Acute augmentation of serotonin suppresses cardiovascular responses to emotional valence

Andrew H. Kemp and Pradeep J. Nathan
Neuropsychopharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, Hawthorn, Victoria 3122, Australia

Abstract
A key component in visceral reactivity to emotional states is heart rate (HR), however little is known about how HR response to emotional stimuli is modulated by neurochemicals. The present study investigated the way in which acute enhancement of serotonin (5-HT) function with a selective serotonin reuptake inhibitor (SSRI) modulates the HR associated with differently valent images (pleasant, neutral, unpleasant). Sixteen healthy participants viewed 75 images whilst HR was recorded. Participants were tested under two single-dose treatment conditions: placebo and citalopram (20 mg). Our findings suggest: (1) HR is able to differentiate differently valent images during placebo treatment and, (2) administration of citalopram suppresses the differences in HR between differently valent images. These results suggest that 5-HT may modulate the cardiovascular HR response to visual emotional stimuli and indicate that 5-HT may have a protective effect on the cardiovascular responses to emotional stimuli.

Key words: Antidepressants, cardiovascular system, citalopram, emotional valence, heart rate, serotonin.

Introduction
Emotion is regarded as consisting of multiple components including cognitive processes, physiological responses, motivational changes, motor expression and subjective feeling. William James proposed that an emotion was a direct function of feedback from the periphery or viscera (James, 1884) and a key component of such visceral reactivity to emotional states are changes in heart rate (HR). Changes in HR have been reported to be able to differentiate pleasant from unpleasant visual stimuli (Aftanas et al., 2001; Palomba et al., 1997) and load onto a valence dimension (Lang et al., 1993). Previous studies have generally reported larger HR decelerations to unpleasant stimuli compared to pleasant stimuli relative to a blank screen prior to image onset, and these deceleratory changes in HR are believed to reflect an orienting reaction which purportedly reflects milder emotional stimulations (see Palomba et al., 1997 for discussion).

Although the cardiovascular response to images differing on emotional valence has been demonstrated, little is known about how these responses are modulated by neurochemicals including serotonin (5-HT). Although results from extensive retrospective analyses demonstrate a small reduction in HR following chronic selective serotonin reuptake inhibitor (SSRI) treatment (Rasmussen et al., 1999), cardiovascular reactivity to emotional stimuli following administration of SSRIs is unknown. This is an important research area given that (1) HR is a key component in emotional responsiveness, (2) the serotonergic system is implicated in a range of disorders including depression, anxiety, social phobia, and premenstrual dysphoria (for a review, see Jones and Blackburn, 2002), (3) depression and anxiety have been associated with an increase in the likelihood of sudden cardiovascular death (Roose, 2001; Sheps and Sheffield, 2001) and (4) SSRIs have been reported as having ‘cardio-protective effects’ (Yeragani et al., 2002a).

The aim of the present study was, therefore, to investigate how increases in 5-HT with a SSRI (citalopram) modulates the HR associated with the viewing of differently valent images selected from the International Affective Picture System (IAPS). Previous literature suggests that HR is able to differentiate differently valent stimuli, thus in this study we will employ a within-subjects repeated-measures design to investigate differences between categories during placebo and citalopram conditions. We hypothesize...
that HR will differentiate differently valent images during both treatment conditions. Specifically, we hypothesize that HR during unpleasant images will be less than HR during pleasant images. We also hypothesize that there will be a small reduction in the HR for all image categories during the citalopram condition.

**Methods**

**Participants**

Sixteen healthy, non-smoking, medication-free volunteers (8 males, 8 females) participated in the current study (mean age \( \pm \) S.D. = 22.94 \( \pm \) 4.75 yr). Potential participants were carefully screened by a medical physician and excluded from the study if found to have a history of psychiatric disorders, neurological or other physical (i.e. cardiovascular) conditions. The study was approved by the Swinburne Human Research Ethics Committee at Swinburne University.

**Procedure**

All participants were requested not to eat breakfast or to drink any caffeinated beverage prior to arrival for testing. Participants arrived at the institute at 08:00 hours and were then provided with a standard breakfast in order to control for diet variability between and within subjects across both testing sessions of the study. The study was a double-blind, placebo-controlled design in which participants were tested under two single-dose treatment conditions: placebo and citalopram (20 mg). Participants were tested 2 h following administration of either substance to coincide with approximate peak plasma levels of citalopram (Noble and Benfield, 1997) and the order in which either placebo or citalopram were administered was counter-balanced. These conditions were separated by a minimum washout period of 1 wk.

