Published in final edited form as:

Am J Addict. 2019 January ; 28(1): 16–21. doi:10.1111/ajad.12828.

Neuroactive Steroid Levels and Cocaine Use Chronicity in Men and Women with Cocaine Use Disorder Receiving Progesterone or Placebo

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Abstract

Purpose/Background: Neuroactive steroids (NAS) may play a role in addiction, with observed increases in response to acute stress and drug use, but decreases with chronic substance use, suggesting that NAS neuroadaptations may occur with chronic substance use. However, levels of NAS in addicted individuals have not been systematically examined. Here, we evaluated a panel of NAS in men and women with cocaine use disorder (CUD) who participated in a clinical laboratory study of progesterone.

Methods/Procedures: Forty six CUD individuals were enrolled in a randomized placebo-controlled laboratory study to evaluate progesterone effects on levels of various NAS. On day 5 of a 7-day inpatient treatment regimen of 400mg/day progesterone (15M / 8F) or placebo (14M / 9F), plasma levels of NAS known to be downstream of progesterone (allopregnanolone, pregnanolone), and NAS not in the progesterone synthesis pathway (androstanediol, testosterone, dehydroepiandrosterone [DHEA] and the NAS precursor, pregnenolone) were analyzed using highly sensitive gas chromatography/mass spectrometry (GC/MS). The relationship between each of the NAS and chronicity of cocaine use was also assessed.

Findings/Results: Progesterone vs placebo significantly increased the GABAergic NAS allopregnanolone and pregnanolone in both CUD men and women. Levels of pregnenolone, testosterone, its GABAergic metabolite androstanediol, and the non-GABAergic DHEA were unaffected by progesterone treatment, and testosterone and androstanediol levels were significantly higher in men than women. Importantly, lower pregnenolone and androstanediol levels were associated with greater years of cocaine use.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Implications/Conclusions: GABAergic NAS that are upstream from the progesterone synthesis pathway appear susceptible to chronic effects of cocaine use.

Keywords

neuroactive steroids; cocaine use disorder; pregnenolone; androstenediol; progesterone

Introduction

Cocaine use disorder (CUD) is a common and serious health problem [1], yet we do not have a complete understanding of the biological adaptations that occur with chronic cocaine use. This presents a significant challenge to the development of effective treatment targets. One neuroadaptation that has been observed in addiction, yet is still largely underexplored in individuals with CUD, is the down-regulation in GABAergic transmission [2] and a decrease in levels of neuroactive steroids (NAS) in the brain and periphery [3–5]. NAS are endogenous modulators of neurotransmission in the brain, and GABAergic NAS are potent allosteric modulators of GABA_A receptors. Moreover, chronic drug use has been shown to result in blunted drug-related NAS and GABA levels, as well as altered responses to stress [2, 6, 7]. These adaptations, in turn, have been associated with behavioral changes critical to drug use outcomes, such as greater emotion dysregulation and compulsive drug seeking [8]. For example, chronic alcohol exposure reduces both plasma and brain levels of the potent GABAergic NAS allopregnanolone (ALLO) [4] in rats and ALLO administration attenuates drug-primed reinstatement of cocaine [9] and cue-induced reinstatement [10] in cocaine dependent animals. Moreover, ALLO administration decreased cocaine-primed reinstatement in female, but not in male rats [11], and decreased yohimbine-induced cocaine reinstatement in female rats only [12], suggesting that ALLO's effects on reducing stress-induced cocaine relapse may be sex-specific. A human laboratory study found that high levels of ALLO, as induced by progesterone administration in CUD men and women, reduced craving in the laboratory, improved negative mood in response to stress, and improved cognitive performance [13]. In addition, acute cocaine administration has been shown to increase serum and brain levels of ALLO in male and female rats [14].

Other NAS such as dehydroepiandrosterone (DHEA) have been examined in CUD. However, unlike ALLO, DHEA is a negative modulator of GABA and therefore an excitatory NAS [17], and may have opposite effects to those of GABAergic NAS. For example, while a preclinical study found DHEA to be effective in reducing cocaine use and reinstatement [15], a placebo-controlled 12 week pilot study of a high dose of DHEA found it to increase cocaine use [16] in individuals with CUD, suggesting that high dosages of DHEA do not effectively reduce symptoms of cocaine use disorder. While these studies demonstrate that NAS play a role in CUD, the impact of chronic cocaine use on the NAS system has not been systematically examined in humans. As such, there is a lack of understanding of the potential adaptive changes in NAS levels that may happen with chronic cocaine use, and tonic levels of different NAS have not been systematically examined in individuals with CUD. Therefore, the purpose of this study was to evaluate a panel of NAS in men and women with CUD who participated in a clinical laboratory study of progesterone, and assess the association between NAS levels and chronicity of cocaine use.

