

# Effects of Acute Progesterone Administration Upon Responses to Acute Psychosocial Stress in Men

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Animal studies suggest that neuroactive steroids, in particular progesterone and its metabolites, have stress-dampening effects. However, few studies have explored these effects in humans. In this study, we investigated the effects of acute progesterone administration on responses to the Trier Social Stress Test (TSST). Healthy men participated in the TSST 3.5 hrs after intramuscular injection of 0, 50, or 100 mg progesterone ( $N = 16, 14,$  and  $14$ ). We measured cardiovascular (heart rate, blood pressure), hormonal (plasma adrenocorticotrophic hormone, cortisol, and noradrenaline), and subjective (e.g., anxiety, arousal) responses to stress in the three groups. Before the TSST, progesterone injections increased plasma levels without altering physiological or subjective states. Stress produced its expected physiological and subjective effects among placebo-treated individuals. Progesterone 50 mg attenuated peak increases in plasma cortisol and reduced changes in negative mood and alertness after stress, yet it increased plasma noradrenaline and systolic blood pressure. Progesterone 100 mg also attenuated stress-induced increases in alertness and arousal, yet it potentiated stress-induced increases in diastolic pressure. Thus, progesterone dampened some of the psychological effects of stress but produced inconsistent effects on physiological stress responses.

*Keywords:* progesterone, allopregnanolone, stress, TSST

An acute physiological or psychological threat initiates a cascade of events called the stress response, which serves to counteract the threat. The stress response is crucial to survival and must be readily activated, but must also be limited in duration to avoid harmful effects (McEwen, 2008). One mechanism thought to regulate the activity of stress systems is the release of neuroactive steroids (Girdler & Klatzkin, 2007). In particular, progesterone and its metabolites allopregnanolone and pregnanolone, which bind potently to the GABA<sub>A</sub> receptor (Majewska, Harrison, Schwartz, Barker, & Paul, 1986; Paul & Purdy, 1992), have been implicated in restoring normal GABAergic tone and hypothalamic-pituitary-adrenal (HPA) axis activity after a stressor (Barbaccia et al., 1996b). Thus, it might be expected that high levels of progesterone and its neuroactive metabolites might dampen stress responses in humans.

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Several lines of evidence suggest that neuroactive steroids may play a role in returning homeostasis after a stressful event. First, neuroactive steroids are released in response to acute stress; animal and human studies show that progesterone and allopregnanolone are elevated after stress (Barbaccia et al., 1996a, 1996b, 1996c, 1996b, 1996c; Barbaccia, Serra, Purdy, & Biggio, 2001; Childs & de Wit, 2009; Droogleever Fortuyn et al., 2004; Purdy, Morrow, Moore, & Paul, 1991) and that stress increases brain levels of enzymes that convert progesterone to allopregnanolone (Sanchez, Torres, Gavete, & Ortega, 2008). Second, the physiological effects of these agents oppose hormonal stress responses; animal studies show that allopregnanolone attenuates stress-induced increases in adrenocorticotrophic hormone and corticosterone (Patchev, Hassan, Holsboer, & Almeida, 1996). Finally, the behavioral effects of these agents are also consistent with a role in combating the subjective effects of stress; progesterone, via its metabolite allopregnanolone, produces sedative effects in humans (de Wit, Schmitt, Purdy, & Hauger, 2001; Freeman, Purdy, Coutifaris, Rickels, & Paul, 1993; Soderpalm, Lindsey, Purdy, Hauger, & de Wit, 2004) and decreases anxiety-like behaviors in animals (Bitran, Shiekh, & McLeod, 1995). Thus, the available evidence suggests that stress-induced increases in progesterone and allopregnanolone may be an endogenous mechanism that counteracts increases in anxiety and limits hypothalamic pituitary adrenal axis activation.

In this exploratory study, we investigated the antistress effects of progesterone in humans. Using a randomized, double-blind, between-subjects design, healthy male volunteers ( $N = 44$ ) received intramuscular injections of 0, 50, or 100 mg progesterone 3 hrs before participating in a stan-

standardized psychosocial stress task, the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). We assessed the effects of the treatments and TSST on cardiovascular (heart rate, blood pressure), hormonal (plasma adrenocorticotrophic hormone = ACTH, cortisol, and noradrenaline) and subjective measures. We hypothesized that progesterone would attenuate stress-induced increases in cortisol and subjective distress.

