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Low dose hydrocortisone has acute enhancing effects on verbal learning in HIV-infected men

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Abstract

Objective—Glucocorticoids are released in response to stress and alter cognition and brain function through both rapid, nongenomic and slow, genomic mechanisms. Administration of glucocorticoids in the form of hydrocortisone enhances aspects of learning and memory in individuals with PTSD, but impairs these abilities in healthy individuals. We examine the time-dependent effects of glucocorticoids on cognition in HIV-infected men.

Methods—In a double-blind, placebo-controlled, cross-over study, we examined the time-dependent effects of a single low dose of hydrocortisone (10mg; LDH) on cognition in 45 HIV-infected men. Participants were randomized to receive either LDH or placebo, and one month later were given the opposite treatment. At each intervention session, cognition was assessed 30 minutes (assessing nongenomic effects) and 4 hours (assessing genomic effects) after pill administration. Self-reported stress/anxiety and cortisol/cytokines in saliva were measured throughout each session.

Results—Compared to placebo, LDH doubled salivary cortisol levels. Cortisol returned to baseline 4 hours post-administration. At the 30-minute assessment, LDH enhanced verbal learning compared to placebo. Greater increases in cortisol were associated with greater enhancements in verbal learning. LDH did not affect subjective stress/anxiety or any other cognitive outcomes at the 30-minute or 4-hour time point.

Conclusion—The rapid effects of LDH on verbal learning suggests a nongenomic mechanism by which glucocorticoids can enhance cognition in HIV-infected men. The non-enduring nature of

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this enhancement may limit its clinical utility, but provides insight into mechanisms underlying the effects of acute glucocorticoids on learning.

Keywords

hydrocortisone; cognition; HIV; men

INTRODUCTION

Even in the era of combination antiretroviral therapy (cART), HIV-infected individuals show deficits in executive function, complex attention, processing speed, learning, and memory^{1–3}. Associated dysfunction of fronto-striatal networks⁴ and alterations in hippocampal and prefrontal brain regions^{5–7} may reflect the distribution of HIV-related neuropathology, neuroinflammation, and/or selective neuronal vulnerability to HIV-mediated damage in these regions^{8–12}. The hypothalamic-pituitary-adrenal (HPA) axis may also be an important contributor to HIV-associated cognitive manifestations. As a key mediator of the effects of stress on the hippocampus and prefrontal cortex, the HPA axis exerts cognitive effects via release and action of its primary steroid hormone, cortisol¹³. HIV-infected compared to HIV-uninfected individuals demonstrate HPA axis alterations which may contribute to their cognitive difficulties including elevated basal cortisol levels^{14–19}, attenuated diurnal cortisol variations¹⁹, and reduced cortisol responsivity to challenges²⁰. Thus, investigations into the causal role of the HPA axis in HIV-associated cognitive perturbations may indicate its importance as an additional treatment target.

Pharmacologic challenge studies with hydrocortisone, the exogenous form of cortisol, allow for evaluation of the direct link between the HPA axis and cognition in HIV, independent of psychological stress. Although no studies to date have evaluated the effects of hydrocortisone on cognition in HIV, low dose hydrocortisone (LDH) enhances aspects of learning and memory in PTSD^{21–24}, has no effect in current depression^{25,26}, and often impairs these abilities in healthy individuals²⁷ although these effects are dependent on the timing of assessments in relation to LDH administration^{27–29}. Traditionally, LDH effects on cognition are studied approximately 30–45 minutes post-LDH administration. This approach models the physiological effects of acute stressors on cognition and addresses the immediate, rapid effects of LDH. Recent studies; however, have assessed cognition four hours post-LDH administration to examine the delayed, slow effects of LDH, effects that are attributable to genomic factors. The 4-hour assessment is clinically meaningful as it occurs post-peak, when cortisol levels are steady and typical of the broader daily cortisol profile in individuals treated with LDH³⁰.

In a randomized, double-blind, placebo-controlled cross-over design, 45 HIV-infected men received 10mg of hydrocortisone (LDH), a widely used dose in prior cognitive studies^{28,31,32}, or placebo prior to testing which occurred 30-minutes and 4-hours post-pill administration. We hypothesized that LDH relative to placebo would impair learning and memory at both time-points. Given LDH may affect cognition by inducing immune change^{33,34}, we also examined whether any cognitive changes were related to immune changes.

