The indirect serotonergic agonist D-fenfluramine and prepulse inhibition in healthy men∗

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Abstract

The specific serotonin (5-HT) releaser, D-fenfluramine (DFEN) was used as a probe of serotonergic effects on prepulse inhibition (PPI). We wished to explore the notion that increased central serotonergic transmission was in part responsible for the psychotomimetic effects of hallucinogens using a relevant and objective physiological measure. Disruption of PPI is considered a valid pharmacological model of some aspects of the behavioural abnormalities in schizophrenia. The aim of this study was to test the hypothesis that increasing central 5-HT neurotransmission with DFEN would produce disruption of PPI. Eighteen healthy male subjects received 45 mg of DFEN or placebo in a random order, within-subject, double-blind, and cross-over design. Prepulse to pulse intervals were 30 ms and 120 ms. The Brief Psychiatric Rating Scale (BPRS) was administered. Although mean PPI at the two prepulse intervals was not significantly different, DFEN prevented the increase in PPI usually seen at the 120 ms interval and significantly increased startle magnitude, but did not alter habituation. There were no significant associations between PPI effects and behaviour.

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1. Introduction

Serotonin (5-HT) has been implicated in the pathophysiology of schizophrenia since the observation that 5-HT agents produce psychosis in healthy subjects (Wooley and Shaw, 1954). More recent studies suggest that hallucinogens are agonists or partial agonists at 5-HT2 receptors (e.g. Glennon, 1990) and that stimulation of cortical 5-HT2A/2C receptors is responsible for their psychotomimetic effects (Marek and Aghajanian, 1998). It is suggested that there may be a functional increase in brain 5-HT transmission in schizophrenia whose behavioural effects may or may not be dopamine (DA) dependent (for review see Marek and Aghajanian, 1998; Dean, 2003). We have previously reported an increase in D-fenfluramine (DFEN)-mediated prolactin (PRL) responses in never-treated schizophrenia (Abel et al., 1996) which supports the notion of increased central 5-HT function (Dean, 2003), at least in the acute stages of the illness. Although alone the pure 5-HT2A antagonist MDL-100 907 has no efficacy as an antipsychotic (de Paulis, 2001), second generation antipsychotic agents (SGAs) have approximately 10 times the affinity for the 5-HT2A receptor (Meltzer et al.,...
chronic schizophrenia (Braff et al., 1992; Ludewig et al.,
communication). Habituation of startle may also be impaired in
view) and acute illness (Cadenhead, personal commu-
2003), although some studies do not find this (Braff et al.,
sensory or motor inhibition (Geyer and Braff, 1987).
prevent the cerebral cortex being inundated (and over-
conceptualised as key filtering or ‘gating’ processes which
an intense startling stimulus. Both PPI and habituation are
transiently suppress a motor response (Ison and Hoffman,
PPI as seen in schizophrenia.
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measured by PPI of startle, is deficient in schizophrenia
hypothesis that 5-HT plays a crucial role in sensory gating
mechanisms and may suggest that changes in serotonergic
transmission in acute, drug na
1993) and amesergide (Coccaro et al., 1996a).
Disruption of PPI is considered a reliable pharmacologi-
cal model of some aspects of the behavioural abnormalities
in schizophrenia (Braff et al., 1999). Abnormalities of hu-
man startle reflex modulation have been described repeatedly
in schizophrenia. Most prominently, sensorimotor gating, as
measured by PPI of startle, is deficient in schizophrenic
patients with chronic (Braff et al., 1992; Grillon et al.,
1992; Ludewig et al., 2003; see Braff et al., 2001 for re-
view) and acute illness (Cadenhead, personal commu-
nication). Habituation of startle may also be impaired in
chronic schizophrenia (Braff et al., 1992; Ludewig et al.,
2003), although some studies do not find this (Braff et al.,
1999; Kumari and Sharma, 2002). Habituation is the sim-
plest form of learning and is essential for the selectivity
of attention. Having reported evidence of raised 5-HT neuro-
transmission in acute, drug naïve schizophrenia, we wished
to use PPI to assess whether increasing 5-HT transmission
in healthy subjects would produce similar disruption of
PPI as seen in schizophrenia.