## Method

### Participants

Healthy, nonsmoking men ( $N = 44$ ) aged 18 to 35 years participated in the study. The exclusion criteria included serious medical conditions, current or prior diagnosis of Axis I disorder, body mass index outside of 19–26 kg/m<sup>2</sup>, abnormal blood pressure or electrocardiogram, and night shift work. Participants were told that the aim of study was to investigate the effects of a drug upon responses to a verbal task; they were not told the specific nature of the drug or task.

### Procedure

The University of Chicago Institutional Review Committee approved the protocol. Subjects participated in a single, 7-hr session. On arrival at the General Clinical Research Center (GCRC) at 8 a.m., participants submitted breath and urine samples to test for recent use of drugs or alcohol; no one tested positive. Participants ate a standard breakfast and then a snack at 11:15 a.m. prepared by the GCRC staff. At 8:30 a.m., an intravenous catheter was placed in the participant's nondominant arm for collection of blood samples. At 9 a.m., baseline samples of blood and measures of blood pressure and mood were obtained. Heart rate was measured continuously (Mini-Logger, Mini Mitter/Respironics®, Bend, OR). At 9:15 a.m., participants received an intramuscular (IM) injection of 0, 50, or 100 mg progesterone. These doses have been previously administered to healthy individuals and were well tolerated (de Wit et al., 2001). Higher doses (e.g., 200 mg) are likely to produce sedative effects (Soderpalm et al., 2004), which would complicate the interpretation of this study. Individuals were randomly assigned to treatment groups. Progesterone was administered intramuscularly because there is a higher relative bioavailability in comparison to orally administered progesterone (Simon et al., 1993) and also because oral administration produces highly variable plasma levels of progesterone (Freeman, Weinstock, Rickels, Sondheimer, & Coutifaris, 1992) because of individual differences in first pass metabolism. Allopregnanolone was not accessible in a bioavailable form to administer directly. Physiological, subjective, and hormonal measures were collected hourly until 12:15 p.m. At 12:45 p.m. (3.5 hrs after progesterone injections) individuals were taken to an adjacent room to perform the TSST, a mock job interview that consisted of 5 min of public speaking and 5 min of mental arithmetic (Childs & de Wit, 2009). Plasma progesterone peaks approximately 3.5 to 5 hrs after an

intramuscular injection at the doses used here (de Wit et al., 2001), and in our previous acute stress study, progesterone peaked 20 min after stressor onset (Childs & de Wit, 2009). Thus, peak plasma progesterone levels from the injections in the present study were expected to coincide with the peak poststress levels (at approximately 4 hrs). At the end of the task, the participant was escorted back to the patient room. Physiological, subjective, and hormonal measures were obtained immediately and then at 10, 20, 30, and 60 min after the task. Participants were fully debriefed and received payment at a debriefing session.

### Dependent Measures

The GCRC Core Laboratory determined levels of cortisol in plasma (Immulite® 1000 Cortisol, sensitivity = 0.2ug/dl, Siemens Healthcare Diagnostics, Deerfield, IL). The University of Chicago Medical Endocrinology Laboratory determined levels of ACTH and progesterone in plasma (Immulite® 2000 Progesterone, sensitivity = 0.1 ng/ml). Mayo Medical Laboratories determined levels of plasma noradrenaline (test code 8532, NA sensitivity = 70 pg/ml). Participants reported subjective mood using an experimental version of the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971) and Visual Analogue Scales (VAS; Folstein & Luria, 1973).

### Statistical Analysis

Sample size calculations were based upon responses to the TSST in untreated healthy nonsmoking males (Childs & de Wit, 2009). Demographic characteristics were compared between groups using independent samples  $t$  tests and Pearson's  $\chi^2$  tests. Among placebo-treated individuals, the effects of the TSST upon dependent measures were assessed by comparing prestress values with those obtained immediately after the stress task using Student's paired  $t$  tests. Treatment effects before and after stress were analyzed using two-factor analysis of variance (ANOVA) for repeated measures, with time as the within-subjects factors and treatment group as the between-subjects factor. Significant interactions were further investigated by one-factor ANOVA and Student's paired  $t$  tests with Bonferroni correction for multiple comparisons. Peak change scores, that is, the maximum positive or negative change from the pretask baseline at any time point after the TSST, were analyzed by Student's unpaired  $t$  tests. The effects of progesterone were analyzed separately for each dose because previous studies report paradoxical and bimodal effects of progesterone and its metabolites (Andreen, Sundstrom-Poromaa, Bixo, Nyberg, & Backstrom, 2006; Fish, Faccidomo, DeBold, & Miczek, 2001; Andreen et al., 2009).

