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Response of Rabbit Ear and Femoral Arteries to 5-Hydroxytryptamine During Cooling

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Abstract

The effects of cooling on the response of cutaneous and non-cutaneous arteries to 5-hydroxytryptamine (5-HT) were analysed.

Segments 2-mm long from rabbit central ear (cutaneous) and femoral (non-cutaneous) arteries were prepared for isometric tension recording in an organ bath at 37 and 24°C (cooling). 5-HT (10^{-9}–3×10^{-4} M) induced concentration-dependent contraction of the arteries. The sensitivity and maximal contraction of ear arteries and only the maximal contraction of femoral arteries to this amine were reduced at 24°C.

Endothelium removal or pretreatment with the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME, 10^{-5} M) did not affect the response at 37°C but reversed the decreased sensitivity at 24°C in ear arteries, and neither procedure modified the reactivity at 24 or 37°C in femoral arteries to 5-HT. At both temperatures, the response of ear arteries to 5-HT was shifted to the right by phentolamine (10^{-6} M) more than by the 5-HT antagonist, ketanserin (3×10^{-7} M), and that of femoral arteries was shifted to the right by ketanserin or the 5-HT_1/5-HT_2 antagonist methysergide (3×10^{-7} M) more than by phentolamine, in arteries with and without endothelium.

These data concur with the proposition that the contraction to 5-HT is mediated mainly by α-adrenergic receptors in ear arteries and mainly by 5-HT-ergic receptors in femoral arteries, and suggest that cooling reduces the sensitivity of cutaneous, but not of deep arteries to 5-HT, probably by endothelium-nitric oxide-dependent mechanisms.

The vascular actions of 5-hydroxytryptamine (5-HT) seem to depend on the location and type of vessel, and in many blood vessels this amine can produce constriction by activation of 5-HT_2 or 5-HT_1 receptors, by direct activation of α-adrenergic receptors (Black et al 1981), as well as by releasing noradrenaline from adrenergic nerves (Garrison 1990). Also, the role of the endothelium in the vascular effects to 5-HT seems to vary with the type of vessel (Houston & Vanhoutte 1988; Nyborg & Mikkelsen 1990; Schoeffter & Hoyer 1990; Foy et al 1992; Seager et al 1992). Experiments on the effects of 5-HT on cutaneous blood vessels have shown that this amine induces contraction of human hand veins by activation of the 5-HT_2-receptor subtype (Bodelsson et al 1990), contraction of rabbit (Van Heuven-Nolsen et al 1990) and dog (Feniuk et al 1985) saphenous veins by activation of the 5-HT_1-like-receptor subtype, and contraction of rabbit ear arteries mainly by stimulation of α-adrenergic receptors (Apperley et al 1976).

In cutaneous blood vessels it appears that cooling specifically alters the contraction to adrenergic activation (Vanhoutte & Flavahan 1986; Gómez et al 1991; García-Villalón et al 1992) and to endothelin-1 (Monge et al 1991) as well as the relaxation to cholinergic stimulation (Monge et al 1993). Some of these studies (Monge et al 1991, 1993; García-Villalón et al 1992) suggest that the effects of cooling on reactivity of cutaneous vessels are dependent on endothelial nitric oxide. The effects of cooling on the cutaneous vascular response to 5-HT remain elusive. It has been reported that cooling increases the constriction of dog cutaneous veins to 5-HT (Vanhoutte & Shepherd 1970) and that the cooling-increased contraction to 5-HT in rabbit tibial arteries (Van Neuten et al 1984) and in human hand veins (Bodelsson et al 1990) are inhibited by ketanserin (a 5-HT_2-receptor antagonist). From studies in the rat jugular vein, Bodelsson et al (1989) suggest that the increased effects of cooling on the response to 5-HT depend on the endothelium. As 5-HT has been involved in pathophysiology of some vascular diseases, such as cold-induced cutaneous vasoconstriction (i.e. Raynaud's phenomenon) (Seibold 1985), and the plasma levels of this amine are increased in Raynaud patients (Reilly et al 1986), studies for examining the effects of cooling on the response of cutaneous arteries to 5-HT could be of interest.

