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PII: S0924-977X(13)00213-7
DOI: http://dx.doi.org/10.1016/j.euroneuro.2013.07.013
Reference: NEUPSY10713

To appear in: European Neuropsychopharmacology

Received date: 21 January 2013
Revised date: 27 July 2013
Accepted date: 29 July 2013

Cite this article as: Peter D. Drummond, Kate Minosora, Gretta Little, Wendy Keay, Topical ibuprofen inhibits blushing during embarrassment and facial flushing during aerobic exercise in people with a fear of blushing, European Neuropsychopharmacology, http://dx.doi.org/10.1016/j.euroneuro.2013.07.013

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Topical ibuprofen inhibits blushing during embarrassment and facial flushing during aerobic exercise in people with a fear of blushing

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Short title: topical ibuprofen inhibits blushing

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Word count: (abstract, text, table, figure legends): 3,677
References: 46
Abstract

The flush that develops during whole-body heat stress depends partly on prostaglandins production in the skin. Variations in the strength of this local mechanism may contribute to individual differences in susceptibility to blushing and associated anxiety. To investigate this in the present study, the anti-inflammatory agent ibuprofen (which blocks prostaglandins formation) was applied topically to a small area of the cheek in 16 participants with a fear of blushing and in another 14 without this fear. Changes in skin blood flow were monitored at the ibuprofen-treated site and at a mirror image control site while participants sang (to induce embarrassment and blushing) and during aerobic exercise (to induce flushing). The topical ibuprofen treatment inhibited increases in cheek blood flow in both groups during both of these tasks. However, increases in cheek blood flow were greater in participants with high than low fear of blushing immediately after exercise. These findings suggest that prostaglandins contribute to dilatation of facial blood vessels both during emotional arousal (embarrassment) and aerobic exercise. Furthermore, fear of blushing may be associated with mechanisms that delay the resumption of normal vascular tone after a period of vasodilatation. Whether topical ibuprofen gel is suitable for intermittent or long-term use as an aid for blushing control requires further investigation.

Keywords: blushing; flushing; embarrassment; exercise; skin blood flow; prostaglandins
Introduction

Blushing refers to the transient facial redness that develops during emotions such as embarrassment, guilt or shame (Leary et al., 1992), whereas flushing refers to more-enduring facial redness triggered not only by strong emotions but also by vasodilators such as alcohol and by thermoregulatory adjustments to physical exercise and heat. Transient blushing involves an accumulation of red blood cells in the superficial venous plexus of the facial skin due to sympathetically-mediated dilatation of the arterial supply (Mellander et al., 1982; Drummond and Lance, 1987; Drummond, 1997; Drummond, 2013). Similarly, the flush that develops during whole-body heating and exercise involves active sympathetic dilatation of cutaneous blood vessels (Drummond and Lance, 1987; Drummond and Finch, 1989; Charkoudian, 2010). These neurally-mediated increases in blood flow liberate substances such as nitric oxide from the vascular endothelium and prostaglandins from cutaneous cells which heighten and prolong the flush (Kellogg et al., 2003; Kellogg et al., 2008; McCord et al., 2006; Pyke and Tschakovsky, 2005).

During social encounters, people with social anxiety frequently experience autonomic and motor signs of anxiety, including blushing (Bögels et al., 2010). A subgroup of socially anxious people are particularly frightened of blushing (Voncken and Bögels, 2009; Pelissolo et al., 2012), primarily because they fear that others who notice the blush will regard them with derision or contempt. Surprisingly, during the majority of embarrassing laboratory tasks, the actual intensity of blushing is unrelated to perceived intensity or susceptibility to blushing (Drummond, 1997; Mulkins et al., 1997; Drummond and Su, 2012; but see Drummond, 2001) or to fear of blushing (Mulkins et al., 1999; Gerlach et al., 2001; Voncken and Bögels, 2009; but see Dijk et al., 2009). Nevertheless, blushing appears to build up over repeated episodes in people who report that they
blush frequently (Drummond et al., 2003) or who are frightened of blushing (Drummond et al., 2007). The aetiology of this is unknown, but is consistent with a physiological predisposition that might delay recovery after a blush.

