Immersion of the Hand in Ice Water Releases Adrenergic Vasoconstrictor Tone in the Ipsilateral Temple

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Abstract

Immersion of the hand in painfully-cold water induces cutaneous vasodilatation in the temples, more so ipsilaterally than contralaterally. To investigate the mechanism of this response, guanethidine or saline was administered by transcutaneous iontophoresis to a recording site in the temple of ten participants before they immersed one of their hands in ice water. Guanethidine displaces noradrenaline from sympathetic nerve terminals and inhibits sympathetic noradrenergic neurotransmission. Therefore, it was hypothesized that guanethidine pretreatment would block vasodilatation mediated by release of sympathetic vasoconstrictor tone in cutaneous vessels in the temple. During hand immersion, increases in the amplitude of the pulse waveform detected by laser Doppler flowmetry were greater in the ipsilateral than contralateral temple (86% versus 34% above baseline, $p<0.05$), and pretreatment with guanethidine prevented this asymmetric response (ipsilateral response 21% above baseline and contralateral response 32%, difference not significant). Guanethidine also inhibited ipsilateral increases in cutaneous blood flow during hand immersion in responsive participants. These findings suggest that limb pain inhibited ipsilateral adrenergic vasoconstrictor outflow in the temple. Thus, the findings challenge the concept of the sympathetic nervous system as a “mass action” system that discharges in unison to meet environmental demands. Instead, they suggest that the sympathetic nervous system is highly differentiated, with separate control of discrete reflex pathways on each side of the body.

Introduction

At least four neural mechanisms influence blood flow through the facial circulation of humans. First, sympathetic vasoconstrictor tone limits flow through superficial vessels in exposed parts of the face (particularly the ears, lips and nose, and less so in other parts of the face) (Fox et al., 1962; Drummond and Finch, 1989). Second, active sympathetic vasodilatation increases facial blood flow when body temperature rises and during emotions such as embarrassment (Drummond and Finch, 1989; Drummond and Lance, 1987). Third, irritation of the sensitive tissues of the eyes, nose and mouth triggers trigeminal-parasympathetic vasodilator reflexes that increase peri-oral and peri-ocular blood flow (Drummond, 1992; Izumi, 1999). Fourth, antidromic (axon reflex) release of vasoactive substances such as calcitonin gene-related peptide from trigeminal nerve terminals contributes to neurogenic vasodilatation in the facial skin (Drummond et al., 1983; Lambert et al., 1984; Goadsby et al., 1988).

The amplitude of the cutaneous pulse waveform increases in the temples during immersion of the hand in painfully-cold water (Drummond and Granston, 2003), indicating that limb pain induces extracranial vasodilatation. Curiously, this response is greater ipsilateral than contralateral to limb immersion, implying the involvement of one or more of the supra-spinal autonomic reflexes listed above.

The aim of the present study was to determine whether release of sympathetic vasoconstrictor tone contributes to extracranial vasodilatation during limb pain. To achieve this aim, guanethidine was administered by iontophoresis to a recording site in the temple before participants immersed their hand in painfully-cold water (the cold pressor test). Guanethidine displaces noradrenaline from sympathetic nerve terminals (Chang et al., 1965), and may also inhibit neural release of noradrenaline (Fabiani and

Story, 1996). Thus, it was hypothesized that guanethidine pretreatment would block extracranial vasodilatation mediated by release of sympathetic vasoconstrictor tone during the cold pressor test.

Method

Subjects

The sample consisted of six women and four men aged between 18 and 48 years (mean age ± S.D. 33.2 ± 12.7 years). Apart from oral contraceptives, none of the participants took prescribed medication for any medical condition. Each participant provided their informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee.

Procedures

The procedures were carried out in a temperature-controlled laboratory maintained between 20-22^{o}C. Participants attended the laboratory on two days separated by one week.

