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Additional dopamine reuptake inhibition attenuates vigilance impairment induced by serotonin reuptake inhibition in man

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There is evidence for a specific impairment of human vigilance following enhancement of serotonergic activity by antidepressant drugs. In the present study, we investigated the putative role of serotonergic–dopaminergic interactions in diminished vigilance by comparing the attentional effects of sertraline, a selective serotonin reuptake inhibitor (SSRI) with additional mild dopamine stimulating effects, with those of paroxetine, a SSRI without dopamine activity, using a placebo-controlled, double-blind, three-way cross-over design. Twenty-one (of 24) healthy middle-aged subjects completed the three treatment periods of 2 weeks in which sertraline (50 mg, days 1–7; 100 mg, days 8–14), paroxetine (20 mg, days 1–7; 40 mg, days 8–14) and placebo were administered. Vigilance (Mackworth Clock Test), selective (Stroop, Dichotic Listening) and divided attention (Dichotic Listening) were assessed at baseline and on days 7 and 14 of each treatment period. Selective and divided attention were unaffected by SSRI treatment. Subchronic administration of paroxetine impaired vigilance performance at each investigated dose. Sertraline did not produce a significant decline in vigilance performance, presumably due to its concomitant effects on dopamine activity, counteracting the negative effects of serotonin on dopamine neurotransmission. It is concluded that a serotonergically mediated reduction of dopamine activity plays an important role in the reduction of human vigilance following SSRI administration.

Key words: attention-drug-effects, dopamine, paroxetine, serotonin-drug-effects, sertraline, vigilance

Introduction

The majority of psychoactive medication poses the potential problem of sedation, a condition generally conceived as decreased or suboptimal wakefulness. The maintenance of wakefulness is a brain function that is no longer considered a unitary construct. Different neuroanatomical, neurochemical and behavioural functions characterize its multidimensional nature. Stimulus-mediated arousal, tonic readiness to respond, voluntary effort and behavioural inhibition have been outlined as functions controlling wakefulness, distinctly mediated by noradrenergic, dopaminergic, cholinergic and serotonergic neurochemical modulation (Robbins and Everitt, 1995; Riedel *et al*., 1998; Robbins, 1997). Noradrenaline (NA) is mainly involved in rapid but transient changes in cortical arousal in response to outside stimuli, whereas dopamine (DA) and acetylcholine (Ach) are thought to be primarily associated with an internally driven energetic state, which varies more slowly and is not readily modulated by external stimulation (McGuiness and Pribram, 1980; Robbins, 1984). Serotonin (5-HT) is thought to dampen the activity of each of these neurotransmitter systems, thereby promoting behavioural inhibition and cortical de-arousal (Robbins, 1997).

In accordance with this latter notion, augmentation of serotonergic activity in humans has been associated with a reduced ability to remain alert over longer periods of time. In healthy volunteers, administration of the 5-HT reuptake inhibitor (SSRI) fluoxetine, an antidepressant drug which stimulates serotonergic neurotransmission, impaired performance on a 45-min vigilance task (Mackworth Clock Test). The effect was present at a therapeutic daily dose of 20-mg and lasted throughout the 3-week treatment period (Ramaekers *et al*., 1995). A similar reduction of vigilance was observed following subchronic administration of the 5-HT promoting antidepressant venlafaxine in therapeutic doses (75–150 mg) in healthy subjects (O'Hanlon *et al*., 1998). The authors of the latter study proposed that serotonergic anxiolytics and antidepressants may consistently impair vigilance without affecting other attentional functions.

The dampening action of 5-HT on various neurotransmitter systems that modulate arousal functions and vigilant behaviour (i.e. NA, Ach and DA) comprises the putative neuronal mechanism underling the observed 5-HT-induced vigilance impairment. The behavioural effect is analogous to that of direct receptor blockade by, for example, older tricyclic antidepressants, albeit expectedly less pronounced. However, little is known about the relative

