ELSEVIER

European Journal of Pharmacology 328 (1997) 41–44

ejp

Short communication

Nociception from blood vessels is independent of the sympathetic nervous system under physiological conditions in humans

Detlef Kindgen-Milles *, Holger Holthusen

Heinrich-Heine-Universität Düsseldorf, Institut für Experimentelle Anaesthesiologie, Gebäude 23.02.01, Postfach 10 10 07, D-40001 Düsseldorf, Germany

Received 6 February 1997; revised 9 April 1997; accepted 11 April 1997

Abstract

To test the hypothesis that vascular pain depends on sympathetic drive under physiological conditions we studied the effects of both α-adrenoceptor stimulation by noradrenaline and α-adrenoceptor blockade by phentolamine on the intensity of physicochemically evoked pain from veins in humans. In seven healthy volunteers, a vascularly isolated hand vein segment was perfused continuously with noradrenaline (6×10^{-9}–6×10^{-6} M), or phentolamine (1.24×10^{-4} M). Pain was evoked by intraluminal electrostimulation or by injection of hyperosmolar saline during control perfusion of isoosmolar saline and after each noradrenaline concentration, as well as after perfusion of phentolamine. Subjects rated pain intensity continuously on an electronically controlled visual analogue scale (VAS) between 0% VAS (no pain) and 100% VAS (tolerance maximum). Intravenous electrostimulation as well as hyperosmolar solutions evoked pain in each subject. The intensity of pain was neither influenced by noradrenaline, nor by phentolamine, so that nociception from blood vessels is unlikely to be modulated by the sympathetic nervous system under physiological conditions in humans.

Keywords: Pain; Vein; Noradrenaline; Phentolamine; (Human)

1. Introduction

In certain pain syndromes, pain depends on sympathetic drive, as is evidenced by experiments in which α-adrenoceptors were either stimulated or blocked. Intracutaneous application of noradrenaline, for instance, induces thermal hyperalgesia, aggravates ongoing pain, and can even evoke strong pain requiring pain-relieving treatment (Torebjörk et al., 1995). Accordingly, regional anaesthesia of sympathetic ganglia (Bonica, 1990), catecholamine depletion by guanethidine (Wahren et al., 1991), or systemic α- but not β-adrenoceptor blockade (Raja et al., 1991) alleviates pain in these syndromes. From such observations, it was concluded that the sympathetic nervous system via α-adrenoceptor action modulates nociception at least in pathological pain states (Campbell et al., 1992).

However, it is currently not known whether such a functional link also exists under physiological conditions in humans. In animals, the influence of sympathetic drive on nociception from skin, muscles and pulpa is rather low (Jänig and Koltzenburg, 1992) and, if present, even inconsistent. Sympathetic stimulation of C-polymodal nociceptors in the rabbit pinna, for instance, lowers the firing threshold to heat but not to noxious pressure (Barasi and Lynn, 1986). Surprisingly, however, nociceptors of blood vessels have never been tested for dependency on sympathetic activity, neither in animals nor in humans, although such a link appears a natural option for the following reasons. First, in blood vessels, which are the main target organ for sympathetic nerve fibers, efferent and afferent nerve endings are in close vicinity (Pletchkova and Khaisman, 1976). Second, sympathetic stimulation still increases the spike activity from other receptors in blood vessels, e.g., from mechanoreceptors in the aorta or carotid artery (Kunze et al., 1984; Munch et al., 1987). Finally, in certain chronic pain states, pain increases with increasing intravascular pressure (Jänig and Koltzenburg, 1992), which also points to a link between the sympathetic nervous system and nociception from blood vessels.

Superficial hand veins of humans are well suited to test this hypothesis, as their sensory innervation subserves

* Corresponding author. Tel.: (49-211) 81-13610; Fax: (49-211) 81-13954.

nociception exclusively (Arndt and Klement, 1991) and as they are substantially innervated by sympathetic efferents (Arneklo-Nobin and Owman, 1985). Furthermore, their vasomotor response to noradrenaline has been shown to be increased in certain pain syndromes (Arnold et al., 1993) indicating the ability of receptors of veins to change sensitivity to noradrenaline in response to pain. Therefore, to look for a physiological link between the sympathetic nervous system and vascular nociception we evaluated the effect of both α-adrenoceptor stimulation and blockade on pain from superficial hand veins in healthy humans.

2. Materials and methods

Seven healthy men volunteered and consented to this study, which was performed in accordance with the recommendations of the declaration of Helsinki and approved by the Institutional Committee of Medical Ethics. The subjects were studied on two different days (at least 2 weeks apart) depending on the kind of stimulation. Each experiment started at 9.00 a.m. with the subjects sitting semi-recumbent in an easy chair at a thermoneutral ambient temperature of 24°C.