Purpose-built iontophoresis capsules (internal diameter 2 cm) were taped to the skin of the temples 1-2 cm above the level of the eyebrows and 3 cm in front of the ears. The ground electrode (a silver plate that covered gauze swabs soaked in saline) was taped to the centre of the forehead. On one occasion, the capsule ipsilateral to the hand to be used later for the cold pressor test contained 20 mM guanethidine hydrochloride (Sigma Chemical Company, Sydney, Australia) in de-ionized water, whereas the capsule on the contralateral temple contained 0.9% saline to control for any nonspecific effect of iontophoresis. A syringe attached to each capsule held a 2 mL reservoir of the solution. On the other occasion, both capsules contained 0.9% saline. Five of the ten participants received guanethidine on the first occasion. A constant current (0.1 mA) passed through the solution in each capsule for

30 minutes to repel positively-charged ions from the solution into the underlying skin. The dose of guanethidine delivered by this current completely blocks the local cutaneous vasoconstrictor effect of tyramine (which liberates neural stores of noradrenaline) for several days (Lipnicki and Drummond, 2001). Displacement of neural stores of noradrenaline by guanethidine is complete within three hours (McKain et al., 1983).

Four hours after the guanethidine or saline pretreatment, extracranial vascular responses to a cold pressor test were recorded. Probe holders for wide surface area laser Doppler flow probes were taped to the treated sites in the temples. Bilateral changes in skin blood flow before, during and after each cold pressor test were detected by an MBF3D laser Doppler flowmeter (Moor Instruments, Axminster, UK). Signals were sampled at 200 Hz by an MP100 data acquisition system (Biopac Systems Inc, Goleta, CA) and displayed and analyzed on a personal computer with Biopac AcqKnowledge software. After several minutes of stable vascular recordings, the participant immersed one hand to the wrist in water cooled to 2^{o}C (or 7^{o}C for one participant who could not tolerate the pain provoked by 2^{o}C water), and moved the hand around slowly for two minutes. Five participants immersed their dominant hand and the other five participants immersed their non-dominant hand. After the cold pressor test, the participant sat quietly for two minutes with his or her hand wrapped in a towel while vascular recordings continued.

Data reduction

A pulse waveform, representing the beat-by-beat difference between arterial inflow and venous outflow, was superimposed on the slowly changing component of the laser Doppler flux signal (Figure 1). Since gravitation and systemic factors such as cardiac output and blood pressure should exert symmetrical effects on arterial inflow

and venous outflow, asymmetrical changes in extracranial blood flow and pulse amplitude during the cold pressor test (Drummond and Granston, 2003) most likely reflect changes in regional vascular tone. Mean blood flow levels were averaged for five consecutive one-minute intervals starting one minute before the hand was immersed in the cold water (the baseline). To quantify the amplitude of the pulsatile component, frequencies below 0.5 Hz were digitally filtered to remove slow changes in blood flow. In addition, frequencies above 15 Hz were digitally filtered to remove electrical artifact. The peak-to-trough amplitude of the filtered pulse waveform was then calculated and averaged minute-by-minute.

Preliminary analyses indicated that blood flow and pulse amplitude (measured in arbitrary units) did not differ between the saline- and guanethidine-treated sites before the cold pressor test. Laser Doppler flow techniques detect relative changes in vascular activity but do not measure blood flow in absolute terms. Therefore, changes in blood flow and pulse amplitude during and after each cold pressor test were expressed as a percentage of levels recorded during the baseline. The effect of guanethidine on these vascular indices was investigated in Treatment (guanethidine, saline) x Side (ipsilateral or contralateral to pain) x Time (four consecutive minutes during and after the cold pressor test) repeated measures analyses of variance. Where necessary, degrees of freedom were adjusted with the Greenhouse-Geisser ε to correct for violations to the assumption of sphericity.

Results

An example of changes in blood flow in the temples during immersion of the right hand in cold water is shown in Figure 1. In this particular case, the cold pressor test provoked large increases in blood flow and pulse amplitude in the ipsilateral temple that were inhibited by the guanethidine pretreatment. There was considerable

individual variation in the magnitude of response among the ten participants. Nevertheless, as noted below, statistically significant effects of hand immersion and guanethidine pretreatment were identified in the group as a whole.

As shown in Figure 2, ipsilateral increases in pulse amplitude were greater than contralateral increases during the cold pressor test after the bilateral saline iontophoreses (Figure 2). Pretreatment with guanethidine blocked local ipsilateral increases in pulse amplitude during and after the cold pressor test [Treatment x Side x Time interaction, $F(1.7, 15.4)=6.30$, $p<0.05$] (Figure 2).

Blood flow asymmetry was less consistent than pulse amplitude asymmetry during the cold pressor test (Figure 3). Nevertheless, after the bilateral saline iontophoreses, blood flow increased by more than 100% in the ipsilateral temple during the cold pressor test in four of the ten participants. The increase was greater in younger than older participants [$r(8) = -0.78$, $p<0.01$], but was unrelated to the participant's gender, whether the right or left hand was immersed, or whether the saline pretreatment was administered on the first or second occasion. In the four most responsive participants, pretreatment with guanethidine inhibited the ipsilateral increase in temple blood flow (Figure 4).