Seventy-five images were selected from the IAPS, categorized as either pleasant (P), neutral (N) or unpleasant (U) (25 images in each category) and presented to participants in three blocks (P-N-U or U-N-P). Following the 6-s presentation of each image, the participant was presented with the Self-Assessment Manikin (SAM) rating scales for valence and arousal dimensions, which allow participants to rate each image in terms of how they actually felt during the presentation of the previous image. These scales range from 1 to 9, in which valence reflects the degree of pleasantness (1 = unpleasant; 9 = pleasant) and arousal, the degree of stimulation or excitement (1 = low arousal; 9 = high arousal). A thorough description of image selection and task instructions has been previously provided by Kemp et al. (2002).

Valence and arousal ratings for each image were averaged across categories so that each subject was associated with three valence and three arousal ratings which were then used in repeated-measures ANOVA statistics. HR was recorded from the upper left arm and referenced to linked ear electrodes as part of the set up for the recording of brain electrical activity. After the recording, cardiac interbeat intervals during picture presentation were converted to beats per minute (bpm) in half-second bins for each image category. The bpm over the 6-s epochs were then averaged for each category and treatment condition creating 6 bpm per subject for use in a repeated-measures ANOVA statistic.

**Statistics**

Behavioural SAM ratings were analysed using a 2 (placebo, citalopram) \( \times \) 3 (P-N-U) within-subjects repeated-measures ANOVA for valence and arousal dimensions separately to determine whether citalopram modified the participants’ reports of how they felt whilst they viewed differently valent images. HR data was also analysed using a 2 (treatment) \( \times \) 3 (category) within-subjects repeated-measures ANOVA to determine whether citalopram modified HR to the viewing of differently valent images. In addition, three paired-measures \( t \) tests were conducted to examine the citalopram-treatment effects on each of the differently valent image categories separately. One-tailed \( t \) tests were used for the HR analysis, as explicit hypotheses were made for differences between valent categories (repeated-measures ANOVA) as well as between treatment conditions (repeated-measures ANOVA and paired-measures \( t \) tests) (\( \alpha \) therefore is set at 0.10, two-tailed).

**Results**

Means and standard deviations for the participants’ ratings of images on the SAM rating scales for both treatment conditions are provided in Table 1. Within-subjects repeated-measures ANOVAs were conducted for both valence and arousal dimensions separately. Significant category effects were found for both valence \( [F(1.19, 17.78) = 109.45, p < 0.001, \eta^2 = 0.88] \) (Greenhouse–Geisser adjusted) and arousal \( [F(2.30) = 23.72, p < 0.001, \eta^2 = 0.61] \) ratings. However, no main treatment effect or a category \( \times \) treatment effect was found for either valence or arousal rating scales, indicating that treatment had
Table 1. Self-Assessment Maniken (SAM) mean ratings and standard deviations for pleasant, neutral and unpleasant categories in placebo- and citalopram-treatment conditions

<table>
<thead>
<tr>
<th></th>
<th>Pleasant</th>
<th>Neutral</th>
<th>Unpleasant</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Citalopram</td>
<td>Placebo</td>
</tr>
<tr>
<td>Valence</td>
<td>6.40 ± 0.62</td>
<td>6.13 ± 0.52</td>
<td>5.04 ± 0.23</td>
</tr>
<tr>
<td>Arousal</td>
<td>3.37 ± 1.73</td>
<td>2.86 ± 1.33</td>
<td>1.92 ± 0.96</td>
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Mean beats per minute (bpm) means and standard deviations for pleasant, neutral and unpleasant images in placebo- and citalopram-treatment conditions

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Citalopram</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>69.30 (8.96)</td>
<td>68.05 (8.87)</td>
<td>66.45 (10.56)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>66.48 (11.53)</td>
<td>67.20 (10.70)</td>
<td>67.17 (10.29)</td>
</tr>
</tbody>
</table>