In prepulse inhibition (PPI), a brief weak sensory cue can
transiently suppress a motor response (Ison and Hoffman,
1983), for example reducing the magnitude of an eyelink to
an intense startling stimulus. Both PPI and habituation are
conceptualised as key filtering or ‘gating’ processes which
prevent the cerebral cortex being inundated (and over-
whelmed) with sensory information, with resultant lack of
sensory or motor inhibition (Geyer and Braff, 1987).

In rodents, the majority of studies using drugs which
release synaptic 5-HT, i.e. 5-HT receptor agonists, impair
both PPI and habituation in a manner similar to that seen in
schizophrenia (Mansbach et al., 1989; Kehne et al., 1996;
Dulawa et al., 2000a; Martinez and Geyer, 1997; Vollenweider
et al., 1999; see Geyer et al., 2001 for review). PPI is disrupted
by acute administration of 5-HT receptor agonists which
activate 5-HT$_{1A}$ (Rigdon and Weatherspoon, 1992; Sipes
and Geyer, 1994; Fletcher et al., 2001; Prinsen et al., 2002)
5-HT$_{1B}$, and 5-HT$_{2A}$ receptors (Padich et al., 1996; Sipes
and Geyer, 1997; Farid et al., 2000) except in mice, where
5-HT$_{1A}$ receptor activation appears to increase PPI (see
Dulawa et al., 2000b). These studies are consistent with the
hypothesis that 5-HT plays a crucial role in sensory gating
mechanisms and may suggest that changes in serotonergic
neurotransmission, postulated in (acute) schizophrenia (Abel
et al., 1996; Dean, 2003), are also associated with deficits of
PPI observed in schizophrenia.

To date, studies in humans using either indirect mixed
serotonergic and dopaminergic agonists, such as psilocybin
(Ouzouzis-Mayfrank et al., 1998), or releasers of presynap-
tic 5-HT, such as MDMA (3,4-methylenedioxy-N-methylam-
phetamine or ‘ecstasy’) (Vollenweider et al., 1999; Liechti
et al., 2001), have been reported to increase PPI. In addition,
the non-selective 5-HT$_{2}$ antagonist, ketanserin, reduced PPI
in humans (Graham et al., 2002). Results from these studies
may be limited for several reasons: (1) psilocybin is a mixed
direct agonist at DA as well as 5-HT$_{1A/2}$ receptors (e.g.
Vollenweider et al., 1998) and compared to direct 5-HT re-
ceptor agonists, releasers may be considered a more ‘natural’
serotonergic stimulus as they maintain the normal physiolog-
ical relationship between transmitter, synapse and receptor;
(2) small numbers limited the psilocybin study; (3) only
one study (Liechti et al., 2001) controlled for the effects of
smoking, which has independent effects on PPI (Della Casa
et al., 1998); (4) similarly, only one study (Liechti et al.,
2001) controlled for effects of menstrual phase, which also
has independent effects on PPI in women (Swerdlow et al.,
1997); and (5) ketanserin is an $z_{2}$ receptor antagonist which
may have independent effects on PPI. One recent study
(Gogos et al., 2006) has used a specific 5-HT agonist, buspir-
one, and controlled for menstrual phase in healthy women.
These authors reported a PPI deficit with buspiron stretched
for the 120 ms prepulse interval. We chose to administer the
selective 5-HT$_{1}$ receptor agonists, DFEN, in a larger sample of healthy,
non-smoking subjects. We used a random order, double-
blind, placebo-controlled, within-subject design to test the
hypothesis that indirect 5-HT receptor agonists disrupt PPI
habituation in healthy humans.

2. Methods

2.1. Ethics

Ethical approval was obtained from the Research Ethics Committee of the
Institute of Psychiatry and Maudsley Hospital. The procedures and possible
side effects were fully explained to subjects by a psychiatrist or physician
(KMA or MA) and subjects were given opportunities to ask questions before,
and on the day of, testing. Written informed consent was obtained. DFEN was
obtained under license from Servier Pharmaceuticals (France) prior to its with-
drawal, which followed reports of pulmonary hypertension in prolonged/repet-
titive use as an appetite suppressant. We continued our studies, with ethical
approval of the single dosing, until approximately 2000.