METHODS

Participants

Participants were recruited through HIV primary care clinics and the surrounding community via advertisements/websites. Inclusion criteria were confirmed HIV seropositive by medical record, age 18–45 years, English as a first language, and use of same cART three months. Exclusion criteria were DSM-IV SCID diagnosis of mood disorders in the past year or history of anxiety/psychotic disorders, current use of psychiatric medications; reported neurological conditions impacting cognition (e.g., stroke), BMI >40, history of substance abuse/dependence in the past 6 months excluding alcohol/nicotine, and inability to abstain from illicit substances 24 hours prior to testing via urine toxicology screen.

Procedures

Qualifying participants visited UIC for an initial visit (Session 1) and provided informed consent, completed a DSM SCID interview, vitals assessment, toxicology screen, and questionnaires including Childhood Trauma Questionnaire (CTQ)³⁵, Schedule of Life Events checklist³⁶, PTSD Checklist–Civilian version (PCL-C)³⁷, Perceived Stress Scale (PSS-10)³⁸, Center for Epidemiologic Studies Depression Scale (CES-D)³⁹, Pittsburgh Sleep Quality Index⁴⁰, and Medication Adherence Self-Report Inventory⁴¹.

Forty-five HIV-infected men (Table 1) returned for two parallel visits (Sessions 2&3) nested in a randomized, double-blind, placebo-controlled, cross-over pharmacologic challenge study. UIC's Investigational Drug Service randomized participants to receive either LDH or placebo at Session 2; opposite treatment at Session 3. Sessions 2&3 entailed a toxicology screen, blood draw, vitals assessment, questionnaires, cognitive assessments, and collection of saliva samples. Session 2 occurred within 1 week of Session 1 and Session 3 occurred ~1 month after Session 2. Sessions 2&3 occurred between 12:00 pm (±30min) and 6:00 pm (±30min) to control for diurnal cortisol variations⁴².

Cognitive Measures

Learning/memory: Hopkins Verbal Learning Test (HVLT-R; learning outcome= Trial 1 learning, total learning; memory=delayed recall)⁴³; **Attention/concentration:** WAIS IV Letter-Number Sequencing (LNS) control condition (outcome=total correct)⁴⁴, Trail Making Test (TMT) Part A (outcome=time to completion)⁴⁵, congruent trials on the computerized Stroop (outcome=accuracy)⁴⁶; **Executive function:** LNS experimental condition (outcome=total correct)⁴⁴, TMT Part B (outcome=time to completion)⁴⁵, incongruent Stroop trials (outcome=accuracy); **Visuospatial ability:** RBANS Line Orientation (outcome=total correct)⁴⁷.

The battery administered 30 minutes post-pill administration included HVLT, LNS, TMT, Stroop, and RBANS (administration time= 35–45 minutes); 4 hours post-pill administration included HVLT, LNS, and TMT (administration time= 35–45 minutes). Four alternate versions of HVLT, LNS, and TMT were used to minimize carryover effects^{48–50}; all forms were counterbalanced. Stroop was only administered 30 minutes post-pill administration because of greater susceptibility to practice effects⁵⁰.

Physiological and Psychological Measures

During Sessions 2&3, salivary samples were taken 35 and 20 minutes pre-pill administration and 30, 60, 90, 180, 210, 240, 270, and 300 minutes post-pill administration^{31,32,35}. Saliva was collected via straws into Nalgene tubes, stored at -80° , and samples were batch shipped to Salimetrics and assayed for cortisol (EIA kit, sensitivity $<0.007\mu\text{g/dL}$).

