Neuropsychopharmacology (2006) 31, 885–889

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Estrogen Prevents 5-HT_{1A} Receptor-Induced Disruptions of Prepulse Inhibition in Healthy Women

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The sex steroid hormone, estrogen, has been proposed to be protective against schizophrenia. This study examined the effects of estrogen treatment on modulation of prepulse inhibition (PPI) by the serotonin-1A (5-HT_{1A}) receptor partial agonist, buspirone. PPI is a model of sensorimotor gating, which is deficient in schizophrenia and other mental illnesses. A total of 11 healthy women were tested following four acute treatment conditions: placebo, buspirone (Buspar; 5 mg), estradiol (Estrofem; 2 mg), and combined buspirone and estradiol. Electromyogram activity was measured across three interstimulus intervals (ISI): 30, 60, and 120 ms. There was no significant effect of either drug treatment on startle amplitude or habituation. At 120 ms ISI, buspirone caused a significant disruption of PPI and pretreatment with estrogen prevented this disruption. Estrogen treatment, administered in the appropriate experimental conditions, prevented PPI deficits induced by 5-HT_{1A} receptor activation and may therefore also play a protective role in sensorimotor gating deficits in schizophrenia.

Neuropsychopharmacology (2006) **31,** 885–889. doi:10.1038/sj.npp.1300933; published online 19 October 2005

Keywords: schizophrenia; serotonin; estradiol; EMG; buspirone; human

INTRODUCTION

Gender differences exist in schizophrenia, where compared to men, in women the disease tends to first occur several years later and be less severe (Canuso *et al*, 1998; Häfner *et al*, 1993). Thus, it has been suggested that the 'female' sex steroid hormone, estrogen, plays a neuroprotective role in schizophrenia (Häfner *et al*, 1993; Seeman and Lang, 1990); however, the exact mechanism remains unknown. Clinical trials suggest that adding estrogen treatment to antipsychotic medication accelerates the improvement of symptoms compared to antipsychotic medication alone (Kulkarni *et al*, 2001). The present study focused on the interaction of estrogen with central serotonin-1A (5-HT_{1A}) receptor function. Evidence for the importance of 5-HT_{1A} receptors in schizophrenia includes post-mortem research (Burnet *et al*, 1997; Simpson *et al*, 1996) and some atypical antipsychotics having high affinity for 5-HT_{1A} receptors (Bantick *et al*, 2001).

Prepulse inhibition (PPI) of the acoustic startle response is a measure of sensorimotor gating, a protective mechanism in the brain that functions to filter irrelevant information, allowing for coherent thought (Kodsi and Swerdlow, 1994). PPI is disrupted in schizophrenia patients and such deficits can be pharmacologically induced in animals and healthy humans (Braff *et al*, 2001). For example, in healthy men, depletion of the 5-HT precursor, tryptophan, has been found to disrupt PPI (Phillips *et al*, 2000). It is well established that systemic administration of the selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-di-propylaminotetralin (8-OH-DPAT), causes a disruption of PPI in rats (Gogos and Van den Buuse, 2003, 2004; Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1995; Sipos *et al*, 2000). However, it has not been established whether 5-HT_{1A} receptors play a role in modulating PPI in humans. Similarly, although the effect of natural variations in estrogen has been investigated (Jovanovic *et al*, 2004; Kumari *et al*, 2004; Swerdlow *et al*, 1997), the specific effect of estrogen administration on PPI in women has not been tested. We previously found that chronic estrogen treatment in ovariectomized female rats prevented 8-OH-DPAT-induced disruptions of PPI (Gogos and Van den Buuse,

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[5]Financially supported by the National Health and Medical Research Council of Australia and Alzheimer's Australia

[6]Supported by the Griffith Senior Research Fellowship of the University of Melbourne. The Mental Health Research Institute is a Stanley Research Centre supported by the Stanley Medical Research Institute, Bethesda, MD, USA

Received 15 July 2005; revised 11 August 2005; accepted 22 August 2005

Online publication: 9 September 2005 at http://www.acnp.org/citations/Npp090905050457/default.pdf

2004). The present study examined the effects of 5-HT$_{1A}$ receptor activation on startle and PPI in healthy women, using the partial 5-HT$_{1A}$ receptor agonist, buspirone. Furthermore, we examined whether acute estrogen treatment modulates the 5-HT$_{1A}$ receptor-mediated responses on startle and PPI.