A vein segment on the dorsum of the hand was cannulated from distal and proximal between two valves (Venflon, outer diameter 2.0 mm; Ohmeda, Helsingborg, Sweden) and, for blood-free perfusion, vascularly isolated by fastening external occluders of foam rubber on the puncture sites (Arndt and Klement, 1991). For applying either hyperosmolar saline or electrostimuli, a single-lumen catheter (Cavafix, Braun Melsungen, Germany) or a bipolar stimulation catheter with circular platinum-iridium electrodes (Vygon, Aachen, Germany) was advanced via the distal cannula into the segment.

After isolation of the segment, either noradrenaline was perfused at increasing concentrations between 6×10^{-9} and 6×10^{-6} M, each for 10 min, or phentolamine at 1.24×10^{-4} M for 20 min. At the end of each perfusion period either hyperosmolar saline (4000, 5000 mosM; 1 ml) or electrostimuli (rectangular pulses of constant current, duration 2 ms, frequency 20 Hz, impulse strength 1.5, 3.0, 4.5 mA, randomised order) were tested for their pain-evoking property.

The subjects rated pain intensity continuously with the help of an electronic visual analogue scale (VAS) between threshold and individual tolerance maximum by moving the handle of a linear potentiometer from the left (0 V corresponding to 0% VAS = no pain) to the right (10 V = 100% VAS = maximal tolerable pain). Voltages, proportional to pain intensities, were continuously recorded on a Gould TA 550 Polygraph. Maxima of pain intensity were extracted from these recordings and tested for difference using the Wilcoxon-rank-sum test (level of significance $P < 0.05$).

3. Results

Neither noradrenaline nor phentolamine changed pain from veins in humans regardless of whether pain was evoked by electrostimulation or hyperosmolar saline. The lack of effect of adrenoceptor stimulation by noradrenaline to influence pain from veins is shown by the pain intensity/concentration curves in Fig. 1 (mean ± standard deviation). In each subject, electrostimuli intravenously applied during the control perfusion of isoosmolar saline evoked pain of low, medium and high intensity corresponding to the stimulus strength of 1.5, 3.0 and 4.5 mA (Fig. 1A). Pretreatment of the vein segment with noradrenaline between 6×10^{-9} M and 6×10^{-6} M did not change pain ratings, neither on stimulation near threshold nor near tolerance maximum. Likewise, chemically induced pain by hyperosmolar saline was not influenced by noradrenaline treatment (Fig. 1B).

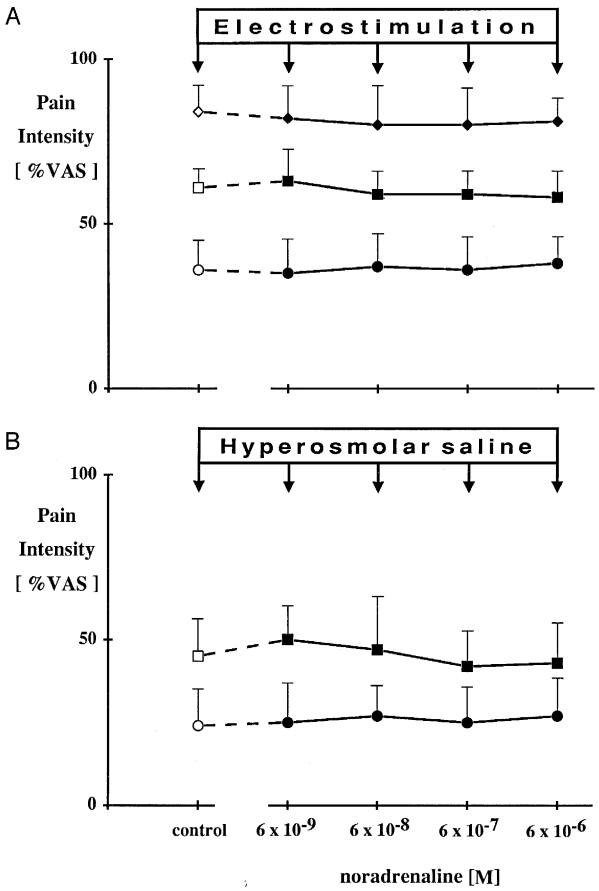

Fig. 1. Maximum pain intensities after application of electrostimuli (A) or hyperosmolar saline (B) to vascularly isolated human hand vein segments in relation to α-adrenoceptor stimulation by noradrenaline ($n = 7$; mean ± S.D.). Pain evoked by intravenously applied electrostimuli (1.5 mA: ●, 3.0 mA: ■, 4.5 mA: ♦) or hyperosmolar saline (4000 mosM: ●, 5000 mosM: ■) was not changed by pretreatment with noradrenaline (perfusion of 6×10^{-9}–6×10^{-4} M for 15 min; filled symbols); 'control' = application of isoosmolar saline (open symbols).