contribution and importance of these various serotonergic interactions with other neurotransmitter systems in the induction of vigilance impairment. Inhibition of noradrenergic activity is probably not a key factor. Venlafaxine, in addition to its 5-HT promoting effects, also potently stimulates noradrenegic neurotransmission (Richelson, 1996), but this did not prevent a reduction of vigilance performance due to the 5-HT stimulating actions of venlafaxine (O'Hanlon *et al*., 1998). There is also accumulating evidence from animal studies that NA is not the critical neurotransmitter specifically associated with the maintenance of vigilance (Delagrange *et al*., 1993; McGaughy *et al*., 1997; Sarter *et al*., 2001). Another potential mediator is DA, and manipulation of dopaminergic neurotransmission is known to affect human vigilant behaviour. For example, DA receptor antagonism by pimozide impaired performance on a sustained attention task in healthy volunteers, whereas DA stimulation by pemoline improved sustained attention (Nicholson and Pascoe, 1990). Furthermore, facilitation of performance on sustained attention tasks in humans by amphetamine is well established (for a review, see Koelega, 1993), and the behavioural effect of amphetamine is thought to be primarily mediated by dopaminergic mechanisms (Servan-Schreiber *et al*., 1998). Levy and Hobbes (1996) showed the beneficial effect of methylphenidate on a continuous performance test could be attenuated by haloperidol coadministration, indicating that improved vigilance was mediated by DA systems.

Sertraline is an SSRI that inhibits 5-HT reuptake into the presynaptic neurone and thus stimulates serotonergic neurotransmission. Additionally, sertraline possesses a relatively high affinity (among SSRIs) for the human DA transporter (Tatsumi *et al*., 1997) and may also facilitate dopaminergic neurotransmission. It should be noted, however, that its dopaminergic reuptake blocking properties are still 100-fold lower than its 5-HT reuptake blockade properties. Nevertheless, sertraline was demonstrated to inhibit DA reuptake *in vitro* with one-third the potency of *d*-amphetamine (Bolden-Watson and Richelson, 1993). Furthermore, in contrast to other SSRIs, sertraline does not generally increase prolactine levels in humans (Gordon *et al*., 1998). Since prolactine release is stimulated by serotonergic input but inhibited by dopaminergic input, the DA activity of sertraline may have attenuated the serotonergic effects on prolactine release. In a similar fashion, dopaminergic stimulation by sertraline may attenuate vigilance impairment by 5-HT, if this effect is mediated by diminished activity of DA systems. Thus, the dual pharmacodynamic property of sertraline renders it particularly useful in the investigation of the putative role of 5-HT– DA interactions in SSRI induced vigilance impairment.

The aim of the present study was to confirm and further dissect the serotonergically mediated reduction of vigilance performance in human volunteers. Based on above considerations, it was hypothesized that vigilance impairment following serotonergic stimulation is primarily mediated by an associated reduction of dopaminergic activity. To test this hypothesis, we compared the effects of paroxetine, a SSRI without dopaminergic activity, to those of sertraline, a SSRI with mild stimulating effects on dopaminergic neurotransmission. Specifically, it was expected that serotonergic stimulation by paroxetine would impair vigilance performance, whereas the additional dopaminergic activity of sertraline would attenuate the serotonergically mediated reduction of vigilance performance. A secondary objective was to investigate the specificity of the effect in terms of attentional functioning. To this end, we included two tests of selective and divided attention, which were recently demonstrated to be sensitive to serotonergic manipulation by tryptophan depletion (Schmitt *et al*., 2000). Since SSRI administration may alter sleep architecture, and this in turn may affect daytime vigilance performance, we measured drug-related changes in sleep quality to control for this potential confounder.

Materials and methods

Subjects

Twenty-four healthy volunteers (13 men, 11 women), aged 30–50 years (mean 37.8 years), were recruited through advertisements in local newspapers. The mental and physical health of each subject were assessed by means of a health questionnaire, medical examination, routine electrocardiogram, blood haematology and chemistry, and standard urine screening. A urine test for drug abuse and, for women, a urine pregnancy test were conducted. Excluded were those volunteers who suffered from, or had a history of cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, haematological or psychiatric illness. All subjects completed the Zung Depression Scale (Zung, 1965) and scored well below depression threshold (score < 50). Other exclusion criteria were excessive drinking (> 20 units of alcoholic a week) pregnancy or lactation, use of medication other than oral contraceptives, use of drugs, and any sensory or motor deficits which could reasonably be expected to affect test performance. The study was approved by the Medical Ethics Committee of Maastricht University and the Maastricht University Hospital's Board of Directors. All subjects gave their written informed consent prior to participation.