2.2. Study subjects

Twenty-one male subjects (medical students and employees of the Institute
of Psychiatry, London) were recruited by local advertisement. They were
screened for psychiatric and medical illness by a psychiatrist (KMA). All sub-
jects were screened with audiometry and had no impairment of hearing. All
were naïve to DFEN. Three subjects with negligible baseline startle responses
(mean amplitude < 10) were excluded from the study. Eighteen subjects with
a mean age of 26.8 years (range 22–33) completed both days of testing.

2.3. $\alpha$-fenfluramine and placebo administration

Subjects attended at 8.30 a.m. on each testing day having fasted from
midnight the night before. Drug administration was initially double-blind,
but the psychotropic effects of DFEN ensured that both subjects and investigators were usually able to distinguish placebo from the active drug. Test days were separated by at least a week and test order was randomised. Subjects were asked to lie on a couch and were cannulated in a forearm vein. Subjects were asked to rest supine for about 30 min before baseline bloods were drawn from the cannula and then DFEN (45 mg) or placebo was administered orally. This dose of DFEN was chosen because it has been demonstrated (McBride et al., 1990) to give a more robust response in male subjects than the more usual dose of 30 mg. The first 1.5 ml of blood was discarded as contaminant. Baseline samples were considered as time 0 minute samples. These and all subsequent samples were taken in 5 ml aliquots for PRL estimation.

Subjects remained semi-recumbent for the ensuing 5 h during which samples of blood were taken as for the baseline in two 5 ml aliquots at 1.3, 4 and 5 h. After each sampling, the cannula was flushed with 5 ml saline. After the baseline sample a standard light breakfast was given to subjects consisting of two pieces of toast and a hot drink. Hypoglycaemic effects on PRL secretion were controlled by asking subjects to eat a light lunch of a sandwich and fruit. Subjects were not allowed to sleep during the testing.

2.4. Startle paradigm

The blink component of the acoustic startle response was measured by taking electromyographic (EMG) recordings from the right orbicularis oculi using two silver/silver chloride disk electrodes filled with Dracard electrolyte gel attached to the skin. A ground electrode was placed over the right mastoid process. The startle system (San Diego Instruments (SDI), San Diego, CA: modified SR-Lab system) recorded, and band-pass filtered, EMG activity at 1 kHz for 250 ms from the onset of startle stimulus. Startle magnitude was measured in arbitrary analog-to-digital units and peak latency to response in milliseconds. Acoustic stimuli consisted of 40 ms bursts of 116 dB broadband noise with nearly instantaneous rise time over a continuous background noise of 70 dB broadband noise presented binaurally through headphones. The prepulses were 20 ms duration noise bursts of 80 dB, i.e. 10 dB above background. After a 5 min acclimatisation period with the background noise, the first block of six 116 dB 40 ms noise bursts was presented alone (pulse alone). These pulse-alone trials were followed by 24 trials consisting of two blocks of 12 trials each. Each of these 12-trial blocks included four pulse-alone trials, four trials with 30 ms, and four trials with 120 ms prepulse to pulse intervals, presented in a pseudorandom order. The final block was identical to the first block, consisting of six pulse-alone noise bursts. The comparison of startle magnitudes in the first versus the final blocks was used as a measure of habituation, in addition to the trend in startle magnitudes across all blocks. The total session included 36 trials and lasted approximately 11 min. The order of the trials did not vary, once randomised, across sessions or between subjects.

Subjects remained lying down or semi-recumbent throughout the procedure and we used a passive attention paradigm in which subjects were not given any instruction to attend to the prepulse, but simply asked to fixate on a visual locator (a cross on the wall in front of them). PPI testing was performed between hours 4 and 5 to coincide with peak neuroendocrine responses.