We hypothesized that a) progesterone administration would increase the progesterone metabolites ALLO and pregnanolone, and not have an effect on the NAS precursor pregnenolone which is upstream of progesterone's synthesis pathway, and testosterone and its metabolites; and b) that lower NAS levels will be associated with a greater cocaine use history.

Materials and Methods

Participants

Forty six treatment-seeking cocaine dependent individuals (29M/ 17F) were recruited from the community through local advertisements and enrolled in a previously published randomized placebo-controlled clinical trial to evaluate the efficacy of progesterone to decrease stress- and cue-induced craving in the laboratory in men and women with cocaine dependence [18]. All subjects from this study were included in the current analysis, and the current sample further included 4 more participants over the parent study. Participants met DSM-IV criteria for current cocaine dependence and tested positive for cocaine in urine toxicology screens upon entry into inpatient treatment and study at the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC) for a 3–4 week inpatient admission. The CNRU is a locked inpatient treatment facility with no access to alcohol or drugs and very limited access to visitors. Alcohol and drug testing was conducted 3 times per week, to ensure drug abstinence. Participants were excluded if they met criteria for any other current psychiatric disorder or current and/or lifetime dependence on substances other than cocaine, alcohol or nicotine, determined using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID IV; [19]). Women were excluded from the study if they were using any birth control or were peri- or postmenopausal. Participants were excluded if they required any prescribed medications or were not in good health. All participants gave both written and verbal informed consent and the study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Neuroactive Steroids

Blood samples for neuroactive steroid analysis were obtained on the fifth day of placebo/ progesterone treatment. Plasma levels of pregnenolone, allopregnanolone, pregnanolone, testosterone, androstenediol, and DHEA were measured using the highly sensitive gas chromatography/ mass spectrometry (GC/MS) with electron capture- negative chemical ionization as previously described [13, 20, 21].

Blood samples for progesterone levels were obtained in serum collection tubes and kept at room temperature for 2 h prior to being centrifuged. All samples were then shipped to Graham Massey Analytical Lab, Inc (Shelton, CT) for measurement of progesterone using immune-assay procedures [18].

Statistical Analysis

All statistical analyses were conducted using SPSS software (version 24). Chi-square analyses and independent t-tests were used to compare demographic characteristics.

Independent t-tests were used to assess NAS levels as a function of progesterone vs placebo treatment. Gender differences were examined using ANOVAs. Linear regression models, where NAS levels were the independent variable and years of cocaine/alcohol use were the dependent variable, assessed whether each of the NAS were associated with severity of cocaine or alcohol use.

Results

Participants:

Participants in the progesterone vs placebo groups were matched on all demographic characteristics (Table 1). The groups did not differ in sex or race distribution. Participants in both groups were similar in age and majority of participants were regular smokers. There was no difference in years of cocaine use and in years of alcohol use. Lastly, participants in both groups did not differ in their prevalence of lifetime depression and lifetime anxiety, with or without PTSD.

Neuroactive steroid levels:

As shown in Table 2, levels of progesterone were significantly higher in the progesterone vs the placebo group ($F(1,39)=48.24$; $p<0.001$). Levels of the neuroactive steroid precursor pregnenolone were not affected by progesterone administration and hence did not differ between the two groups ($p>.05$). Similarly, levels of testosterone, its GABAergic NAS androstenediol, and the non-GABAergic DHEA were not affected by progesterone administration and did not differ between the groups ($p>.05$). However, men displayed higher levels of testosterone ($F(1,42)=126.24$; $p<0.001$) and androstenediol ($F(1,42)=75.50$; $p<0.001$) than women (data not shown). Finally, as expected, progesterone significantly increased levels of the potent GABAergic NAS pregnanolone ($F(1,44)=24.21$; $p<0.001$) and ALLO ($F(1,44)=106.43$; $p<0.001$) that are downstream to progesterone in the NAS synthesis pathway.