Field of view no effect on ratings generally, nor did treatment modulate the participants’ ratings to specific image categories. For the valence dimension, planned comparisons revealed that the participants’ ratings of both pleasant and unpleasant images were significantly different from ratings of neutral images $[F(1,15) = 91.10, p < 0.001, \eta^2 = 0.86$ and $F(1,15) = 94.31, p < 0.001, \eta^2 = 0.86$ respectively]. For the arousal dimension, planned comparisons revealed that ratings of arousal for both pleasant and unpleasant images were significantly different from ratings of neutral images $[F(1,15) = 14.16, p = 0.002, \eta^2 = 0.49$ and $F(1,15) = 45.95, p < 0.000, \eta^2 = 0.75$ respectively]. In addition, ratings of arousal for unpleasant images were significantly different to those of pleasant images $[F(1,15) = 9.56, p = 0.007, \eta^2 = 0.39]$.

Means and standard deviations for the participants’ HR (in bpm) during viewing of pleasant, neutral and unpleasant valence categories for both placebo- and citalopram-treatment conditions are provided in Table 2.

A 2 (treatment) × 3 (category) repeated-measures ANOVA on bpm revealed a significant main effect for category $[F(2,30) = 3.92, p = 0.031, \eta^2 = 0.21$ and a treatment × category interaction $[F(1,43,21.51) = 4.54, p = 0.033, \eta^2 = 0.23$] (Greenhouse–Geisser adjusted). No main effect for treatment was evident. Planned comparisons for category indicated a significant difference between HR during viewing of unpleasant images and HR during viewing of pleasant images $[F(1,15) = 9.00, p = 0.009, \eta^2 = 0.38]$; a significant difference between HR during viewing of unpleasant images and HR during viewing of neutral images $[F(1,15) = 3.81, p = 0.070, \eta^2 = 0.20]$; and no statistical difference between HR during pleasant images and HR during viewing of neutral images.

Post-hoc one-way within-subject ANOVA statistics were conducted on placebo- and citalopram-treatment conditions separately to determine the nature of the treatment × category interaction. Significant category effects were found for the placebo-treatment condition $[F(2,30) = 6.69, p = 0.004, \eta^2 = 0.31]$, but not for the citalopram condition, suggesting that although HR is modulated by differently valent images within the placebo condition, the ability for differently valent images to modulate HR during the citalopram-treatment condition is suppressed. Planned comparisons for category within the placebo-treatment condition revealed a significant reduction in HR during viewing of unpleasant images relative to that during the viewing of pleasant images $[F(1,15) = 8.88, p = 0.009, \eta^2 = 0.37]$; a significant reduction in HR during viewing of unpleasant images relative to that...
during the viewing of neutral images \( [F(1, 15) = 4.53, p = 0.050, \eta^2 = 0.23] \); as well as a significant reduction in HR during viewing of neutral images relative to that during the viewing of pleasant images \( [F(1, 15) = 4.47, p = 0.052, \eta^2 = 0.23] \) (Figure 1).

Paired-sample t tests were conducted on each of the three valent categories separately to examine the differences between the placebo- and citalopram-treatment conditions. Differences between treatment conditions for unpleasant and neutral images were not significantly different, however there was a trend for a statistically significant difference between placebo- and citalopram-treatment conditions for pleasant images \( [t(15) = 1.61, p = 0.129] \) (Figure 1).

### Discussion

The study examined the modulatory effect of serotonergic augmentation on cardiovascular HR changes associated with the viewing of differentially valent images selected from the IAPS. The major findings were (1) that HR was able to differentiate differently valent images within the placebo condition and, (2) that HR was no longer able to differentiate differently valent images after increasing 5-HT with the SSRI citalopram. In addition, although we hypothesized there would be a reduction in HR for all image categories, results suggest that there was no main effect for citalopram.

During the placebo condition, HR differentiated all three valent image categories. HR during viewing of unpleasant images was significantly less than that during the viewing of neutral images and the HR during the viewing of neutral images was significantly less than that during the viewing of pleasant images. These findings support the previously reported effects of emotional valence on HR, believed to reflect a mild emotional stimulation (Aftanas et al., 2001; Lang et al., 1993; Palomba et al., 1997).