All analyses were conducted using SPSS version 16.0 for Windows. Repeated-measures ANOVAs were performed with Greenhouse Geisser correction where violations of sphericity were observed. Differences were considered to be significant if  $p < .05$ . Effect sizes are reported using partial eta squared ( $\eta_p^2$ ) for analyses of variance; 0.01, 0.06, and 0.14 are considered respectively small, medium, and large effect sizes.

## Results

### Demographic Characteristics

Most participants were European American (68%) full-time students (70%) in their early twenties ( $21.9 \pm 3.1$  year). The groups did not differ in demographic characteristics (see Table 1).

### Effects of Progesterone Before Stress

At baseline (before injections), the mean concentration of progesterone in plasma was  $0.89 \pm 0.11$  ng/ml among all participants and did not differ between the three treatment groups. There were also no differences between the groups in other physiological and subjective measures before injections. Progesterone injections significantly increased plasma progesterone in comparison to placebo injections [50 mg Treatment\*Time,  $F(3, 75) = 32.8$   $p < .001$   $\eta_p^2 = 0.57$ ; 100 mg Treatment\*Time,  $F(3, 75) = 54.7$   $p < .001$   $\eta_p^2 = 0.69$ ]. Before stress, mean plasma progesterone was respectively  $0.57 \pm 0.04$ ,  $30.58 \pm 4.32$ , and  $38.97 \pm 3.98$  ng/ml among individuals in the 0, 50, and 100 mg progesterone groups. Progesterone injections did not significantly influence cardiovascular and hormonal measures or self-reported subjective state before the tasks, although individuals in the placebo group reported feeling more Drowsy overall that is, both before and after administration of progesterone, in comparison to the 100 mg treatment group before participating in the stress tasks, Treatment  $F(1, 26) = 5.1$   $p < .05$   $\eta_p^2 = 0.16$ .

### Effects of the TSST

As expected, the TSST significantly increased heart rate, blood pressure, and levels of cortisol, ACTH, noradrenaline, and progesterone in plasma among individuals in the pla-

cebo treatment group (see Table 2). Stress also produced an increase in feelings of anxiety and negative mood (POMS Anger, Anxiety, Confusion, and Depression).

### Effects of Progesterone on Responses to the TSST: Cardiovascular Measures

In comparison to placebo, 50 mg progesterone increased systolic blood pressure overall, Treatment  $F(1, 28) = 4.8$   $p < .05$   $\eta_p^2 = 0.15$ , but did not significantly alter TSST-induced increases. Progesterone 100 mg potentiated and prolonged TSST-induced increases in diastolic blood pressure [Treatment\*Time  $F(5, 140) = 2.5$   $p < .05$   $\eta_p^2 = 0.08$ ]; blood pressure remained significantly elevated above baseline for 10 min after the TSST among individuals treated with 100 mg progesterone, and the peak change from pre-task baseline was significantly greater after 100 mg compared with placebo,  $t(28) = -2.7$   $p < .05$  (Figure 1). Progesterone treatments did not significantly alter TSST-induced changes in heart rate.

### Hormonal Measures

In comparison to placebo, progesterone 50 mg significantly attenuated peak increases in plasma cortisol after the TSST,  $t(28) = 2.1$   $p < .05$ , and there was a trend to a reduced response over time [Treatment\*Time  $F(5, 140) = 2.2$   $p = .06$   $\eta_p^2 = 0.10$  (Figure 2)]. ACTH responses to the task did not differ among the groups, although there was a trend to potentiated responses by 100 mg progesterone [Treatment\*Time  $F(5, 95) = 2.0$   $p = .08$   $\eta_p^2 = 0.10$  (Figure 2)]. In comparison to placebo, progesterone 50 mg significantly elevated plasma noradrenaline overall [Treatment  $F(1, 24) = 4.1$   $p = .05$   $\eta_p^2 = 0.15$  (Figure 2)]. The TSST significantly increased plasma progesterone among individuals who received placebo

Table 1  
Demographic Characteristics of Participants in Each Treatment Group

	0 mg (N = 16)	50 mg (N = 14)	100 mg (N = 14)
Age <sup>a</sup>	21.8 ± 0.9	21.2 ± 0.7	22.6 ± 0.8
Body mass index <sup>a</sup> (kg/m <sup>2</sup> )	22.0 ± 0.6	23.6 ± 0.6	23.6 ± 0.4
Full-time Student (#)	11	12	8
Education (%)			
High school	13	7	14
Partial college	56	93	57
College degree	31	0	29
Caffeine consumption <sup>a</sup> (cups/week)	3.9 ± 1.0	5.0 ± 1.6	6.0 ± 2.2
Alcohol consumption <sup>a</sup> (drinks/week)	4.7 ± 1.0	5.3 ± 0.9	4.9 ± 1.7
Race (%)			
White	63	79	64
Black	12	0	14
Asian	6	14	8
Other	19	7	14
Drug use (% ever used)			
Cannabis	69	50	64
Stimulants	25	0	7
Opiates	31	7	21
Tranquilizers	0	0	0
Hallucinogens	19	7	14

<sup>a</sup> Data is presented as mean ± SEM.

