the World Health Organisation (WHO) estimating that the total number of people infected with HIV rose in 2004 to its highest level ever: an estimated 39.4 million. This figure includes the 4.9 million people who became infected with HIV in 2004. Worldwide there have been 3.1 million deaths from AIDS in 2004, with the death toll rising daily. In Western and Central Europe, the estimated figure of those infected with the virus was 610,000 (Joint United Nations Program on HIV/ AIDS, 2004).

HIV Neuroinvasion

It appears that the main cell types infected by HIV in the central nervous system

(CNS) and in particular the brain are microglia and macrophages (Clayton *et al.* 1990, Gonzalez-Scarano & Martin-Garcia 2005, Fischer-Smith *et al.* 2004). There is a growing body of evidence which suggests that in addition to these two cell types there are other cells within the brain such as astrocytes, which can be infected (Brack-Werner 1999, Bagasra *et al.* 1996, Trillo-Pazos *et al.* 2003). However, if astrocytes are infected they are unable to sustain viral replication and are limited to producing early viral regulatory proteins only, and as such, it has been challenging to establish the direct link between astrocytes and neuropathogenesis of HIV. Infection of the CNS can be proven in about 80% of HIV-infected individuals (Speth *et al.* 2005). The virus enters the brain after systemic infection of CD4^{+} lymphocytes (An *et al.* 1999). CD4^{+} together with chemokine receptors CXCR4 and CCR5 are the main membrane bound receptors that facilitate attachment of the virus and fusion of viral and cellular membranes, leading to entry of the virus into the cell; for review, see (Zaitseva *et al.* 2003). These cells migrate across the blood brain barrier in order to replenish the pools of macrophages (Gonzalez-Scarano & Martin-Garcia 2005). In the process of differentiating into macrophages, the virus-infected monocytes encounter mainly perivascular macrophages and microglia, which become infected and contribute to the increasing viral load. The HIV envelope glycoproteins that are expressed at the surface of infected cells, mediate cell to cell fusion of macrophages and microglia, resulting in the formation of multinucleated giant cells (MNGC) (Sharer *et al.* 1985). MGNCs, as well as functioning as cellular sites of virus production, also serve as a morphological hallmark of HIV encephalitis (HIVE).

Neuropathological and Clinical Aspects of HIV infection

The neuropathological consequences of HIV brain infection are well characterized and include neuronal loss (Everall *et al.* 1993, Everall *et al.* 1991), dendritic and synaptic damage (Masliah *et al.* 1992, Everall *et al.* 1999), as well as astrocytosis and microgliosis (Figure 1) (Budka 1993). Mechanisms by which neurodegeneration occur are still being elucidated but are postulated to include both direct and indirect avenues. Numerous studies have demonstrated neurotoxicity induced directly by various viral proteins, including the envelope protein, GP120 (Lipton *et al.* 1991) and regulatory proteins TAT (Nath *et al.* 2000) and nef (Trillo-Pazos *et al.* 2000). For GP120 and TAT, excitotoxicity has been implicated (Lipton 1994, Nath *et al.* 1995). However, infection of the brain is also associated with prolonged cytokine dysregulation, which may be a potential mediator of indirect virally mediated neurodegeneration (Corasaniti *et al.* 2001, Ensoli *et al.* 1999). Many other putative neurotoxic pathways have been proposed and all of these avenues of neurotoxicity are likely to be interactive and not acting in isolation (Fine *et al.* 1996, Vitkovic & Tardieu 1998).

