Society on NeuroImmune Pharmacology (SNIP)
25th Annual Scientific Conference
April 10 - 13, 2019, Portland, OR

Late Breaking Abstracts & Posters – Wednesday

W53 Impact of pharmacological activation of glycolytic enzyme pyruvate kinase isoform M2 (PKM2) on HIV replication in macrophages.

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Human pyruvate kinase isoform M2 (PKM2) is a glycolytic enzyme involved in the irreversible transphosphorylation between phosphoenolpyruvate (PEP) and adenosine diphosphate, which produces pyruvate and ATP. We have shown that it moonlights as a co-activator of HIV-1 LTR by interacting with the p65 subunit of NF-kappaB. Furthermore, we demonstrated an increase in the nuclear dimeric form of PKM2 in the PMA-induced U1 cells in comparison to PMA-induced U937 cells. Since the active form of PKM2 is a tetramer and is involved in glycolysis, we assessed the impact of pharmacological activators of PKM2 such as TEPP-46 and DASA-58 that promotes tetramerization of PKM2 on HIV-1 replication in U1 cells. Our results demonstrate that both TEPP-46 and DASA-58 induces tetramer form of PKM2 and also reduces nuclear translocation of PKM2. Furthermore, both the activators inhibit HIV-1 replication in U1 cells. These observations, taken together suggest that small molecule activators of PKM2 can be used to attenuate HIV-1 biogenesis in macrophages.

Supported by NIH/NIDA

W54 The Integrated National NeuroAIDS Tissue Consortium: A Rich Platform for HIV Research

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Those living with HIV with access to antiretroviral therapy (ART) are living longer, healthier lives. However, neurocognitive disorders persist, and new areas of concern and research exist. One is cerebrospinal fluid (CSF) escape, where virus can be present in the CSF but not in the plasma. Another is viral reservoirs in those with suppressed virus, key for efforts to cure HIV. A third is that people living with HIV may be at higher risk for developing chronic, non-HIV related conditions. A fourth is interaction with issues related to drugs of abuse. To help scientists address these issues, the National NeuroAIDS Tissue Consortium (NNTC) is an outstanding resource. The NNTC has enrolled over 3000 participants with a wealth of data and specimens. Our biobank also includes a set of brains, other organs, and biofluids from 57 cases of subjects on ART with viral suppression that show exceptional utility for HIV eradication research. The NNTC also manages the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study of over 1600 participants. Data and biospecimens from CHARTER and NNTC cohorts are available to qualified researchers upon request. Data generated by requestors are returned to the NNTC, annotated, curated, and added to the database, thereby extending the utility of each case. Furthermore, a new platform, the Global CSF Escape and Reservoir Consortium for HIV-1 (Global CERCH) has been initiated to provide information and facilitate research and collaborations on CSF escape and other HIV reservoir issues. Access is at www.nntc.org and neuroaids-dcc.unmc.edu.

Supported by NIMH, NINDS

W55 Itaconic and Glutaconic Acid Effects on Neuronal Dendritic Spine Morphology in the Rat Medial Prefrontal Cortex and Nucleus Accumbens: Translational Results of a Metabolomic Study of HIV-Associated Neurocognitive Disorder

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HIV-associated neurocognitive disorder (HAND) remains an important problem, despite otherwise effective antiretroviral therapy (ART). While the etiology of HAND is only partly understood, synaptodendritic simplification is one of its known hallmarks. We performed an untargeted cerebrospinal fluid (CSF) metabolomics analysis in 60 adults with HIV on ART without active substance use, lifetime substance dependency, or neuro-confounding conditions (mean age 47, median nadir CD4 167 cells/µl, 75% with undetectable plasma virus). Thirty (50%) had HAND, defined by a Global Deficit Score >0.5, and 30 were stably unimpaired adults with HIV, who were comparable to cases on age, ART, and plasma virus detectability. Two compounds, itaconic acid (IA) and glutaconic acid (GA) were significantly associated with HAND (false-discovery-rate-adjusted $p<0.05$). The effects of purified IA and GA on synaptic complexity were then assessed in F344/N rat brain slices containing the medial PreFrontal Cortex (mPFC) and Nucleus Accumbens core (NAcc). Compared to controls, exposure to either GA or IA at 300µM for 30 minutes significantly reduced numbers and types of spines of medium spiny neurons in the NAcc; GA had a greater adverse impact on dendritic spines in mPFC than IA, with a significant reduction in the branch order of cortical neurons. We identified 2 novel CSF metabolites associated with HAND, IA (produced by activated microglia) and GA (a gut microbiome derivative), which also induced synaptodendritic damage in the rat mPFC and NAcc. These compounds may mediate development of HAND in humans.

