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Allopregnanolone Association with Psychophysiological and Cognitive Functions during Acute Smoking Abstinence in Premenopausal Women

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Abstract

Nicotine response may predict susceptibility to smoking relapse. Allopregnanolone, a neuroactive steroid metabolized from progesterone, has been shown to be associated with several symptoms of nicotine response. We sought to explore the association between allopregnanolone and response to nicotine during acute smoking abstinence in premenopausal women. Participants completed 2 nicotine response laboratory sessions, 1 in their follicular (low allopregnanolone) and 1 in their luteal (high allopregnanolone) menstrual phase, on the fourth day of biochemically confirmed smoking abstinence. During the laboratory sessions, participants self-administered a nicotine nasal spray and completed a timed series of cardiovascular, cognitive, and subjective assessments of response to nicotine. The relationships of allopregnanolone with baseline values and change scores of outcome measures were assessed via covariance pattern modeling. Study participants (n = 77) had a mean age of 29.9 (SD = 6.8) years and smoked 12.2 (4.9) cigarettes per day. Allopregnanolone concentration measured before nicotine administration was positively associated with systolic (β = 0.85, p = .04) and diastolic blood pressure (β = 1.19, p < .001); and self-report of physical symptoms (β = 0.58, p < .001), dizziness (β = 0.88, p < .01), jitteriness (β = 0.90, p = .04), and pleasantness (β = 2.05, p = .04). Allopregnanolone also had significant positive associations with change in cognition following nicotine nasal spray administration, specifically discriminability as a measure of attention (β = 1.15, p = .05) and response bias as a measure of impulsivity (β = 0.13, p = .02). These data suggest that allopregnanolone may be related to cardiovascular and subjective physical state during acute smoking abstinence, as well as cognitive response to nicotine.

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Contributors Statement

All authors have contributed in a significant way to this manuscript and all authors have read and approved the final manuscript.

Conflicts of Interest

There are no conflicts of interest to report.

Keywords

Women; Smoking; Nicotine; Response; Allopregnanolone

Nicotine response, defined as the physiological, cognitive, and psychological reaction to nicotine, reinforces cigarette-smoking behavior (Stolerman & Jarvis, 1995). Nicotine response is also an indicator of sensitivity to nicotine, susceptibility to nicotine dependence, and risk for smoking relapse (Marks, Pomerleau, & Pomerleau, 1999; Pillitteri, Kozlowski, Sweeney, & Heatherton, 1997; Pomerleau, 1995). In premenopausal women, risk for smoking relapse has been observed to vary by menstrual phase (Allen, Bade, Center, Finstad, & Hatsukami, 2008; Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2008; Mazure, Toll, McKee, Wu, & O'Malley, 2011). These observations may be related to differences in response to nicotine by hormonal fluctuations during identified menstrual phases, as suggested by recent research. Specifically, after overnight abstinence, a delivery of nicotine intravenously led to a greater reduction in craving as well as a greater increase in heart rate in the follicular phase as compared to the luteal phase (DeVito, Herman, & Sofuoglu, 2013). Furthermore, in non-depressed women, after four days of abstinence, the absorption of nicotine was significantly greater in the follicular phase than in the luteal phase (Allen, Allen, Kotlyar, et al., 2013). These data suggest that the luteal phase may be associated with a blunted response to nicotine; however, the specific mechanisms involved remain unknown.

One possible factor that may influence response to nicotine is allopregnanolone. Because allopregnanolone is a metabolite of progesterone, endogenous concentrations vary by menstrual phase in premenopausal women, with low concentrations occurring in the follicular phase and high concentrations in the luteal phase (Zheng, 2009). Allopregnanolone has been shown to be dose-dependently related to both dopamine and gamma aminobutyric acid type A (GABAa) release (Zheng, 2009). Thus, given that both dopamine and GABAa play important roles in the reward processes associated with drug abuse behavior, allopregnanolone may modify the effect response to nicotine(Anker & Carroll, 2010). In fact, preclinical research indicates that allopregnanolone may limit nicotine withdrawal (Thakre, Tundulwar, Chopde, & Ugale, 2013). However, the association between nicotine response and allopregnanolone has yet to be directly investigated in a clinical sample. Prior studies have observed associations between allopregnanolone and cardiovascular, cognitive, and mood. For example, regarding the physiological aspect of nicotine response, allopregnanolone has been shown to have a positive correlation with diastolic blood pressure (Childs, Dlugos, & De Wit, 2010). Regarding cognition, animals injected with allopregnanolone learned significantly less compared to those who were not injected with allopregnanolone (Sundstrm-Poromaa, 2008). Further, in clinical research, changes in saccadic eye movement patterns and subjective scores of sedation were correlated with increasing serum allopregnanolone levels (Sundstrm-Poromaa, 2008). Allopregnanolone is also associated with several psychological conditions including major depressive disorder, depressive symptoms, and a sense of well-being (Klatzkin, Morrow, Light, Pedersen, & Girdler, 2006; Nappi et al., 2001). Finally, in a clinical sample of male smokers, allopregnanolone was significantly correlated with cotinine, a byproduct of nicotine (Marx