We recently reported that a local vascular mechanism may, in part, contribute to individual differences in susceptibility to blushing and associated anxiety. In particular, we found that a low dose of the vasodilator nicotinic acid (niacin) provoked greater increases in facial blood flow in people with high than low fear of negative evaluation (a cardinal feature of social anxiety), both when they sat quietly (Drummond and Lazaroo, 2012a) and during an embarrassing task (singing a children’s song) (Drummond and Lazaroo, 2012b). Niacin dilates superficial blood vessels by releasing prostaglandin D₂ from epidermal Langerhans cells and prostaglandin E₂ from keratinocytes (Benyo et al., 2006; Hanson et al., 2010). Prostaglandins are potent vasodilators (Nagai, 2008; Shimura et al., 2010; Matsushima et al., 2011); thus, an exaggerated release or a heightened response to prostaglandins might amplify vasodilatation or delay resolution of blushing in people with social anxiety (Bouwer and Stein, 1998).

Non-steroidal anti-inflammatory drugs such as ibuprofen inhibit cyclooxygenase, an enzyme that mediates the production of prostaglandins (Ricciotti and Fitzgerald, 2011). When applied topically to the skin in a gel, ibuprofen inhibits the inflammatory processes involving prostaglandin formation that contribute to musculoskeletal pain (Massey et al., 2010). Hence, to determine whether prostaglandins might contribute to blushing or exercise-induced flushing, ibuprofen gel was applied topically to a small area of the cheek in the present study. Changes in blood flow were measured at this site and at a comparable site in the contralateral cheek while participants sang (to induce embarrassment and blushing) and exercised (to evoke thermoregulatory flushing). It was hypothesized that ibuprofen would inhibit increases in cheek
blood flow when participants exercised by blocking prostaglandins-mediated vasodilatation. As social anxiety is associated with a heightened response to prostaglandins (Drummond and Lazaroo 2012a; 2012b), it was hypothesized that the inhibitory effect of ibuprofen would be greater in people with a fear of blushing than in people without this fear. We expected that participants who were frightened of blushing would report more embarrassment when they sang than participants without this fear, due to greater social anxiety in the high- than low-fear group (Voncken and Bögels, 2009; Dijk et al., 2009). Whether this heightened emotional arousal would augment blushing due to prostaglandins production was also explored.

**Experimental procedures**

**Participants**

Participants were selected from 286 undergraduate university students who rated their concerns about blushing on a screening questionnaire (Bögels and Reith, 1999; Heinrichs et al., 2006). The high fear group consisted of 12 women and four men aged between 17 and 37 years (mean ± S.D., 22 ± 5 years) who scored between 29 and 55 out of a possible total of 60 on the screening questionnaire (i.e., between the 83rd and 100th percentile of the total group), and the low fear group consisted of six women and eight men aged between 18 and 53 years (27 ± 11 years) who scored between 0 and 9 on the screening questionnaire (i.e., between the 1st and 33rd percentile of the total group). None of the participants was pregnant, had asthma or other respiratory problems, liver or kidney disease, mental difficulties, took prescription medication for high blood pressure, regularly took ibuprofen or other analgesics, had a previous sensitivity to non-steroidal anti-inflammatory drugs or had inflamed facial skin. Participants each provided informed consent for the procedures, which were approved by Murdoch University Human Research Ethics Committee.
Measures and instruments

The screening questionnaire consisted of six items from the Blushing, Trembling and Sweating Questionnaire that measured the extent to which individuals were afraid of and hindered in their daily functioning by blushing (Bögels & Reith, 1999). Each item was rated on a 10 cm visual analogue scale, thus providing a total score between 0 and 60. To evaluate perceptions of blushing propensity and other broader aspects of social anxiety, participants filled out the Blushing Propensity Scale (Leary and Meadows, 1991) and the Fear of Negative Evaluation Scale (Watson and Friend, 1969). The Blushing Propensity Scale measures the degree to which people expect to blush in situations such as “talking to someone about a personal topic” and “when I’ve looked stupid or incompetent in front of others” (Leary & Meadows, 1991). Blushing propensity scores relate closely to measures of social anxiety (Leary et al., 1992; Edelmann & Skov, 1993). The Fear of Negative Evaluation Scale contains 30 items that assess apprehension and distress about being evaluated negatively by others, a fundamental component of social anxiety. The participants also completed the Social Interaction Anxiety and Social Phobia Scales which, respectively, assess anxiety associated with initiating and maintaining conversations and anticipatory and performance-related social anxiety (Mattick and Clarke, 1998). For each of these scales, the internal consistency and test-retest reliability over short intervals is high (Bögels & Reith, 1999; Leary & Meadows, 1991; Mattick & Clarke, 1998; Watson & Friend, 1969).