Design

The study was conducted according to a randomized, double-blind, placebo-controlled, three-way cross-over design. Treatment periods lasted 14 days and were separated by washout periods of at least 14 days. Treatment order was counterbalanced over the three treatment periods.

Treatment

In the respective conditions, subjects were treated orally for 14 days with the following medications: paroxetine 20 mg once daily, increasing to paroxetine 40 mg once daily on the eighth day; sertraline 50 mg once daily, increasing to sertraline 100 mg once daily on the eighth day; and placebo once daily. At the investigated daily doses both SSRIs are equally efficacious in the treatment of major depression (Goodnick and Goldstein, 1998). Medication was taken in the morning in one capsule during the first week and two capsules during the second week.

Procedure

Approximately 1 week prior to the first treatment period the subjects practiced the tests to minimize learning effects. Assessments were performed on the day preceding each treatment period (day 0), and on days 7 and 14 of each treatment period. All measurements were carried out between 12.00 h and 18.00 h. Subjects were instructed to arrive at the laboratory well rested.

During the treatment period, subjects were not allowed to drink alcoholic beverages. Consumption of alcohol was limited to two glasses a day during the washout period. Female subjects were tested for pregnancy before the start of each treatment period.

Upon arrival, subjects completed the Groningen Sleep Quality Scale (see below) and were then seated in a soundproof test room. They first completed a cognitive test battery, which included the Stroop Colour Word Test and Dichotic Listening Task (see below). Subsequently, vigilance performance was assessed using a 45-min Mackworth Clock Test (see below). Finally, a 10-ml blood sample was taken.

Attention tests

Mackworth Clock Test

This test has been extensively used in studies on human vigilance performance (Mackworth, 1961) and is sensitive to the effects of various drugs (Koelega, 1989, 1993), including antidepressants (Ramaekers *et al*., 1995; O'Hanlon *et al*., 1998). Subjects were seated in front of a computer screen displaying a circular arrangement of 60 dots simulating the second marks on a clock. Dots were briefly illuminated in clockwise rotation at a rate of one per 500 ms. Usually, the rotation proceeded with a 6′-jump. Subjects were instructed that at rare, irregular intervals the target would proceed with a 12′- jump by skipping one of the dots in the normal sequence. This double jump was the signal to which subjects were required to respond by pressing a button as quickly as possible. A response made within 4 s after the occurrence of a signal was registered as a correct detection. A total of 30 signals were presented during the 45-min task. Ten signals occurred within each successive 15-min period, with intervals ranging from 8 s to 7.2 min. Outcome measures were the number of correct detections and the corresponding reaction times, and the number of false detections.

Stroop Colour Word Test

The Stroop Test has often been used to test selective attention (Stroop, 1935). The test consists of three cards. First, a card with a hundred colour names must be read as quickly as possible, followed by a card in which the same number of colored patches must be named. On the third card colour names are printed in incongruously colored ink. The colour of the ink must be named, without paying attention to the word itself. The outcome parameters of this test are the time needed to complete each card and the interference measure. The latter denotes the percentage of extra time needed to complete card III, relative to the average of card I and II: (time card III/[(time card I + time card II)/2]) × 100%.

Dichotic Listening Task

Dichotic listening is used to test selective attention and divided attention for auditory stimuli. Subjects receive two different auditory stimuli simultaneously though stereo headphones, one stimulus on each side. The stimuli are numbers ranging from 1 to 200, presented at random and natural-speech spoken by a male voice. The test consists of three subtasks in which subjects are instructed to focus on either the right channel, the left channel or on both channels, and to remember these numbers. The subtasks requiring focusing on stimuli from one side, while ignoring the other side, is a selective attention task. The subtask in which stimuli from both sides have to be remembered is a divided attention task. Each of the three subtasks consists of nine trials, in which 2, 3, or 4 stimuli pairs are presented in random order. After each trial, subjects must identify the appropriate numbers from a list of numbers on a computer screen. This list is composed of all presented numbers, plus the same amount of other numbers. Outcome variables are the total number of correctly identified stimuli, total number of stimuli identified from the wrong side and number of false alarms (numbers which were not presented). Performance on each subtask is assessed by calculating nonparametric sensitivity measure A' using the formula: $A' = 1–1/4[fr/cr + (1 - cr)/(1 - fr)]$, in which cr denotes the proportion of correctly identified numbers and fr the proportion of falsely recognized words. Because of its skewed distribution A' is arcsin transformed before statistical analysis.

