Effects of Sympathectomy on Endothelin-1 and Histamine Responses of Rabbit Carotid Artery

T. Utkan,* T. Kaya and Y. Sarioglu

DEPARTMENT OF PHARMACOLOGY, FACULTY OF MEDICINE, CUMHURIYET UNIVERSITY, SIVAS, TURKEY

ABSTRACT. 1. The effects of chronic sympathectomy on contractile responses of rabbit common carotid artery were studied in vitro.
2. Endothelin-1 (ET-1), histamine, KCl and papaverine concentration–response curves of sympathectomized and sham-operated (control) vessels were recorded and analyzed. Effects of endothelium removal also were investigated.
3. The contractions elicited by ET-1 and histamine in sympathectomized preparations did not change when compared with controls. Papaverine, which produces endothelium-independent relaxation, and KCl, which produces endothelium-independent contraction, did not differ from controls. No significant difference was observed between the contractile responses of sympathectomized vessels and those of control vessels to ET-1 and histamine after the removal of endothelium.
4. These results indicate that chronic sympathectomy did not affect the sensitivity to exogenous ET-1 and histamine of the vascular smooth muscle.

KEY WORDS. Sympathectomy, endothelin-1, histamine, carotid artery, rabbit

INTRODUCTION

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by vascular endothelial cells (Tanagisawa et al., 1988). Its plasma levels are very low in normal subjects but are augmented in many disease states such as in certain patients with hypertension (Loscher et al., 1992) and cerebral vasospasm (Masaoka et al., 1989), suggesting that it may play a pathophysiological role in these situations. Factors contributing to the development and maintenance of cerebral vasospasm include changes in the sensitivity of cerebral arteries to vasoactive substances such as noradrenaline, serotonin and ET-1 (Alabadi et al., 1994; Alafaci et al., 1990; Lobato et al., 1980; Sahlin et al., 1990). It is also known that histamine produces contractions in cerebral arteries (White et al., 1975). However, mechanisms underlying the development of the chronic cerebral vasospasm remain uncertain, and definitive therapy to prevent or reverse the arterial narrowing is not yet available. Cervical or periartrial sympathectomy are occasionally used in the prophylaxis or treatment of vasospasm and chronic occlusive cerebrovascular disease (Yasargil, 1984). Chronic sympathectomy of the common carotid artery in rabbit has been shown to affect both contractile function and endothelium-dependent relaxation (Kars et al., 1993), and it is of interest to determine if the contractile responses to ET-1 and histamine following sympathectomy differ from those of the normally innervated arteries. The present work was therefore undertaken to determine the long-term effects of cervical and periartrial sympathectomy on ET-1- and histamine-induced contractions in both endothelium-intact and endothelium-denuded common carotid arteries of rabbit.

MATERIALS AND METHODS

Albino rabbits of either sex weighing 2.5–3.0 kg were used. Animals in the experimental group (n=10) were subjected to right cervical sympathetic chain excision and periartrial sympathectomy of the right common carotid artery. Rabbits were anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg) and were allowed to breathe spontaneously. The cervical sympathetic chain, including all the ganglia, was excised. Periartrial sympathectomy of the common carotid artery was performed and the adventitia was sheared. Rabbits in the control group (n=10) were subjected to a sham operation. Removal of the sympathetic chain was confirmed by microscopic examination. The right carotid artery was excised in its full length on the 21st postoperative day in the experimental group and in the control group. The artery was removed rapidly, then cut into rings and placed in Krebs-Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.7; NaHCO3, 24.9; KHPO4, 1.2; CaCl2, 1.6; MgSO4, 1.2 and glucose, 11.1. Concentration-response curves for ET-1 and histamine were obtained by cumulatively increasing the total concentration of each drug in the bath. Isometric tension was recorded on a Grass model 79E polygraph with the use of Grass FT03 force-displacement transducers. Endothelium was destroyed mechanically by cotton thread rubbing. The integrity of the endothelium was checked functionally by the presence or absence of acetylcholine-induced relaxation in endothelium-denuded arterial preparations. For the relaxation studies, arterial tone was first increased with 80 mM KCl to a submaximal level, after which 10−5–10−4 M papaverine was added in a cumulative fashion. The relaxations induced by papaverine were expressed as a percentage of the tonic phase of contraction induced by KCl.