MATERIALS AND METHODS

Participants

At least 40 female participants were screened for inclusion in this study. Based on the exclusion criteria, we selected 14 healthy, female participants aged 20–38 years (mean: 26 ± 2 years), who completed the study. Participants were excluded if they were on any medication (particularly hormone treatment), pregnant, had a history of psychiatric illness, an irregular menstrual cycle, or if they reported hearing difficulties, use of smoking or illicit drugs.

Study Design

The Swinburne University of Technology Human Research Ethics Committee approved this study. Prior to testing, participants read the full description of each drug treatment, signed the informed consent form, were given a numerical identifier to ensure confidentiality, and were screened by a physician to ensure they were without any medical conditions that may cause danger or violation of the study criteria. All participants were tested within 10 days from menstruation onset, when estrogen levels are low (ie during the early follicular phase). Depending on the availability of the equipment and the participant within the 10 days of menstruation onset, some participants were tested once per menstrual cycle (ie testing occurred over 4 months), whereas other participants were tested more than once per menstrual cycle, so that two tests (7 days apart) were completed within 10 days from menstruation onset (ie testing occurred over 3 months).

A repeated measures, double-blind, randomized design was used, with four treatment conditions: placebo/placebo, estradiol/placebo, placebo/buspirone, and estradiol/buspirone. Drug treatments were orally administered: placebo (gelatin capsule filled with flour); Estrofem® (17β-estradiol, Novo Nordisk Pharmaceuticals, NSW, Australia, 2 mg); and Buspar® (buspirone hydrochloride, Bristol-Myers Squibb, VIC, Australia, 5 mg). This dose of estradiol produces physiological concentrations of 17β-estradiol (Fink and Christensen, 1981; Furuhjelm *et al*, 1984). The dose of buspirone has been shown to exert pharmacodynamic effects in humans (Hellewell *et al*, 1999; Mizuki *et al*, 1994). Time of testing after drug administration was chosen to coincide with peak pharmacokinetic effects of both buspirone (ie 60–90 min) and estradiol (ie 4–6 h).

Prepulse Inhibition of the Acoustic Startle Response

Participants were tested for a number of tasks, presented in a random order, including PPI, P50, mismatch negativity, and loudness dependence (only the PPI data will be reported here).

Eye muscle activity (electromyogram, EMG) was recorded as the difference between two 6 mm electrodes placed below the right eye (orbicularis oculi muscle). The data were recorded and stimuli presented using NeuroScan equipment with Synamp amplifiers and STIM Audio System and software (NeuroScan Labs, Sterling, VA), and sounds were applied to the participant binaurally by EAR insert earphones (Aearo Company Auditory System, Indianapolis, IN). EMG activity was continuously digitized at 2000 Hz, amplified, and band-pass filtered (0.05–500 Hz).

The PPI session included 48 trials presented in a pseudorandom order, with intertrial intervals ranging from 16 to 24 s (mean: 20 s). There was an initial 1 min acclimation period of 70 dB white noise that continued as background noise. There were three groups of eight startling pulses (40 ms bursts of 108 dB white noise) that were used to obtain a measure of startle amplitude and habituation; presented at beginning, middle, and end of session. There were three groups of eight prepulse–pulse trials with varying interstimulus intervals (ISI): prepulse intensity 15 dB (20 ms burst of white noise) above the 70 dB background, followed by the 108 dB startle pulse 30, 60, or 120 ms later. All stimuli had a rise and fall time <1 ms. This PPI session was based on a review of the human PPI literature (Braff *et al*, 2001) and is similar to the protocols used by others (Cadenhead *et al*, 1993; Kumari *et al*, 2000; Parwani *et al*, 2000). During the PPI paradigm, a task was given to the participants to avert their attention. Participants were instructed to look at a screen and press a keypad when a complete, four-sided square appeared, as opposed to an incomplete square.

For EMG activity, the data were epoched (-80 to 300 ms poststimulus), band-pass filtered (10–200 Hz), rectified, smoothed (over five adjacent data points and three consecutive passes), and baseline corrected (Anokhin *et al*, 2003). The magnitude of the startle response was defined as the peak EMG response within 20–120 ms poststimulus (Anokhin *et al*, 2003), as determined by the NeuroScan software. The % PPI was calculated as (startle response to middle eight pulse-alone trials minus response to prepulse–pulse trials, divided by response to pulse-alone trials) $\times$ 100%. Three participants were classified as 'non-responders' and excluded from any further data analysis, as the peak startle amplitude was less than 10 (arbitrary units) when administered placebo treatment.

Statistical Analysis

We conducted ANOVA with repeated measures, using the statistical software SYSTAT (SPSS, Chicago, IL). For PPI data, factors (within-subject) were pretreatment (placebo or estrogen), treatment (placebo or buspirone), and ISI (30, 60, and 120 ms).