Table 2

Effects of the Trier Social Stress Test (TSST) Among Placebo-Treated Individuals.  
Data Represent Mean  $\pm$  SEM at Baseline (Prestress) and Immediately After the TSST (Poststress)

Measure	Prestress	Poststress	$t(df)$
Systolic blood pressure (mmHg)	115.8 $\pm$ 3.1	130.3 $\pm$ 2.9	-8.0 (15)***
Diastolic blood pressure (mmHg)	64.1 $\pm$ 1.6	70.2 $\pm$ 2.2	-2.8 (15)*
Plasma cortisol (ug/dl)	7.9 $\pm$ 0.8	14.7 $\pm$ 1.1	-5.3 (15)***
Plasma ACTH (pg/ml)	16.4 $\pm$ 1.4	28.6 $\pm$ 5.4	-2.4 (13)*
Noradrenaline (ng/ml)	173.0 $\pm$ 15.5	347.6 $\pm$ 43.4	-5.4 (14)***
Progesterone (ng/ml)	0.6 $\pm$ .04	0.7 $\pm$ .06	-2.5 (12)*
STAI	35.0 $\pm$ 2.4	46.1 $\pm$ 2.6	-4.4 (15)***
POMS Anger	0.2 $\pm$ .09	0.5 $\pm$ 0.1	-3.4 (15)**
POMS Arousal	0.6 $\pm$ 0.3	1.3 $\pm$ 0.4	-2.1 (15)*
POMS Confusion	0.6 $\pm$ 0.2	1.2 $\pm$ 0.2	-2.6 (15)*
POMS Depression	0.4 $\pm$ 0.2	0.8 $\pm$ 0.3	-2.6 (15)*
Heart rate baseline	71.5 $\pm$ 2.4	89.9 $\pm$ 3.8	-7.2 (14)***

Note. ACTH = Adrenocorticotrophic hormone; STAI = State Trait Anxiety Inventory; POMS = Profile of Mood States.

\* indicates a significant difference between pre- and poststress measurements (Student's paired  $t$ -test, \*  $p < .05$ . \*\*  $p < .01$ . \*\*\*  $p < .001$ ).

[Treatment\*Time  $F(5, 60) = 5.5$   $p < .001$   $\eta_p^2 = 0.32$  (Figure 3b)]. Among progesterone-treated individuals, plasma progesterone continued to rise after the TSST; levels peaked and reached a plateau at 10 to 20 min poststress, a time coinciding with peak increases in progesterone in the placebo group (Figure 3a, b).

### Subjective Measures

In comparison to the placebo group, individuals treated with progesterone 50 mg exhibited less negative mood after the TSST; peak increases in POMS Anger did not differ between the groups but mood returned to baseline much