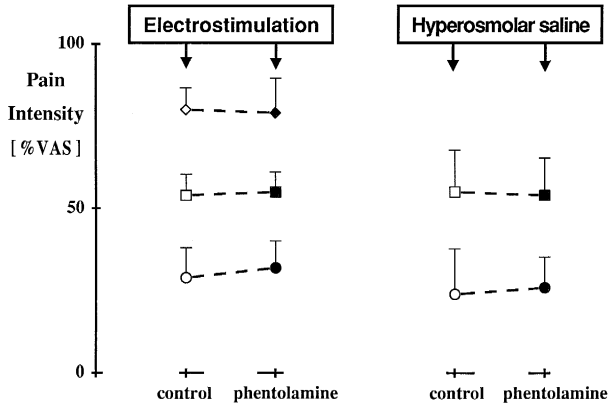

Fig. 2. Maximum pain intensities after application of electrostimuli or hyperosmolar saline to human hand veins in relation to α-adrenoceptor blockade by phentolamine ($n = 7$; mean ± S.D.). Pain evoked by intravenously applied electrostimuli (1.5 mA: ●, 3.0 mA: ■, 4.5 mA: ♦) or hyperosmolar saline (4000 mosM: ●, 5000 mosM: ■) was not changed by pretreatment with phentolamine (perfusion of 1.24×10^{-4} M for 20 min; filled symbols); 'control' = application of isoosmolar saline (open symbols).

Finally, blockade of α-adrenoceptors by phentolamine at a concentration of 1.24×10^{-4} M had no significant effect on pain from veins evoked by electrostimulation or hyperosmolar saline (Fig. 2).

Noradrenaline and phentolamine never evoked pain per se.

4. Discussion

Neither stimulation by noradrenaline nor blockade by phentolamine of α-adrenoceptors changed pain from superficial hand veins in humans. Therefore, the sympathetic nervous system does not influence vascular nociception under physiological conditions.

Pain, in our experiments, undoubtedly originated from stimulation of venous nociceptors, since pain is the only sensation to be evoked by intravenous application of various kinds of stimuli including electrostimuli and hyperosmolar saline regardless of the state of innervation of the surrounding tissue (Arndt and Klement, 1991). Both noradrenaline and phentolamine ought to have reached venous nociceptors in our experiments, since on intravenous application both drugs obviously act on vascular smooth muscles (Arnold et al., 1993) and thus on structures far beyond the venous nociceptors, which are sandwiched between the smooth muscle and the endothelial layer (Flöel and Staubesand, 1978). Because of the small diffusion distance of only a few micrometers, concentrations at the nociceptors should have been by and large equal to those applied, particularly after perfusion periods of 10 min (Arndt et al., 1993). Additionally, the noradrenaline concentrations applied exceeded by far those reached endogenously, even under extreme conditions (Hörnchen et al., 1992), and the phentolamine concentrations needed for effective α-adrenoceptor blockade (Raja et al., 1991), respectively. Finally, intravascularly applied noradrenaline at similar concentrations has been shown to exert direct excitatory and inhibitory effects on other receptors in the vessel wall (Munch et al., 1987). In conclusion, our approach was appropriate to stimulate venous nociceptors exclusively and for the drugs applied to reach the nociceptors at pharmacologically active concentrations. Therefore, α-adrenoceptor modulation of nociception from intact veins should have been detectable, if present. However, neither stimulation nor blockade of α-adrenoceptors changed pain from veins.

This result is in parallel with experiments on nociception from skin in animals. Noradrenaline, for instance, although physiologically modulating the sensitivity of cutaneous mechanoreceptors (Kissin et al., 1987), does not change responsiveness of cutaneous nociceptors unless the skin area stimulated is inflamed (Sato et al., 1993), or has been injured (Sato and Perl, 1991). In humans, sympathectomy does not alter acute pain from skin on injection of bradykinin (Raja, 1995), whereas after tissue trauma or during inflammation, intracutaneously applied noradrenaline aggravates mechanical and thermal-induced pain (Torebjörk et al., 1995; Drummond, 1995). Thus, a preceding trauma or onset of inflammation is apparently the crucial step for cutaneous nociceptors to become sensitive to the α-adrenergic action of drugs, whereas in normal skin, sympathetic influence on nociception is negligible. Our observations suggest that the same holds true also for nociceptors of blood vessels. It is not clear, whether α-adrenoceptors are resident at nociceptors or nociceptive afferents, but are unresponsive unless the tissue milieu has changed in the wake of injury or inflammation, or whether there is a de novo synthesis of α-adrenoceptors (Jänig and Koltzenburg, 1992). The time course of sensitization and the de novo synthesis of opiate receptors during inflammation (Stein, 1993) likely point to the latter possibility.

However, regardless of the exact mechanism of how the sympathetic nervous system gains access to nociceptive input during pathological pain states, our results show for the first time that there is no α-adrenoceptor modulation of nociception from normal veins in humans.

Acknowledgements

The support of the Deutsche Forschungsgemeinschaft (Ar 64/8-1) is gratefully acknowledged. We also thank Professor Dr. J.O. Arndt (Department of Experimental Anaesthesiology, Heinrich-Heine-University) for his advice.

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