Immersing the foot in painfully-cold water evokes ipsilateral extracranial vasodilatation

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Abstract

Temporal pulse amplitude was recorded bilaterally in 56 participants before, during and after three ice-water immersions of the foot. Half of the participants were told that prolonged exposure to freezing temperatures could cause frostbite. Increases in pulse amplitude were greater in the ipsilateral than contralateral temple during and after the three foot-immersions. Although pulse amplitude decreased after threatening instructions and repeated immersion of the foot, the vasodilator response persisted during all three immersions. These findings suggest that nociceptive stimulation of the foot evokes an ipsilateral supra-spinal extracranial vasodilator response, possibly as part of a broader defense response.

Key words: extracranial vasodilatation; nociceptive reflex; fear; cold pressor test; sympathetic nervous system

Introduction

Immersing the hand in painfully-cold water provokes extracranial vasodilatation that is more pronounced in the ipsilateral than contralateral temple (Drummond & Granston, 2003; Drummond & Granston, 2004). The response appears to involve loss of sympathetic vasoconstrictor tone, because local pretreatment with guanethidine (which inhibits sympathetic noradrenergic neurotransmission) prevents the response (Drummond, 2006a). The functional significance of this nociceptive vasodilator response is uncertain but could be worth exploring, as loss of sympathetic vasoconstrictor tone may aggravate the extracranial vascular component of pain in disorders such as cluster headache and migraine (Drummond, 1991; Drummond, 2006b).

The present study had two aims. The first was to establish whether immersion of the foot in ice water would also provoke ipsilateral extracranial vasodilatation. If so, this would imply that hemilateral nociceptive processing involves a supra-spinal mechanism. The second aim was to determine whether fear-evoked constriction of facial blood vessels would counteract the vasodilator response.

Methods

Participants and ethics approval

The sample consisted of 16 male and 40 female undergraduate psychology students aged between 19 and 55 years (mean age of 25 ± 8 years) who earned course credits for participating. The gender imbalance reflects differences in the proportions of women and men enrolled in undergraduate psychology classes at Murdoch University. None of the participants had cardiovascular or psychiatric disorders or took prescribed medication for any other medical complaint. Each participant provided informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee.

Procedures

The experiments were carried out in a temperature-controlled room maintained at 23 ± 1^{o}C. To monitor changes in facial blood flow, pulse transducers (photoplethysmographs, Grass Instruments, Quincy, MA) were attached with adhesive washers to the left and right fronto-temporal region in the distribution of branches of the superficial temporal artery. The pulse transducers were covered with a black elastic headband to reduce interference from random illumination of the recording site. The headband was stretched slightly to hold the pulse transducers in place but was not tight enough to interfere with skin blood flow. Signals were sampled at 200 Hz by a Biopac MP100 data acquisition system and displayed and analyzed using Biopac AcqKnowledge software on a personal computer.

After a physiological baseline was established, participants were assigned randomly to receive threatening or neutral information about the up-coming cold pressor tests. In the threatening condition, they were informed by the female experimenter (CC) that "Prolonged exposure to freezing temperatures may lead you to experience persistent shivering, display signs of inflammation such as blistering or skin peeling and, in more severe cases, may lead to frostbite. Frostbite is defined as freezing of the tissue in the exposed part of the body. In particular, ice crystals which form inside the skin can damage the tissues, and you could lose skin or part of a finger or toe. Before the tissue freezes, you may experience sensations of tingling, pain and numbness in exposed skin. Additionally, your skin may become hard or waxy and may blister or peel; and it may turn purple. Because the tissues feel numb, most victims only realize that he or she has frostbite when someone else brings it to their attention." Both groups were then told "In a short while, I will ask you to immerse your foot in cold water at approximately 2ºC for one minute. I would obviously like you to keep your foot in the water for the full minute. However, please note that you are free to withdraw your

foot at any point if the discomfort is too much for you to tolerate. I will ask you to repeat the procedure two more times at 4-minute intervals".

Participants placed their left or right foot to approximately 2.5 cm above the lateral malleolus into a container of water maintained at 32^{o}C for four minutes, then into another container of water maintained at 2^{o}C for 60 seconds, then back into the 32^{o}C water. This cycle was repeated two more times. Half of the participants placed their right foot into the water and the remainder placed their left foot into the water. None of the 56 participants who completed the experiment withdrew their foot early. However, one additional participant withdrew from the experiment after the first cold pressor test. Participants who received threatening instructions were told afterwards that frostbite takes approximately 100 minutes to develop after prolonged exposure to freezing temperatures.