The present experiments were mainly designed to study the effects of moderate cooling on the response of cutaneous and non-cutaneous arteries to 5-HT, with analysis of the role of the endothelium in these effects. To achieve this, central ear and femoral arteries from rabbits were mounted in an organ bath at 37 and 24°C (cooling), and the response to 5-HT was isometrically recorded in arteries with and without endothelium or treated with an inhibitor of nitric oxide synthesis. The response of the arteries to this amine was also tested in the presence of phentolamine (10^{-6} M), ketanserin (3×10^{-7} M) or methysergide (3×10^{-7} M) to examine the possible role of α-adrenergic mechanisms and subtype of 5-HT-ergic receptors involved in the 5-HT-induced contraction at both temperatures. The central ear

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artery is a superficial artery that is easily accessible and used as a model of cutaneous blood vessels (Patton & Wallace 1978; Roberts & Zygmunt 1984; Harker & Vanhoutte 1988).

Materials and Methods

Nineteen male New Zealand White rabbits, 2–2·5 kg, were killed by intravenous injection of sodium pentobarbitone (100 mg kg^{-1}). Central ear and femoral arteries were dissected free and cut into cylindrical segments 2 mm in length. Each segment was prepared for isometric tension recording in a 6-mL organ bath containing modified Krebs–Henseleit solution with the following composition (mM): NaCl 115, KCl 4·6, KH_2PO_4 1·2, $MgSO_4$ 1·2, $CaCl_2$ 2·5, $NaHCO_3$ 25, glucose 11·1. The solution was equilibrated with 95% O_2 and 5% CO_2 to give a pH of 7·3–7·4. Briefly, the method consists of passing two fine, stainless-steel pins, 150 μm in diameter, through the lumen of the vascular segment. One pin is fixed to the organ bath wall while the other is connected to a strain gauge for isometric tension recording, thus permitting the application of passive tension in a plane perpendicular to the long axis of the vascular cylinder. The recording system included a Universal Transducing Cell UC3 (Statham Instruments, Inc.), a Statham Microscale Accessory UL5 (Statham Instruments, Inc.) and a Beckman Type RS Recorder (model R-411, Beckman Instruments, Inc.). A resting tension of 0·5 g was applied to the tissue and the segments were allowed to equilibrate for 60–90 min before any drug was added.

Part of the ear and femoral arteries were kept in the bath at a temperature of 37°C throughout the experiment, and the others were kept at 24°C (cooling). In some of the arterial segments, at 37 or 24°C, the endothelium was removed before mounting the vessels in the organ bath. The removal of the endothelium was accomplished by gently rubbing the lumen of the vessel with a roughened steel rod. The presence of the endothelium in non-rubbed arteries as well as the adequacy of endothelium removal in rubbed arteries was functionally tested by recording the response to acetylcholine (10^{-6} M) in arteries precontracted with 5-HT (10^{-6} M), and at the end of the experiments by morphological observation after en-face silver staining. In non-rubbed, intact arteries acetylcholine produced relaxation and exhibited more than 60–70% of the luminal surface covered by endothelium. In rubbed arteries, acetylcholine did not cause any response and exhibited less than 5% of the luminal surface covered by endothelium.

Cumulative concentration-response curves for 5-HT (10^{-9}–3×10^{-4} M) were determined in central ear and femoral arteries with and without endothelium, under resting conditions at 37°C and at 24°C. To analyse the possible role of α-adrenergic receptors, as well as the subtype of 5-HT-ergic receptors involved in the response to 5-HT, responses to this amine were determined in the presence of the α-adrenergic antagonist phentolamine (10^{-6} M), of the 5-HT_2-receptor antagonist ketanserin (3×10^{-7} M), or of methysergide (3×10^{-7} M), an antagonist for both 5-HT_1 and 5-HT_2 receptors.

To analyse the possible role of nitric oxide in the vascular response, concentration-response curves to 5-HT were also performed in ear and femoral arteries in the presence of N^G-nitro-L-arginine methyl ester (L-NAME, 10^{-5} M), a nitric oxide-synthase inhibitor (Moore et al 1990; Rees et al 1990) at 37 and 24°C. This drug was added to the bath 30 min before the beginning of the experiments.