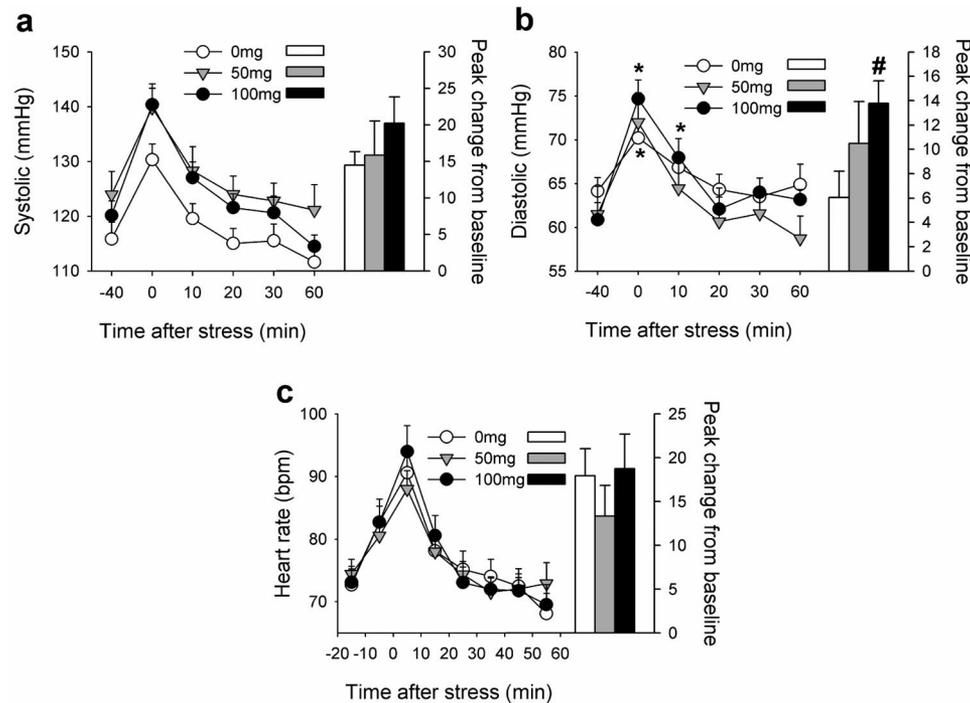


Figure 1. Effects of the Trier Social Stress Test (TSST) on systolic blood pressure (a), diastolic blood pressure (b), and heart rate (c) among individuals treated with 0, 50, and 100 mg progesterone. Data points indicate mean  $\pm$  SEM values at repeated times before and after the TSST (left axis) and bars indicate the peak change from -40 min (right axis). Asterisks indicate a significant difference from -40 min (Student's paired  $t$  test with Bonferroni correction,  $p < .001$ ). # indicates a significant difference from 0 mg (Student's unpaired  $t$  test,  $p < .05$ ).

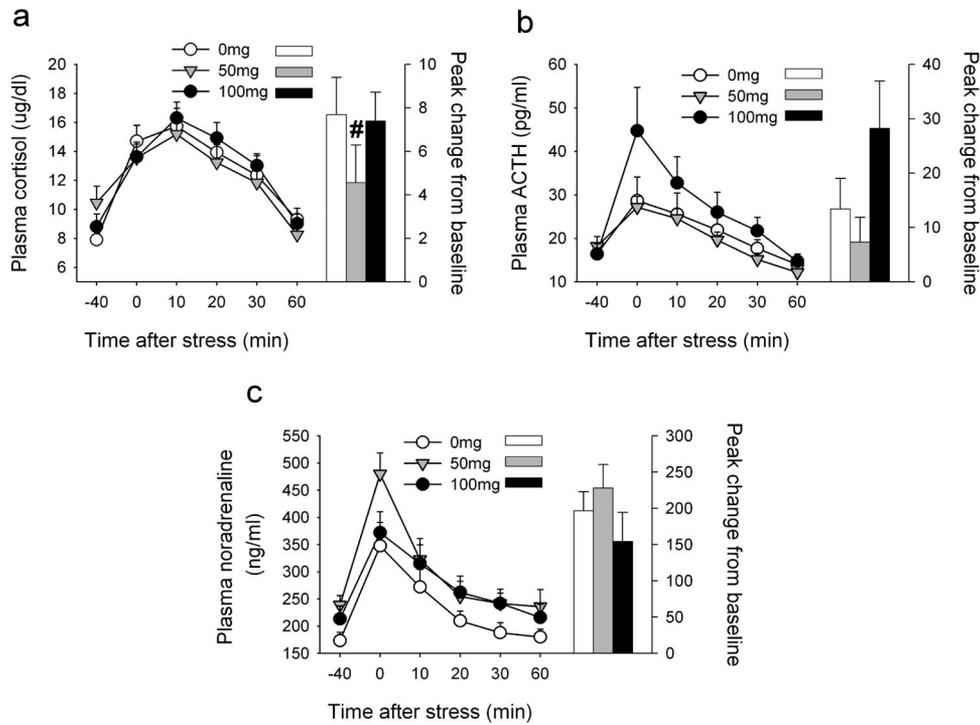


Figure 2. Effects of the Trier Social Stress Test (TSST) upon plasma cortisol (a), ACTH (b), and noradrenaline (c) among individuals treated with 0, 50, and 100 mg progesterone. Data points indicate mean  $\pm$  SEM values at repeated times before and after the TSST (left axis) and bars indicate the peak change from -40 min (right axis). # indicates a significant difference from 0 mg (Student's unpaired *t* test,  $p < .05$ ).

