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ORIGINAL PAPER

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Acute treatment with the antidepressants bupropion and sertraline do not influence memory retrieval in man

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Abstract *Objective* Several evidences implicate that monoamines play a modulatory role in the brain mechanisms underlying encoding and retrieval of emotional memories. Recent experiments demonstrate that acute monoaminergic potentiation with the antidepressants bupropion or sertraline enhance the retrieval of long-term emotional memory in rodents. In the present study, we tested the hypothesis that acute monoaminergic re-uptake inhibition with these antidepressants might enhance retrieval of emotional memory in man. *Methods* The central monoaminergic system was stimulated with either bupropion or sertraline in a double-blind, randomized, placebo-controlled design with 105 healthy adult subjects divided in three groups (placebo, 150 mg-bupropion and 50 mg-sertraline). Memory was evaluated with a 'surprise' memory test 7 days after the presentation of an emotional story and with a word-cued autobiographical memory test. *Results* A total of 99 volunteers completed the experimental procedures. Contrasting to our prediction, we found no memory enhancing effect for either drug in both memory tests. All groups showed the expected heightened memory performance to the middle 'emotive' phase of the story. *Conclusion* Stimulation of the central monoaminergic system with the antidepressants bupropion and sertraline did not enhance the retrieval of long-term emotional memories in man.

Key words memory · emotions · bupropion · sertraline · biogenic monoamines

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Introduction

A large body of animal literature implicates the neurobiological processes involved in the stress response in the modulation of memory to emotional events [18]. The monoaminergic stress system is one of a number of neurobiological systems believed to play a role in the complex array of mediators involved in this process. This suggests that the response to stress may either enhance or impair memory for stimuli that either elicit the stress response or occur concomitantly to that physiological reaction. Studies have repeatedly found that post-training injections of substances that are released during and immediately after the training event modulate retention of the training session at different training-test intervals [9, 14]. A model from these observations has been proposed in which hormones and neurotransmitters systems interact to regulate memory consolidation for emotionally arousing events [18]. The model postulates that following an emotional stimulus, the body releases stress hormones which activate a central adrenergic system that projects to the amygdala. The activated noradrenergic pathway within the amygdala influences the storage of memories in other brain regions involved in long-term memory. Additional evidence also implicates that activation of dopaminergic D1/D5 [5] and 5-HT_{1A} [15] receptors modulates the consolidation of long-term emotional memory.

Studies of human declarative memory for emotional material during pharmacological manipulation of biogenic monoamines are necessary to determine the degree to which those animal findings apply to humans. Cahill and coworkers reported that blocking the adrenergic system using the β-adrenergic antagonist propra-

nolol impaired memory for an emotional 11-slide story presentation [7]. In these memory studies, subjects do not know that the real focus of the study is to test their memory, until they return and respond to a 'surprise' multiple-choice recognition test of the story presented one week before. Typically, the healthy volunteers display a peak memory performance to the emotional components of the story [7, 19–21, 25]. This paradigm was employed in subsequent studies with minor modifications. These studies suggest that activation of the central adrenergic system specifically enhance memory for the emotionally arousing phase of the story [7]. Conversely, acute noradrenergic re-uptake inhibition with the antidepressant reboxetine at the time of encoding worsened memory performance, while the subjects continued to display the heightened performance for the 'middle' emotional phase of the story [20].

Recent research has started to focus on the mechanisms underlying retrieval to long-term emotional memory [4]. Retrieval is a means to assess memory function, and is, of course, fundamental for our life as individuals [16]. Our group demonstrated that retrieval for long-term emotional memory is simultaneously modulated by dopaminergic D1, β-adrenergic and serotonergic 5-HT_{1A} receptors [2]. When infused into different areas of the rodent brain, just 10 min prior to the retention test, agonists/antagonists of these neuroreceptors modulate memory retrieval. D1 receptors and β-adrenergic receptors enhance, whereas 5-HT_{1A} receptors diminish retrieval [2]. Thus, it is possible that specific monoaminergic mechanisms should be necessary for the modulation of retrieval to long-term emotional memories at least in the rodent brain.