To test the functional status of the vascular segments used, the contraction in response to potassium chloride (50 mM) was recorded in both types of arteries, with and without endothelium, at 37 and at 24°C.

Concentrations of 5-HT causing 50% of the maximal response (EC50) were calculated from each individual concentration-response curve under the different conditions, and the geometric mean of EC50 and its 95% confidence interval was obtained for each group of experiments. At 37 and 24°C the logarithms of the EC50 value obtained in vascular segments with or without endothelium, and in the presence of L-NAME or the adrenergic or 5-HT-ergic antagonists were compared statistically. The data are expressed as means ± s.e.m., and were evaluated by analysis of variance applied to each group of data, followed by Student-Newman-Keuls test to compare each experimental condition with its control. $P < 0.05$ was considered significant.

Drugs used were: 5-HT, creatinine sulphate (Sigma, St Louis, MO), phentolamine hydrochloride (Sigma), L-NAME (N^G-nitro-L-arginine methyl ester hydrochloride, Sigma), ketanserin (Sigma) and methysergide bimaleate (Sandoz Pharmaceuticals, Hanover, NJ).

Results

Ear arteries

Response to potassium chloride. Potassium chloride contracted ear arteries in every experimental condition tested. In intact arteries, this contraction was lower at 24°C (0·9 ± 0·05 g, $P < 0.001$) than at 37°C (1·9 ± 0·1 g). Removal of the endothelium did not modify the contraction to potassium chloride at 37°C ($P > 0.05$), but it increased the contraction at 24°C (1·3 ± 0·09 g, $P < 0.001$) compared with intact arteries at the same temperature.

Response to 5-HT. The effects of 5-HT on ear arteries with and without endothelium at 37 and 24°C are summarized in Fig. 1. At 37°C, 5-HT (10^{-9}–3×10^{-4} M) produced a concentration-dependent contraction that was similar in intact arteries (EC50 = 2.0×10^{-6} M, 95% confidence interval = 9.9×10^{-7}–4.2×10^{-6} M; maximal contraction = 3·2 ± 0·14 g) and in arteries without endothelium (EC50 = 2.2×10^{-6} M, 95% confidence interval = 1.2×10^{-6}–3.9×10^{-6} M; maximal contraction = 3·3 ± 0·13 g) ($P > 0.05$).

During cooling, the sensitivity of intact arteries (EC50 = 8.5×10^{-6} M, 95% confidence interval = 3.3×10^{-6}–2.2×10^{-5} M) was 25% ($P < 0.05$), and the maximal effect (2·5 ± 0·14 g) was 80% ($P < 0.01$) the value at 37°C. At 24°C, ear arteries without endothelium were more sensitive (3·2 times, $P < 0.05$) than intact arteries, and the maximal contraction was similar in intact and endothelium-deprived ear arteries to 5-HT. At 37°C ear arteries pretreated with L-NAME (10^{-5} M) exhibited a comparable response ($P > 0.05$) with non-treated arteries, whereas at 24°C, treatment with L-NAME induced a parallel leftward shift

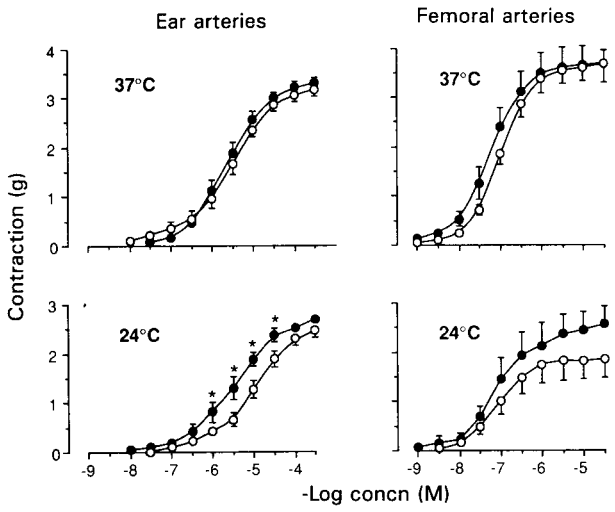

FIG. 1. Contractile response to 5-HT of rabbit ear (left panels) and femoral (right panels) arteries with (○) and without (●) endothelium at 37°C (upper panels) and at 24°C (lower panels). Data are means ± s.e. from 10–15 animals. *$P < 0.05$ compared with arteries with endothelium.