Changes in skin blood flow were detected with wide surface area laser Doppler flow probes (Moor Instruments, Axminster, UK) which were inserted into probe holders attached with double-sided adhesive washers to prepared sites in the cheeks. Signals were processed by a Moor
Instruments MBF3D laser Doppler flowmeter and sampled at 200 Hz by a Biopac MP100 data acquisition system (Biopac Instruments, Goleta, California).

**Procedures**

The experiments were carried out in a temperature controlled room maintained at 22 ± 1°C. The procedures were delivered by three female postgraduate psychology students who were unaware of the participant’s previously rated fear of blushing.

Initially, 5% ibuprofen gel (Nurofen gel, Reckitt Benckiser Healthcare, Sydney, Australia) was rubbed into a 1 cm diameter patch on the participant’s right or left cheek for one minute to assist absorption, as recommended by the manufacturer. The site chosen was approximately 2 cm below the zygomatic arch, as blushing often develops in this region of the face. As a control, a saline-based ultrasound gel (Medical Equipment Services, Melbourne, Australia) was rubbed into a similar site on the contralateral cheek. The prepared sites were then covered with capsules (10 mm internal diameter) filled with the ibuprofen or control gel for 60 minutes to further assist absorption (Drummond, 2011). While waiting for the ibuprofen to be absorbed, participants completed the Blushing Propensity Scale, Fear of Negative Evaluation Scale and the Social Interaction Anxiety and Social Phobia Scales.

The capsules and excess gel were then removed, and laser Doppler flow probes were placed over the prepared sites in the cheeks. Once stable blood flow had been recorded for two minutes, participants were asked to rate their embarrassment and blushing on 10 cm visual analogue scales that ranged from “not embarrassed at all” and “not blushing at all” through to “extremely embarrassed” and blushing extremely”. They were then instructed to sing along for five minutes to “I will survive” by Gloria Gaynor while being video-recorded. The song lyrics were displayed on a chart in front of the participant. During the song the experimenter remained
in the room to observe the participant and, to heighten their embarrassment, commented now and then on the participant’s performance with the following statements: “make sure you sing in tune”, “sing in melody”, “sing nice and loudly”, “be expressive” and “sing in time with the music”. When the song had finished the participant was asked to again rate their embarrassment and blushing on the 10 cm visual analogue scales. The participant then sat quietly for a further two minutes while their blood flow was monitored.

Next, the participant was asked to stand in front of a 18.5 cm step for two minutes before stepping up and down as fast as possible for five minutes. Participants were encouraged to keep going throughout the five-minute period. After five minutes of exercise, the participant was asked to sit quietly while their blood flow was monitored for a further two minutes.

**Data reduction and statistical approach**

As laser Doppler flow probes detect relative rather than absolute changes in skin blood flow, mean changes in blood flow during each minute of each task were expressed as a percentage of the level recorded during the baseline before the task. To remove movement artefacts, the blood flow signal was filtered with a low pass filter at 0.5 Hz.

To determine whether physiological responses to each task differed between participants with a high or low fear of blushing, changes in facial blood flow were investigated in analyses of variance with a between-subjects factor of Fear of Blushing (high, low) and within-subjects factors of Drug (ibuprofen, control) and Time (the five consecutive minutes of the task). Self-reported ratings of embarrassment and blushing before and after each task were investigated in similar analyses. Blood flow recovery after each task was investigated in analyses of variance with a between-subjects factor of Fear of Blushing (high, low) and a within-subjects factor of Drug (ibuprofen, control). Where appropriate, Greenhouse-Geisser’s $\varepsilon$ was used to adjust the
degrees of freedom to correct for violations of the sphericity assumption. Results are reported as the mean ± standard error of the mean, and p < 0.05 was the criterion of statistical significance.

Results

Group characteristics

Fear of blushing averaged 35.1 ± 1.7 in the high fear group and 4.2 ± 0.8 in the low fear group. Age and sex distributions were similar in both groups [for age, t(17.3) = 1.58, not significant; for sex, χ²(1) = 3.21, not significant] (Table 1). Overall, participants in the high fear group had greater scores than the low fear group on self-reported measures of blushing propensity, fear of negative evaluation, social interaction anxiety and social phobia (Table 1).