For cytokines, saliva was collected 20 minutes pre-pill administration and 30 and 240 minutes post-pill administration. We computed the median cytokine value across three saliva samples from the placebo day⁵¹ and change from the median cytokine value during placebo to acute and delayed time points during the LDH session ((placebo – LDH acute)/placebo)). We assessed IL-6, TNF- α , IL-8, IL-1 β , CRP, macrophage migration inhibitory factor (MIF), chemoattractants interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein (MCP)-1, monokine induced by interferon (MIG), cell surface receptor TNF receptor type 2 (TNFR2), matrix metalloproteinase MMP-9, and MMP-2. Saliva was batch assayed in duplicate using a MILLIPLEX MAP human high sensitivity T-cell panel immunology multiplex assay (Millipore, Billerica, MA) for IL-1 β , IL-6, IL-8 and TNF- α (standard curves 0.18–7500pg/mL; average interplate CV 9.9%); MILLIPLEX MAP standard sensitivity cytokine for IP-10 and MCP-1 (3.2–10,000 pg/mL; average interplate CV 9%); R&D systems (Minneapolis, MN) singleplex to detect TNFR2 (12–50,000 pg/mL; average interplate CV 5.75%), and R&D systems custom 5-plex for CRP, MIP, MIG, MMP-2, and MMP-9 (144–96,000 pg/mL; average interplate CV 12.7%). Milliplex results were acquired on a Labscan 200 analyzer (Luminex, Austin, Tx) using Bio-Plex manager software 6.1 (Bio-Rad, Hercules, CA). Undetectable samples were assigned one-half the lowest detectable value. Cytokine values were log transformed due to non-normality.

Concurrent with saliva sampling, participants completed the 6-item State-Trait Anxiety Inventory and a two-item Visual Analogue Scale measuring how “anxious” and “stressed” participants felt.

Statistical Analysis

Mixed-effects regressions (MRM, random intercept) were conducted in SAS (v.9.4 for Windows) to examine LDH effects on physiological, psychological, and cognitive measures. For cortisol/psychological measures, predictors were Treatment (LDH, placebo), Time (treated categorically), and Treatment x Time interaction. For cognition, predictors included Treatment, Time (Acute, Delayed), and Treatment x Time interaction. Models adjusted for sequence of cognitive testing forms and treatment sequence to account for potential bias due to carry-over effects. MRMs also were used to examine LDH-induced changes in immune cytokines with treatment sequence as a covariate.

Correlations were conducted to determine whether cognitive changes (LDH - placebo) and/or immune changes were associated with cortisol responsivity to LDH (computed area under the curve-AUC⁵²). Exploratory correlations were conducted between individual difference factors (CTQ, PSS-10, PCL-C, CES-D, SLE), HIV-related clinical characteristics (CD4 count, viral load), and AUC. Factors correlating with AUC were examined in a series

of multivariable linear regressions to determine if those factors mediated cognitive changes by their effects on cortisol responsivity to LDH^{53,54}.

RESULTS

Mean salivary cortisol levels at 30 and 45 minutes before LDH and placebo (i.e., baseline) was 0.20ug/dl (5.1 nmol/L). Levels changed across study duration during LDH but not placebo. Compared to baseline, levels increased at 105 and 150 minutes post-LDH administration (p 's<0.001), the time frame when the "acute" cognitive battery was administered. Cortisol levels returned to baseline levels at the 315 and 360 minute time points following LDH (p 's>0.68), the time frame when the "delayed" cognitive assessment was obtained. Self-reported anxiety and stress levels remained stable across study duration and Session (p 's>0.88). IL-8 and MMP-2 decreased from baseline with LDH at the 30-minute time point (p 's<0.05).

Participants showed significant improvement only in learning after receiving LDH compared to placebo at the 30-minute time point (Table 2). There were no effects of LDH on any outcome at the 4-hour time point. At the 30-minute time point, the greater the increase in cortisol following LDH, the better the scores on trial 1 (r =0.35, p =0.02) and total learning (r =0.38, p =0.01) during LDH relative to placebo. Associations remained after controlling for cortisol levels during placebo (p 's<0.05). Changes in IL-8 or MMP-2 did not correlate with acute learning changes.

More stressful life events (r =0.32, p =0.03) and greater emotional abuse (r =0.30, p =0.04) were associated with greater increases in cortisol following LDH but not placebo. While these measures were not related to learning, mediational analyses indicated that stressful events influenced changes in total learning indirectly through cortisol responsivity to LDH (97% of the total effect (12%) was explained by the indirect effect). The same pattern was seen with childhood emotional abuse (98% of the total effect (11%) was explained by the indirect effect). CD4 count and viral load were not associated with LDH cortisol changes (p 's>0.36).