(9·6 times, $P < 0.05$) of the concentration-response curve to 5-HT in comparison with non-treated arteries (Fig. 2). Thus, endothelium removal or treatment with L-NAME reversed the reduced sensitivity of control arteries at 24°C and the response of the arteries without endothelium or treated with L-NAME was similar at 37 and 24°C.

At 37°C, phentolamine (10^{-6} M) shifted to the right in a parallel way (19 times) the concentration-response curve to 5-HT, and at 24°C, it depressed the contraction to this amine (Fig. 3).

Ketanserin (3×10^{-7} M) produced a parallel rightward shift of the concentration-response curve to 5-HT which was similar at 37 and 24°C, both in intact arteries (7·1 times at 37°C, and 5·1 times at 24°C) and in arteries without

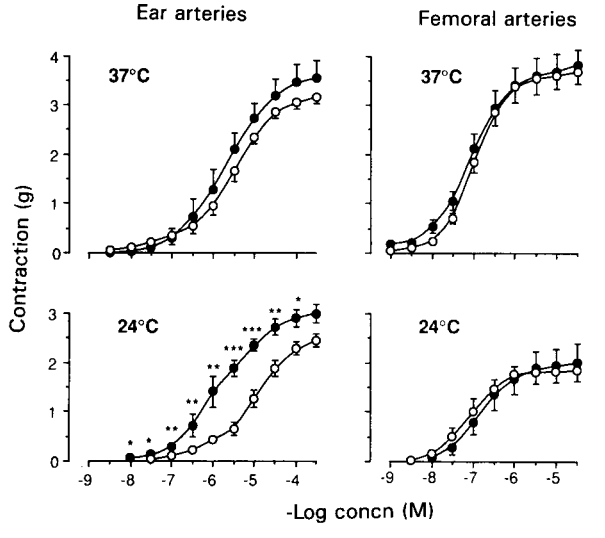

FIG. 2. Contractile response to 5-HT of rabbit ear (left panels) and femoral (right panels) arteries in the absence (○) and in the presence (●) of L-NAME (10^{-5} M) at 37°C (upper panels) and at 24°C (lower panels). Data are means ± s.e. from 6–7 animals. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with control.

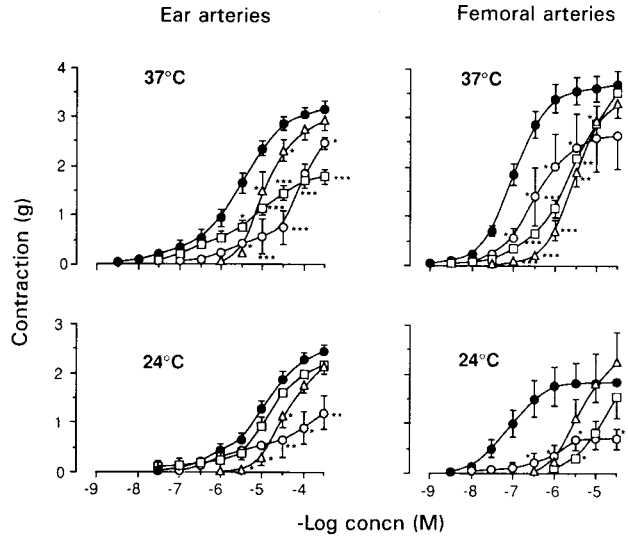

FIG. 3. Contractile response to 5-HT of rabbit ear (left panels) and femoral (right panels) arteries in the absence (●) and in the presence of phentolamine (10^{-6} M, ○), methysergide (3×10^{-7} M, □) or ketanserin (3×10^{-7} M, △), at 37°C (upper panels) and at 24°C (lower panels). Data are means ± s.e. from 4–7 animals. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with control.

endothelium (6·4 times at 37°C, and 6·8 times at 24°C) (Fig. 3).