Cocaine use chronicity:

Levels of NAS measured in this study were used to assess whether they were associated with years of cocaine use, as well as years of alcohol use in this co-morbid population. Standard linear regression analyses indicated that levels of pregnenolone ($\beta = -0.46$, $t = -3.4$, $p < 0.001$) and androstenediol ($\beta = -0.29$, $t = -2.0$, $p < 0.05$) were significantly associated with years of cocaine use, specifically in that lower levels of both NAS were associated with more years of cocaine use. There were no associations with years of alcohol use in this population, and all other NAS did not correlate with either years of cocaine or alcohol use. Moreover, we examined the effects of age on all NAS. Linear regression analysis showed that only levels of DHEA ($\beta = -0.45$, $t = -3.4$, $p < 0.002$) were significantly associated with age, in that DHEA levels decreased with age.

Discussion

The goal of the current study was to more closely examine the neuroactive steroid (NAS) synthesis pathway in individuals with chronic cocaine use, as the dynamic changes and

adaptations that may occur to this neuroendocrine system are not well understood in individuals with CUD. Preclinical evidence demonstrates that multiple NAS are active in the brain. As such the goal of this study was to assess those that are impacted by progesterone and those that are not. The findings in the current study illustrated distinct progesterone-related neuroactive steroids and those that are precursors of progesterone and unrelated to progesterone in the NAS synthesis pathways. Furthermore, findings showed that chronic cocaine use was associated with lower levels of specific GABAergic NAS, pregnenolone and androstenediol. On the other hand and as expected, progesterone administration increased levels of the potent GABAergic NAS pregnanolone and allopregnanolone, while having no effect on the NAS precursor pregnenolone as well as other NAS that are not in the progesterone pathway (see Figure 2).

The role of progesterone and its 3 α -reduced neuroactive metabolites in addiction has been assessed in our laboratory and in that of others [11–13, 18, 22–26]. The novel finding in this study is that lower levels of pregnenolone were significantly associated with years of cocaine use in men and women with CUD. Pregnenolone is the precursor to all downstream steroids and neurosteroids, i.e. those that influence neuronal functioning via extracellular receptors. It is metabolized from cholesterol, and then converted into all steroids, including progestins, estrogen and testosterone, as well as glucocorticoids such as cortisol. Recent basic science and clinical evidence indicate that GABAergic NAS such as ALLO and their neuroactive precursor pregnenolone normalize the HPA axis stress response and reduce drug craving, anxiety, and drug intake [5, 9, 13, 27, 28], suggesting that pregnenolone may be acting by normalizing stress system upregulation and potentially decreasing related compulsive drug seeking [13]. Although the precise role of pregnenolone in addiction is only emerging, preclinical evidence shows that it reduces alcohol self-administration in alcohol-preferring rats [28] and leads to reductions in cannabis intoxication effects in mice and rats [29]. In other clinical populations, pregnenolone has demonstrated significant improvements in clinical outcomes, such as improved negative symptoms, cognitive deficits, and functional capacity in schizophrenia, as compared to placebo [30, 31]. Pregnenolone-induced increases in ALLO also enhanced activation of the emotion regulation neurocircuitry in healthy controls [32]. A randomized placebo-controlled trial of pregnenolone in men and women with bipolar depression improved depressive symptoms [33]. The precise mode of action for pregnenolone remains an open question [34]. While it has been shown to act via Sigma 1 receptors [35], cytoplasmic microtubules and cannabinoid system (CB1) receptors [36], it is also rapidly metabolized into downstream neuroactive steroids, making it difficult to distinguish the effects of pregnenolone versus its metabolites.

The current findings also show that increased years of cocaine use predict lower levels of the NAS androstenediol. Androstenediol is a testosterone-derived, powerful anticonvulsant and highly potent positive allosteric modulator of GABA_A receptors [37]. Acute doses of cocaine have been shown to significantly increase concentrations of androstenediol in the frontal cortex of male rats in a dose-dependent way [38]. This finding also suggests that repeated cocaine exposure could promote chronic adaptations that lead to decreased tonic levels of androstenediol, as is observed in the current study. Moreover, a human study found that genetic variation in a neurosteroid synthesis gene previously found to be associated with risk for alcohol dependence [39] was shown to also be associated with lower synthesis of

androstenediol [21], implying that lower levels of androstenediol may be associated with increased risk of alcohol and/or drug use disorders.