Discussion

The main finding was that guanethidine pretreatment blocked signs of ipsilateral extracranial vasodilatation provoked by immersing the hand in painfully-cold water. Guanethidine displaces noradrenaline from sympathetic nerve terminals (Chang et al., 1965) and inhibits sympathetic noradrenergic neurotransmission (Fabiani and Story, 1996). Thus, the reduction in response after guanethidine administration implies that vasodilatation was mediated by sympathetic vasoconstrictor neurons that employ noradrenaline as a neurotransmitter. As

sympathetic adrenergic neurons apply a tonic vasoconstrictor influence on cutaneous vessels in the face (Drummond and Finch, 1989), release of this vasoconstrictor tone apparently contributed to extracranial vasodilatation during the cold pressor test.

Limb immersion in ice water triggers sympathetic vasoconstrictor discharge in the extremities, which reduces cutaneous blood flow (Fagius and Blumberg, 1985) and increases blood pressure in proportion to muscle sympathetic nerve activity (Fagius et al., 1989). The combination of a vasoconstrictive response in the limbs and an increase in facial blood flow is reminiscent of the pattern of vascular response during emotions such as anger and embarrassment (Drummond, 1997; Drummond, 1999), and also resembles the response evoked by microinjections of the synaptic excitant D,L homocysteic acid into the pretentorial part of the lateral periaqueductal gray of decerebrate cats (Carrive and Bandler, 1991). The extracranial vasodilator response to midbrain stimulation forms part of a threat display characterized behaviourally in cats by vocalizations such as hissing and howling and by facing and backing away from the source of threat or pain (Bandler and Shipley, 1994). This behavioural display is a component of the “confrontational defense reaction” to attack that also involves increases in blood pressure due to widespread sympathetic discharge. Noxious cutaneous stimulation excites cells within the lateral periaqueductal gray (Keay and Bandler, 1993). In turn, injection of excitatory amino acids into this part of the periaqueductal gray produces non-opioid-mediated antinociception in association with defensive behaviours and hypertension (Bandler and Shipley, 1994).

The mechanism of extracranial vasodilatation during confrontational defense reactions to threat and pain is uncertain. Parasympathetic neurons that project from the inferior and superior salivatory nuclei in the facial and glossopharyngeal nerves to

the sphenopalatine and otic ganglia form the efferent limb of trigeminal-parasympathetic vasodilator reflexes (Izumi, 1999). These reflexes can be evoked by stimulation of brainstem centres such as the nucleus raphe dorsalis and locus coeruleus (Goadsby et al., 1984; Goadsby et al., 1985a; Goadsby et al., 1985b), which communicate closely with neurons in the periaqueductal gray. Parasympathetic vasodilator reflexes might contribute to vasodilatation around the mouth and eyes during defense reactions. However, some other mechanism must mediate pain-evoked extracranial vasodilatation in regions of the face not supplied with parasympathetic vasodilator fibres (Drummond, 1992; Izumi, 1999). Preganglionic and postganglionic lesions in the cervical sympathetic pathway inhibit increases in facial blood flow during body heating and embarrassment (Drummond and Lance, 1987), suggesting that heightened sympathetic discharge during social threat contributes actively to extracranial vasodilatation. An emotional response to pain, or pain itself, might evoke a similar response. In addition, the present findings indicate that pain triggers the release of sympathetic vasoconstrictor tone in extracranial vessels.

The asymmetry of the extracranial vascular response suggests the involvement of lateralized neural pathways. After they enter the spinal cord, most nociceptive signals ascend contralaterally in multiple spinal pathways to the thalamus, to autonomic centres such as the parabrachial nucleus, and to pain modulation centres in the rostroventral medulla, caudal pons and midbrain periaqueductal gray (Millan, 1999). Neurons from the parabrachial nucleus project to the amygdala and hypothalamus, which regulate autonomic responses to pain via programmes in the periaqueductal gray that exert opposing influences on extracranial and limb blood flow (Carrive and Bandler, 1991). The present findings suggest that a decrease in

sympathetic vasoconstrictor outflow to the extracranial vasculature contributes to ipsilateral extracranial vasodilatation during cold-pain.