Methysergide (3×10^{-7} M) by itself contracted intact arteries (1·6 ± 0·24 g) and arteries without endothelium (2·4 ± 0·16 g) at 37°C, but it did not produce any effect in the arteries at 24°C. At 24°C, methysergide (3×10^{-7} M) did not affect the response, and at 37°C it only reduced the maximal response to 5-HT, both in arteries with (1·8 ± 0·15 vs 3·2 ± 0·14 g) and without endothelium (1·5 ± 0·12 vs 3·3 ± 0·13 g) (Fig. 3).

Femoral arteries

Response to potassium chloride. The contraction to potassium chloride (50 mM) in intact femoral arteries was also lower at 24°C (2·5 ± 0·16 g) than at 37°C (3·7 ± 0·16 g). At 37 and 24°C, the response to potassium chloride in the arteries without endothelium was not significantly different from that in intact arteries.

Response to 5-HT. This amine (10^{-9}–3×10^{-4} M) induced contraction of intact femoral arteries in a concentration-dependent manner. At 37°C, intact femoral arteries showed a higher sensitivity (EC50 = $1·2 \times 10^{-7}$ M, 95% confidence interval = $8·8 \times 10^{-8}$–$1·6 \times 10^{-7}$ M) and similar maximal contraction (3·7 ± 0·27 g) than intact ear arteries (Fig. 1). Cooling (24°C) reduced the maximal effect (1·9 ± 0·39 g) and did not modify the sensitivity ($8·1 \times 10^{-8}$ M, 95% confidence interval = $2·6 \times 10^{-8}$–$2·6 \times 10^{-7}$ M) of intact femoral arteries as compared with 37°C.

At 37 or 24°C, endothelium removal did not modify the sensitivity or the maximal effect to 5-HT in femoral arteries. Likewise, the response of femoral arteries to 5-HT was similar in the absence and in the presence of L-NAME (10^{-5} M), both at 37 and 24°C (Fig. 2).

Phentolamine (10^{-6} M) shifted to the right the concentration-response curve and reduced the maximal contraction to

5-HT (Fig. 3). The shift induced by phentolamine was not significantly different at 37 and at 24°C either in intact arteries (3·6 times at 37°C, and 9·8 times at 24°C) or in arteries without endothelium (6·0 times at 37°C, and 5·7 times at 24°C).

Ketanserin (3×10^{-7} M) shifted to the right in a parallel way the concentration-response curve to 5-HT and this shift was significantly greater than that produced by phentolamine. In intact arteries, ketanserin shifted the response to 5-HT 27 times at 37°C and 123 times at 24°C, and in arteries without endothelium it shifted the response 31·6 times at 37°C and 41·3 times at 24°C (Fig. 3).

Methysergide (3×10^{-7} M) by itself contracted femoral arteries at 37°C ($0{\cdot}93 \pm 0{\cdot}14$ g in intact arteries and $1{\cdot}3 \pm 0{\cdot}12$ g in arteries without endothelium), but did not affect them at 24°C. In arteries with and without endothelium, methysergide (3×10^{-7} M) shifted to the right in a parallel way the concentration-response curve to 5-HT, and this shift was higher at 24°C (270 times for arteries with, and 245 times in the arteries without endothelium) than at 37°C (21·5 times for arteries with, and 44·6 times in the arteries without endothelium) (Fig. 3).

