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ORIGINAL INVESTIGATION

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Acute administration of citalopram facilitates memory consolidation in healthy volunteers

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Abstract *Objectives:* Decreasing serotonergic neurotransmission in humans has been found to impair memory consolidation. Such effects may be relevant to the memory deficits seen in major depression and the cognitive actions of antidepressant drugs used to treat them. However, the improvement in cognitive function often found following successful pharmacological treatment in depression may be confounded by symptom improvement. *Rationale:* The present study assessed the effects of an acute challenge with the selective serotonergic re-uptake inhibitor citalopram in healthy (non-depressed) females. *Methods:* Immediate and delayed recall/recognition was assessed using the auditory verbal learning test following 10 mg (intravenous) citalopram or placebo in a double-blind between groups design. *Results:* Immediate recall on the verbal memory test was unaffected by citalopram administration. However, volunteers receiving citalopram showed enhanced long-term memory performance in terms of delayed recall and recognition relative to those receiving placebo. Sustained attention performance was also comparable in the two groups of subjects suggesting that non-specific increases in information processing are not responsible for this effect. *Conclusions:* These results indicate that augmentation of serotonergic neurotransmission is associated with increased memory consolidation, which may be relevant to its therapeutic and cognitive actions in acutely depressed patients.

Keywords SSRI · Citalopram · Memory consolidation · Serotonin

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Introduction

Serotonergic circuits have long been held to play a role in learning and memory processes. However, results from animal studies have yielded inconsistent findings concerning the direction of its effect (Altman and Normile 1988). While there is evidence that stimulation of serotonin activity impairs, whereas blockade of its activity enhances, learning and memory (see McEntee and Crook 1991), the opposite findings have also been reported (e.g. Bammer 1982; Flood and Cherkin 1987). These inconsistencies may relate to interactions between the type of memory assessed, dose and specificity of agents used and the timing of the serotonergic manipulations (Altman and Normile 1988).

In humans, decreasing serotonergic neurotransmission, using the method of tryptophan depletion, has been reported to decrease memory and learning (Park et al. 1994; Riedel et al. 1999; Schmitt et al. 2000). In particular, long-term, as opposed to short-term, memory appears to be primarily affected. In the study by Riedel et al. (1999), immediate recall of verbal items was unaffected by tryptophan depletion, but delayed recall and recognition of these same items was significantly impaired. In a subsequent investigation, only tryptophan depletion given prior to learning affected delayed recall. Administration of the tryptophan-free drink 1 h after presentation of a word list did not affect the storage or retrieval of this verbal material (Schmitt et al. 2000). The involvement of serotonin in memory does not appear to be restricted to verbal material, as tryptophan depletion has also been reported to impair performance in non-verbal memory tasks, such as paired associate learning and pattern recognition memory (Park et al. 1994; Rubinsztein et al. 2001).

A role for serotonin in learning and memory may be relevant to clinical conditions such as depression, Alzheimer's disease and the symptoms associated with prior ecstasy (MDMA) use. Major depressive disorder has been associated with impaired recall both on immediate and delayed measures (Austin et al. 1992; Brown et al. 1994),

and memory deficits are usually seen to improve following recovery from the disorder with antidepressant treatment (Peselow et al. 1991), particularly selective serotonergic reuptake inhibitors (SSRIs) (Keegan et al. 1991; Bondareff et al. 2000). This improvement may be related to direct actions of the antidepressant on memory or may be a non-specific effect of symptom improvement. Similarly, deficits in immediate and delayed memory have been reported to occur in individuals with past history of ecstasy use with associated abnormalities of serotonergic functioning (e.g. Reneman et al. 2000, 2001).

The effects of increased, as opposed to decreased, serotonin levels have not been investigated to the same degree in humans. Such results may help confirm the role of serotonin in memory processes and also provide a possible mechanism for the cognitive effects of antidepressant treatment in major depression. The present study therefore investigated the effects of an acute challenge with the SSRI, citalopram, on verbal short and long-term memory in non-depressed female subjects. Sustained attention was also examined to assess whether more global changes in information processing were found following SSRI treatment. Based on the effects of tryptophan depletion in humans, it was postulated that citalopram would specifically facilitate long-term memory recall and recognition, without affecting immediate recall and mood.

Materials and methods

Subjects

Twenty-four healthy female volunteers between the ages of 21 and 59 years took part in this study. Participants were screened to exclude those with a current or previous history of psychiatric disorder (assessed using semi-structured interview for DSM IV), current medication (apart from the contraceptive pill), current or previous substance use, or significant physical illness. All gave their written consent to participate in this study, which was approved by the local ethical committee. Volunteers were randomly allocated to receive citalopram (10 mg, IV) or placebo in a double-blind between groups design. These two groups were matched in terms of age (mean age: 40.1±3.6 and 37.3±3.7 years, respectively) and years of education (mean: 13.4±0.7; 14.6±0.7). All volunteers were tested within the follicular phase of their menstrual cycle.