Subjective sleep quality

Subjective quality of sleep was assessed using the Groningen Sleep Quality Questionnaire (Mulder-Hajonides-van-der-Meulen, 1981). This questionnaire consists of 14 statements regarding the quality of sleep over the past week. Subjects agreed or disagreed with each of the statements. Maximum score is 14, indicating severely disturbed sleep, and minimum score is 0, indicating no sleeping problems.

Blood sampling

Blood (10 ml) was collected by venipuncture on days 0, 7 and 14 at the end of each cognitive test battery. Blood samples obtained in the paroxetine and sertraline periods were assayed for the appropriate drug using a reverse phase high-performance liquid chromatography procedure with ultraviolet detection, with a detection limit of 10 ng/ml for the paroxetine assay and 5 ng/ml for the sertraline assay.

Statistical analysis

Results of the attention tests and subjective sleep questionnaire were analysed using repeated-measures analyses of variance (SPSS 6.1, SPSS Inc., Chicago, IL, USA). Within subjects factors were Treatment (paroxetine, sertraline, placebo) and Day of assessment (day 7, day 14). Respective baseline values of each treatment period (day 0) were entered as covariates to correct for pretreatment level of performance.

For analyses of the Mackworth Clock Test, the additional factor Time on task (performance at 15, 30 and 45 min) was included and data were tested for a main effects of Time on task and Treatment by Time on task interactions. Main effects of treatment ($p < 0.05$) were further investigated using separate comparisons between drug and placebo and between paroxetine and sertraline. In this case, analyses were rerun using two levels of the factor Treatment (drug–placebo or paroxetine–sertraline).

Sex was entered as a between-subject factor in each initial overall analysis, but was omitted in subsequent comparisons if no significant gender differences were apparent. False detections in the Mackworth Clock Tests were not normally distributed and were analysed using Friedman's non-parametric ANOVA.

Results

Dropouts and missing data

Twenty-one subjects completed the study. One woman withdrew in the first period during paroxetine treatment, with complaints of

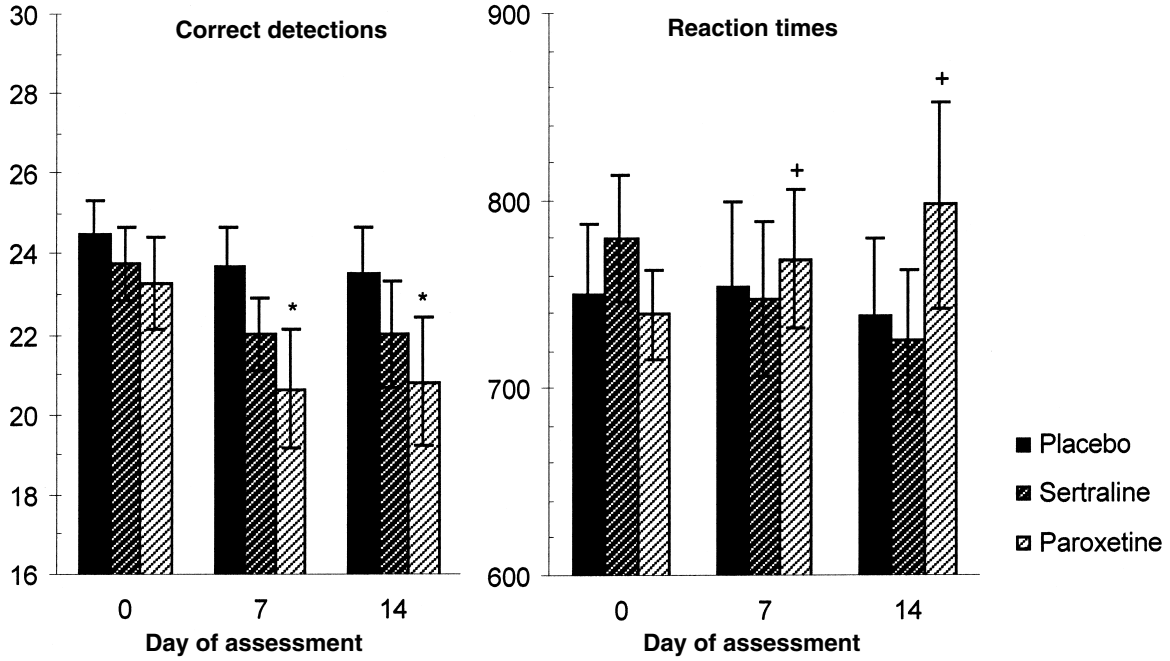

Figure 1 Mean (SE) number of correct detections (left) and reaction times for the correct detections (right) in the Mackworth Clock Test, at baseline (day 0) and after 7 and 14 days of treatment with paroxetine, sertraline or placebo. *$p < 0.05$ versus placebo, +$p < 0.05$ versus sertraline