The magnitude of extracranial vasodilatation to cold-pain varied markedly among individual participants, possibly because of age-related variation in tonic vasoconstrictor discharge. Indeed, pilot studies on a few individuals in our laboratory indicated that vasodilatation to limb pain was minimal when the cold pressor test was administered during body heating (unpublished observations). These observations are consistent with reports that vasoconstrictor tone is weak and variable in most parts of the face except the nose, lips and ears (Fox et al., 1962).

Implications

Before the 1970's, the sympathetic nervous system was generally regarded as a "mass action" system that discharged in unison to meet the demands of exercise, changes in posture, the thermal environment, and psychological stress. However, this concept was revised when microelectrode recordings in conscious humans demonstrated a difference in the pattern of sympathetic neural discharge to muscle and skin (Delius et al., 1972; Hagbarth et al., 1972). In particular, sympathetic neural discharge to muscle was found to be associated with baroreflex activity whereas arousal, emotions and changes in environmental temperature evoked sympathetic neural discharge in cutaneous nerves.

The present findings suggest that the concept of "mass action" requires further revision to recognize lateralized sympathetic reflex activity to nociceptive stimulation. Although not widely acknowledged as a general characteristic of the sympathetic nervous system, bilateral asymmetry in indices of sweating and blood flow seems to be typical rather than atypical of healthy humans (Varni et al., 1971). Autonomic innervation of organs such as the heart is asymmetric, as is cortical control of

autonomic activity (Craig, 2005). Rhythmic changes in congestion and decongestion of opposing nostrils may reflect alternating lateralized autonomic influences on the nasal microcirculation; furthermore, lateralized influences on sweating and skin colour have been described in relation to posture, asymmetry of cerebral hemisphere activity, and psychological state (Shannahoff-Khalsa, 1991; Hugdahl, 1984). Merely staring at one side of the face increases blood flow on that side of the face, even when staring through a glass window from an adjacent room (Drummond and Mirco, 2004). Importantly, Magerl et al. (1996) reported that sympathetic vasoconstrictor reflexes to sustained nociceptive stimulation of the forearm were greater in the ipsilateral than contralateral hand. Although Magerl et al. (1996) attributed the asymmetry of this response to a segmental somatosympathetic reflex, the present findings suggest the involvement of a lateralized supraspinal reflex.

These observations support the notion that the sympathetic nervous system is highly differentiated, and that distinct patterns of reflex activity to different effector organs can be modulated at various points along discrete functional pathways from the brain to the periphery (Jänig and McLachlan, 1999). Furthermore, they point to separate control of these reflex pathways on each side of the body. This may be important for the pathophysiology of painful disorders such as migraine and complex regional pain syndrome, which appear to involve asymmetry of autonomic tone (Avnon et al., 2004; Baron et al., 2002).