et al., 2006), suggesting that allopregnanolone may be related to absorption and/or metabolism of nicotine. Overall, these data suggest that there may be an association between allopregnanolone and nicotine response.

The overall goal of this study was to assess the association between allopregnanolone and nicotine response during short-term smoking abstinence. Using data from a recently completed controlled cross-over trial (Allen et al., 2014) of premenopausal women who completed two 6-day testing sessions, one during their follicular (low allopregnanolone) and one during their luteal (high allopregnanolone) menstrual phase, we tested the hypothesis that allopregnanolone concentration is inversely related to cognitive measures and positively associated with cardiovascular and favorable subjective measures. We expected that these associations would be related to both the absolute levels and the response to a nicotine challenge.

Methods

Study Sample

Women between the ages of 18 and 40 years were recruited via mass media advertising to participate in a larger controlled cross-over study that was designed to test the effect of depressive symptoms and menstrual phase on short-term smoking cessation outcomes (Allen et al., 2014). Eligibility was assessed over the phone initially and then at an in-person screening visit. To be eligible, women had to have smoked at least five cigarettes per day for at least the past year, have had regular menstrual cycles for at least the past 3 months, and be in stable physical and mental health. Subjects were excluded if they used exogenous hormones or psychotropic medications, and if they had a history of breastfeeding or pregnancy within the past 3 months. All procedures were approved by the Institutional Review Board of the University of Minnesota. This report is a secondary data analysis of participants who had additional blood samples available for analysis (participants who had a missing blood sample or had an insufficient volume of blood collected were not included).

Study Procedures

At screening, participants were randomly assigned to one of two test sequences: F-L = first test during the follicular phase and second test during the luteal phase; L-F = first test during the luteal phase and second test during the follicular phase. This allowed testing when allopregnanolone concentrations were naturally low (follicular phase), as well as when they were naturally high (luteal phase). The 6-day test period started on the day after the onset of menses for the follicular phase, and 2 days after ovulation for the luteal phase. Ovulation was determined based on urinary luteinizing hormone tests as previously described (Allen et al., 2008). If schedule conflicts occurred, the entire testing week was shifted by 1 day in either direction.

Each test period consisted of daily clinic visits for 6 consecutive days. On Days 1 and 2, participants smoked ad libitum. At midnight on testing Day 2, participants quit smoking and remained abstinent for the rest of the test period. On Days 3–6, participants attended clinic visits, and smoking status was biochemically confirmed, with abstinence indicated by the

following values: daily breathalyzer results for carbon monoxide <5 ppm, salivary cotinine concentration <15 ng/ml on Day 6, and serum nicotine concentration <2 ng/ml on Day 6, (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009; Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987) (Data not presented). On the fourth day of smoking abstinence (Day 6) for each test period, participants completed a 4-hour nicotine laboratory session (described below). Upon completion of the first laboratory session, participants resumed ad libitum smoking for 1.5 menstrual cycles (approximately 6 weeks depending on cycle length), until they arrived at the alternate menstrual phase, when the identical data collection procedures were repeated.

The nicotine laboratory sessions included a timed protocol in which the study participants self-administered a nicotine nasal spray (2-mg dose) at Time 0. Physiological, cognitive, and subjective responses to nicotine were assessed during the time from 30 minutes before administration (Time-30 minutes) through 90 minutes after administration (Time 90 minutes). To assess the response to nicotine, we focused on the change from baseline to expected peak time points.

Assessments

All data for the present analysis were from the nicotine laboratory sessions on Day 6 (e.g. the fourth day of biochemically verified smoking abstinence) of each test period.