more quickly among those treated with 50 mg [Treatment\*Time  $F(5, 140) = 2.6$   $p < .05$   $\eta_p^2 = 0.09$ ]. Post hoc tests showed that scores for POMS Anger were significantly elevated above baseline immediately after the TSST among progesterone-treated individuals yet remained significantly elevated for 30min after stress among placebo-treated individuals (see Figure 4). Progesterone treatment

attenuated TSST-induced increases in POMS Vigor [50 mg Treatment\*Time  $F(1, 28) = 4.9$   $p < .05$   $\eta_p^2 = 0.15$ ; 100 mg Treatment\*Time  $F(5, 140) = 2.5$   $p < .05$   $\eta_p^2 = 0.08$ ] and decreases in VAS Drowsy [100 mg Treatment\*Time  $F(5, 130) = 3.0$   $p < .05$   $\eta_p^2 = 0.10$ ]. Similarly, progesterone attenuated peak changes in POMS Vigor [50 mg  $t(24) = -2.7$   $p < .05$ ; 100 mg  $t(26) = -2.1$   $p < .01$ ] and VAS Drowsy [50

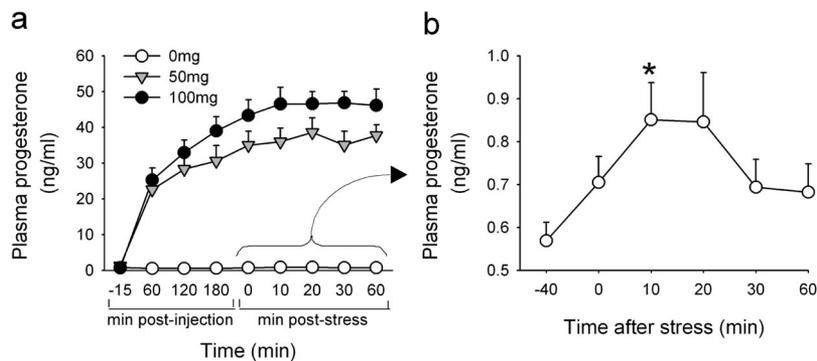
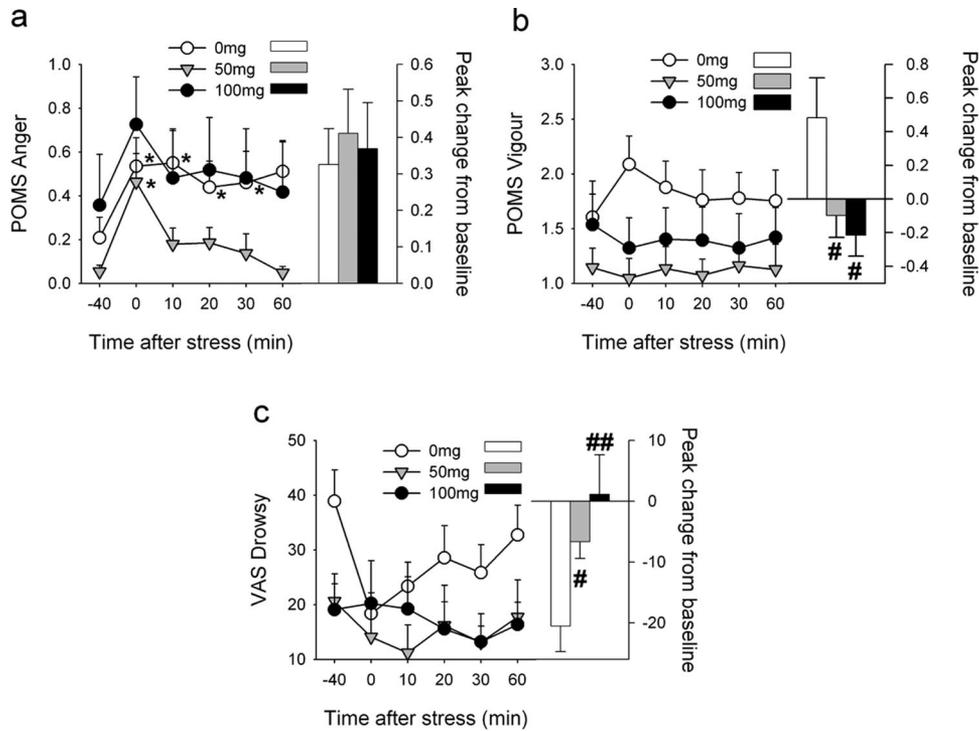


Figure 3. Plasma progesterone levels as a function of time among individuals treated with 0, 50, and 100 mg progesterone (a) and changes in plasma progesterone after the TSST among individuals treated with 0 mg progesterone (b). Data points indicate mean  $\pm$  SEM values at repeated times before and after the Trier Social Stress Test (TSST). Asterisks indicate a significant difference from -40 min (Student's paired *t* test with Bonferroni correction,  $p < .001$ ).