Effect of ibuprofen on cheek blood flow

Blood flow in the cheeks increased 53 ± 11% (95% confidence interval 30% to 75%) at the control site and 21 ± 5% (95% confidence interval 11% to 32%) at the ibuprofen-treated site when participants sang [main effect for Drug, F(1,27) = 9.67, p = 0.004]. The inhibitory effect of ibuprofen on cheek blood flow persisted throughout the task in both groups (none of the main effects or interactions that involved Group or Time were statistically significant). This inhibitory effect also persisted in both groups during the recovery period after singing [main effect for Drug, F(1,27) = 9.08, p = 0.006; neither the main effect for Group nor the Drug x Group interaction was statistically significant] (Figure 1).

During the two-minute period before exercise, cheek blood flow remained 16 ± 6% above the baseline before singing when averaged over sites and groups (95% confidence interval 4% to 28%). However, at this stage of the experiment, blood flow was similar at both sites in both groups (neither the main effects for Drug or Group nor the Drug x Group interaction were statistically significant). During the exercise step-test, cheek blood flow increased 44 ± 12%
(95% confidence interval 19% to 68%) at the control site but decreased 3 ± 6% (95% confidence interval -15% to +10%) at the ibuprofen-treated site [main effect for Drug F(1,28) = 22.2, p < 0.001]. In both groups and drug conditions, cheek blood flow increased gradually over the course of the task [main effect for Time, F(2.29, 64.18) = 6.65, p = 0.002; none of the interactions that involved Time were statistically significant] (Figure 2). However, when averaged across sites and time, vasodilatation during exercise was marginally greater in the high than low fear of blushing group [main effect for Group, F(1,28) = 3.15, p = 0.087] (Figure 2).

The inhibitory effect of ibuprofen on cheek blood flow persisted after exercise [main effect for Drug F(1,28) = 9.32, p = 0.005] (Figure 2). Importantly, however, cheek blood flow was greater after than before exercise both at the control site (mean increase 56 ± 12%, 95% confidence interval 30% to 81%) and the ibuprofen-treated site (mean increase 31 ± 10%, 95% confidence interval 11% to 51%). In addition, cheek blood flow was greater in the high than low fear of blushing group at this stage of the experiment [66 ± 14% versus 21 ± 15%, main effect for Group, F(1,28) = 4.59, p = 0.041; Drug x Group interaction not significant] (Figure 2).

**Ratings of blushing and embarrassment during singing**

Increases in embarrassment while singing were greater in the high than low fear group [main effect for Time, F(1,28) = 11.4, p = 0.002; main effect for Group, F(1,28) = 2.96, p = 0.097; Group x Time interaction, F(1,28) = 4.63, p = 0.04] (Figure 3). However, ratings of blushing did not increase in either group during singing (none of the effects were statistically significant for Time or Group).

**Discussion**

We expected that prostaglandins production during aerobic exercise would augment facial flushing in people who were frightened of blushing, and that topical ibuprofen treatment
would inhibit this response. Although increases in cheek blood flow were similar in both groups when they exercised, increases were greater in the high- than low-fear group when they rested immediately after exercise. Importantly, topical ibuprofen treatment inhibited flushing in both groups during exercise, and also inhibited blushing during and after an embarrassing task (singing). These findings indicate that prostaglandins mediate flushing in the cheeks during brief aerobic exercise, and also contribute to blushing evoked by singing. They also suggest that cumulative or exercise-induced increases in facial blood flow delay the resolution of flushing in people with a fear of blushing. Prostaglandins might contribute, in part, to this delay (Drummond and Lazaroo, 2012a; 2012b) because cheek blood flow remained higher at the control than ibuprofen-treated site after exercise in the high-fear group.

Interestingly, the ibuprofen treatment completely eliminated increases in cheek blood flow during the self-paced aerobic exercise, indicating that prostaglandins production was the primary driver of vasodilatation. However, an additional prostaglandins-independent mechanism contributed to blushing during and after singing and to flushing immediately after exercise, as blood flow was greater than baseline both at the ibuprofen-treated and control sites at these points in the experiment. Possibilities include release of sympathetic vasoconstrictor tone (Drummond, 1997), active sympathetic vasodilatation (Drummond and Finch, 1999), or mediation by acetylcholine (Shibasaki et al., 2002), neuronal nitric oxide (Kellogg et al., 2003; Kellogg et al., 2008), vasoactive intestinal polypeptide (Bennett et al., 2003; Kellogg et al., 2010), histamine (Wong et al., 2004), or a neurokinin receptor agonist such as substance P (Wong and Minson, 2006). Beta-adrenergic vasodilatation might also have contributed to blushing (Drummond, 1997). After exercise, the vasodilator mechanism appeared to be more prominent in participants who were frightened of blushing, suggesting that this fear might be
associated with mechanisms that delay the resumption of normal vascular tone. As this may also apply after repetitive bursts of psychological arousal (Drummond et al., 2007), a slow rate of recovery after an episode of blushing or flushing could result in physiological or social cues that add to social discomfort and help to maintain a fear of blushing.