We also examined the effects of age on levels of all NAS assessed in the current study, and found that only DHEA levels decreased with age, whereas DHEA levels did not associate with years of cocaine use, arguing that in the current study we were able to measure distinct effects of chronicity of cocaine use rather than age on levels of NAS. While age is an important factor to always consider when assessing steroids, it is possible that the current sample was fairly young with a mean age of 41 years and therefore age did not confound the results.

It is important to note that an association between pregnanolone and ALLO levels and years of cocaine use was potentially not observed in the current study due to the fact that both NAS were exogenously elevated by progesterone administration and hence did not represent a natural state. Therefore, a study in which endogenous levels of ALLO and pregnanolone are measured in cocaine dependent individuals and then assessed for associations with cocaine use chronicity is needed. While we tested this association in the placebo group (data not shown), no effect was observed likely due to an underpowered sample.

One limitation of this study is that it did not include a control sample. A comparison group of healthy individuals without a history of cocaine use would have informed us on the relative changes in the examined NAS levels that occur with chronic cocaine use, and such a study is timely and necessary. In the current study, we also assessed whether amounts of both cocaine and alcohol associated with NAS levels but didn't find any significant associations. The important limitation here was that we only had information on amounts used in the past month, which may not accurately represent an individual's pattern over the years of use, and a more extensive history of amounts and patterns of use might have been more informative. This should be assessed in a future study. However, the present findings are of value in that they highlight that chronic cocaine use may impact select NAS and result in neuroadaptations in the neuroactive steroid pathway.

Acknowledgements

This research was supported by grants P50-DA016556 (Dr. Sinha), P60 AA03510 (Dr. Covault; UConn Alcohol Research Center) and 5T32DA007238-24 and K12-DA-000167 (Dr. Milivojevic), from the National Institutes of Health and the State of Connecticut. We would like to thank the staff at The Clinical Neuroscience Research Unit (CNRU), The Substance Abuse Center at The Connecticut Mental Health Center and the Yale Center for Clinical Investigation (YCCI) supported by the Yale Clinical and Translational Science Award (Yale CTSA, UL1-RR024139) for their assistance in completing this study.

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Figure 1. Association of years of cocaine use with levels of pregnenolone (left) and androstenediol (right).

Regression analyses show that more years of cocaine use predict lower levels of pregnenolone and androstenediol.

Figure 2. Neuroactive steroid synthesis pathway.

The neuroactive steroids assessed in the study are shown in bold font. The progesterone pathway is highlighted in shaded grey area.

TABLE 1.

Demographic and Clinical Characteristics

	Placebo (n=23)	Progesterone (n=23)
Gender – no. of males	14 (61%)	15 (65%)
Race		
African American	16 (70%)	18 (78%)
Caucasian	6 (26%)	4 (18%)
Hispanic	1 (4%)	1 (4%)
Age ^a	41.1 ± 7.9	41.9 ± 6.0
No. of regular smokers	21 (91%)	22 (96%)
Years of cocaine use ^a	14.3 ± 8.3	12.2 ± 5.9
Years of alcohol use ^a	13.9 ± 8.6	15.6 ± 10.4
Lifetime depression	1 (4%)	1 (4%)
Lifetime anxiety (incl. PTSD)	4 (17%)	6 (26%)
Lifetime anxiety (without PTSD)	3 (13%)	2 (9%)

^aData indicate means and standard deviations.

All variables: $p > .05$.

TABLE 2.

Plasma Neuroactive Steroid Levels in CUD Individuals Receiving Placebo vs Progesterone

Neurosteroid (pg/ml)	Placebo (n=23) Mean (SD)	Progesterone (n=23) Mean (SD)	<i>p</i>	Effect Size (F)
Pregnenolone	1292 (565)	1286 (950)	.202	1.67
Pregnanolone	145 (153)	6677 (4836)	.000	24.21
Allopregnanolone	126 (140)	9202 (8569)	.000	106.43
Testosterone	4037 (3137)	3820 (3036)	.754	0.09
Androstenediol	219 (137)	216 (144)	.738	0.11
DHEA	7932 (6624)	5535 (3420)	.093	2.94
Progesterone* (ng/ml)	0.64 (0.25)	25.52 (17.91)	.000	48.24

Shaded areas: $p < 0.001$ main effect of medication group

* Levels of progesterone were assessed using Radioimmunoassay (RIA), whereas all other NAS were assessed using gas chromatography/mass spectrometry (GC/MS).