nausea and light-headedness. Two men dropped out for reasons unrelated to the study; one man was in the sertraline condition, the other withdrew before starting the first treatment period. The subjects who completed the study provided complete data, with the exception of one man who could not be tested on day 7 during placebo because of unforeseen personal circumstances.

Attention tests

Mackworth Clock Test

The number of correct detections (Fig. 1) of the Mackworth Clock Test showed main effects of Treatment [$F(2,35) = 3.49$, $p < 0.05$] and Time on task [$F(2,35) = 6.04$, $p < 0.01$], but no main effects of Day or Sex. There were no significant interactions. Lack of a significant Treatment by Time on task interaction lead to the use of the total number of correct detections over 45 min for subsequent analysis of the correct detections. These drug–placebo comparisons revealed that paroxetine reduced the number of correct detections [$F(1,18) = 7.58$, $p < 0.05$], whereas sertraline did not significantly affect this task parameter. No main effect of Day or a Treatment by Day interaction was found in either comparison. Furthermore, no main effects or interactions were found in a comparison between paroxetine and sertraline.

Reaction times of the correct detections (Fig. 1) showed a main effect of Time on task [$F(2,35) = 5.45$, $p < 0.01$]. In addition, the main effect of Treatment approached a significant level [$F(2,35) = 2.90$, $p = 0.07$]. No main effects of Day or Sex were found, and no significant interactions between Treatment, Time on task, Day and Sex were present. The observed trend for a main effect of treatment leads us to perform additional analyses to explore this effect. No significant main effects or interactions were found in separate drug–placebo comparisons. However, paroxetine showed a trend to prolong reaction times [$F(1,18) = 4.21$, $p = 0.06$], whereas sertraline appeared to speed up responses [$F(1,18) = 3.97$, $p = 0.06$]. A separate comparison between sertraline and paroxetine revealed a main effect of Treatment [$F(1,19) = 7.03$, $p < 0.05$], but no main effect of time or a Treatment by Day interaction. No effects were found for the number of false detections (Table 1).

Stroop Colour Word Test

The results of the Stroop test are summarized in Table 1. No main effects of Treatment, Day or Treatment by Day interactions were found for card I, card II, card III or the interference measure of the Stroop Test. None of these analyses showed a main effect of Sex or a Sex by Treatment interaction.

Dichotic Listening Task

The results of the dichotic listening task are summarized in Table 1. No main effects of Treatment or Time, or Treatment by Time interactions were present for the performance on subtasks ‘left’, ‘right’ or ‘both’. No main effects of Sex or Sex by Treatment interactions were found.

Subjective Sleep Quality

Subjective sleep quality showed a main effect of Treatment [$F(2,37) = 7.76$, $p < 0.01$] but no main effect of Day or a Treatment by Day interaction. The analysis further revealed a significant Treatment by Sex interaction (Fig. 2). Consequently, analyses were conducted for men and women separately. Treatment did not affect sleep quality of the male subjects, but the sleep quality for women showed a main effect of Treatment [$F(2,17) = 10.24$, $p < 0.001$]. No main effects of Day or Day by Treatment interactions emerged from these analyses. Separate drug–placebo comparisons for women revealed that paroxetine significantly reduced women’s sleep quality compared to placebo [$F(1,8) = 15.44$, $p < 0.01$]. Sertraline did not significantly affect women’s sleep quality. No

Table 1 Mean ± SD number of false alarms of Mackworth Clock Test, and outcome variables of the Stroop Colour Word Test and Dichotic Listening task on day 0 (baseline) and after 7 and 14 days of treatment with placebo, paroxetine or sertraline