RESULTS

There was no significant effect of either drug treatment on startle amplitude or habituation (Figure 1). There was a significant main effect of block ($F_{(2,20)} = 6.3$, $p = 0.008$), reflecting the significant habituation of the startle response over repeated exposure to the startling stimuli (Figure 1).

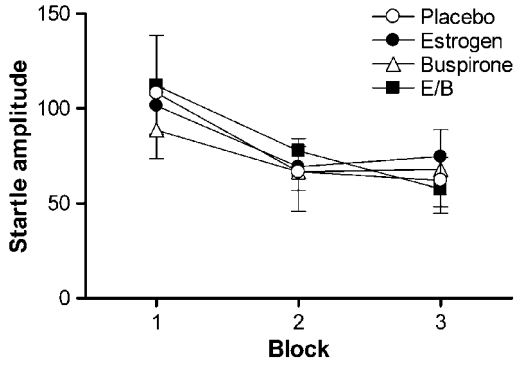

Figure 1 Mean ± SEM startle responses (in arbitrary units) of healthy women ($n = 11$) treated with placebo (open circles), estrogen (2 mg; black circles), buspirone (5 mg; open triangles), or both estrogen and buspirone (E/B, black squares). Habituation to the startle response is shown for the three blocks of eight 108 dB startling pulses presented throughout the PPI session.

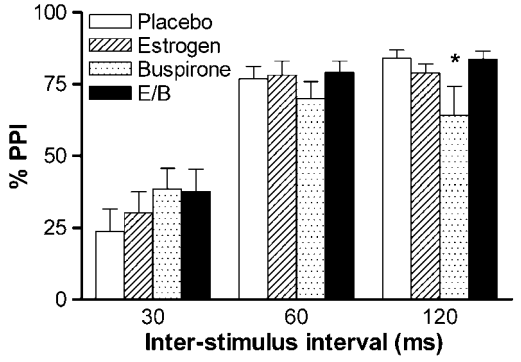

Figure 2 Mean ± SEM % PPI of healthy women ($n = 11$) treated with placebo (open bars), estrogen (2 mg; hatched bars), buspirone (5 mg; spotted bars), or both estrogen and buspirone (E/B, black bars). % PPI is shown for the three types of prepulse-pulse trials, that is, a prepulse of 85 dB presented either 30, 60, or 120 ms before the 108 dB startling pulse. *$p < 0.05$.

Overall, there was a significant main effect of ISI ($F_{(2,20)} = 54.3$, $p < 0.001$), reflecting reduced startle with increasing ISI (Figure 2). There was no significant main effect of either pretreatment or treatment, suggesting that neither drug treatment affected PPI overall. While there was no interaction of pretreatment (placebo or estrogen) with ISI, there was however a significant treatment (placebo or buspirone) by ISI interaction ($F_{(2,20)} = 7.1$, $p = 0.005$). Furthermore, there was a significant pretreatment by treatment by ISI interaction ($F_{(2,20)} = 5.6$, $p = 0.012$). Further separate ANOVAs for each ISI indicated that there was no significant effect of pretreatment or treatment at ISI 30 or 60 ms. However, there was a significant pretreatment by treatment interaction at ISI 120 ms ($F_{(1,10)} = 8.0$, $p = 0.018$). Further analysis of the drug treatments at ISI 120 ms revealed that, compared to placebo treatment, buspirone treatment caused a significant disruption of PPI ($F_{(1,10)} = 5.3$, $p = 0.044$). In addition, when comparing buspirone treatment with combined estrogen and buspirone (E/B) treatment, there was a strong trend for a significant difference in PPI ($F_{(1,10)} = 4.6$, $p = 0.058$), indicating the lack of a buspirone-induced disruption of PPI with E/B treatment (Figure 2). There were no significant effects of estrogen or E/B treatment on PPI, compared to placebo treatment.

DISCUSSION

To our knowledge, this is the first study to examine the effects of 5-HT$_{1A}$ receptor modulation on PPI and how this response is affected by estrogen in humans. This study found that at an ISI of 120 ms, administration of the partial 5-HT$_{1A}$ receptor agonist, buspirone, significantly disrupted PPI. Furthermore, pretreatment with estrogen prevented this effect of buspirone. These results support our previous findings in female rats that 8-OH-DPAT-induced PPI deficits were prevented by estrogen treatment (Gogos and Van den Buuse, 2004).