Acute treatment with the antidepressants bupropion and sertraline enhance the retrieval of long-term emotional memory for the one-trial inhibitory avoidance task in rodents [3]. Burpropion acts as a dual inhibitor of dopamine and noradrenaline reuptakes, whereas sertraline acts as a selective serotonin reuptake inhibitor [19, 26]. These actions lead to the accumulation of these respective monoamines in the synaptic cleft. More importantly, these treatments enhance the retrieval in a wide range of training-test intervals. These effects persisted even for very remote (e. g., 19 month-old) memories [3]. The extent to which these newly reported effects of the involvement of biogenic monoamines in the modulation of retrieval to long-term memory apply to humans deserves investigation.

Sertraline and bupropion are devoid of any significant antagonist effects at the adrenergic alpha-1, alpha-2, beta, or muscarinic receptors [1, 19], which are associated with cardiovascular, anticholinergic and sedative effects of other antidepressants. Accordingly, no adverse cognitive or sedative effects have been observed for sertraline [9, 27] and bupropion [6] in clinical studies or in studies with healthy adults. Thus, both drugs are suitable for the study of the role of monoamines in human memory retrieval.

The present study aims to test the hypothesis that acute potentiation of the central monoaminergic system with the antidepressants bupropion and sertraline might enhance retrieval to long-term emotional memory in man. Since bupropion and sertraline enhance the retrieval of remote memories in rats [3], we also tested the acute effects of these drugs on the performance of an emotional word-cued autobiographical memory test.

Materials and methods

Subjects of either sex with ages between 18 and 35 years-old were recruited through written advertisements placed around the university campus of Universidade Federal do Rio Grande do Sul. Students attending various academic courses of the Universidade Federal do Rio Grande do Sul (160 subjects) contacted the study team through telephone calls. Subjects who were currently taking any medications apart from oral contraceptives were not allowed to participate in this study. A sample of 123 volunteers was then screened to exclude current or previous history of a major psychiatric disorder, substance abuse, and serious medical and neurological diseases by a research psychiatrist (AF Carvalho). Elegible subjects were randomly allocated to one of three groups, to receive placebo, 50 mg sertraline, or 150 mg bupropion.

This study protocol was approved by the local ethical committee of Universidade Federal do Rio Grande do Sul. After complete description of the study to the subjects, signed written informed consent was obtained.

Procedures

Eligible volunteers (116 subjects) had a baseline mood measurement by the aid of the Beck Depression Inventory [10]. Subjects were then individually exposed to an emotionally arousing story [7, 21]. The entire presentation consisted of a set of 11 slides accompanied by narration [7]. The slide presentation shows a boy who leaves home with his mother to visit his father. On their way, the boy is involved in a serious car accident and is transported to a nearby hospital were his legs, severed during the accident, need to be reattached. The story was divided into three phases: the first including the slides 1–4, the second including slides 5–8, and the final slides 9–11. The first and third phases of the story were neutral, whereas the second phase of the story comprised the emotionally arousing stimuli (i. e., the time when the boy's legs are reattached) [7]. Since a previous study involving a similar Brazilian population found that this story was rated as highly emotional [21], we did not ask the study participants to rate how emotional they thought the story was.

Second session, 7-day interval: assessment of memory function

Subjects were asked to come to a second visit, one week later. Due to unknown reasons, eleven subjects did not return after one week. The remaining 105 study participants were then randomly allocated in a sex-matched design to receive a single-dose of bupropion sustained release (150 mg; Libbs Framaceutica), setraline (50 mg; Pfizer), or sugar-containing placebo. Each treatment was administered as manufactured capsules of identical appearance. The study followed a double-blind design through the generation of random numbers by a study investigator who did not participate in the application of the study tests (M Chaves). The subjects fasted and came back after 3 hours (for bupropion), 6 hours (for sertraline), or either 3 or 6 hours for placebo to complete a final testing session. These times are those described for these drugs to achieve peak serum levels following a single *per os* administration [17, 23]. At these times, subjects answered the Beck Depresion Inventory [10] and then had their memory assessed. The double-blind design of the study was maintained throughout the experiment. A flowchart of the study subjects and design is presented in Fig. 1.

