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HIV-1 Tat-induced increases in depression-like effects were linked to oxidative stress

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Dr. McLaughlin and colleagues published a very interesting and potentially impactful manuscript titled “Conditional human immunodeficiency virus transactivator of transcription protein expression induces depression-like effects and oxidative stress”.[1] Performing animal behavior studies is difficult and doing behavior studies properly is very easy to do badly. This group and the careful behavioral analyses no doubt led by the behavioral neuroscientist Dr. Paris gives confidence that the data and the associated analyses are robust. The principal findings of this work were that expression of the HIV-1 transactivator of transcription (Tat) protein in HIV-1 Tat transgenic mice produced depression-like effects including increased tail suspension immobility time and decreased saccharin consumption. Mechanistically, their studies implicated oxidative stress in these behavioral effects by showing that HIV-1 Tat expression increased measures of oxidative stress and that the administration of the pro-oxidant methylsulfonylmethane increased immobility time thus mimicking the effects of HIV-1 Tat while administration of the anti-oxidant diethylmaleate decreased immobility time and protected against the effects of HIV-1 Tat.

Depression, as diagnosed using DSM-V criteria, is a serious but in many cases treatable neuropsychiatric disorder. The 12-month prevalence of major depressive episodes among adults in the USA was reported in 2015 to be 10.3% among 18–25 year olds, 7.5% among 26–49 year olds, and 4.8% in people 50 years of age or older. Thus, the prevalence is higher in young adults than in older adults. Furthermore, the prevalence of major depressive episodes across all age groups was much higher in females (8.5%) than males (4.7%). Of great concern to HIV-1 infected individuals and their families, friends and coworkers are findings that the prevalence rates of major depression in HIV-1 infected individuals ranges from 30 to 50%; clearly these rates are much higher than those observed in the general (HIV negative population). Furthermore, it is difficult in many cases to separate HIV-1 and depression from the ingestion of drugs of abuse because these are highly interlinked and because HIV-1 infected individuals have a high degree of substance abuse issues. Indeed, they commonly ingest tobacco products, alcohol, marijuana, psychostimulants and opioids, and it is clear that drugs of abuse increase the prevalence and severity of neurological complications associated with the virus.[6]

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HIV-1 Tat protein, the focus of this study, can directly excite neurons, can decrease neuronal cell viability, can decrease mitochondrial function, and can increase oxidative stress. Substantial evidence exists that HIV-1 Tat plays an important role in the perpetuation of a chronic neuroinflammatory state in brain and in the pathogenesis of HIV-1 associated neurological disorders. Indeed, HIV-1 Tat levels have been shown to be elevated even when HIV-1 replication is effectively controlled by anti-retroviral therapy.[3] As was shown by McLaughlin et al., the effects of HIV-1 Tat on depression-like behavior persisted long after HIV-1 Tat levels were no longer detectable; findings consistent with the so called 'hit and run' phenomena described by Nath and colleagues almost two decades ago.[4]

The implications of this work to neuropsychiatric complications in the HIV-1 infected population are of obvious importance. Therefore, it is of no surprise that this work raises many more issues and questions that no doubt McLaughlin and colleagues have considered. Here we will draw attention to some of the follow-up studies that they might be conducting even as we read this commentary. First, in this study, they used only male mice and the mice studied were quite young (8 to 13 weeks of age). Because the mice were used soon after conditional expression of HIV-1 Tat was initiated their model might be more closely related to acute and early HIV-1 infection and not to the more chronic neuroinflammatory condition associated with HIV-1 infection and HIV-1 associated neurological disorders. Indeed, in acute and early infected individuals in their early to mid 30's of both genders the incidence of overall mood disorders compared to HIV-1 negative individuals increased from 15.4 to 61.8% and of major depressive disorders increased from 12.8% to 47.1%.[2] Thus, in subsequent studies it would be important and clinically relevant to determine the extent to which age and gender play roles in the involvement of oxidative stress in the depression-like effects of HIV-1 Tat, the possibility that enhancing endogenous anti-oxidants or administering exogenous anti-oxidants can reverse these depression-like effects, and to test these issues in models of acute and early versus chronic HIV-1 infection. Second, as they pointed out, they only tested a single dose of the anti-oxidant methylsulfonylmethane and the pro-oxidant diethylmaleate and thus additional studies might be focused more on the pharmacokinetics and pharmacodynamics of these (and possible additional) agents for translational significance. Third, it would be interesting to know if antidepressants without anti-oxidant properties could also reverse depression-like behavior induced by HIV-1 Tat. Fourth, HIV-1 Tat is but one of the HIV-1 proteins possibly involved in the pro-oxidative state that exists in the context of HIV-1 infection; increased levels of reactive oxygen species that been described as well for gp120, Nef and Vpr.[5] Therefore, examining the effects of these proteins alone and in combination with HIV-1 Tat on depression-like effects will be important. Fifth, the findings that HIV-1 Tat increased depression-like behavior raises many important questions that need addressing including the necessity to determine the extent to which HIV-1 and HIV-1 proteins through actions on dopaminergic systems cause anhedonia and thereby increase depression, drug seeking behavior and substance abuse. Already, much is known about HIV-1 Tat interacting with dopamine transporters and it would be fascinating to know the extent to which oxidative stress is involved in these complex interactions.

This manuscript contained experiments that were carefully constructed and performed, data that were thoughtfully analyzed and described, and descriptions of discussion points that

were clinically relevant. We look forward to additional manuscripts possibly addressing some of the issues raised in this commentary.

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