2.5. Definition of percent PPI and habituation

Percent PPI was measured using the average of the peak startle responses and was defined by the formula: \[
\%\text{PPI} = 100 \times \frac{\text{magnitude of pulse-alone trials} - \text{magnitude on prepulse trials}}{\text{magnitude on pulse-alone trials}}
\]. Percent habituation of the startle response magnitude was measured by assessing the decrement in the magnitude of the startle response to pulse-alone (PA) trials (block 1 to block 4 magnitudes) defined by the following formula: \[
\%\text{HAB} = 100 \times \frac{\text{magnitude block 1 – magnitude final block}}{\text{magnitude block 1}}
\]. If a response fell outside the physiological range for a reflex blink (onset < 20 ms or beyond 90 ms) it was discarded. Startle magnitudes, peak latencies and PPI were calculated using Microsoft Excel 7.0 for Windows 2000. To assess differences in PPI and habituation with drug condition a repeated-measures ANOVA was performed.

2.6. Neurobehavioural measures

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was administered between hours 4 and 5. The total BPRS and BPRS factor scores were recorded. A short battery of cognitive tests was administered during the steady state infusion (at the same time as the BPRS): verbal fluency (FAS); Category Instance Generation; Mini-Mental State Examination (MMSE); and Backwards Digit Span. Subjects were also asked to report any symptoms they noticed as a result of taking the capsules. These were recorded for each subject.

2.7. Analyses

All analyses were performed using SPSS 8.0.1 (SPSS, Chicago, USA). A repeated-measures multivariate analysis of variance (RMANOVA) was performed with trial type, block and drug condition (placebo or n-fenfluramine) as within-subject factors. Hormonal responses between the two drug conditions were compared using independent samples t-test. Correlational analyses were performed using Pearson’s correlations and results from DFEN and placebo condition were examined separately.

3. Results

3.1. Neurobehavioural data

On mental state evaluation, subjects reported elevation of mood, increased talkativeness, social disinhibition, reduced appetite and agitation with DFEN. DFEN produced a significant increase in the total BPRS score (Wilcoxon’s signed ranks test: \( Z = 2.60; \ p = 0.009 \)). The following factor scores were also increased by DFEN: thought disorder (\( Z = -2.12; \ p = 0.034 \)); withdrawal (\( Z = -2.00; \ p = 0.046 \)); anxiety/depression (\( Z = -2.71; \ p = 0.007 \)); agitation/activation (\( Z = -2.97; \ p = 0.003 \)); and hypomania (\( Z = -2.72; \ p = 0.007 \)). The factor ‘hostility’ was not significantly altered by DFEN (\( Z = -1.00; \ p = 0.317 \)) (see Table 1). There were no significant correlations between the change in BPRS factor scores with DFEN and change in habituation or change in PPI at 30 ms and 120 ms inter-stimulus intervals (Spearman’s rho; \( p > 0.05 \)).

### Table 1

| BPRS factor scores [mean (SD)] in DFEN and placebo conditions |
|-----------------|-----------|-----------|-----------|
| BPRS factor scores | Drug condition | Mean (SD) | \( Z \) | \( p \) |
| Thought disorder | Placebo | 0.00 | -2.12 | 0.034 |
|                 | DFEN | 0.47 (0.8) | | |
| Withdrawal | Placebo | 0.00 | -2.00 | 0.046 |
|               | DFEN | 0.27 (0.46) | | |
| Anxious depression | Placebo | 0.05 (0.2) | -2.71 | 0.007 |
|                   | DFEN | 0.73 (0.88) | | |
| Hostility | Placebo | 0.00 | -1.00 | 0.317 |
|            | DFEN | 0.68 (0.26) | | |
| Agitation and activation | Placebo | 0.05 (0.2) | -2.97 | 0.003 |
|                       | DFEN | 0.8 (0.68) | | |
| Hypomania | Placebo | 0.00 | -2.72 | 0.007 |
|            | DFEN | 1.2 (1.15) | | |

Wilcoxon’s signed ranks test.

BPRS, Brief Psychiatric Rating Scale.

DFEN, n-fenfluramine.
3.2. Cognitive tests

None of the cognitive tests, nor the mini-mental state examination, were significantly affected by this dose of DFEN, with testing carried out at the 4 h time point on each occasion (paired t-tests; p > 0.05) (see Table 2).