Measure	day 0	day 7	day 14
Mackworth Clock Test			
(no. false alarms)			
Placebo	2.05 ± 3.42	1.00 ± 1.45	0.70 ± 1.13
Paroxetine	1.40 ± 1.90	0.70 ± 1.03	0.75 ± 1.25
Sertraline	1.00 ± 2.05	0.85 ± 1.39	0.70 ± 0.87
Stroop Colour Word Test			
Time card I (s)			
Placebo	35.6 ± 4.5	35.5 ± 6.0	36.2 ± 6.0
Sertraline	35.4 ± 4.4	35.9 ± 5.2	36.9 ± 8.8
Paroxetine	35.7 ± 4.9	35.2 ± 5.1	36.0 ± 7.7
Time card II (s)			
Placebo	42.6 ± 8.7	41.8 ± 7.9	41.1 ± 7.2
Sertraline	42.1 ± 7.5	41.8 ± 7.0	41.7 ± 9.8
Paroxetine	42.6 ± 9.0	41.3 ± 7.9	42.0 ± 9.7
Time card III (s)			
Placebo	61.9 ± 13.4	61.2 ± 13.0	60.2 ± 13.8
Sertraline	64.3 ± 14.7	60.4 ± 12.4	59.6 ± 12.6
Paroxetine	62.2 ± 15.8	60.6 ± 16.2	60.1 ± 15.5
Interference (%)			
Placebo	57.8 ± 15.7	58.2 ± 17.3	55.2 ± 20.9
Sertraline	64.9 ± 21.7	55.3 ± 18.8	52.2 ± 14.8
Paroxetine	57.8 ± 17.3	57.4 ± 20.7	53.8 ± 17.6
Dichotic Listening Task			
Left side sensitivity (%)			
Placebo	89.4 ± 6.2	90.4 ± 7.1	90.5 ± 6.1
Sertraline	86.4 ± 9.1	90.9 ± 6.2	91.3 ± 6.1
Paroxetine	89.5 ± 10.2	90.1 ± 4.5	91.1 ± 4.8
Right side sensitivity (%)			
Placebo	91.2 ± 6.2	92.7 ± 5.8	92.8 ± 7.5
Sertraline	91.7 ± 8.3	92.2 ± 7.6	91.7 ± 9.4
Paroxetine	91.7 ± 8.1	93.5 ± 5.4	92.7 ± 5.4
Both sides sensitivity (%)			
Placebo	84.3 ± 2.9	84.6 ± 2.8	85.4 ± 3.0
Sertraline	84.0 ± 2.2	85.0 ± 3.3	85.3 ± 3.3
Paroxetine	85.5 ± 2.1	84.9 ± 2.9	85.0 ± 2.7