**Figure 4.** Effects of the Trier Social Stress Test (TSST) upon Profile of Mood States (POMS) Anger (a), Vigor (b), and Visual Analogue Scales (VAS) Drowsy (c) among individuals treated with 0, 50, and 100 mg progesterone. Data points indicate mean  $\pm$  SEM values at repeated times before and after the TSST (left axis) and bars indicate the peak change from  $-40$  min (right axis). Asterisks indicate a significant difference from  $-40$  min (Student's paired  $t$  test with Bonferroni correction,  $p < .001$ ). # indicates a significant difference from 0 mg (Student's unpaired  $t$  test, #  $p < .05$ . ##  $p < .01$ ).

mg  $t(28) = 2.1$   $p < .05$ ; 100 mg  $t(28) = 2.5$   $p < .05$ ] after the TSST. Because baseline values of VAS Drowsy differed significantly between the placebo and 100-mg treatment groups before stress, we also analyzed change from baseline values at each time point. These analyses confirmed that 100-mg progesterone attenuated stress-induced decreases in VAS Drowsy, even after taking into account elevated ratings of Drowsy among placebo-treated individuals before the stress procedure [Treatment\*Time  $F(4, 104) = 2.9$   $p < .05$   $\eta_p^2 = 0.19$ ].

### Discussion

The results of this study are consistent with evidence from recent nonhuman and human studies which suggest that progesterone, perhaps via conversion to allopregnanolone and pregnanolone, modulates responses to stress. In laboratory animals, swim stress elevates central levels of enzymes that convert progesterone to allopregnanolone (Sanchez et al., 2008), and brain and plasma levels of progesterone and allopregnanolone are elevated after acute stressors including swim stress, footshock, and CO<sub>2</sub> inhalation (Barbaccia et al., 1996a, 1996b, 1996c, 1996b, 1996c; Barbaccia et al., 2001; Purdy et al., 1991). Furthermore,

allopregnanolone attenuates stress-induced increases in adrenocorticotrophic hormone and corticosterone (Patchev et al., 1996). In humans, stress induces increases in progesterone and allopregnanolone (Childs & de Wit, 2009; Droogleever Fortuyn et al., 2004). In the present study, we found that progesterone (50, 100 mg) attenuated stress-induced increases in alertness, arousal and negative mood. However, unexpectedly progesterone did not consistently attenuate physiological responses to the stress; 50 mg progesterone attenuated stress-induced increases in plasma cortisol but increased plasma noradrenaline and systolic blood pressure overall, whereas 100 mg progesterone potentiated stress-induced increases in diastolic blood pressure. These results suggest that progesterone may preferentially play a role in psychological or subjective responses to stress in humans.

Progesterone significantly attenuated stress-induced increases in POMS Vigor that is, mental activation, and decreases in VAS Drowsy, which is consistent with a sedative profile of subjective effects. Although previous studies have reported clear sedative effects of progesterone itself in humans (de Wit et al., 2001; Freeman et al., 1992; Soderpalm et al., 2004), it is notable that progesterone in our study did not increase self-reports of sedation before the

stress task began. The plasma levels of progesterone after the 50 and 100 mg doses were comparable to plasma concentrations in the earlier studies that is, up to threefold higher than those observed during the midluteal phase in women (Redei & Freeman, 1995). It is not clear why the participants did not report subjective sedation. However, the subjective effects of progesterone became apparent during the stress challenge. Progesterone attenuated stress-induced increases in anger and frustration and promoted recovery from negative mood changes after stress. These findings are consistent with the idea that progesterone metabolites such as allopregnanolone and pregnanolone play a role in recovery from stress. Although we did not measure plasma levels of the progesterone metabolites in this exploratory study, we and others (de Wit et al., 2001; Freeman et al., 1993; Soderpalm et al., 2004) found high correlations between plasma levels of progesterone, allopregnanolone, and pregnanolone, and that the time course of plasma allopregnanolone closely follows that of plasma progesterone after oral and intramuscular progesterone (Andreen, Spigset, Andersson, Nyberg, & Backstrom, 2006; de Wit et al., 2001; Soderpalm et al., 2004). Moreover, Freeman et al. (1993) found that individual differences in levels of progesterone and its metabolites were correlated with subjective measures and performance in cognitive tasks. Thus, our findings provide support for the theory that progesterone, most likely via conversion to neuroactive metabolites, promotes psychological recovery after stress.