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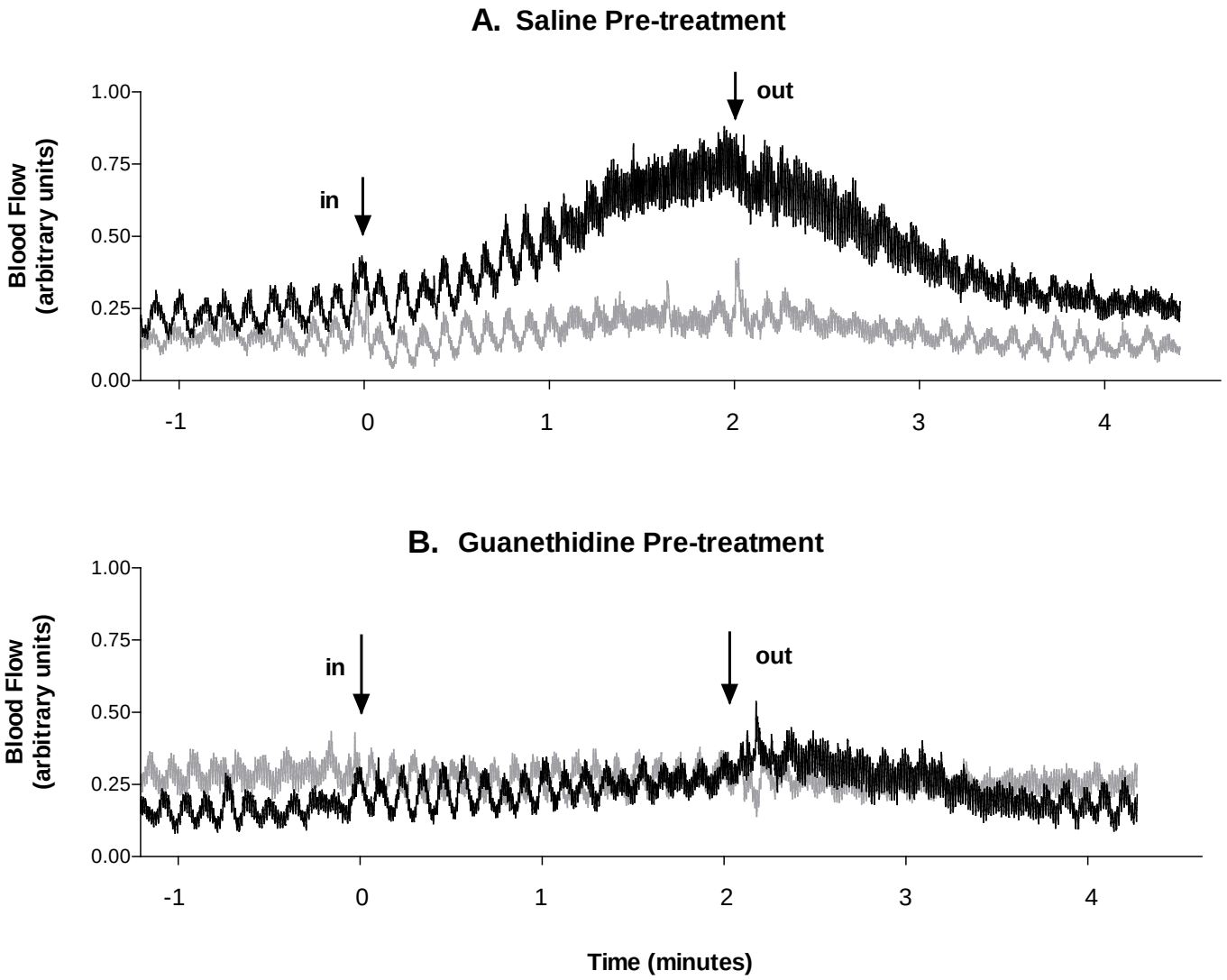
Figure legends

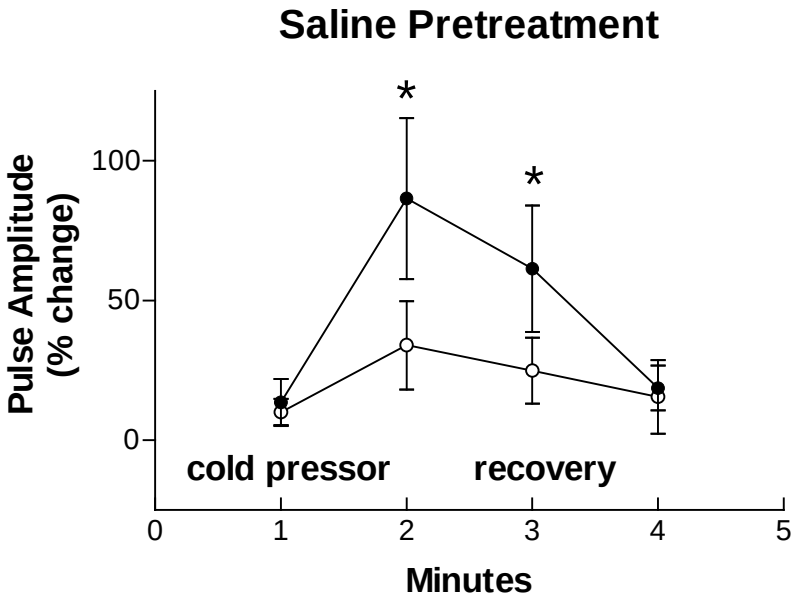
Figure 1. Effect of immersing the right hand in 2^{o}C water for two minutes on blood flow in the right temple (black waveform) and left temple (grey waveform) after bilateral saline pre-treatment (**A**), and after guanethidine pre-treatment to the right temple and saline pre-treatment to the left temple (**B**). The hand was immersed in the water at the arrow marked "in", and removed from the water at the arrow marked "out". The cold-pain-induced increase in blood flow in the right temple after saline pretreatment was inhibited by guanethidine pretreatment. Pulse amplitude (indicated by the thickness of the blood flow signal) also increased in the right temple after saline pretreatment, and this response was inhibited by guanethidine pretreatment.