Data reduction and statistical approach

To minimize movement artifacts, the pulse waveform was filtered with a low pass filter at 15 Hz and a high pass filter at 0.5 Hz. Pulse amplitude was measured as the peak-to-trough height of the filtered pulse waveform, with a greater difference indicating greater blood flow. Pulse amplitude was measured for 60 seconds before the threatening or neutral instructions, for 60-second blocks immediately before the participant moved their foot from warm to cold water, and during and immediately after each immersion of the foot in cold water. As pulse amplitude is influenced by individual differences in the density and location of cutaneous vessels and the pressure of application of the transducer against the skin, pulse amplitude was expressed as a percentage of the level before the instructions were given.

In preliminary analyses, effects did not depend on whether the left or the right foot was immersed. Therefore, extracranial vascular responses to the foot immersions were compared in an Instructions (threatening, neutral) x Side (ipsilateral, contraleral) x Block

(before, during or after foot immersion) x Trials (1-3) repeated measures analysis of variance. The multivariate approach was used for factors with more than two levels.

Results

As shown in Figure 1, the amplitude of vascular pulsations increased during and after the cold water immersions [main effect for Block, $F(2,53) = 30.7$, $p<0.001$]. In general, increases were greater ipsilateral than contralateral to the cold water immersion [main effect for Side, $F(1,54) = 4.93$, $p<0.05$] (Figure 1). However, pulse amplitude decreased during the four-minute recovery period between immersions, and generally declined across the course of the experiment [main effect for Trials, $F(2,53) = 5.81$, $p<0.01$]. Vasodilatation during the first trial was greater in participants who received neutral than threatening instructions [Trial x Instructions interaction, $F(2,53) = 3.59$, $p<0.05$] (Figure 1). No other effects achieved statistical significance.

Discussion

Immersing the foot in ice water provoked a bilateral increase in pulse amplitude that was greater in the ipsilateral than contralateral temple. Although threatening instructions and repeated immersion of the foot in ice-water evoked signs of extracranial vasoconstriction, the ipsilateral component of the vasodilator response persisted during all three immersions.

The neural control of the facial circulation is more complex than in most other parts of the body. Noxious stimulation of the eyes, nose, lips, mouth or face triggers trigeminal-parasympathetic vasodilator reflexes in orofacial tissues and the forehead microvasculature, and also initiates antidromic vasodilatation in the terminal distribution of stimulated trigeminal nerve fibres (Izumi, 1999; Drummond, 2006b). In addition, increases in body temperature (Drummond & Finch, 1989) and emotions that provoke blushing (Drummond & Lance, 1987; Licht & Pilegaard, 2008) generate active sympathetic vasodilatation of facial vessels, whereas sympathetic vasoconstrictor tone limits blood flow through exposed parts of

the face in cold environments, particularly the nose, lips and ears (Blair et al., 1961; Fox et al., 1962; Drummond & Finch, 1989).

Cutaneous blood flow decreases in the limbs during emotions such as fear and surprise (Turpin & Siddle, 1983; Hayashi et al., 2009). Similarly, blood flow through the facial artery of conscious rabbits decreases in response to unexpected noises and noxious cutaneous stimulation (Roatta et al., 2009). These responses are inhibited by alpha-adrenergic blockade and prevented by unilateral cervical sympathectomy (Blessing, 2003; Roatta et al., 2009). In humans, facial blood flow generally increases in response to loud noises (Turpin & Siddle, 1983) and verbal provocation (Drummond, 1999), but does not change when participants watch frightening movie clips (Hayashi et al., 2009). Nevertheless, the pallid face of fear suggests that facial blood flow decreases during more intense or prolonged threat.

In the present study, the amplitude of vascular pulsations was lower in participants who received threatening instructions than in the control group before, during and after the first immersion of the foot in ice-water, consistent with fear-evoked vasoconstriction. In addition, pulse amplitude decreased across the experiment in both groups, possibly in response to recurrent pain. Despite this, pulse amplitude increased by much the same amount during each immersion in both groups, indicating that heightened vasoconstrictor tone did not alter transient extracranial vasodilatation to noxious stimulation of the foot. As the extracranial vasodilator response appears to involve release of sympathetic vasoconstrictor tone, blood vessels would have to be at least partly constricted for the response to proceed (Drummond, 2006a). Although vasoconstrictor tone may be required, the present findings suggest that the response does not increase further as vasoconstrictor tone intensifies.