As in previous studies (e.g., Drummond et al., 2007), a fear of blushing was associated with high blushing propensity scores, a fear of negative evaluation, high social interaction anxiety and social phobia scores, and elevated embarrassment while singing. However, a physiological index of blushing (the increase in cheek blood flow) was similar in the high and low fear groups during this task. Emotional distress often is out of step with physiological signs of blushing, both in people who believe that they blush easily and in those who are frightened of this response (see review by Drummond, 2013). Convergent findings from several studies suggest that people with social anxiety focus more intently than usual on internal sensations during social interactions, and thus might overestimate autonomic responses such as blushing (Gerlach et al., 2001; Edelmann and Baker, 2002; Chen and Drummond, 2008). Nevertheless, there is some support for the view that anxiety associated with heightened expectations of blushing actually augments blushing (Dijk et al., 2009; Drummond and Su, 2012; Drummond, 2013). As people generally are unaware of how intensely they are blushing, contextual or emotional pointers might combine with physiological cues to reinforce blushing in people who are frightened of this response.

Several limitations apply to the findings of this study. First, as singing always preceded exercise, carry-over effects from singing might have influenced the response to exercise. In particular, we are unsure whether the delay in recovery in the high-fear group after exercise was due to exercise alone or whether repetitive increases in facial blood flow during singing and
exercise boosted residual flushing. This will need to be investigated in further studies. Second, as exercise was relatively brief, it probably did not evoke a full thermoregulatory response involving maximal increases in skin blood flow. Thus, whether prostaglandins entirely mediate increases in facial blood flow during the later stages of exercise is unknown. Third, no therapeutic recommendations can be drawn from the findings of this study as the participants were recruited from a student population rather than a clinical setting; furthermore, ibuprofen was applied to only a small region of the cheek on only one occasion and did not completely block increases in cheek blood flow when participants sang.

Nevertheless, the findings provide preliminary support for a pharmacological approach to blushing control that might be relevant not only for people who are frightened of blushing but also for inflammatory dermatological conditions such as rosacea. As topical ibuprofen gel is associated with only minor side effects (Massey et al., 2010), it may be suitable both for intermittent and long-term use as an aid for blushing control. In particular, knowing that ibuprofen suppresses blushing might help people who are frightened of blushing engage in social encounters that they otherwise would have avoided. This could provide an opportunity to habituate to anxiety-provoking cues and allow the fear of blushing to subside.
References


Drummond, P.D., Lazaroo, D., 2012b. The effect of facial blood flow on ratings of blushing and negative affect during an embarrassing task: preliminary findings. J. Anxiety Disord. 26,


Figure legends

**Figure 1.** Percent change ± S.E. in cheek blood flow during and after singing at control and ibuprofen-treated sites (* p<0.05 for differences between sites) in participants with low or high fear of blushing.

**Figure 2.** Percent change ± S.E. in cheek blood flow during and after exercise at control and ibuprofen-treated sites (* p<0.05 for differences between sites) in participants with low or high fear of blushing.

**Figure 3.** Embarrassment and blushing ratings ± S.E. before and during singing in participants with low or high fear of blushing. Embarrassment ratings were greater in participants with high than low fear of blushing during singing (* p<0.05).
Table 1

Blushing propensity, fear of negative evaluation, social interaction anxiety and social phobia scores in participants with high or low fear of blushing

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<td></td>
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<td></td>
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Role of the funding source

No funding was provided for this study.

Acknowledgements

None.

Conflicts of interest

None of the authors has a conflict of interest with the contents of this paper.

Contributors

Peter Drummond designed the study, undertook the statistical analysis and wrote the first draft of the manuscript. Kate Minosora, Gretta Little and Wendy Keay managed literature searches, collected the data, and contributed to and approved the final manuscript.
Figure 2

Low Fear of Blushing

Cheek Blood Flow (% change)

Minutes of Exercise

High Fear of Blushing

Cheek Blood Flow (% change)

Minutes of Exercise
Figure 3