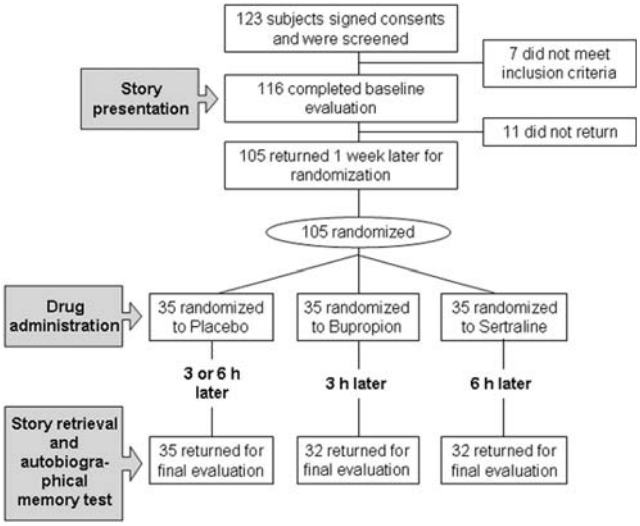

Fig. 1 Flowchart of participants across the study

Autobiographical memory test

Ten cue-words with both negative and positive valences were then presented to study participants. The words were obtained from Williams & Scott [27]. The words were translated into Portuguese (by AF Carvalho) and then back-translated into English (by I. Izquierdo). A consensus resolved the inequalities and the final list of five positive words and five negative words was obtained. Prior to the commencement of the present study, the experimenters tested this instrument in a series of five unrelated volunteers. Words were read aloud to participants (ordered to alternate 'positive' and 'negative' words). Subjects were given 60 seconds for each word to retrieve a specific personal memory. The latency to the first word of each individual response was recorded with a stopwatch. If the participant did not respond within 60 s, a time of 60 seconds was recorded for that specific trial, and the next cue-word was presented. If subjects responded with a non-specific memory (e. g. to the cue word 'happy': 'My childhood was happy'), then the memory was considered general. In any doubtful case, the procedure adopted by Williams & Broadbent [26] was followed. That is, a memory was considered specific whenever the subject was later able to give a date, day of week, or time of a day when the episode occurred. The investigators were careful to ensure that each subject understood the nature of this task, and practice words were given until the participants understood the requirement to be specific. The final list of words obtained is available upon request to the authors. A study investigator (AF Carvalho) homogenized the classification of different memory types (i. e., specific or general) retrieved by the subjects.

Long-term emotional memory test

The learning related to the emotional story was assessed following a 7-day interval by the means of a 'surprise' memory-recall test that consisted of 80 multiple-choice questions. The questionnaire was composed of 5–8 questions to each slide and was presented in the same order of the story. Each question was presented just once and the subject was asked to choose one answer and then immediately go to the next question.

Statistical analysis

Data are presented as mean ± SEM. Data from the story retrieval test were analyzed with repeated measures analysis of variance (ANOVA) models, with group (sertraline, bupropion, or placebo) as between-subject factor. Data from the autobiographical memory test were analyzed with two-way ANOVA, with valence and group as between-subject factors. Data that followed a non-normal distribution were analyzed with appropriate non-parametric tests. The sample size of this study (N = 105) was calculated to allow the detection of a difference of at least 10 % in the number of correct answers in the long-term emotional memory test with a statistical power level of 0.8 and an alpha level of 0.05. Analyses were performed with the aid of the SPSS statistical package (version 10.0 for Windows).

Results

Subject characteristics

After the completion of the trial, we observed that three subjects of the bupropion group and three of the sertraline group did not return for the final testing session. One subject in the sertraline group reported nausea, two participants from the bupropion group reported headaches, and the other subjects failed to participate due to late arrival. Baseline data from participants demonstrate that subjects who participated in each specific arm of the study did not significantly differ in any baseline characteristic (Table 1).

Mood measurements

The final Beck depression inventory scores were 3.65 ± 0.6 for the placebo group, 3.86 ± 0.6 for the sertraline group and 3.80 ± 0.6 for the buproprion group. Paired Student's t-tests were carried out in each group and revealed no significant differences from baseline measures (all p-values > 0.2). Furthermore, there were no differences between groups ($F(2,96) = 0.414$, $p = 0.66$) in the final scores.