Supported by NIH R01 HD043680; MH106392, DA013137, and NS100624 (to RB and CM)

W56 CANNABIS USE AND CLINICALLY SIGNIFICANT IMBALANCE IN PEOPLE LIVING WITH HIV

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Background: Falls are a leading cause of fatal and nonfatal injuries among older adults. HIV+ adults are at greater risk of sustaining injury from a fall. Cannabis use, common among HIV+ adults, may contribute to imbalance and risk for fall. The contribution of cannabis to this risk has not been investigated. Objective: To evaluate the contribution of recent cannabis use to balance disturbance (BD) in HIV+ and HIV- adults. Methods: Ambulatory HIV+ (N=2,887) and HIV- (N=761) adults were subgrouped by cannabis last use within seven days of the interview (recent use) or more than seven days prior to the interview (remote/never). Self- reported BD with onset within the past 10 years were coded as none-minimal and mild-moderate. Multivariable analysis were adjusted for age, gender, HIV disease and treatment characteristics, diabetes, neuropathy, and medication (sedative, opioid, antihypertensive). Results: Onset of BD within the past ten years was endorsed by 11.9% of participants. BD was more common among HIV+ (13.5%) than HIV- (5.5%) adults. Recent cannabis use was more common among HIV+ adults (26.4% versus 19.3%). There was no difference in the frequency of BD among HIV+ with and without recent cannabis use. However, HIV- adults with recent cannabis use had significantly more BD than those with no recent cannabis use. Conclusion: Unlike in HIV- adults, recent cannabis use does not increase risk of BD in HIV+ adults. These data imply that cannabis does not significantly alter risk of fall in HIV+ persons. The reason for this finding is unclear and further study is warranted.

Supported by National Institute of Health

W57 Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO): A Data and Biospecimen Resource for Researchers

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The Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) stimulates research and encourages new collaborations with the NIDA-funded longitudinal cohorts studying substance abuse in the context of HIV transmission and progression. C3PNO fosters innovative science powered by a combined sample size of 12,000 active participants and data for 20,000 historical participants. Our work

includes: Facilitating scientific cooperation and initiatives between cohorts and outside investigators; sharing of specimens, data, and methods; developing methods to link data and measures across cohorts and consortia; promoting measurement tools and data collection instruments standardization; providing expertise in biostatistics, epidemiology, and clinical research About the Cohorts: C3PNO cohorts span the U.S. and Canada with the earliest founded in 1987. The cohorts follow a diverse group of mostly street-based HIV- and HIV+ persons in and out of care, including gender diverse substance users, people who inject drugs, racial/ethnic minorities, viremic HIV+ persons. About the Data: Linked clinical, behavioral, and biological data collected over multiple timepoints. Substances of focus include alcohol, cannabis, cocaine, methamphetamine, opioids, (e.g., prescription drugs, heroin, and fentanyl), and tobacco. Biospecimens include: plasma, sera, PBMCs, hair, nails, and rectal swabs. About C3PNO: A collaboration of the NIDA cohorts (ACCESS, ALIVE, Heart Study, HYM, JHHCC, MASH, mSTUDY, RADAR, and V-DUS), UCLA, and Frontier Science. Learn more at www.c3pno.org.

Supported by National Institute on Drug Abuse/U24DA044554

W58 Perkin Elmer Poster 1

Late Breaking Abstracts & Posters – Thursday

T53 Fibroblast Growth Factor 21 (FGF21) Attenuates the Preference for Morphine in Conditioned Place Preference Assay

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Fibroblast growth factor 21 (FGF21) is a member of the endocrine family of growth factors. FGF21 crosses the blood-brain barrier and exerts many effects on the central nervous system. Previous studies showed that FGF21 reduced alcohol consumption and saccharin preference in a 2-bottle choice assay with mice (Talukdar et al., 2016). Initially, we investigated whether there was epigenetic regulation of FGF21 synthesis in C6 glioma cells. HDAC and GSK-3beta inhibitors increased FGF21 mRNA in a time- and concentration- dependent manner. FGF21 transgenic (FGF21-Tg) mice were found to have a 2400-fold higher FGF21 protein serum level than wildtype littermates. FGF21-Tg mice had approximately a 50% reduction in the preference for 10 mg/kg morphine in the conditioned place preference assay in comparison to wildtype littermates. At a dose of 3 mg/kg, wildtype mice still had a preference for morphine, while the FGF21-Tg female mice did not exhibit any preference for morphine. Differences between male and female mice were observed.