Blood samples were collected approximately 30 minutes prior to the start of the nicotine laboratory session. Plasma was separated via centrifugation. Plasma samples were then sent to Dr. Richard Hauger's laboratory at the University of California, San Diego, for determination of allopregnanolone concentration in serum and ether-extracted plasma samples via an in-house ^{3}H-radioimmunoassay (de Wit, Schmitt, Purdy, & Hauger, 2001). The coefficient of variation was approximately 5% for intra-assay and 8% for interassay samples. The assay sensitivity was about 200 pg/ml, with a standard range of 0.2 to 50.0 ng/ml. Given there was aextraction recovery of 78%, final values were multiplied by 1.28.

Cardiovascular response was determined by simultaneously measuring systolic and diastolic blood pressure and heart rate at Times -1 and 5 minutes with an automatic blood pressure machine using a blood pressure cuff placed above the antecubital fossa region of the arm.

Cognitive response was assessed with the following three measures: (a) The Mathematical Skills Task (Math Task) is a revised version of the serial addition/subtraction task from the Walter Reed Performance Assessment Battery (Thorne, Genser, Sing, & Hegge, n.d.). The math task was performed at Times -30 and 20 minutes to assess cognition, specifically general information processing. In each trial, solutions to 50 simple addition or subtraction problems were presented, and the participant indicated whether the solution was true or false; the score was the total number of correct answers, as well as response time. (b) The Finger Tapping Task (FT) was performed at Time -30 and 20 minutes to measure motor speed, which was expected to increase in response to nicotine. Using the index finger on the dominant hand, participants tapped a key on a computer as quickly as possible for 30 seconds for two successive trials (Hindmarch, 2004). (c) The Immediate Memory Task (IMT) was performed at Times -30 and 10 minutes to measure attention and impulsivity

(Dougherty, Marsh, & Mathias, 2002). A series of randomly generated 5-digit numbers (e.g., 54983) was displayed on a computer monitor for half a second at a rate of one per second, and participants were instructed to push a button when the number displayed was identical to the preceding number. Variables from this task included IMT-*A′* (a measure of attention based on the ability to discriminate between target and error stimuli; range 0 to 1, where 1 is perfect discrimination) and IMT-*B* (a measure of impulsivity based on willingness to endorse an item as correct; range 0 to 2, where 0 is liberal and 2 is conservative response bias).

Subjective response to nicotine was assessed with two measures: (a) Visual analog scales (VAS) were completed at Times -30 and 5 minutes to measure potentially rapid changes in negative or positive drug effects (Jones, Garrett, & Griffiths, 1999). The participants indicated the degree to which they felt alert, dizzy, jittery, pleasant, relaxed, stimulated, and whether they experienced a head rush or an urge to smoke, by marking a 100-mm line labeled “not at all” on one end and “very much” on the other. (b) The Subjective State Scale (al’Absi, Hatsukami, Davis, & Wittmers, 2004; al’Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003) was completed at Times -30 and 5 minutes using a six-point Likert-type scale, participants responded to 24 items to assess five subscales (positive affect, negative affect, physical symptoms, withdrawal and craving).

Statistical Analysis

Descriptive statistics were calculated for demographic and smoking behavior variables, including mean and standard deviation (SD) for continuous variables, and counts and percentage for categorical variables. To measure the response to nicotine, change scores for each item were calculated by subtracting the baseline value (i.e., Time -30 or -1 min) from the expected peak value (i.e., Time 5, 10, or 20 min). The relationships between allopregnanolone and the baseline values and change scores of outcome measures were assessed via covariance pattern modeling with an unstructured pattern, where β estimated the average difference or change in these variables associated with a one-unit difference in allopregnanolone. To allow for the identification of the effect of allopregnanolone levels, rather than other hormonal changes that occur during the menstrual cycle, all models were adjusted for menstrual phase (follicular vs. luteal), and testing order (first test period vs. second test period). Linear regression models, adjusting for testing order, were conducted to assess phase specific associations between allopregnanolone and study outcomes. Log transformation was used for variables with a non-normal distribution (IMT-*A′*, VAS Dizzy, and VAS Jittery). *P* values less than 0.05 were deemed statistically significant. No adjustments for multiple comparisons were made. SAS V9.1.3 (SAS Institute, Cary, NC) was used for the analyses.