Clinically, affected individuals can suffer a range of neuropsychiatric disorders from mild cognitive impairment to severe HIV associated dementia (HAD). The essential features of HAD are marked cognitive impairments usually accompanied by motor dysfunction and behavioural changes. Cognitive impairment is characterised by mental slowness, forgetfulness, and poor concentration. Behavioural changes may include apathy, lethargy and

diminished spontaneity and emotional responses. Motor symptoms include loss of fine motor control, clumsiness, unsteady gait and tremor. Clinico-pathological studies have to date identified dendritic and synaptic damage, and selective neuronal loss as factors mediating cognitive impairment (Asare *et al.* 1996) as well as being related to rising brain viral load (Everall *et al.* 1999).
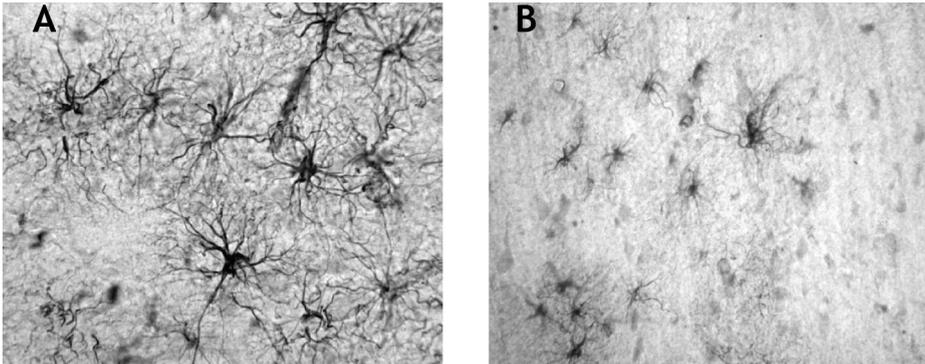

Figure 1. Immunoperoxidase staining for glial fibrillary acidic protein (GFAP) in post-mortem frontal cortex. Increased cellular GFAP staining is observed in the advanced HIV+ disease demonstrating inflammation (A) compared to non-HIV infected control case (B). (Magnification x1000).

The Emergence of Methamphetamine as an HIV Co-factor

Methamphetamine Neurotoxicity

Attempts to understand the mechanisms mediating HIV neurotoxicity have been further complicated with the findings that co-factors, such as drugs of abuse may exacerbate HIV neurodegeneration. The stimulant drug methamphetamine (MA) is a cationic lipophilic molecule readily capable of crossing the blood brain barrier and therefore has a potent action on the CNS. MA induces the release of dopamine (DA) from pre-synaptic terminals and causes the decrease in the number of DA transporters (Westphalen & Stadlin 2000, Stadlin *et al.* 1998). Clinically, MA has been found to reduce fatigue, increase alertness and cause a sense of confidence and euphoria in the user (Hanson *et al.* 2004). *In-vitro* and human neuroimaging studies, have shown MA to be detrimental to the dopaminergic (DA) metabolism (Davidson *et al.* 2005, Volkow *et al.* 2004, Vollm *et al.* 2004). In addition, glutamatergic cells in the hippocampus and neocortex (Ohmori *et al.* 1996, Marshall *et al.* 1993, Bae *et al.* 2005), serotonergic cells in the raphe nucleus, and GABAergic interneuron's in the neocortex, basal ganglia and hippocampus (Jernigan *et al.* 2005, Hanson *et al.* 2004) have all been shown to be adversely affected by MA. This MA induced neurotoxicity may in part be related to the generation of reactive oxygen or nitrogen species (Davidson *et al.* 2001). For example, the acute administration of MA to rodents resulted in production of oxidative stress as demonstrated by reduced glutathione and increased oxidized glutathione levels in the rat striatum and pre-

frontal cortex (Acikgoz *et al.* 1998, Harold *et al.* 2000). MA induced oxidative stress in mice has also been observed to activate redox-responsive transcription factors such as activator protein-1 (AP-1) and cAMP-responsive element binding protein (CREB) (Lee *et al.* 1999).