Auditory verbal learning test (AVLT)

The auditory verbal learning test assesses a number of different components of learning, recall, and recognition (Rey 1964). In the immediate recall phase, a 15-item word list was read to the subject five times, and after each trial the subject was asked to repeat back as many items as they could remember in any order. Immediate recall on a distracter list was then assessed, providing a short delay after which free recall of the original list was tested. Fifteen minutes later, subjects were tested for long delay free recall, followed by a recognition test, where they were asked to respond with a "Yes" or "No" to each item on a list comprising the 15 targets plus 35 distractors. Data were analysed with respect to four dependent variables: learning over trials 1–5, short-delay and long-delay free recall (expressed as a percentage of performance on the final learning trial), and recognition. Signal detection theory was applied to the data from the recognition test to derive a measure of accuracy corrected for the subject's response tendency. The proportion of correctly recognized words (cr) and the proportion of falsely recognized (fr) constitute the non-parametric sensitivity measure: A'=1–1/4(fr/cr+(1–cr)/(1–fr)).

Sustained attention

A measure of sustained attention was also given, adapted from a test by Wesnes and Warburton (1984) and Sahakian et al. (1989). In this task, digits between 1 and 9 were presented in the centre of the screen at a rate of 200 per minute (pseudo-random order) for 7 min. Subjects were asked to monitor the digits for any one of three specified digit sequences (3–5–7, 2–4–6 or 4–6–8), which they should respond to by pressing a button on a key pad. A practice session was given initially, with target sequences appearing in red, to familarise volunteers with the nature of the task. In the testing phase all digits were given in black on a white screen. This task yields three measures: speed of correct detections, number of correct detections and responses made in the absence of appropriate stimuli (false alarms). Signal detection analysis can also be applied to these results, giving two independent measures of performance: response sensitivity and response bias.

Subjective state

Subjective state was recorded using visual analogue scales for the following variables: happiness, sadness, fear, disgust, anger, alertness and anxiety. The Befindlichkeits scale (BFS: von Zerrsen et al. 1974) was also given to provide an additional measure of mood.

Procedure

Subjects attended the laboratory at midday, having fasted from breakfast, and an IV cannula was inserted. After a 30-min rest period subjects received infusion of either citalopram (10 mg, IV) or placebo given over 30 min. The immediate recall part of the AVLT was given 45 min after the end of the infusion, by which time effects of citalopram on serotonin function have been reported (Attenburrow et al. 2001). In between the distraction and delayed recall, subjects were given the sustained attention task. Subjective state was assessed at baseline and prior to the psychological testing.

Statistical analysis

Performance in these tasks was analysed using two-way split-plot analysis of variance (ANOVA), with group and learning trial as factors (for immediate and delayed recall). Significant main effects were completed using simple main effect analyses. Recognition memory was analysed using one-way ANOVA.

Results

Immediate recall

Recall of the 15-item word list improved over the five repetitions in both groups of subjects [Fig. 1: main effect of trial: $F(4,88)=108.7$, $P<0.001$]. However, there was no effect of group or group by trial interaction in this analysis ($F<1$, NS), suggesting that citalopram administration had no effect on acquisition and short term recall.

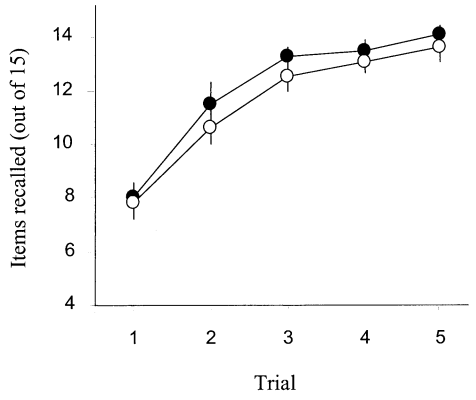

Fig. 1 Immediate recall over the five learning trials following citalopram (*black*) or placebo (*white*). Values represent mean number correct±1 SEM

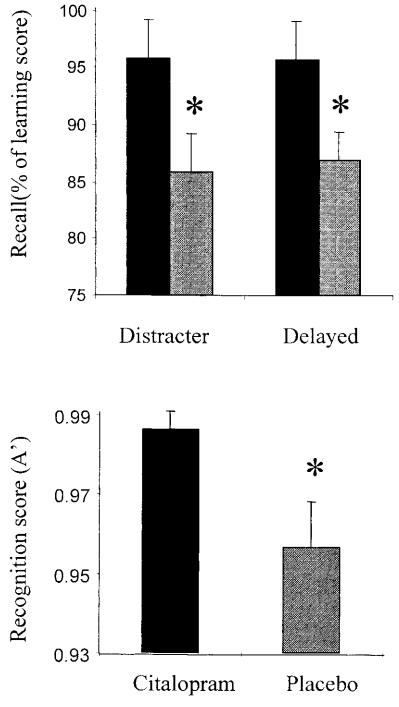

Fig. 2 Delayed recall and recognition following citalopram (*black bars*) or placebo (*grey bars*). *Top graph*: following distracter list and 15-min delay. Values represent mean number of items recalled, expressed as a percentage of each subjects' final score on the immediate recall component of the AVLT. *Lower graph*: recognition memory. Values represent signal detection score, *A'* ±1 SEM. *Asterisks* represent statistical comparison of the two groups: **P*<0.05