Treatment with buspirone disrupted PPI without affecting startle amplitude or habituation. Similarly, in healthy men, acute tryptophan depletion disrupts PPI, without affecting startle amplitude (Phillips *et al*, 2000). Tryptophan depletion causes a depletion of 5-HT levels in the entire brain (Phillips *et al*, 2000). Buspirone treatment, at doses similar to those used in the present study, reduces plasma 5-HT and its metabolite concentrations (Mizuki *et al*, 1994). An acute dose of buspirone in the rat significantly reduces 5-HT synthesis in the brain (Okazawa *et al*, 1999) and completely inhibits dorsal raphe nucleus firing (VanderMaelen *et al*, 1986), most likely by its action at presynaptic 5-HT$_{1A}$ receptors. Together, this suggests that a reduction in 5-HT concentration in the human brain, as caused by tryptophan depletion or buspirone treatment, results in a disruption of PPI.

The present findings, together with our previous results (Gogos and Van den Buuse, 2004), suggest that estrogen may interact with 5-HT$_{1A}$ receptors in the modulation of PPI in both rats and humans. It is unlikely that the 'interaction' involves estrogen altering 5-HT$_{1A}$ receptor density or affinity, as estrogen treatment in ovariectomized rats does not alter 5-HT$_{1A}$ receptor density or affinity in various brain regions, including the raphe nuclei, hippocampus, or prefrontal cortex (Flugge *et al*, 1999; Jackson and Etgen, 2001; Landry and Di Paolo, 2003). The most likely mechanism responsible for the observed PPI effects is that estrogen treatment altered signalling of the 5-HT$_{1A}$ receptor. Acute estrogen treatment in ovariectomized rats desensitized 5-HT$_{1A}$ receptor function, as indicated by a reduction in [^{35}S]GTPγS binding (Mize and Alper, 2000; Mize *et al*, 2001). Further studies are required to investigate if similar mechanisms occur in humans.

Estrogen treatment alone did not induce any changes in PPI or startle. This suggests that the reversal of the buspirone-induced disruption of PPI is not due to any effects of estrogen itself on PPI. The dose of estrogen used results in a plasma estradiol concentration of 100 pg/ml (Fink and Christensen, 1981), the average concentration of estrogen during the luteal phase (Ganong, 1979). Others have found that, compared to the early follicular phase of the menstrual cycle, PPI was reduced during the luteal (high estrogen) phase (Jovanovic *et al*, 2004; Swerdlow *et al*, 1997). The apparent discrepancy between these studies and

ours may be attributed to the type of estrogen stimulation: natural cyclical estrogen (Jovanovic *et al*, 2004; Swerdlow *et al*, 1997) *vs* acute oral administration. Moreover, during the menstrual cycle, levels of progesterone also vary, which could be another factor in the menstrual cycle effects.

In the present study, the significant PPI findings occurred only at the 120 ms ISI. The use of different ISI can result in different effects on PPI (Swerdlow *et al*, 2001). While PPI is generally thought of as an automatic process, at an ISI greater than 120 ms, attentional influences may also play a role (Braff *et al*, 2001). For example, Filion *et al* (1993) found that a greater inhibition occurred at the 120 ms interval when the prepulse was attended to compared to when it was ignored, but there was no difference at the 60 ms interval. The 120 ms interval is on the border between automatic and attentional forms of PPI. Therefore, in the present study, it is possible that both processes were involved in modulating buspirone-induced PPI deficits, suggesting why a significant effect was observed only at the 120 ms ISI. However, this idea requires further investigation in order to clarify the different roles of varying ISI on PPI. It should be noted that participants were given another 'distraction' task to complete during the PPI paradigm, in an attempt to deter attention from the prepulse trials.

While buspirone is known as a partial 5-HT$_{1A}$ receptor agonist, at higher doses it has some antagonist activity at dopamine D$_2$-like receptors and indirect agonist activity at adrenergic receptors (Lechin *et al*, 1998). However, the disruptive effect of buspirone treatment on PPI in humans was similar to that of 8-OH-DPAT treatment in rats (Gogos and Van den Buuse, 2004), while administration of dopamine D$_2$-like receptor antagonists increased PPI in rats (Johansson *et al*, 1995).

In conclusion, acute estrogen treatment prevented buspirone-induced PPI deficits. Thus estrogen treatment, administered in the appropriate experimental conditions, prevented 5-HT$_{1A}$ receptor-induced sensorimotor gating deficits. Therefore, estrogen treatment may also play a role in sensorimotor gating deficits in schizophrenia through its effects on 5-HT$_{1A}$ receptor function.

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