Cognitive Decline in HIV Infected Methamphetamine Using Population

The HIV infected drug user group is the fastest growing population living with HIV in Western Europe and the USA (Gibson *et al.* 2002, Nath *et al.* 2001). In recent years, the HIV infected MA using population has contributed significantly to this trend, with studies suggesting that MA use presents a serious problem due to its relationship with the high risk sexual behaviours associated with HIV transmission (Urbina & Jones 2004, Chesney *et al.* 1998). While the separate neuropsychological effects of either HIV or drug abuse is well documented, less is known about these factors in combination. At the HIV neurobehavioural research centre (HNRC), University of California, San Diego, studies have demonstrated that the combination of HIV and MA use is associated with excess neurocognitive disorder, highlighting that individuals with both HIV and a current history of MA use exhibit the highest rates of cognitive impairment when compared to controls and non MA using HIV infected subjects. Alongside this, those with HIV and a current history of MA use are more likely to show continued cognitive decline at 1-4 year follow up (Rippeth *et al.* 2004). A recent MRI study examining the effects of MA use and HIV on cerebral morphology indicate that there is an additive significant brain structure alterations associated with both HIV and MA

use. There were distinct regional patterns of changes associated with either HIV or MA. These changes were mainly atrophy but for MA they also included regional caudate volume enlargement, probably due to an increase in the neuropil. Certain cortical regions were doubly affected by both HIV and MA (Jernigan *et al.* 2005).

Patterns of Neurodegeneration

An emerging synergism between HIV and MA is the neurotoxic effects of these two agents together on the CNS. Clinically, as stated above MA use worsens HIV neurocognitive deficits (Rippeth *et al.* 2004) and it can amplify brain viral load (Gurwell *et al.* 2001, Maragos *et al.* 2002). As previously mentioned, the neurotoxic effects of MA on the brain monoamine systems are well characterised and can result in neuronal loss, loss of dendritic processes and decreases in synaptic densities (Phillips *et al.* 2000). Similarly, HIV infection has been shown to mediate toxic effects in selective neuronal populations (Masliah *et al.* 1994). These effects also include neuronal damage, loss of dendritic processes and synaptic simplification (Masliah *et al.* 1994, Wiley *et al.* 1991, Everall *et al.* 1999). Since HIV and MA are both capable of causing degeneration of DAergic neurons as well as other neuronal cell types, recent studies have focused on understanding the neuropathology of the HIV infected, MA using population. In our analysis of neurodegeneration we assessed the effect of HIV and MA on all neurons, as visualized with the neuronal dendritic marker, microtubule associate protein-2, as well as markers of specific interneuronal and pyramidal neuronal populations which selectively express the calcium binding proteins, Calbindin (CB) or Parvalbumin (PV). We observed a an extensive

loss of CB interneurons in the neocortex (Figure 2), accompanied by aberrant sprouting and axonal damage in HIV infected MA using brain tissue, compared to HIV infected and HIVE tissue (Langford *et al.* 2003). It has previously been demonstrated that CB interneurons regulate the firing rate of pyramidal neurons and contribute to cognitive function (Hof *et al.* 1999, Blatow *et al.* 2003). A decrease in the numbers of CB immunopositive neurons may therefore partially account for the diminished neurocognitive functions exhibited by HIV infected MA using patients. The molecular mechanisms through which MA and HIV interact to injure neuronal populations is unclear, however common paths of convergence are beginning to be elucidated.
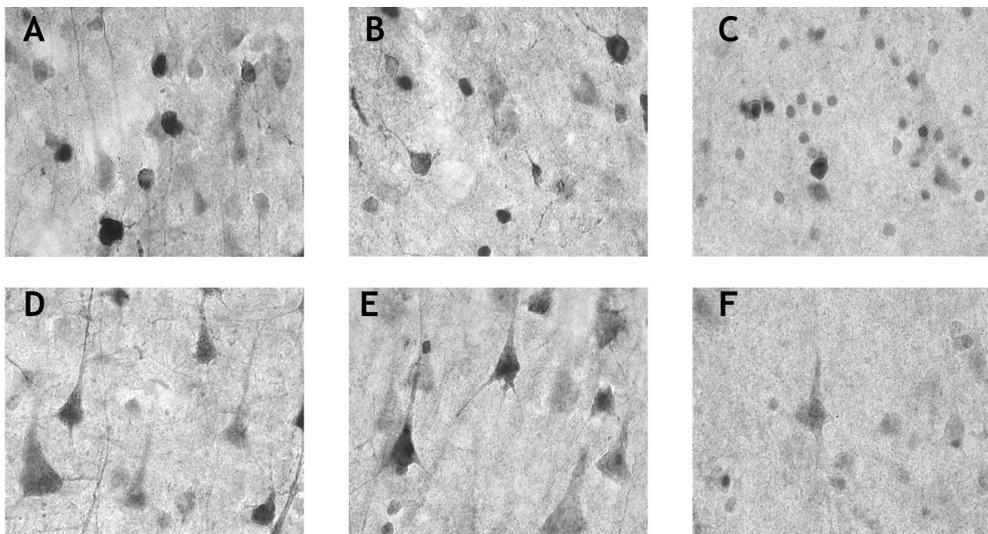