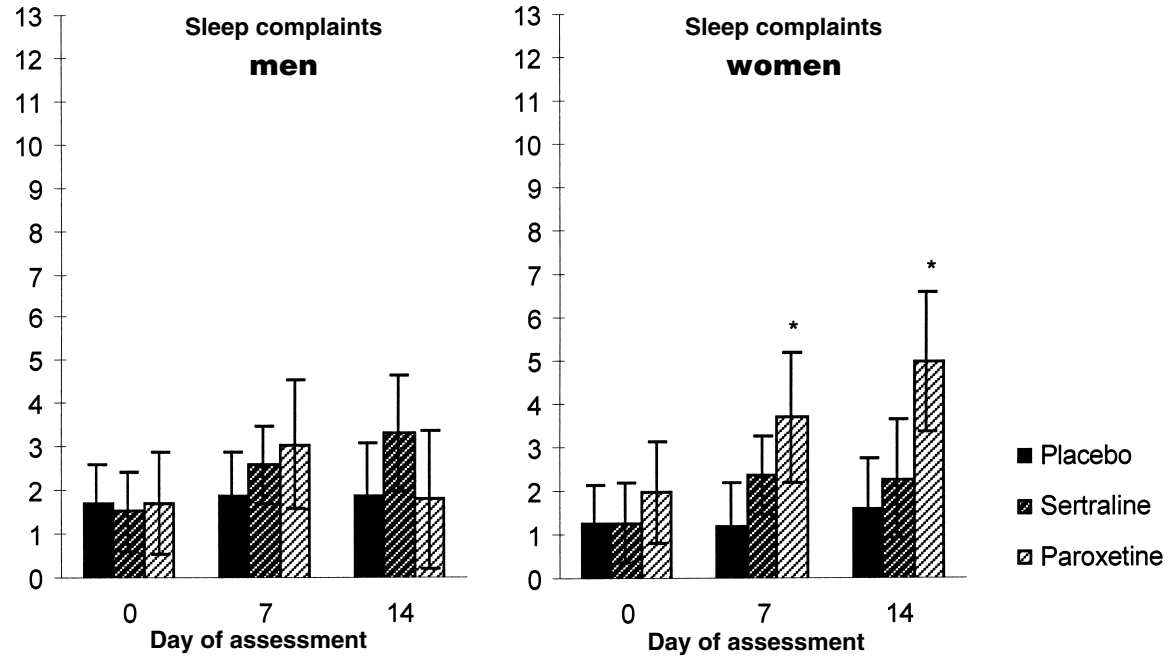

Figure 2 Mean (SE) subjective sleep quality at baseline (day 0) and after 7 and 14 days of treatment with paroxetine, sertraline or placebo, broken down by sex. *$p < 0.01$ versus placebo

main effect of Day or Treatment by Day interaction was found for paroxetine or sertraline. A comparison between paroxetine and sertraline revealed a main effect of treatment [$F(1,8) = 7.89$, $p < 0.05$] but no main effect of Day or a Treatment by Day interaction.

Plasma drug levels

Mean (± SD) plasma paroxetine concentrations were 36.7 (± 24.7) ng/ml on day 7 and 70.4 (± 54.2) ng/ml on day 14. Sertraline concentrations were 17.8 (± 7.9) ng/ml on day 7 and 41.6 (± 23.0) ng/ml on day 14. No detectable drug concentrations were present on day 0.

Discussion

In accordance with our hypothesis, performance on a vigilance task was adversely affected by subchronic administration of the SSRI paroxetine in healthy volunteers. Paroxetine reduced the number of correct detections in the Mackworth Clock Test by approximately 11% compared to the pretreatment level of performance. In addition, the speed of the correct detections appeared to be decreased with paroxetine, although this effect just failed to reach significance. Sertraline had no significant effect on the number of correct detections, although the data showed a non-significant reduction of the number of correct detections with sertraline as well. However, in contrast to paroxetine, sertraline administration was associated with a trend to increase response speed.

Enhancement of serotonergic neurotransmission appears to be consistently associated with a reduction of human vigilance performance. This effect has now been demonstrated in three separate studies with the serotonergic stimulants venlafaxine, fluoxetine and, now, paroxetine. Performance on the vigilance task appeared to be specifically affected by serotonergic stimulation as no effects could be detected on other attentional measures (i.e. divided and selective attention). The latter findings are in line with the prevailing opinion that SSRIs are generally devoid of adverse cognitive effects, although the sensitivity of the Stroop and Dichotic Listening task must ideally be validated by use of a verum. It has been argued that short-term, high demanding cognitive assessment may not be sensitive to subtle adverse drug effects, as subjects may temporarily allocate greater or lesser amounts of compensatory effort depending on drug condition or state (Kahneman, 1973; Oken *et al*., 1995; Sanders, 1998). Such compensatory mechanisms are unlikely to be maintained during long lasting vigilance tasks (O'Hanlon, 1981), and vigilance tasks have been characterized as the most sensitive tasks in cognitive and psychomotor test batteries (Koelega, 1993). Diminished vigilance is certainly compatible with the numerous reports of increased subjective drowsiness following SSRI administration (Hindmarch and Bhatti, 1988; Mattila *et al*., 1988; Saletu and Grünberger, 1988; Robbe and O'Hanlon, 1995; Hawley *et al*., 1997).

As for vigilance, the overall pattern of results is in line with the general hypothesis that the dopaminergic activity of sertraline was able to at least partially attenuate a serotonergically induced vigilance decrement. We propose that SSRI-induced impairment of vigilance performance is primarily mediated by neural circuits modulated by opposing influences of 5-HT and DA. There is abundant anatomical and experimental evidence indicating an inhibitory influence of the serotonergic system on DA activity. In short, serotonergic projections arising from the dorsal nucleus raphe exert a tonic inhibitory influence over the mesocortical DA system, involved with cognitive functioning, as well as the nigrostriatal DA system, involved in the modulation of motor behaviour (Kapur and Remington, 1996). Similarly, the mesolimbic DA system, involved in motivation and reward, is under inhibitory influence of serotonergic neurones from the median nucleus raphe, projecting to the ventral tegmental area (Bonhomme and Esposito, 1998; Di Mascio *et al*., 1998). The inhibitory effects are mediated mainly via 5-HT_{2C} inhibitory receptors on DA cell bodies in the ventral tegmental area and substantia nigra, and at terminal endings in striatum and cortex.