DISCUSSION

Our primary goal was to examine the time-dependent effects of LDH on cognition in HIV-infected men. Secondary goals were to examine the mechanisms underlying these effects and determine who might benefit most from LDH. We demonstrated that relative to placebo, LDH has only acute cognitive enhancing effects. The benefit was observed on measures of learning but not memory, attention/concentration, executive function, or visuospatial abilities. The enhancement was observed in the early but not later time point and the magnitude of the enhancement was associated with the magnitude of cortisol response. Those findings suggest that LDH may work acutely through nongenomic mechanisms to normalize stress-induced alterations in the HPA axis and enhance learning in HIV-infected men. Those who showed the greatest cognitive enhancement had more stressful life events and a greater degree of emotional abuse those showing less enhancement. Mediational analyses revealed that the association between these individual difference factors and

cognition was due to the individual differences in cortisol response following LDH. Thus, HIV-infected men experiencing more stress/trauma may showed the greatest acute cognitive benefits from LDH because LDH in these men may increase glucocorticoids to levels supporting learning.

Our findings provide further evidence that the cognitive effects of LDH depend on dose, administration timing, cognitive domains assessed, and mental health factors^{21,27}. Although participants had no history of PTSD, they reported above-average levels of stress compared to healthy men in other studies⁵⁵ as well as exposure to violence/abuse. Broadly, our findings of acute LDH learning improvements are consistent with studies in PTSD^{23,24}. Although we did not find improvements in attention and working memory which others have demonstrated⁵⁶, those changes were noted 75 minutes post-LDH in PTSD^{21,22}. We did not test during this time frame therefore it is possible that learning remains elevated for some time and that other abilities might be enhanced at that time point. The generalizability of these findings across different doses and duration and to the broader population of HIV warrants further study.

In sum, administration of LDH in HIV-infected men increased cortisol and enhanced learning acutely but not in the longer term. The absence of cognitive benefit in the delayed time point, when cortisol levels returned to baseline, indicates that LDH may have limited clinical utility for treating cognitive impairments in HIV-infected men. However, our findings provide insights into mechanisms and individual difference factors underlying the effects of acute glucocorticoids on learning.

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Table 1

Demographic and clinical characteristics for HIV-infected men at enrollment visit, Session 1 (n=45).

Variables	M (SD) or n (%)	Median (IQR)	Range
<i>Socio-demographic factors</i>			
Age	32.36 (8.77)	30 (18)	18–45
Education			
<High school	23 (51)		
High school graduate	12 (27)		
>High school	10 (22)		
Race/Ethnicity			
Black, not Hispanic	42 (93)		
White, not Hispanic	-		
Other	3 (7)		
Unemployed	32 (71)		
Sexual identity			
Only straight/heterosexual	7 (15)		
Mostly straight/heterosexual	3 (7)		
Only gay	22 (49)		
Mostly gay	4 (9)		
Bisexual	9 (20)		
<i>Risky health behaviors</i>			
Smoking			
Never	9 (20)		
Former	4 (9)		
Current	32 (71)		
Number of Alcohol drinks/week	1.31 (1.71)	1 (1.5)	0–9
Current use			
Marijuana	27 (60)		
Number of times used/week	3.26 (4.78)	2 (3)	0–25
Urine toxicology screen positive for marijuana	22 (49)		
Cocaine	1 (2)		
Heroin	0 (0)		
Methadone	0 (0)		
Methamphetamines	1 (2)		
Ever dependent/abuse alcohol	11 (24)		
Ever dependent/abuse substances	15 (33)		
<i>Psychological profile</i>			
Major depression [†] in lifetime but not past year	15 (33)		
Depressive symptoms (CES-D)(range: 0–60)	11.67 (7.09)	10 (11)	1–28
Perceived stress (PSS-10)(range: 0–40)	19.38 (5.44)	20 (5)	2–39