Results

Participant Characteristics

A total of 77 women were included in this analysis. Participants’ demographic characteristics, smoking behavior, and allopregnanolone concentration just before nicotine administration are presented in Table 1. Slightly more than half of the participants were non-

Hispanic white and a high school (or equivalent) education. Mean cigarettes smoked per day was 12.2 (S.D. = 4.9) with the first morning cigarette smoked within 40.9 (S.D. = 42.0) minutes of waking. As expected, allopregnanolone levels (range: 0.20–8.60 ng/mL) were significantly higher in the luteal phase as compared to the follicular phase (3.82±1.68 ng/mL vs. 0.79±0.31 ng/mL; t-value=16.32; p-value<0.0001).

Association Between Allopregnanolone and Baseline Measures

As shown in Table 2, a one-unit increase in allopregnanolone was associated with a 0.8% increase in systolic blood pressure ($p = 0.037$), a 1.7% increase in diastolic blood pressure (p<0.001), a 13.0% increase in physical symptoms on the Subjective State Scale ($p < 0.001$), an 8.7% increase in the VAS score for feeling dizzy (p=0.008), a 5.3% increase in the VAS score for feeling jittery (p=0.041), and a 3.1% increase in the VAS score for a pleasant feeling ($p = 0.041$). Higher allopregnanolone concentrations appeared to be related to the following variables, but the associations did not reach statistical significance: greater response time on the math task (β = 0.078, $p = 0.065$), a higher VAS score for head rush (β = 1.391, $p = 0.094$), and a lower VAS score for urge to smoke (β = −2.228, $p = 0.087$).

Between subject analyses noted four significant associations between allopregnanolone and subjective response to nicotine that varied by menstrual phase. Specifically, during the follicular phase but not the luteal phase, higher allopregnanolone levels were associated with greater withdrawal (β=5.57, p=0.025), greater craving (β=2.18, p=0.010), greater urge to smoke (β=25.67, p=0.027) and less stimulation (β=−23.73, p=0.008) prior to the administration of nicotine. No other significant associations were found.

Association Between Allopregnanolone and Response to Nicotine

As shown in Table 2, higher allopregnanolone levels were associated with significant increases in IMT-*A′*, indicating a heightened ability to discriminate (β = 1.154, p = 0.047), and in IMT-*B*, indicating that response bias became more conservative (β = 1.132, $p = 0.022$). Higher allopregnanolone concentrations appeared to be associated with a decrease in the Subjective State Scale score for negative affect after using the nicotine nasal spray (β = −0.354, $p = 0.086$), but the association was not statistically significant.

Menstrual phase specific associations indicated that during the follicular, but not the luteal phase, higher allopregnanolone levels were associated with a less change in heart rate after nicotine administration (β=−6.80, p=0.039) and stimulation (β=12.26, p=0.034). Further, during the luteal phase but not the follicular phase, higher allopregnanolone levels were related to a more conservative response bias (via IMT-B; β=0.10, p=0.039). No other significant observations were noted.

Discussion

This was a controlled cross-over study in which premenopausal smokers completed two nicotine response laboratory sessions after 4 days of biochemically verified smoking abstinence. We observed several significant associations between allopregnanolone and the subjective, cardiovascular, and cognitive response both prior to and after the delivery of nicotine.

First, we observed associations between allopregnanolone and subjective responses at baseline. Overall, regardless of menstrual phase, higher allopregnanolone levels at baseline were associated with a more desirable state for several subjective measures (i.e., more pleasantness and, possibly, desire to smoke). Higher levels of allopregnanolone were significantly associated with a greater decrease in negative affect from baseline to five minutes. We also noted that during the follicular phase, but not the luteal phase, higher allopregnanolone levels during the were associated with baseline levels of greater craving, withdrawal and urge to smoke No other changes in subjective responses were associated with allopregnanolone levels. The overall effect of allopregnanolone appears to suggest that higher levels of allopregnanolone may be associated with an improved sense of mood during acute nicotine withdrawal. Conversely, during follicular phase, higher allopregnanolone levels appear to be associated with greater withdrawal. Specific mechanisms involved in these observations are unknown. In prior work, menstrual phase, progesterone and/or estradiol were not identified as significant predictors of subjective response to nicotine (Allen, Allen, Lunos, et al., 2013). Therefore, these data suggest that allopregnanolone may play an independent role in smoking-related symptomatology during acute smoking abstinence and that allopregnanolone's role may vary by menstrual phase.