Contrary to our hypothesis, progesterone did not consistently attenuate physiological responses to stress. Although 50 mg progesterone attenuated the increase in cortisol after stress, the 100 mg dose tended to potentiate ACTH responses. This is in contrast to animal data showing that progesterone attenuated stress-induced increases in ACTH (Patchev et al., 1996). Indeed, there is accumulating evidence to show that the effects of progesterone, allopregnanolone and other GABA<sub>A</sub> modulators are bimodal and paradoxical (Andreen et al., 2009). For example, there are biphasic effects of GABA<sub>A</sub> steroids upon mood in humans (Andreen, Bixo, Nyberg, Sundstrom-Poromaa, & Backstrom, 2003; Andreen et al., 2005; Andreen, Sundstrom-Poromaa, et al., 2006; Bjorn et al., 2002) and behavioral effects in animals (Beauchamp, Ormerod, Jhamandas, Boegman, & Beninger, 2000; Fish et al., 2001; Gourley, Debold, Yin, Cook, & Miczek, 2005; Miczek, DeBold, van Erp, & Tornatzky, 1997; Yoshimura & Ogawa, 1989) that is, low doses increase negative mood, aggression and anxiety-like behaviors while high doses are calming and reduce aggressive and anxiety-like behaviors. Thus, it follows that there may also be bimodal effects of GABA<sub>A</sub> steroids upon HPA axis activation. The precise mechanism of the biphasic action is unknown but may involve disinhibition and specific effects at certain GABA<sub>A</sub> receptor subtypes (see Andreen et al., 2009). It is also interesting that the 100 mg dose increased plasma progesterone only slightly above that seen in the 50-mg group which may indicate that progesterone was converted to other mineralocorticoids for example, aldosterone, in this group.

Progesterone 50 mg increased noradrenaline and systolic blood pressure overall although it did not alter response to stress in these measures. These findings are in line with previous findings in animal studies, which have also shown that progesterone increases noradrenaline (Sandoval, Gong, & Davis, 2007) and systolic blood pressure (Sharkey et al., 2005). Yet, they are in contrast to previous human studies which reported that progesterone reduced plasma noradrenaline (Tollan, Oian, Kjeldsen, Eide, & Maltau, 1993) and cardiovascular measures (Evans & Foltin, 2006; Rylance et al., 1985; Sofuoglu, Mitchell, & Kosten, 2004). Thus, our results suggest that the beneficial effects of progesterone administration upon subjective responses to stress are counterbalanced by its less advantageous hypertensive action.

A limitation of this study is that the sample size is relatively small. There is rather large interindividual variation in the effects of stress (Kudielka, Hellhammer, & Wust, 2009), and there was also modest variability in the plasma levels of progesterone. Thus, the sample may not have been large enough to demonstrate small-medium size drug effects. Furthermore, we used a similar pretreatment period for each dose of progesterone. Since there is variation in the time to peak plasma levels between different progesterone doses after intramuscular injection (de Wit et al., 2001; Soderpalm et al., 2004), the effects of progesterone may have been assessed at different phases of absorption that is, approaching peak plasma levels with 50 mg versus following peak plasma levels with 100 mg. Although it appeared that peak levels of progesterone were achieved at approximately the same time in the 50 and 100 mg groups, subtle differences in the time to peak plasma concentrations between the groups may be related to the differential effects of progesterone doses upon hormonal measures. In this exploratory study we chose to study the effects of progesterone upon stress responses in men only. First, we previously reported clear differences in levels of progesterone after stress in men (Childs, Dlugos, & de Wit, 2009), and these differences in women varied with menstrual cycle (Childs and de Wit, in press). Also, there are sex differences in stress responses between men and women and in women between different phases of the menstrual cycle, which may influence progesterone-stress interactions. In addition, animal studies show that the effects of progesterone and other GABA<sub>A</sub> modulators differ depending upon the length of exposure (Biggio et al., 2006; Brot, Akwa, Purdy, Koob, & Britton, 1997; Gulinello & Smith, 2003), and therefore differences in baseline levels of progesterone between men and women are also likely to influence progesterone-stress interactions. Thus, the findings of this experiment cannot be generalized to the effects of progesterone upon stress responses in women, which remain to be studied.

In conclusion, administration of progesterone dampened subjective responses to acute stress without altering mood alone. The effects of progesterone upon other physiological and hormonal responses to stress were not dose dependent and provide mixed support for the role of progesterone and its metabolites in restoring homeostasis after a stressful event. These results should be extended to other populations that is, women and anxiety-sensitive individuals.

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