3.3. Neuroendocrine data

RMANOVA (drug condition (twofold) × time (fivetfold)) revealed that DFEN induced an increase in PRL levels in all except one subject within the subsequent 5 h period of testing. There was a significant treatment effect (DFEN or placebo) [F(1,33) = 25.4; p < 0.001], time effect [F(4,30) = 8.1; p < 0.001], and drug condition × time interaction [F(4,30) = 4.7; p < 0.005] on PRL release (see Fig. 1). Mean Area Under the Curve (AUC) PRL (mU/h/L) was significantly higher for the DFEN condition (mean 302.0, SD 337.8) than for the placebo condition (mean −15.5, SD 61.3) (t = −3.9, df = 18.2; p < 0.001). Similarly, ΔPRL (mU/L) was significantly higher following DFEN administration (mean 128.5, SD 124.3) than following placebo (mean 7.95, SD 14.6) (t = −4.3, df = 19.6; p < 0.001). There were no correlations between change in PPI (30 ms and 120 ms inter-stimulus intervals) or habituation and change in prolactin after DFEN (Pearson’s rho; p > 0.05).

3.4. Startle magnitude

RMANOVA (block (fourfold) × drug condition (twofold)) revealed a significant main effect of block on startle magnitude [F(1,17) = 25.8; p < 0.001] and a main effect of drug on startle magnitude [F(1,17) = 5.14; p = 0.037] (Table 3), but no interaction between block and drug condition [F(1,17) = 0.63; NS]. Paired sample t-tests were used to compare placebo and DFEN conditions. Startle magnitude in all blocks was greater in the DFEN condition compared to the placebo condition. This was statistically significant in block 2 (t = −2.10; p = 0.051) and block 3 (t = −2.51; p = 0.022). Habituation was not significantly different between placebo and DFEN conditions (t = 1.57; p = 0.136).

3.5. PPI

PPI data were collapsed across the two blocks of PPI trials. RMANOVA (trial type (twofold) × drug condition (twofold)) showed a main effect of trial type [F(1,17) = 9.42; p = 0.007] but no main effects of drug condition [F(1,17) = 0.206; p = 0.65] or block [F(1,17) = 0.71; NS]. There was a drug condition × trial type interaction [F(1,17) = 4.24; p = 0.05]. Examination of the data shows that DFEN prevented the usual increase in PPI at the 120 ms inter-stimulus interval (Table 3). There were no significant differences between DFEN and placebo conditions for either 30 ms or 120 ms inter-stimulus intervals (Wilcoxon’s signed ranks test; p > 0.05). In the placebo condition, percent PPI increased between 30 ms and 120 ms inter-stimulus intervals by 26.9% (SD = 34.0%). In the DFEN condition this expected increase with the more robust PPI eliciting 120 ms interval was attenuated to 12.5% (SD = 27.8%) although post hoc testing did not reveal this to be statistically significant (Z = −1.50; p = 0.133). There was no correlation between startle magnitude and PPI in the DFEN condition at either 30 ms (r = 0.362; NS) or 120 ms (r = 0.092; NS).

4. Discussion

The specific, but indirect 5-HT receptor agonist, DFEN, administered to healthy, non-smoking men with no family history of psychosis, produced no reduction of PPI, and did not alter startle habituation. However, with DFEN the increase in PPI that is normally elicited by increasing the prepulse to pulse interval (from 30 ms to 120 ms) did not occur. DFEN elicited robust neuroendocrine effects with characteristic elevations of prolactin. It also produced clinical effects including hypomania, activation, and agitation and a subjective perception of subjects of arousal, disinhibition, and elation. No relationship was found between any startle parameters and the increase in either BPRS factors or neuroendocrine parameters with DFEN. DFEN had no significant effect on startle reflex habituation, although it generally increased startle magnitude. PPI was independent of baseline startle in both DFEN and placebo conditions.