Second, as hypothesized, both systolic and diastolic blood pressure (but not heart rate) had a significant positive association with allopregnanolone at baseline. Further, while the change in heart rate was significantly and inversely associated allopregnanolone after nicotine administration, other changes in cardiovascular measures in response to the nicotine nasal spray were not significantly related to allopregnanolone. Overall, these data offer mixed support of prior clinical literature. Specifically, in a study by Childs and colleagues (Childs et al., 2010), a positive although nonsignificant ($p = 0.06$) correlation between diastolic blood pressure and allopregnanolone was observed in a sample of men and women nonsmokers participating in a laboratory session designed to induce a stress response. Given prior work has suggests that follicular phase may be associated with greater sensitivity to nicotine via improved cessation rates with nicotine replacement therapy patch (Carpenter et al., 2008; Franklin et al., 2008), as well as greater absorption of nicotine (Allen, Allen, Kotlyar, et al., 2013), it is possible that allopregnanolone may play a role in these observations. Thus, additional work exploring allopregnanolone as a factor in physiological response to nicotine is warranted.

Lastly, regarding cognition, we observed conflicting results. Specifically, at baseline (Time-30 minutes), a trend suggest that higher allopregnanolone levels appeared related to a slower response time on the Math Task. If true, such an association would indicate that higher concentrations of allopregnanolone may be associated with blunted cognitive functioning. However, after nicotine administration, allopregnanolone concentrations were significantly associated with an increase in both IMT-A'(a measure of attention) and IMT-B (a measure of impulsivity), suggesting that greater increases in discriminability and impulsivity occur if allopregnanolone levels are high when nicotine is administered. Thus, although higher baseline allopregnanolone concentrations may have been unfavorably associated with cognition, allopregnanolone levels were favorably associated with cognition after delivery of nicotine nasal spray. The former agrees with our hypothesis as well as with

the previous preclinical and clinical literature. For example, a preclinical study found that animals injected with allopregnanolone learned significantly less than those who were not injected. In the clinical literature, pregnant women and women with premenstrual dysphoric disorder had lower levels of memory and concentration with higher levels of allopregnanolone (Birzniece et al., 2006). While the association between allopregnanolone and change in cognition after delivery of nicotine nasal spray may seem to conflict with this prior work, to our knowledge this is the first study to examine the role of allopregnanolone in the response to nicotine among women smokers in a state of nicotine withdrawal. This novel finding may be applicable to risk for relapse in premenopausal women.

The cross-over study design of this study was a major strength because it allowed for a within-subject analysis to isolate the association of allopregnanolone (independent of other menstrually-related hormonal changes) with study outcomes. Additional strengths included a fairly diverse study sample, frequent biochemical confirmation of smoking status, and a well-designed nicotine laboratory session with a variety of both subjective and objective outcome measures. However, some limitations need to be considered. First, the study sample included women who planned to return to smoking after the nicotine laboratory session. It is unknown how this may have affected either allopregnanolone response to the stressful experience of smoking cessation during the days before the laboratory session or the response to nicotine during the laboratory session. Similarly, we excluded women on exogenous hormones (including hormonal contraceptives). Therefore, the results of this study may contain selection bias and cannot be generalized to women who are attempting to quit smoking permanently. Second, we had a fairly small sample size, which limits our ability to detect small effects of allopregnanolone on nicotine response. Third, although allopregnanolone has been shown to increase in response to stress among nonsmoking women in the luteal phase (Childs et al., 2010), we only measured allopregnanolone once before the nicotine exposure laboratory session. However, it is unknown whether allopregnanolone increases in response to stress in women who smoke or whether the nicotine exposure laboratory session acted as an acute stressor. Finally, our previous work demonstrated that absorption of nicotine may vary by menstrual phase (Allen, Allen, Kotlyar, et al., 2013). It is unknown how various levels of absorption may have influenced results of this study. Despite its limitations, the study fills a current void in the literature by being the first to assess the association between allopregnanolone concentration and nicotine response in premenopausal women during short-term smoking abstinence.

In conclusion, allopregnanolone had significant associations with several subjective and objective nicotine response measures. Most of these were found at baseline, before the administration of a nicotine challenge, suggesting that higher allopregnanolone levels, regardless of menstrual phase, may predispose the smoker to experience a more favorable state during withdrawal. Future research should explore the mechanisms of these relationships and how these associations may play a role in smoking cessation efforts.