Autobiographical memory test

There were no between-subjects (drug) effects in the percentage of specific answers elicited by subjects in the autobiographical memory test ($F(2, 192) = 2.931$, $p = 0.056$). No valence effect was observed (F(1,

Table 1 Baseline characteristics of subjects randomly allocated to each treatment group

	Placebo (N = 35)	Bupropion (N = 32)	Sertraline (N = 32)	P value
Age (years)	23.1 ± 0.5	22.5 ± 0.4	23.0 ± 0.4	0.54 *
Sex				0.92**
Male	17	15	14	
Female	18	17	18	
Schooling (years)	15.0 ± 0.4	14.9 ± 0.4	15.0 ± 0.3	0.98 *
Initial BDI score	4.3 ± 0.6	4.1 ± 0.6	3.8 ± 0.7	0.83 *

Continuous data are presented as means ± SEM
BDI Beck Depression Inventory
* One-Way ANOVA; ** Chi-Square Test

192) = 0.981, p = 0.32). There was no overall group-by-valence interaction (F(2, 192) = 2.476, p = 0.087) (see Fig. 2A). Since the drug effects were close to statistical significance, we performed post-hoc analyses with Dunnett test that showed no differences between drugs and placebo (all p values > 0.1).

The measured latencies in the autobiographical memory task did not differ between the three groups (F(2, 192) = 2.38, p = 0.09). There was neither a valence effect (F(1, 192) = 0.013, p = 0.9) nor an overall group-by valence interaction (F(2, 192) = 1.08, p = 0.34) (see Fig. 2B).

Long-term emotional memory test

A repeated measures ANOVA revealed that bupropion and sertraline did not display any effect in the long-term emotional memory task as outlined in Fig. 3 (F(2, 96) = 1.310, p = 0.27). There was a significant phase effect (F(2,192) = 13.89, p < 0.001). Post-hoc comparisons showed that phase 2 differ from the other phases (pairwise comparisons with Bonferroni correction, p < 0.001). No interaction between drug and phase (F(4, 192) = 0.71, p = 0.54) was observed.

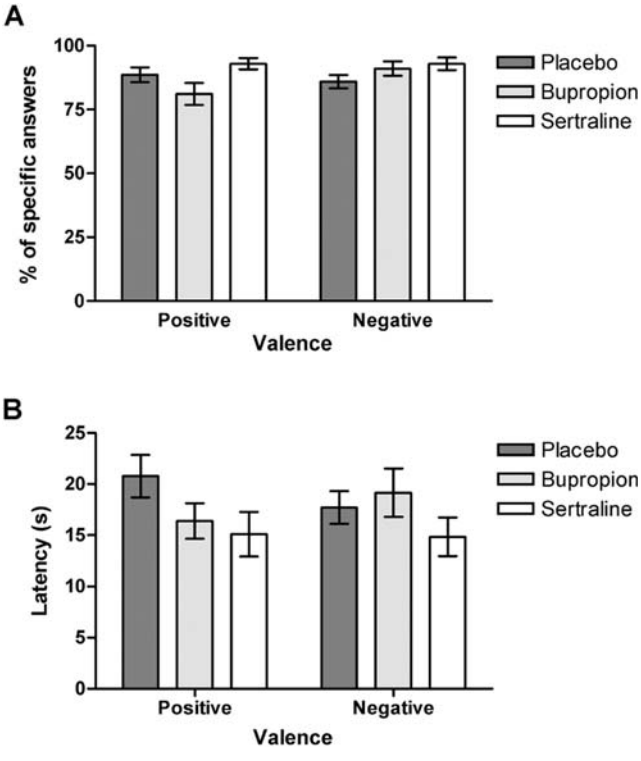

Fig. 2 Effect of acute treatment with bupropion, sertraline and placebo in the performance of the autobiographical memory test. **A** Percentage of specific answers elicited by the subjects across treatment groups. No significant differences were observed (ANOVA, p > 0.05). **B** Latency (in seconds) to retrieve a memory following presentation of cue words with alternating valences. No group effect was observed (ANOVA, p > 0.05). Data are presented as mean ± SEM

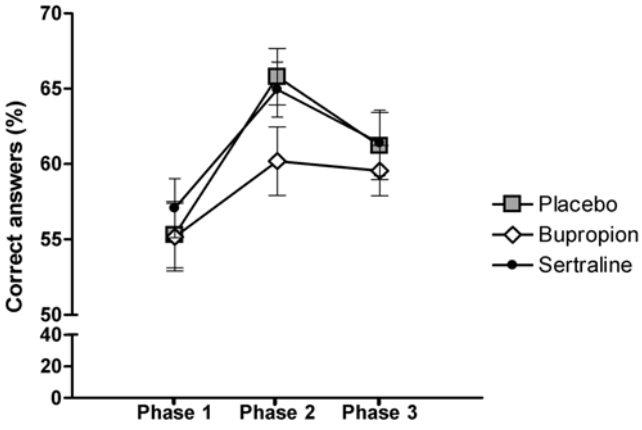

Fig. 3 Long-term emotional memory test. Memory was measured one week after learning. There was a phase effect (repeated measures ANOVA, p < 0.001). No group effect was observed (p > 0.05). Results (mean ± SEM) from different treatments are reported as percentage of correct answers