Sustained pinching of the inter-digital skin of the human hand evokes tonic reflex vasoconstriction in the fingers in proportion to the intensity of pinching (Magerl et al., 1990). In addition, selective excitation of cutaneous nociceptors by application of mustard oil

(burning pain) or histamine (itch) to the human forearm elicits signs of sustained vasoconstriction in the ipsilateral hand (Magerl et al., 1996). Together, these findings suggest that noxious stimulation of the upper limb evokes vasoconstriction in that limb, possibly due to a nociceptive-sympathetic vasoconstrictor spinal reflex. Painful intraneural stimulation of the superficial peroneal nerve evokes vasoconstriction in the palm of the hand (Blumberg & Wallin, 1987). Surprisingly, however, this stimulus also elicits reflex vasodilatation in both feet which is greater on the stimulated than opposite side (Blumberg & Wallin, 1987). The vasodilator response may be mediated by release of sympathetic vasoconstrictor tone as it is enhanced by body cooling. Hence, Blumberg and Wallin's findings suggest that noxious stimulation of the superficial peroneal nerve might paradoxically intensify vasoconstriction in the hands while simultaneously inhibiting sympathetic vasoconstrictor tone in the feet, particularly on the stimulated side. That is, painful stimuli may induce opposing influences on sympathetic vasoconstrictor outflow.

Afferent input from the upper limbs and sympathetic outflow to the head, neck and upper limbs passes through adjacent regions of the thoracic spinal cord. Thus, reciprocal patterned vasomotor responses in cranial and upper limb vessels to nociceptive stimulation of the upper limb (Drummond & Granston, 2003; Drummond & Granston, 2004; Drummond, 2006a) could be organized either at the spinal level or more rostrally. To distinguish between these two possibilities in the present study, we determined whether noxious stimulation of the *lower* limb (which is innervated by lumbar and sacral afferents and thus does not directly cross paths with sympathetic outflow to the face) would also evoke signs of ipsilateral extracranial vasodilatation. Our findings are consistent with a supra-spinal reflex, because noxious stimulation of the foot evoked the ipsilateral vasodilator response in extracranial blood vessels.

The neural pathway of this vasodilator reflex is unclear but may involve passage of nociceptive impulses through the midbrain periaqueductal gray. Stimulation of the lateral pretentorial periaqueductal gray evokes extracranial vasodilatation in association with hindlimb vasoconstriction (Carrive & Bandler, 1991), and triggers non-opioid analgesia and threat displays as part of a defense response in freely-moving cats (Abrahams et al., 1960; Bandler & Carrive, 1988; Bandler and Shipley, 1994). Thus, nociceptive impulses produced by exposure to painfully-cold water might generate this reflex. Alternatively, the extracranial nociceptive vasomotor reflex may originate in the locus coeruleus, a major brainstem pain modulation centre that exerts hemilateral inhibitory influences on nociceptive input in the dorsal horn and trigeminal nuclei (Tsuruoka & Willis, 1996a; Tsuruoka & Willis, 1996b; Tsuruoka et al., 1999; Tsuruoka et al., 2003; Knudsen & Drummond 2009; Knudsen & Drummond, in press). Electrical stimulation of the locus coeruleus evokes intracranial adrenergic vasoconstriction and extracranial trigeminal-parasympathetic vasodilatation (Goadsby et al., 1983; Goadsby et al., 1985). The extracranial vasodilator response to limb pain involves release of sympathetic vasoconstrictor tone (Drummond, 2006a), but whether the trigeminal-parasympathetic reflex also plays a role is unclear.

In conclusion, our findings indicate that immersion of the foot in painfully-cold water evokes ipsilateral increases in extracranial blood flow, possibly as part of a defense response to noxious stimulation. The vasodilator response appears to only partly overcome the inhibitory influence of sympathetic vasoconstrictor tone on facial blood flow. The asymmetry of the response implies the presence of a lateralized supra-spinal mechanism for processing and responding to noxious stimuli. Whether this mechanism contributes to unilateral extracranial vascular disturbances during attacks of migraine or cluster headache requires further investigation.

References

Abrahams, V. C., Hilton, S. M., & Zbrozyna, A. (1960). Active muscle vasodilatation produced by stimulation of the brain stem: its significance in the defence reaction. *J Physiol, 154*, 491-513.

Bandler, R., & Carrive, P. (1988). Integrated defence reaction elicited by excitatory amino acid microinjection in the midbrain periaqueductal grey region of the unrestrained cat. *Brain Res, 439*(1-2), 95-106.

Bandler, R., & Shipley, M. T. (1994). Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? *Trends Neurosci, 17*(9), 379-389.

Blair, D. A., Glover, W. E., & Roddie, I. C. (1961). Cutaneous vasomotor nerves to the head and trunk. *J. Appl. Physiol., 16*, 119-122.

Blessing, W. W. (2003). Lower brainstem pathways regulating sympathetically mediated changes in cutaneous blood flow. *Cell Mol Neurobiol, 23*(4-5), 527-538.

Blumberg, H., & Wallin, B. G. (1987). Direct evidence of neurally mediated vasodilatation in hairy skin of the human foot. *J Physiol, 382*, 105-121.

Carrive, P., & Bandler, R. (1991). Control of extracranial and hindlimb blood flow by the midbrain periaqueductal grey of the cat. *Exp Brain Res, 84*(3), 599-606.