Discussion

Our results at 37°C show that ear (cutaneous) and femoral (non-cutaneous) arteries of rabbits contract to 5-HT, and that the sensitivity of ear arteries is lower than that of femoral arteries. The results with ketanserin (antagonist for 5-HT_2 receptors), methysergide (antagonist for 5-HT_1 and 5-HT_2 receptors) and phentolamine suggest that some differences in the mechanism involved in the 5-HT-induced constriction between both types of arteries exist. In ear arteries, phentolamine and ketanserin shifted to the right the response to 5-HT, but at the concentration used, phentolamine was more effective than ketanserin. Methysergide by itself produced contraction of ear arteries, probably by acting as a partial agonist of 5-HT-ergic (Parsons et al 1989) or α-adrenergic (Apperley et al 1976) receptors, and it reduced the maximal contraction without modifying the sensitivity to 5-HT. This effect of methysergide on the response to 5-HT in ear arteries could be caused by functional antagonism rather than by a competitive blocking effect of methysergide on the 5-HT-ergic receptor. Thus, these results concur with observations in this type of artery which suggest that the contractile response of ear arteries to 5-HT could be mainly mediated by stimulation of α-adrenergic receptors on the smooth muscle, with little or no contribution of the 5-HT_1 or 5-HT_2 5-HT-ergic receptors (Apperley et al 1976). Although ketanserin is considered as an antagonist of 5-HT_2 receptors, its blocking effect on the observed response of ear arteries to 5-HT could be related to the affinity of ketanserin for α-adrenergic receptors (Leysen et al 1981). We tested in ear arteries that ketanserin (3×10^{-7} M) was effective in competitively blocking the response to noradrenaline (10^{-9}–10^{-3} M; not shown).

In femoral arteries, ketanserin and methysergide at the concentrations used were more effective than phentolamine for blocking the constriction to 5-HT. Thus, as methysergide and ketanserin seem to have a higher affinity for the 5-HT_1- and 5-HT_2-receptor subtypes, respectively (Bradley et al 1986), our results in femoral arteries are in agreement with the idea that the response of this type of artery to 5-HT could be mediated mainly by 5-HT_1 and 5-HT_2 receptors (MacLennan & Martin 1992). The observation that phentolamine also reduced the constriction of femoral arteries to 5-HT agrees with that reported previously by others who suggest that this amine may also stimulate α-adrenoceptors in this particular type of artery (Black et al 1981).

With regard to the precise type of receptors involved in the constriction of ear and femoral arteries to 5-HT our study is incomplete and more studies are needed to clarify this issue. Experiments using receptor antagonists complemented with a set of 5-HT-ergic agonists could provide a more clear differentiation of receptors involved in vascular response to 5-HT (Martin & MacLennan 1990).

With regard to the role of the endothelium, we found at 37°C that neither endothelium removal nor L-NAME modified the response of ear and femoral arteries to 5-HT. This suggests that in these arteries the response to 5-HT at physiological temperatures is not modulated by the endothelium or by nitric oxide. Published data indicate that the effects of endothelium on the vascular response to 5-HT differ with the type of vessel. Although the contraction of pig and dog coronary arteries to 5-HT can be reduced by endothelium-dependent mechanisms (Cocks & Angus 1983), the 5-HT-ergic contraction of bovine coronary arteries (Foy et al 1992) or human hand veins (Bodelsson et al 1990) is endothelium-independent. When it exists, the mechanism of endothelial modulation also varies with the type of vessel. In pig (Molderings et al 1989; Schoeffter & Hoyer 1990) and dog (Houston & Vanhoutte 1988) coronary arteries there are 5-HT-ergic receptors of the 5-HT_1 subtype present in the endothelial cells, which stimulate the release of nitric oxide, whereas in rat coronary artery (Nyborg & Mikkelsen 1990), and in rabbit (Trezise et al 1992) and dog (Connor & Feniuk 1989) basilar artery the inhibitory effect of the endothelium to the 5-HT response does not seem to be mediated by 5-HT-ergic receptors and could be due to the existence of a basal release of nitric oxide.

The main objective of the present study was to examine the effect of cooling on the response of ear and femoral arteries to 5-HT, paying special attention to the role of the endothelium in this effect. Cooling affected the contraction of ear and femoral arteries to 5-HT in a different way, as it decreased both the sensitivity and the maximum in ear arteries and decreased only the maximum in femoral arteries to this amine. The mechanisms that are involved in the inhibitory effects of cooling on the 5-HT-induced contraction may also differ between these arteries. In ear arteries the inhibition by cooling could be, at least in part, mediated by an endothelium-dependent mechanism, because removal of the endothelium reversed the reduced effects of 5-HT at 24°C. Treatment of the ear arteries with the nitric oxide-synthase inhibitor L-NAME also reversed the reduced effects of 5-HT at 24°C, suggesting that endothelial nitric oxide could be involved in the inhibition during cooling. The reduction in the maximal contraction of ear arteries to 5-HT during cooling may be endothelium-independent, as this reduction by cooling was comparable in

the arteries with and without endothelium, so that cooling may have also a direct inhibitory effect on the smooth muscle when activated with 5-HT. In femoral arteries, cooling reduced the maximal response to 5-HT without changing the EC50 values, and this effect of cooling was similar in the arteries with and without endothelium. These results suggest that in femoral arteries, cooling reduces the contractility to 5-HT by directly depressing the contraction of the smooth muscle, without involvement of the endothelium.