Figure 2. Immunostaining for Calbindin in the frontal cortex of patients with HIV, HIVE and HIVE plus MA use. Images (A-C) are interneurons; (D-F) are pyramidal neurons. Qualitative reductions in Calbindin immunopositive neurons can be seen in HIVE and even more so in the HIVE plus MA when compared to the HIV(+) sections. (Magnification x1000).

Synergistic Molecular Pathways of HIV and MA Neurodegeneration

The emergence of microarray analysis has facilitated the ability to obtain a comprehensive picture of gene expression changes associated with HIV infection and MA use in order to provide clues to the molecular mechanism by which MA exacerbates HIV neurodegeneration. In order to evaluate the contribution of gene expression alterations to the neurodegenerative process in the HIV infected and MA using population, we undertook a high-density oligonucleotide array study using RNA from the frontal cortex of this patient group, and the Affymetrix Human U95Av2 GeneChip. We initially observed that there were significant alterations in gene expression due to the presence of HIVE in our samples. Of the 12,695 genes analysed, 74 were significantly downregulated and 59 were significantly upregulated in our HIVE group compared to

our controls (Masliah *et al.* 2004). Upon further analysis, we observed that the group of genes induced by Interferons (IFI) were the most significantly elevated, with a 2-fold increase in the HIVE group, and a 3-fold increase in our HIV infected MA using sub-group when compared to our control cases (Everall *et al.* 2005). In order to further qualify and validate these findings, we conducted immunohistochemistry staining on brain tissue followed by optical density counts for two of the upregulated proteins, Interferon stimulated gene 15 (ISG15) and signal transducer and activator of transcription (STAT1). Both these qualitative and quantitative analysis showed significant upregulation of the two proteins in the HIV infected MA using group (Everall *et al.* 2005). In recent years more than 300 IFN genes have been identified (Der *et al.* 1998), and the proteins encoded by these genes have a significant role in the antiviral, immunomodulatory, anti-angiogenic and anti proliferative effects (Stark *et al.* 1998). INF genes such as ISG15 and those involved in the cascade such as STAT1, may not only mediate the antiviral effects, but they may also be involved in promoting pro-apoptotic cascades that can result in neurodegeneration (Chawla-Sarkar *et al.* 2003, Chawla-Sarkar *et al.* 2001, Jung *et al.* 2005). Our studies have shown that both HIVE and MA abuse can lead to a synergistic effect in upregulating IFN inducible genes. We have also shown that in the brains of patients with HIVE, the elevated expression of IFN inducible genes correlates with the severity of cognitive impairments (Masliah *et al.* 2004).

In summary, we have observed that MA use in HIV infected individuals is associated with greater cognitive decline, a decrease in the number of Calbindin containing neurons, (in addition to other selective neuropathology), and a significant up-regulation of IFN inducible genes. Further studies are required to elucidate whether these genes are indeed the molecular substrate to the extra neurodegenerative burden, which could contribute to the excess cognitive decline observed in this increasing population.

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