Supported by Supported by DA044766 from NIDA.

T54 Mephedrone, a psychoactive drug of abuse, exacerbates the effects of HIV-1 gp120 on brain endothelial barrier disruption

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Synthetic cathinones, such as mephedrone, are an emerging class of designer drugs consumed for psychostimulant and hallucinogenic effects. Recently in the US, the use of synthetic cathinones (bath salts) have dramatically increased, especially among adolescent and young adult populations. Several public health reports have also linked cathinone use with outbreaks of HIV-1. Here, we examined the effects that mephedrone, alone or in combination with the HIV-1 envelope protein gp120, may have on human brain endothelial cells. We report that mephedrone application to the endothelial cell monolayer resulted in transient decrease in transendothelial electrical resistance (TEER) indicating compromised barrier integrity. Significant upregulation of ICAM-1 (+80%) but not VCAM-1 was detected in cells exposed to mephedrone, suggesting activation of brain endothelial cells. Although activation of adhesion molecules by gp120 treated cells is marginal, the combination of mephedrone and gp120 increased both

ICAM-1 and VCAM-1 upregulation by +37% and +33% respectively. Our findings suggest that mephedrone triggers brain endothelial activation which may facilitate immune cell transmigration across the BBB. We also showed that mephedrone exposure exacerbates the deleterious effects of gp120 on barrier integrity. Together, these results are the first to suggest that designer drugs, like mephedrone, induce disruption of the BBB. Moreover, our data points to a contributing role for cathinones in HIV-1 CNS infection and neuroinflammation.

T55 Gut Microbiome Dysbiosis is Related with Negative Emotional States in HIV Infection

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People living with HIV (PLWH) commonly experience emotional and social stresses that can impact their quality of life. The biological mechanisms underlying emotional distress are not well understood. Since gut microbiome dysbiosis occurs in PLWH and can affect emotional responses, we investigated their relationship. The analysis included 32 PLWH and 13 people living without HIV (PLWOH) who were assessed at the University of California San Diego. We collected stool, sociodemographic and clinical data, and measured emotional functioning (NIH toolbox emotional battery). We sequenced the 16S rDNA V3-V4 region and analyzed the data using CLC Microbial Genomics Module and R statistical software. PLWH reported significantly more Negative Affect, less Social Satisfaction and less Psychological Well Being than PLWOH ($p<0.05$, for all). The gut microbiome of PLWH had significantly more Prevotella spp. and fewer Bifidobacterium spp. and Bacteroides spp. at the genus level ($p<0.01$, for all). PLWH also had significantly more oral bacteria (facultative anaerobes) in the gut than PLWOH ($p<0.01$). Higher levels of oral bacteria were associated with more Negative Affect ($\rho=0.46$, $p<0.01$), less Social Satisfaction ($\rho=0.42$, $p<0.01$) and less Psychological Well Being ($\rho=0.35$, $p=0.02$). PLWH were more likely to report negative emotional states, which were associated with an increase in oral bacteria in the gut and may reflect worse oxidative stress and barrier defects. This microbial profile could inform therapeutic strategies targeting the microbiome to improve inflammation and emotional distress.

Supported by NIH: Sustained Training on Aging and HIV Research (STAHR) Program 5R25MH108389-02 (PIs: Jeste, Dilip V.; Letendre, Scott L.)

T56 Antiallodynic Effects of Cannabinoid Receptor 2 Agonists on Retrovirus Infection-induced Neuropathic Pain