Drummond, P. D. (1991). Effects of body heating and mental arithmetic on facial sweating and blood flow in unilateral migraine headache. *Psychophysiology, 28*(2), 172-176.

Drummond, P. D. (1999). Facial flushing during provocation in women. *Psychophysiology, 36*(3), 325-332.

Drummond, P. D. (2006a). Immersion of the hand in ice water releases adrenergic vasoconstrictor tone in the ipsilateral temple. *Auton Neurosci, 128*(1-2), 70-75.

Drummond, P. D. (2006b). Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache. *Cephalalgia, 26*(6), 633-641.

Drummond, P. D., & Finch, P. M. (1989). Reflex control of facial flushing during body heating in man. *Brain, 112 (Pt 5)*, 1351-1358.

Drummond, P. D., & Granston, A. (2003). Facilitation of extracranial vasodilatation to limb pain in migraine sufferers. *Neurology, 61*(1), 60-63.

Drummond, P. D., & Granston, A. (2004). Facial pain increases nausea and headache during motion sickness in migraine sufferers. *Brain, 127*(Pt 3), 526-534.

Drummond, P. D., & Lance, J. W. (1987). Facial flushing and sweating mediated by the sympathetic nervous system. *Brain, 110 (Pt 3)*, 793-803.

Fox, R. H., Goldsmith, R., & Kidd, D. J. (1962). Cutaneous vasomotor control in the human head, neck and upper chest. *J Physiol, 161*, 298-312.

Goadsby, P. J., Lambert, G. A., & Lance, J. W. (1983). Effects of locus coeruleus stimulation on carotid vascular resistance in the cat. *Brain Res, 278*(1-2), 175-183.

Goadsby, P. J., Lambert, G. A., & Lance, J. W. (1985). The mechanism of cerebrovascular vasoconstriction in response to locus coeruleus stimulation. *Brain Res, 326*(2), 213-217.

Hayashi, N., Someya, N., Maruyama, T., Hirooka, Y., Endo, M. Y., & Fukuba, Y. (2009). Vascular responses to fear-induced stress in humans. *Physiol Behav, 98*(4), 441-446.

Izumi, H. (1999). Nervous control of blood flow in the orofacial region. *Pharmacol Ther, 81*(2), 141-161.

Knudsen, L., & Drummond, P. D. (2009). Cold-induced limb pain decreases sensitivity to pressure-pain sensations in the ipsilateral forehead. *Eur J Pain, 13*(10), 1023-1029.

Knudsen, L., & Drummond, P. D. (in press). Cutaneous Limb Inflammation Produces Analgesia to Pressure Pain in the Ipsilateral Forehead of Healthy Volunteers. *J Pain*.

Licht, P. B., & Pilegaard, H. K. (2008). Management of facial blushing. *Thorac Surg Clin, 18*(2), 223-228.

Magerl, W., Geldner, G., & Handwerker, H. O. (1990). Pain and vascular reflexes in man elicited by prolonged noxious mechano-stimulation. *Pain, 43*(2), 219-225.

Magerl, W., Koltzenburg, M., Schmitz, J. M., & Handwerker, H. O. (1996). Asymmetry and time-course of cutaneous sympathetic reflex responses following sustained excitation of chemosensitive nociceptors in humans. *J Auton Nerv Syst, 57*(1-2), 63-72.

Roatta, S., Mohammed, M., & Passatore, M. (2009). Acute stress reduces blood flow in the orofacial area, in conscious rabbits. *Arch Oral Biol, 54*(4), 380-388.

Tsuruoka, M., Hitoto, T., Hiruma, Y., & Matsui, Y. (1999). Neurochemical evidence for inflammation-induced activation of the coeruleospinal modulation system in the rat. *Brain Res, 821*(1), 236-240.

Tsuruoka, M., Matsutani, K., & Inoue, T. (2003). Coeruleospinal inhibition of nociceptive processing in the dorsal horn during unilateral hindpaw inflammation in the rat. *Pain, 104*(1-2), 353-361.

Tsuruoka, M., & Willis, W. D., Jr. (1996a). Bilateral lesions in the area of the nucleus locus coeruleus affect the development of hyperalgesia during carrageenan-induced inflammation. *Brain Res, 726*(1-2), 233-236.

Tsuruoka, M., & Willis, W. D. (1996b). Descending modulation from the region of the locus coeruleus on nociceptive sensitivity in a rat model of inflammatory hyperalgesia. *Brain Res, 743*(1-2), 86-92.

Turpin, G., & Siddle, D. A. (1983). Effects of stimulus intensity on cardiovascular activity. *Psychophysiology, 20*(6), 611-624.

Figure legend

Figure 1. Change in the amplitude of vascular pulsations (± S.E.) in the fronto-temporal region before, during and after immersion of the left or right foot into ice water for 60 seconds for participants who received threatening or neutral instructions.