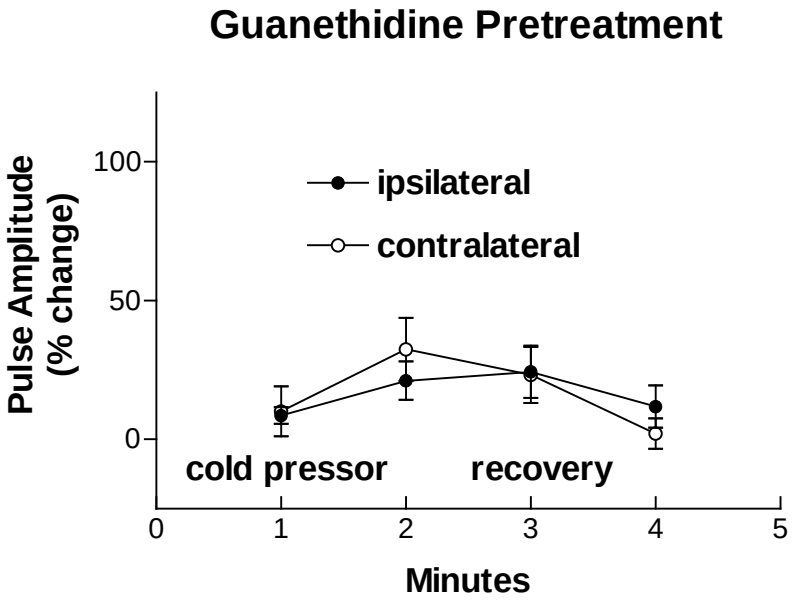
Figure 2. Change in pulse amplitude in both temples during and after immersion of one hand in ice-water. The hand was immersed in the water at Time 0, and taken out two minutes later. Increases in pulse amplitude were greater in the ipsilateral than contralateral temple after bilateral saline iontophoreses (*$p<0.05$). Pre-treatment with guanethidine inhibited the ipsilateral component of response.

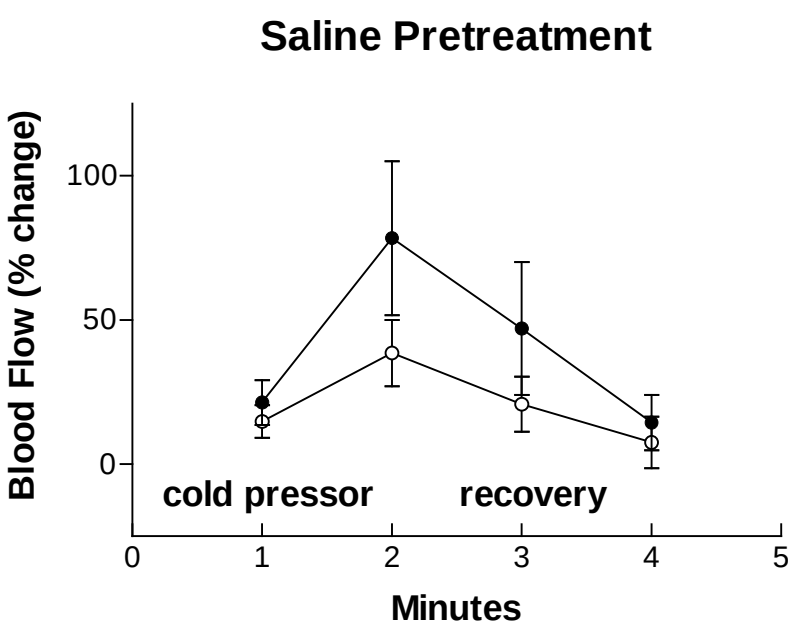
Figure 3. Change in blood flow in both temples during and after immersion of one hand in ice-water for two minutes.

Figure 4. Pain-induced increases in blood flow in the ipsilateral temple after saline and guanethidine pretreatment. Guanethidine pretreatment inhibited increases in blood flow during the cold pressor test in four responsive participants.