Variables	M (SD) or n (%)	Median (IQR)	Range
PTSD symptoms (PCL-C)(range: 17–85)	25.91 (7.85)	23 (9)	17–46
Childhood Trauma (CTQ)			
Emotional abuse (range: 5–25)	9.50 (4.98)	7 (7)	5–24
Physical abuse (range: 5–25)	9.18 (4.89)	7 (4)	5–25
Sexual abuse (range: 5–25)	8.93 (6.01)	5 (7)	5–25
Emotional neglect (range: 5–25)	11.31 (5.16)	10 (8)	5–21
Physical neglect (range: 5–25)	8.64 (3.83)	8 (6)	5–21
Negative Life events (SLE)(range: 0–54)	7.93 (5.87)	6 (7)	1–28
Reported exposure to interpersonal violence [‡]	14 (31)		
Reported exposure to sexual abuse [‡]	10 (22)		
<i>Clinical characteristics</i>			
Body mass index	23.33 (4.39)	23 (5.5)	15.97–38.13
Years living with HIV	8.17 (6.30)	6 (12)	0.40–24.18
Medication adherence (MASRI) missing 1 dose:			
3 days summated before visit	13 (29)		
2 weeks before visit	16 (35)		
Last month [±]	20 (44)		
CD4 Count (cells/ μ l)			
> 500	25 (56)		
200 and 500	14 (31)		
< 200	6 (13)		
Viral Load (HIV RNA (cp/ml))			
Undetectable	18 (43)		
Lowest detectable limit (20 cp/ml)	10 (24)		
< 10,000	10 (24)		
10,000	4 (9)		

Note. IQR=Interquartile Range. Current use=use in the last month. CES-D= Center for Epidemiologic Studies Depression Scale; PSS-10=Perceived Stress Scale; PCL-C=PTSD Checklist-Civilian Version; CTQ=Childhood Trauma Questionnaire; SLE=Schedule of Negative Life Events Checklist; PSQI=Pittsburgh Sleep Quality Index; MASRI= Medication Adherence Self-Report Inventory; sexual identity scale based on ⁵⁷.

[‡] based on the Structural Clinical Interview of Mental Health Disorders (SCID);

[±] visual analogue scale for proportion of doses taken in the last month;

[‡] based on information extracted from the PTSD module on the SCID.

Table 2

Time-dependent effects of Low dose hydrocortisone (LDH) versus placebo on cognition in HIV-infected men.

Outcome measures	Time point tested post-pill					
	Immediate, rapid (30 min)			Delayed, slow (4 hours)		
	Placebo M (SE)	LDH M (SE)	LDH vs Placebo B (SE)	Placebo M (SE)	LDH M (SE)	LDH vs Placebo B (SE)
Learning/Memory						
HVLT						
Immediate Trial 1 Learning	5.20 (0.25)	5.80 (0.25)	0.61 (0.27)*	5.43 (0.25)	5.18 (0.25)	-0.25 (0.27)
Total learning	20.64 (0.80)	21.84 (0.79)	1.20 (0.55)*	20.41 (0.80)	20.13 (0.79)	-0.28 (0.54)
Delay recall	6.41 (0.45)	6.62 (0.44)	0.21 (0.33)	4.59 (0.45)	4.22 (0.44)	-0.37 (0.33)
Executive Function						
LNS experimental condition	13.13 (0.67)	12.39 (0.69)	-0.74 (0.39)	13.25 (0.67)	13.45 (0.67)	-0.21 (0.39)
TMT Part B [#]	4.54 (0.08)	4.57 (0.08)	-0.03 (0.06)	4.45 (0.07)	4.42 (0.08)	-0.03 (0.06)
Stroop Incongruent Trials	0.88 (0.03)	0.89 (0.03)	0.01 (0.03)	-	-	-
Attention/Concentration						
LNS control condition	15.36 (0.59)	15.08 (0.59)	-0.28 (0.38)	15.47 (0.59)	15.79 (0.59)	0.32 (0.38)
TMT Part A [#]	3.59 (0.05)	3.57 (0.05)	0.02 (0.04)	3.52 (0.05)	3.52 (0.05)	0.00 (0.04)
Stroop Congruent Trials	0.99 (0.004)	0.99 (0.004)	0.00 (0.01)	-	-	-
Visuospatial abilities						
Line Orientation Test	13.31 (0.69)	13.44 (0.69)	0.13 (0.48)	-	-	-

Note.

* p<0.05.

[#] Log transformed values.

LDH=Low dose hydrocortisone; HVLT=Hopkins Verbal Learning Test; LNS= Letter-Number Sequencing (LNS) task; TMT=Trail Making Test (higher scores=worse performance).