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Previous data show that distal symmetric polyneuropathy (DSP) develops along with murine acquired immunodeficiency syndrome (MAIDS) following infection with the LP-BM5 retrovirus mixture. In this study, we evaluated whether the exogenous synthetic cannabinoid receptor 2 (CB2R) agonists JWH015, JWH133, Gp1a, and HU308 could control neuropathic pain and neuroinflammation. Using the MouseMet electronic von Frey system, we assessed hind-paw mechanical hypersensitivity in CB2R agonist-treated vs. untreated animals. Multicolor flow cytometry was used to determine effects of CB2R agonists on macrophage activation and T lymphocyte infiltration into dorsal root ganglia (DRG) and lumbar spinal cord (LSC). Results demonstrated that following weekly i.p. injections starting at 5 wk p.i., JWH015, JWH133, and Gp1a; but not HU308 (5 mg/kg), significantly ameliorated mechanical allodynia when assessed 2 h after ligand injection. However, treatment with these same agonists (2x/wk) did not display antiallodynic effects when sensitivity was assessed 24 h after ligand injection. Macrophage activation and T lymphocyte infiltration into DRG and LSC was observed at 12 wk p.i., but was not found to be affected by CB2R agonists. Activation of JAK/STAT3 contributes to development of neuropathic pain in the LSC and pretreatment of primary murine microglia (2 h) with JWH015, JWH133, or Gp1a was found to block IFN-g-induced phosphorylation of STAT1 and STAT3. Taken together, CB2R agonists demonstrated acute, but not long-term, antiallodynic effects on retrovirus infection-induced neuropathic pain.

Supported by National Institute on Drug Abuse/DA-039464

T57 Novel allosteric modulatory effects of SRI-32743 on HIV-1 Tat protein-induced inhibition of human dopamine transporter and potentiation of cocaine reward in HIV-1 Tat transgenic mice

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Cocaine abuse has been shown to increase the incidence of HIV-1 associated neurocognitive disorders. We have demonstrated that HIV-1 Tat allosterically modulates dopamine (DA) reuptake via human DA transporter (hDAT). This study determined whether a novel allosteric modulator, SRI-32743, pharmacologically blocks Tat binding to hDAT and alleviates Tat-potentiated cocaine rewarding effects in inducible HIV-1 Tat transgenic (iTat-tg) mice. SRI-32743 inhibited [3H]DA uptake (IC50, 9.9 µM) with a 17-fold greater inhibition than the potency of [3H]WIN35,428 binding (IC50, 168 µM) with 68.4% and 71.4% of its Emax, respectively. Tat (140 nM) induced 30% and 20% reductions in [3H]DA uptake and [3H]WIN35,428 binding, respectively, which were attenuated by SRI-32743, while SRI-32743 alone did not alter DAT function and binding. SRI-32743 and indatraline, a competitive DAT inhibitor, increased the cocaine IC50 values of [3H]DA uptake by 164% and 280%, respectively. The cocaine (1 µM)-induced dissociation rate (0.238 ± 0.030) of [3H]WIN35,428 binding was similar to that induced by 50 nM SRI-32743 (0.187 ± 0.027); however, SRI-32743 slowed the cocaine-induced dissociation rate to 0.032 ± 0.005. Following a 14 day-doxycycline treatment to induce Tat protein, the iTat-tg mice exhibit a 2-fold potentiation of cocaine-CPP which was dose-dependently ameliorated by pretreatment of SRI-32743 (1 or 10 mg/kg/d, i.p.) prior to CPP. These results demonstrate that developing allosteric modulatory molecules which attenuate cocaine and Tat binding to DAT are of great scientific and clinical potential.

Funding support: NIH/NIDA DA035714 and DA041932

T58 Perkin Elmer Poster 2

T59 Sequencing the microglia translatome during morphine escalation and naloxone precipitated withdrawal: The role of cyclic nucleotide signaling

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Many facets of opioid dependence contribute to the clinical and social crisis that we are now facing. The threat of withdrawal symptoms is a major barrier that stops individuals who would like to discontinue opioids. Furthermore, these symptoms can precipitate relapse to drug taking in order to alleviate withdrawal. In this experiment we investigated the contribution of microglia to withdrawal using RiboTag, a technique which allows for isolation and analysis of RNA that is actively undergoing translation in a specified set of cells. We used male and female transgenic CX3CR1-Cre/RiboTag mice that express HA-tagged rpl22 exclusively in resident microglia. These mice were administered a rapidly escalating, tolerance inducing, non-contingent morphine schedule (versus saline) followed by naloxone-precipitated withdrawal (versus saline), then at 4hrs we sacrificed the mice and immunopurified the ribosome-associated RNA from microglia and then analyzed the RNAs undergoing translation using RNAseq. Gene set enrichment analysis revealed gene sets that are responsive to cyclic nucleotide signaling changing during morphine escalation and withdrawal. Genes related to degradation of cyclic nucleotides are suppressed during morphine escalation, and then increase dramatically during the naloxone precipitated withdrawal. This response by microglia may represent compensatory mechanisms that microglia engage in to combat the cyclic nucleotide storm associated with opioid withdrawal, and may be novel targets for treatment of withdrawal symptoms.

Supported by NIDA 62-8024