Only three other published studies are directly comparable to ours. Using the specific 5-HT1A agonist, buspirone, Gogos et al. (2006) reported a reduction in PPI at the 120 ms inter-stimulus interval, but not at 60 ms (controlling for menstrual phase). Two earlier studies used the 5-HT receptor agonist MDMA. Vollenweider et al. (1999) reported an increase in PPI at both 30 ms and 120 ms inter-stimulus intervals in their 13 healthy subjects after taking MDMA. Although the number of subjects in this study is similar to ours, they did not control for menstrual phase or smoking; nicotine withdrawal may falsely elevate PPI (Della Casa et al., 1998). Second, another study from the same group confirmed the increase in PPI in healthy subjects given MDMA after controlling for both menstrual phase and smoking (Liechti et al., 2001). A related study using psilocybin, a direct receptor agonist with greater affinity at 5-HT1A autoreceptors compared to 5-HT2A receptors, was conducted in a very small sample (n = 7) without control for smoking or menstrual phase (Gouzoulis-Mayfrank et al., 1998), which makes comparison limited. All these studies are consistent in reporting a similar effect on startle magnitude.

Table 2
Phenomenological and cognitive measures in DFEN and placebo conditions [mean (SD)]

<table>
<thead>
<tr>
<th>Drug condition</th>
<th>Placebo mean (SD)</th>
<th>DFEN mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>57.4 (17.2)</td>
<td>57.7 (16.1)</td>
</tr>
<tr>
<td>Category fluency</td>
<td>65.4 (14.1)</td>
<td>67.0 (14.1)</td>
</tr>
<tr>
<td>Backwards Digit Span</td>
<td>10.2 (1.3)</td>
<td>10.5 (1.9)</td>
</tr>
<tr>
<td>MMSE</td>
<td>30.0 (0.0)</td>
<td>30.0 (0.0)</td>
</tr>
</tbody>
</table>
independent of PPI, and no effect on habituation of startle. Our results, and those of Gogos et al. (2006) suggest that 5-HT agonists attenuate PPI, rather than enhancing it. This discrepancy may relate to the methodological differences outlined above, and to the fact that these studies did not use pure 5-HT agonists.

Our results are not inconsistent with studies in rodents where comparable 5-HT releasers reliably disrupt PPI (see Geyer et al., 2001 for reviews). Dulawa et al. (2000a) reported that MDMA inhibits PPI in wild-type mice, but not in 5-HT1B− knockout mice, suggesting that the inhibition of PPI may be mediated by the 5-HT1B receptor. This receptor is found in both mice and humans and acts as a terminal autoreceptor to inhibit neurotransmitter release by 5-HT-containing neurons. In humans, the 5-HT1A receptor agonist, buspirone, acts to reduce serotonergic neurotransmission and PPI; Gogos et al. (2006) suggest that reducing brain 5-HT is responsible for the disruption in PPI. However, this is unlikely to be the explanation in rodents. Dulawa et al. (2000b) have clarified that, in mice at least, the 5-HT1A receptor is not involved in PPI disruption; rather its activation by MDMA increases PPI. The 5-HT2A receptor is also a strong candidate for 5-HT-induced PPI disruption. Padich et al. (1996) reported that, in rats, the 5-HT2A receptor mediates the PPI inhibiting effect of MDMA. Sipes and Geyer (1995) reported that acute administration of the selective 5-HT2 agonist, 2,5-dimethoxy-4-iodo-phenyl-isopropylamine (DOI), caused PPI disruption and that this effect was prevented by the selective 5-HT2A antagonist, MDL-100 907. They concluded that DOI-mediated PPI disruption was an effect at 5-HT2A receptors. Farid et al. (2000) have confirmed disruption of PPI by DOI in both Wistar and Sprague–Dawley rats.