Augmentation of serotonergic activity by SSRI administration can be expected to inhibit dopaminergic transmission and may invoke a 'pseudo-dopaminergic deficiency' (Stahl, 1998). Such a serotonergically induced hypodopaminergic state has been proposed to underlie several side-effects of SSRI treatment (i.e. reduced libido) (Stahl, 1998) and extrapyramidal symptoms, such as akathisia, tremor and dystonic reactions (Kapur and Remington, 1996; Caley, 1997; Stahl, 1998; Jiménez-Jiménez and Molina, 2000). While, in the majority of the individuals, the degree of DA inhibition does not cross the threshold for severe adverse effects such as extrapyramidal symptoms (Lane and O'Hanlon, 1999), a reduction of dopaminergic function may become evident in more subtle behavioural changes, such as a reduced vigilance performance. Indeed, findings that a single dose of fluoxetine or citalopram causes a dose-dependent inhibition of firing rate of ventral tegmental area dopaminergic cells, but not of DA cells in the substantia nigra (Bonhomme and Esposito, 1998), suggest that the cognitive and motivational functions (both important in vigilance) of DA are particularly susceptible to the inhibitory effects of serotonergic stimulation.

A review of both the efficacy and tolerability of SSRIs confirms that the doses used were equipotent (Edwards and Anderson, 1999). From this review, we calculated the average administered daily doses: 78 mg sertraline ($n = 357$) and 30 mg paroxetine ($n = 180$). These doses correspond very well to the average doses that we administered in our study, which were 75 mg sertraline and 30 mg paroxetine. Edwards and Anderson (1999) demonstrated that the calculated efficacy scores of these doses did not differ and similar figures were obtained with respect to tolerability. Therefore, we do not believe it to be very likely that our findings are confounded by non-comparability of doses.

Changes in sleep are often observed during SSRI treatment (Oberndorfer *et al*., 2000) and disturbed sleep may diminish daytime arousal, and consequently vigilance performance (Babkoff *et al*., 1991). Our data show that in women sleep quality was reduced with paroxetine, but not with sertraline. No significant change in sleep quality was found for men with either SSRI. The gender difference in sleep effects of paroxetine and sertraline, however, is not mirrored in the outcome of the vigilance assessments, which showed no sex by treatment interaction. This suggests that the observed differences between paroxetine and sertraline in vigilance effects are not directly associated to their effects on sleep quality. It is also worth mentioning that, among SSRIs, paroxetine has a relatively high affinity for muscarinic Ach receptors. The in-vitro affinity of paroxetine for muscarinic receptors is approximately six-fold higher than that of sertraline (Hyttel, 1994). Theoretically, the direct anticholinergic effects of paroxetine may have contributed to a reduction of vigilance

performance. On the other hand, vigilance impairment was previously found with fluoxetine and venlafaxine; drugs without significant anticholinergic effects. Nevertheless, a more specific serotonergic drug (e.g. citalopram) would provide a better reference drug in future studies on 5-HT and vigilance performance.

In conclusion, the present study sought to identify the underlying neuronal mechanism of reduced vigilance following serotonergic stimulation and provides evidence for an important role of DA in mediating the effect. We propose that enhancement of serotonergic neurotransmission leads to amplified inhibition of dopaminergic neurotransmission, which subsequently results in diminished vigilance. Such an effect would be successfully counteracted by simultaneous stimulation of DA neurotransmission, and it is believed that the absence of a significant vigilance impairment with sertraline is due to its additional intrinsic property to inhibit DA reuptake. However, these findings need to be replicated and confirmed in further studies by using, for example, a dual-manipulation design in which DA and 5-HT activity can be manipulated independently. Also, the relative contribution of the interactions of 5-HT with other neurotransmitter systems (e.g. Ach) needs to be investigated. Furthermore, assessments of the vigilance effects of non-serotonergic antidepressants, such as reboxetine and bupropion that target noradrenergic and dopaminergic systems, respectively, are needed to verify the specific role of 5-HT in impairment of vigilance following antidepressant administration.

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