Delayed recall

Mean performance in the delayed recall and recognition component of the AVLT is given in Fig. 2. Recall following the distracter [$F(1,22)=6.6$, $P<0.05$] and the 15-min delay [$F(1,22)=5.1$, $P<0.05$] was significantly facilitated by citalopram administration. A facilitatory effect of citalopram on long-term memory was also seen in the recognition memory component of the AVLT [$F(1,22)=5.6$, $P<0.05$].

Sustained attention

There was no effect of citalopram on target sensitivity, response bias or reaction time on this measure of sustained attention (see Table 1).

Subjective ratings

The changes in memory occurred in the absence of any subjective alterations in mood and anxiety, as judged by standard visual analogue rating scales and the BFS scale of mood changes (all comparisons, $P>0.08$).

Discussion

Acute administration of citalopram was found to facilitate long-term recall and recognition of verbal material in the absence of effect on immediate recall in healthy females. These results are consistent with previous findings, which suggest decreased memory consolidation following reduction of serotonin activity with tryptophan depletion in healthy volunteers (Riedel et al 1999). These data therefore indicate reciprocal effects of serotonin in long-term memory processes in humans. Citalopram administration did not affect sustained attention performance or subjective ratings of mood and energy, suggesting that the memory effects are unlikely to represent a non-specific action.

Results from animal studies have revealed inconsistent findings concerning the role of serotonin in learning and memory. However, in humans, tryptophan depletion, acting to decrease serotonin neurotransmission, has deleterious effects on memory consolidation. Using a slightly different procedure from the one used here, administration of a tryptophan free mixture prior to learning was found to impair delayed recall and recognition at both 30 min and 18 h after list presentation, whilst leaving short-term memory intact (Riedel et al.

Table 1 Mean performance (with SD in brackets) in the sustained attention task following citalopram (10 mg, IV) or placebo

	Citalopram	Placebo	Significance
Reaction time (ms)	588 (25)	638 (44)	F=0.9, P=0.3
Sensitivity (a')	0.57 (0.01)	0.56 (0.01)	F=0.3, P=0.6
Response bias (b')	0.85 (0.06)	0.92 (0.03)	F=1.1, P=0.3

1999). The present data directly mirror this pattern of results: enhanced long-term, but not short-term, memory performance following citalopram. The present results therefore provide additional evidence for the role of serotonin in memory, and further suggest that increasing serotonin levels can lead to enhancements in memory consolidation.

These findings may have implications for our understanding of the effects of SSRIs on memory processes in depression. Depression is associated with impaired memory performance, which is ameliorated after successful pharmacological treatment (Keegan et al. 1991; Bondareff et al. 2000). The present data suggest that SSRIs are capable of facilitating memory performance, independently from symptom improvement. The volunteers in the current study were free from current or previous depression and reported no changes in mood following citalopram administration. The impaired memory seen in depressed patients may, over time, contribute to the feelings of inadequacy and low self-esteem associated with this disorder. Hence, it is possible that antidepressant drug treatment effects on memory form a valuable process in the response to such treatment. However, while the effects seen here were restricted to delayed recall, depression is associated with more global cognitive deficits including impaired immediate recall and attention (Austin et al 1992; Brown et al 1994). It remains to be assessed whether this acute SSRI administration would have more global effects in volunteers with pre-existing deficits in memory performance. It would also be useful to characterise the effects of these agents on tests tapping into different memory components or subdivisions, such as working memory, autobiographical and emotional memory.

Vigilance performance was not affected by citalopram administration in the current study. Previous studies have reported decreased vigilance performance following oral treatment with SSRIs in tasks demanding more sustained processes of attention than the task used here (such as the 45-min version of the Mackworth clock; Ramaekers et al. 1995; O'Hanlon et al 1998). However, the 7-min task does show a characteristic vigilance decrement over testing and has been shown to be sensitive to other pharmacological manipulations such as clonidine (Coull et al. 1995) and amphetamine (McTavish et al. 2001). This short task was used as a control for the level of sustained attention required by the memory task and the absence of an effect with IV citalopram therefore suggests that alterations in this ability cannot explain the improved memory performance seen in the current sample.

In summary, the current results suggest that administration of a serotonergic agent enhances long-term memory, in the absence of changes in sustained attention or mood. These effects therefore confirm the facilitatory role of serotonin in memory consolidation, as previously suggested by studies investigating the effects of decreased serotonin function in humans.

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