Thus, cooling could inhibit cutaneous vasoconstriction to 5-HT by endothelial nitric oxide-dependent mechanisms, and it also could depress the contractility of cutaneous and non-cutaneous arteries to this amine by acting directly on vascular smooth muscle. This latter action could be an unspecific effect of cooling on vessels as it was also found in ear and femoral arteries when activated with potassium chloride. This feature has been previously reported (Vanhoutte & Flavahan 1986; Monge et al 1993). Our results also suggest that cooling does not affect the sensitivity or affinity of either α-adrenergic receptors or 5-HT_2 receptors to 5-HT in ear and femoral arteries. This suggestion is based on the observation that the sensitivity to 5-HT of ear or femoral arteries without endothelium, or treated with L-NAME, was similar at 37 and at 24°C, and cooling did not affect the blocking effect of phentolamine and ketanserin in either type of arteries as compared with 37°C. We also found that methysergide was more effective at 24°C than at 37°C for antagonizing the response of femoral arteries, but not of ear arteries to 5-HT. The interpretation of this latter observation is difficult, and our data about the effects of cooling on the sensitivity or affinity of 5-HT receptors for agonists and antagonists are not sufficient to draw a definitive conclusion, as the effects of cooling may be related to the efficacy or lipophilicity of agonists and antagonists (see the references in Prentice et al (1991)). Studies on rabbit saphenous veins show that cooling increases affinity of both 5-HT_1-like and 5-HT_2 receptors for 5-HT, but does not alter affinity of these receptors for antagonists and the authors suggest that these different effects of cooling could be related to the different lipophilicity of the agonists and antagonists used (Prentice et al 1991).

It has been reported that cooling can increase the vascular constriction to 5-HT (Vanhoutte & Shepherd 1970; van Nueten et al 1984; Bodelsson et al 1989, 1990). In rabbit tibial arteries (Van Nueten et al 1984) and human hand veins (Bodelsson et al 1990) the potency of 5-HT_2 receptors was increased by cooling, and in human hand veins this phenomenon was endothelium-independent (Bodelsson et al 1990). In the rat jugular vein it has been shown that cooling decreases the relaxation and increases the contraction induced by 5-HT by endothelial mechanisms (Bodelsson et al 1989). In that study the authors suggest that cooling decreases the effectiveness of 5-HT in stimulating the release of EDRF from the endothelium which, in addition to reducing the endothelium-mediated relaxation, contributed to the augmented contraction of the rat jugular vein to this amine during cooling. The discrepancy between that study (Bodelsson et al 1989) and ours may be related to the different way in which cooling affects the venous and arterial endothelium, or to species differences.

Our results with 5-HT agree with previous findings from our laboratory that cooling reduces the contraction of ear arteries, but not of femoral arteries from rabbits to endothelin-1 (Monge et al 1991) and adrenergic stimulation (García-Villalón et al 1992) by endothelial nitric oxide mechanisms. We have also reported that cooling increases the relaxation of ear arteries but not of femoral arteries to cholinergic stimulation by facilitating the stimulated release of endothelial nitric oxide (Monge et al 1993). Thus, cooling might facilitate the release of nitric oxide by the endothelium of cutaneous vessels when activated with constrictor or relaxing substances. This increased release of nitric oxide would inhibit the cutaneous vasoconstriction during cooling to different substances, including 5-HT as suggested from the present study. This effect of cooling might be specific for cutaneous vessels since it has not been observed in femoral arteries, a deep vessel. With the present results we can speculate that in pathological conditions in which a lesion of the vascular endothelium is present, 5-HT might contribute to development of cold-induced cutaneous vasospasm such as Reynaud's phenomenon.

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