Discussion

The present double-blind, placebo-controlled, random allocation study displayed good matching between groups on potentially confounding variables, such as sex, age, schooling and baseline mood. Acute treatment with the antidepressants bupropion and sertraline enhanced the retrieval of long-term memories in a rodent model [3]. Conversely, acute norepinephrine reuptake inhibition with the antidepressant reboxetine did not display such an effect in humans [20]. In the present study, the acute treatment with the antidepressants bupropion and sertraline had no detectable effects in the retrieval of emotionally arousing material learned one week prior to testing or to specific emotional word-cued autobiographical memories.

The impact of emotion on memory performance

Regardless of the treatment group, subjects exhibited the expected heightened performance to the 'middle' emotional phase of the story presented one week prior to the 'surprise' memory recall test. Thus, the negative results reported in the present study cannot be attributed to differences in emotional reactions to stimuli presentations.

Following the presentation of an emotional cue word, subjects from all groups retrieved a high percentage (i. e., at least 80 %) of specific autobiographical memories. The distribution of the data cannot rule out a 'ceiling' effect. Separate statistical analysis (e. g., after exclusion of subjects in who scored at least 2 SD below or above average) are not reported because this procedure undermined the power of the statistical test. Thus, the negative results in this outcome at least in part might be due to a limitation of the instrument to detect differences. Memory performance was also determined by measuring the latency to retrieve autobiographical

memories. All subjects retrieved memories in a very short time (i. e., far less than the 60 s cut-off point of the test). Similarly, we cannot exclude the possibility that a 'ceiling' effect influenced the negative result in this outcome.

Dose-dependent effects?

Another potential explanation for the surprising findings of the present study is dose dependency. The effects that stress mediators exert on memory show a U-shaped curve in which higher concentrations of a given mediator (e. g., noradrenaline) might diminish, whereas lower concentrations of that mediator might enhance arousal-mediated memory performance [22]. It might be possible that smaller doses of these antidepressants (e. g., 75 mg bupropion and 25 mg sertraline) might have affected memory retrieval. A future study comparing the effects of these antidepressants at different doses might shed light on this possibility.

Specific mechanisms underlying memory retrieval?

Other studies investigating the effects of monoaminergic neurotransmission on long-term emotional memory used similar paradigms but pharmacological treatments occurred at the time of encoding [7, 19–21, 25]. The present study examined the effects of monoaminergic potentiation by antidepressants at the time of retrieval. It might be possible that bupropion and sertraline administered at encoding might enhance subsequent retrieval. A recent study failed to demonstrate a memory enhancing effect of reboxetine (4 or 8 mg) on long-term memory performance when the drug was administered at encoding [20]. Contrasting to the biochemical mechanisms involved in the consolidation of long-term emotional memories, the specific mechanisms underlying memory retrieval have been receiving attention just recently [4]. Bupropion and sertraline are retrieval enhancers in a rodent model of long-term emotional memory [3]. Replications of the present study with different designs (e. g., testing these antidepressants at different doses) might determine whether these in animals findings apply to man.

Acute versus chronic effects

Recently, a 'neuropsychological theory' for antidepressant drug action was proposed. This theory resides in the fact that following acute treatment with antidepressants, subjects display a positive cognitive bias, in which they recognize positive emotions with greater accuracy than negative ones as compared to placebo [13]. This recent finding was demonstrated for reboxetine and citalopram [12, 13]. The authors proposed that antidepressant drugs might have mood-independent cognitive effects that might be relevant to their final therapeutic effects. Such findings leave open the possibility that antidepressant drugs with different mechanisms of action could acutely influence other cognitive functions in man.

In agreement with the previous study performed by Papps and coworkers [20], the present study did not demonstrate that the acute treatment with antidepressants improve long-term emotional memory performance. In order to test the acute effects of monoaminergic potentiation in memory retrieval, a single-dose treatment was given to the subjects in this study. We cannot rule out the possibility that such drugs might influence this cognitive function following longer treatment periods when effects on mood might start to appear even in healthy subjects [11].

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