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Table 1

Demographic Characteristics, Smoking Behavior, and Allopregnanolone Concentration (n = 77)

Characteristics	*n*	*%*
Race		
White, non-Hispanic	41	54
Black, non-Hispanic	21	27
Other	15	21
Education		
< High School	26	33
High School (or equivalent)	43	54
> High School	12	16
	M	*SD*
Age	29.9	6.8
Smoking behavior		
Cigarettes/day	12.2	4.9
Time to first morning cigarette (min)	40.9	42.0
Follicular Phase Allopregnanolone[a] (ng/ml)	0.78	0.31 *
Luteal Phase Allopregnanolone[a] (ng/ml)	3.82	1.68 *

[a] Determined before the nicotine laboratory session on Day 6 of each test period.

* Paired t-test: t-value-=16.32, p-value<0.0001

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Table 2

Association Between Allopregnanolone and Nicotine Response During Acute Smoking Abstinence (n = 77)

Variable	Baseline values[a]		Nicotine response (change from baseline)[b]	
	Mean (SD)	Association with allopregnanolone[c]	*Mean (SD)*	Association with allopregnanolone[c]
Cardiovascular				
Blood pressure				
Systolic	108.89 (12.01)	β = 0.846, *p* = .037	3.68 (8.93), *p* < .001	n.s.
Diastolic	68.55 (10.61)	β = 1.188, *p* < .001	4.34 (8.43), *p* < .001	n.s.
Heart rate	68.86 (11.52)	n.s.	9.50 (9.18), *p* < .001	n.s.
Fingertapping				
Number of taps	161.40 (28.26)	n.s.	0.42 (20.52)	n.s.
Immediate Memory				
Task				
Discriminability (*A'*)[d]	0.86 (0.13)	n.s.	0.01 (0.04), *p* < .001	β = 1.154, *p* = .047
Bias (*B*)	1.11 (0.92)	n.s.	0.08 (0.87)	β = 1.132, *p* = .022
Math task				
Correct responses	48.11 (2.35)	n.s.	–0.03 (1.85)	n.s.
Response time	2.15 (1.01)	β = 0.078, *p* = .065	–0.22 (0.70), *p* < .05	n.s.
Subjective State Scale				
Negative affect	6.64 (6.10)	n.s.	1.39 (3.73), *p* < .05	β = –0.354, *p* = .086
Positive affect	20.07 (9.02)	n.s.	–0.67 (4.64)	n.s.
Physical symptoms	4.36 (4.76)	β = 0.580, *p* < .001	–0.11 (3.16)	n.s.
Withdrawal	8.92 (6.45)	n.s.	1.66 (3.78), *p* < .001	n.s.
Craving	3.53 (2.47)	n.s.	0.64 (1.70), *p* < .001	n.s.
Visual analog scale				
Alert	64.75 (23.56)	n.s.	2.70 (19.13)	n.s.
Dizzy[d]	10.82 (17.97)	β = 0.879, *p* = .008	9.94 (22.06), *p* < .001	n.s.
Head rush	12.31 (20.78)	β = 1.391, *p* = .094	18.60 (29.83), *p* < .001	n.s.
Jittery[d]	17.96 (24.31)	β = 0.895, *p* = .041	7.95 (25.20), *p* < .05	n.s.
Pleasant	65.03 (22.13)	β = 2.045, *p* = .041	–0.12 (18.49)	n.s.

Variable	Baseline values[a]		Nicotine response (change from baseline)[b]	
	Mean (SD)	Association with allopregnanolone[c]	*Mean (SD)*	Association with allopregnanolone[c]
Relaxed	62.23 (24.74)	n.s.	0.84 (24.33)	n.s.
Stimulated	50.60 (23.06)	n.s.	5.62 (18.07), $p < .05$	n.s.
Urge to smoke	54.78 (30.58)	$\beta = -2.228$, $p = .087$	–8.42 (21.59), $p < .05$	n.s.

Notes n.s. = not significant.

[a] The nicotine nasal spray was administered at Time 0; baseline values were determined at -30 minutes for all variables except baseline systolic and diastolic blood pressure and heart rate, which were determined at -1 minute.

[b] Change was calculated by subtracting baseline values from the post–nicotine administration values. Post–nicotine administration values were determined for cardiovascular variables, Subjective State Scale, and Visual Analog Scale at Time 5 minutes; for Immediate Memory Task at Time 10 minutes; and for math task and fingertapping at 20 minutes.

[c] Adjusted for menstrual phase, testing order, and baseline value (change only).

[d] Non-normally distributed values were log transformed in the analysis.