A. Saline Pre-treatment
Blood Flow (arbitrary units)
1.00
0.75
0.50
0.25
0.00
in
out
-1
0
1
2
3
4
B. Guanethidine Pre-treatment
Blood Flow (arbitrary units)
1.00
0.75
0.50
0.25
0.00
in
out
-1
0
1
2
3
4
Time (minutes)


Saline Pretreatment
Pulse Amplitude (% change)
100
50
0
*
*
cold pressor
recovery
0
1
2
3
4
5
Minutes


Guanethidine Pretreatment
Pulse Amplitude (% change)
100
50
0
ipsilateral
contralateral
cold pressor
recovery
0
1
2
3
4
5
Minutes


Saline Pretreatment
Blood Flow (% change)
100
50
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cold pressor
recovery
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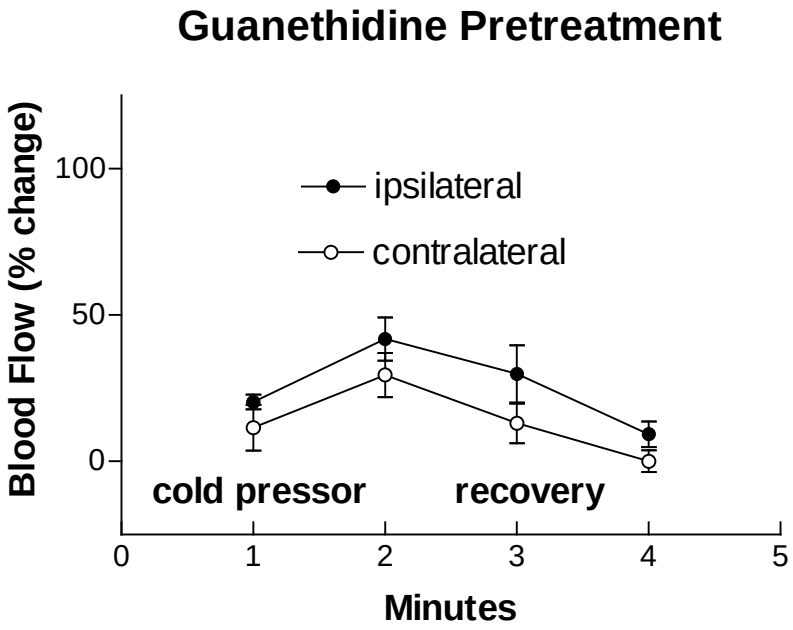
Minutes


Guanethidine Pretreatment
Blood Flow (% change)
100
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ipsilateral
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cold pressor
recovery
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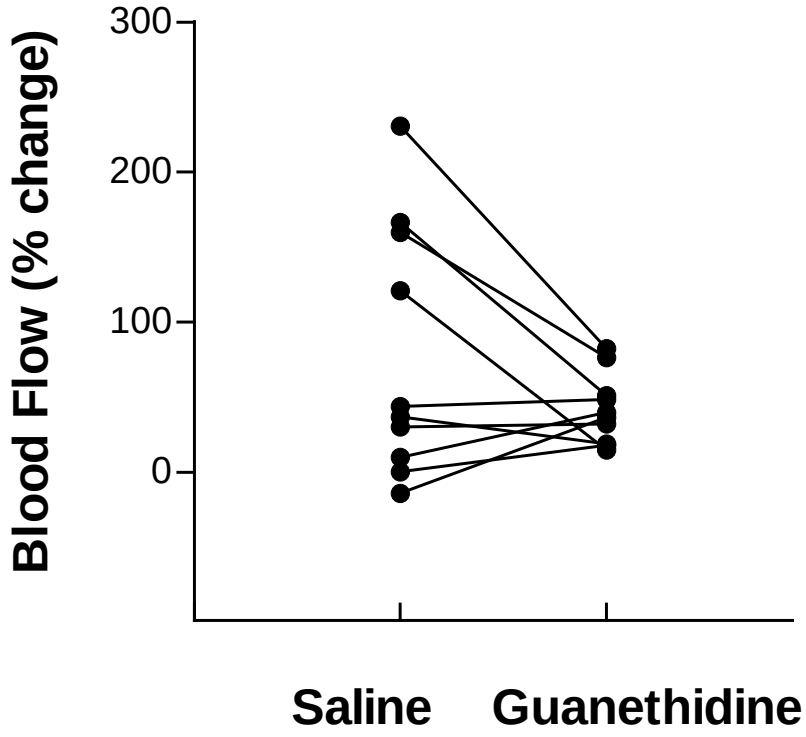
Minutes


Blood Flow (% change)
300
200
100
0
Saline
Guanethidine