Although DFEN is selective for the 5-HT system with little or no dopaminergic activity (unlike MDMA), its exact site of action is unknown (Garattini et al., 1987). DFEN-induced neuroendocrine effects are mediated through a combination of 5-HT2A/C (Goodall et al., 1993; Coccaro et al., 1996a) and 5-HT1A (Palazidou et al., 1995) receptors, but not 5-HT3 receptors (Coccaro et al., 1996b). As a potent releaser of synaptic 5-HT, DFEN is likely to have effects on a range of 5-HT receptors. In our study, we intended that increased central 5-HT transmission would index elevation of peripheral hormone responses (Abel and Cleare, 1999). However, two subjects did not produce significant PRL responses and PRL responses did not correlate with startle parameters. Clinically, subjects treated with DFEN showed increased arousal, activation, markedly elevated mood and behavioural disinhibition. The psychological effects of DFEN are much less pronounced than with either psilocybin or MDMA and are not hallucinogenic at this dose. The difference in DA activity between DFEN and MDMA may be relevant to their different clinical and startle effects; comparison with DFEN effects on PPI may therefore be limited.

5-HT effects in schizophrenia may be associated with increased arousal that occurs especially in the acute stages of psychosis. Perry et al. (2002) reported disruptions of PPI, but no correlation between symptom scores and changes in startle parameters in their acutely psychotic group. In acute

Table 3
Startle magnitudes in all four blocks of startle trials and percent PPI at 30 ms and 120 ms inter-stimulus intervals [mean (SD)] in DFEN and placebo conditions

<table>
<thead>
<tr>
<th>Drug condition</th>
<th>Placebo</th>
<th>DFEN</th>
</tr>
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<tbody>
<tr>
<td>Block 1</td>
<td>109.0 (60.4)</td>
<td>131.6 (78.6)</td>
</tr>
<tr>
<td>Block 2</td>
<td>73.9 (38.3)</td>
<td>98.2 (60.5)</td>
</tr>
<tr>
<td>Block 3</td>
<td>59.3 (32.5)</td>
<td>91.2 (59.5)</td>
</tr>
<tr>
<td>Block 4</td>
<td>61.7 (30.3)</td>
<td>89.0 (61.9)</td>
</tr>
<tr>
<td>Percent PPI 30 ms ISI</td>
<td>18.6 (31.9)</td>
<td>23.5 (28.6)</td>
</tr>
<tr>
<td>Percent PPI 120 ms ISI</td>
<td>45.5 (33.7)</td>
<td>36.0 (28.1)</td>
</tr>
</tbody>
</table>

ISI, inter-stimulus interval.
drug naïve schizophrenia, we have previously reported increased activation and arousal, and elevated PRL responses with DFEN, suggesting increased 5-HT receptor tone (Abel et al., 1996). In the healthy brain, the 5-HT-induced lack of increase in PPI at 120 ms, may be mediated through altered arousal and attention. PPI is consistently shown to be most robust at higher intensity prepulses and at inter-stimulus intervals at or greater than 100 ms. At longer intervals, PPI is found to be abnormal in schizophrenia in active attention paradigms where subjects are asked to attend to the prepulse stimuli (Dawson et al., 1997). It has been speculated that this finding relates to mechanisms involved in the disruption of working memory and attention that may also be important in disrupting gating (Dawson et al., 1997). Such a possibility could be consistent with the lack of PPI increment with DFEN, and the relative attenuation of responses seen only at the longer prepulse interval. Although recent data suggest that serotonergic mechanisms may not explain the cognitive benefits of atypical antipsychotic agents (Wagner et al., 2005), deficits in working memory and attention are both described as part of the cognitive deficits in schizophrenia (Butler et al., 1991). However, tests of cognition with DFEN in this study did not allow detailed assessment of attention.

Conclusions from these data are limited. We have only tested young white men, taken from an academic community and therefore the generalisability of these results to women or other ethnic groups is limited. We did not measure plasma DFEN or nor-fenfluramine levels. Although robust hormonal responses suggest central serotonergic effects (Abel and Cleare, 1999), subject responses were very variable and we did not find a correlation between PPI effects and behavioural or neuroendocrine responses.

5. Conclusions

In healthy adults, we have reported no disruption of PPI with the specific serotonin agonist, DFEN, but modification of the normal increase in PPI at 120 ms inter-stimulus interval. Another recent study suggests that disruption of PPI in humans may be mediated by 5-HT1A receptors. Future studies should attempt to replicate findings with specific 5-HT agents and to map serotonergic effects on PPI using functional imaging.

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