During the citalopram condition, no main treatment effect was found for HR which suggests that the dosage of citalopram administered in the current study (20 mg) may have been too low for this effect to appear, or that the HR reductions hypothesized in the current study are limited to chronic administration. However, we did identify a trend for citalopram to reduce HR during the viewing of pleasant images which is possibly due to these images having the highest HR. More importantly, the citalopram condition was found to modulate the ability for HR to differentiate differently valent stimuli. These findings suggest that the HR changes associated with emotional stimuli are suppressed with acute enhancement of 5-HT. This is a particularly important finding considering that negative feelings have been associated with arterial-wall thickening in treated hypertensive men at high cardiovascular risk (Agewall et al., 1996). Studies suggest that a diagnosis of major depressive disorder in patients with cardiovascular disease is not only associated with poor prognosis (see Yeragani et al., 2002a for discussion), but that the depression is also associated with an increase in the likelihood of sudden cardiovascular death (Roose, 2001; Yeragani et al., 2002a) and have even been regarded as having cardioprotective effects especially in patients with cardiovascular disease (Yeragani et al., 2002a). Our findings imply that 5-HT may have a protective effect on the heart with regards to the fluctuations in HR associated with differently valent stimuli.

Although the mechanisms underlying these effects are unknown, it is unlikely that our findings are the result of a direct 5-HT induced modulation of the noradrenergic system. First, if 5-HT was to directly modulate noradrenaline (NA), HR change would be non-specific to image category, and a main effect for treatment would be reported. Secondly, studies have shown that acute manipulation of 5-HT does not affect NA synthesis (Bystaster et al., 2002) or NA-based neuroendocrine responses (melatonin secretion) (Nathan et al., 1996). On the other hand, it is well-known that the brain modulates HR from descending influences of regions involved in emotional processing, such as the amygdala and the prefrontal cortex (for reviews, see Bernstein et al., 1991; Loewy and McKellar, 1980; Richardson and Chiu, 1983; Thayer and Siegle, 2002). In addition, the serotonergic system is widely distributed throughout the brain (see Barnes and Sharp, 1999 for a review of 5-HT receptors), thus it is therefore possible that 5-HT may modulate the cardiovascular system through actions at multiple sites in the emotional circuitry.

Recently, there has been an increasing interest in the relationship between depression and cardiac mortality using measures of HR variability (HRV) by analysing fluctuations between normal heartbeats using time and frequency domain methods. The usefulness of nonlinear measures has also been reported, although these measures still require critical experimentation. Decreased HRV as indicated by an increase in cardiac sympathetic function or a decrease in vagal function and reported in patients with depression, is now viewed as an important predictor of cardiac mortality (Carney et al., 2001; Stein and Kleiger, 1999; Task...
Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology, 1996; Yeragani, 2000; Yeragani et al., 2002a, b). Although most studies have employed these measures over a long time-frame (usually 24 h), research is beginning to examine their utility in healthy subjects during the processing of emotional stimuli (Lane et al., 2001; Sakuragi et al., 2002). Interestingly, Lane et al. (2001) demonstrate that HRV may be used to index activity within neural structures associated with emotional processing, although how these measures relate to levels of 5-HT remains to be examined (see Thayer and Siegel, 2002 for discussion).

Finally, we should note a few limitations of the present study and provide some directions for future research. First, the sample size of the current study is small and is less than previous studies which have investigated HR response to emotional images (Aftanas et al., 2001; Lang et al., 1993; Palomba et al., 1997). Secondly, we were unable to provide measures of ‘deceleration’ (as reported in previous studies) as the protocol for the current study did not involve presentation of a blank screen prior to slide onset. Despite these limitations however, our findings display a similar trend which suggests that unpleasant images are associated with a lower HR than pleasant images with neutral images falling in between. In order to more fully understand the role of cardiovascular responsiveness to emotional stimuli and the effects of neurochemicals on this processing, it will be important for future research to examine other HR measures, such as HRV.

In conclusion, the current findings indicate that in addition to the known psychotropic effects, citalopram may modulate the HR associated with the viewing of emotional stimuli. Specifically acute enhancement of 5-HT appears to suppress the normal fluctuations in HR associated with different emotional stimuli. These findings suggest a possible neurophysiological mechanism which may contribute to the safe cardiovascular profile of SSRIs.

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Statement of Interest

None.

References


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