Drugs

Endothelin-1, acetylcholine chloride, papaverine hydrochloride, phenylephrine hydrochloride, histamine dihydrochloride were purchased from Sigma Chemical Company, St. Louis, MO, USA.

Data analysis

The data were expressed as means±standard error of the mean (SEM). Statistical comparisons between responses of rings in the
presence of different drugs and with and without endothelium were made by using Student's t-test. P value of <0.05 was considered significant.

RESULTS

Acetylcholine produced concentration-dependent relaxation of both sham-operated and sympathectomized arteries with intact endothelium. This effect was abolished in both vessels by removal of the endothelium. ET-1 produced concentration-dependent contractions at $10^{-10}$--$10^{-8}$ M. The ET-1-induced contraction of rabbit carotid artery rings is long lasting and difficult to wash out. Histamine ($10^{-8}$--$10^{-4}$ M) did not relax but contracted common carotid arteries under resting conditions or when partially contracted with submaximal concentrations of phenylephrine. ET-1, and histamine-induced contractions were not changed by sympathectomy in arterial rings obtained from the rabbits (Fig. 1). Endothelium removal did not cause a significant change in the contraction responses caused by histamine and ET-1 when compared with endothelium-intact control rings (Fig. 2). Sympathectomy and endothelium removal did not cause a significant change in KCl-induced contraction and papaverine-induced relaxation of the arterial preparations (Fig. 3).

DISCUSSION AND CONCLUSION

ET-1 is a potent vasoconstrictor peptide produced by vascular endothelial cells (Yanagisawa et al., 1988). Two endothelin receptors that mediate the vascular effects of ET-1 have been characterized. ET$_A$ receptors appear to be present mainly on vascular smooth muscle cells, mediating the vasoconstrictor effects of ET-1, whereas ET$_B$ receptors on the vascular endothelium mediate the transient vasodilator response to ET-1 and ET-3 (De Nucci et al., 1988; Dohi et al.
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1992). Histamine is stored in secretory granules of mast cells (Edvinsson, 1976) and blood vessels (Abboud et al., 1982). According to our findings, histamine produces contractions in the rabbit carotid arteries and both ET-1-induced and histamine-induced contractions do not require intact endothelium.

It is known that sympathectomy produces structural and functional changes in the cerebral arteries. Muscular hypertrophy with increased protein synthesis in the arterial wall after sympathectomy has been reported by Dimitridou et al. (1988). However, it is generally believed that denervation of smooth muscle produces little morphological change (Thonen and Tranzer, 1963). In this study, papaverine-induced endothelium-independent relaxation and KCl-induced contraction responses in the isolated rabbit carotid artery were not significantly altered after sympathectomy. Therefore, our results remove the possibility of functional and morphological damage on smooth muscle cells following sympathectomy within 3 weeks. An increase in the contractility of isolated arteries was reported by some authors (Aubineau et al., 1993; Bevan and Tsurow, 1981), and this phenomenon observed after sympathectomy is explained by denervation hypersensitivity. Supersensitivity to sympathetic mimetic amines can occur through pre- and postjunctional changes (Fleming, et al., 1973; Trendelenburg, 1986). Prejunctional supersensitivity describes the potentiation that occurs after any procedure that results in a greater concentration of agonist at the receptor sites, such as inhibition of monoamine oxidase (MAO) or catechol-o-methyltransferase (COMT) and extraneuronal or neuronal inhibition. Postjunctional supersensitivity describes the potentiation that occurs after any procedure that results in a change in the number of adrenoceptors or a change that occurs at some point beyond the receptor level (Fleming et al., 1973). In our preliminary studies, the denervated carotid artery showed an increased sensitivity to exogenous noradrenaline and serotonin as well as a decreased sensitivity to acetylcholine (Kars et al., 1993), which is in agreement with other authors (Mangiarua and Bevan, 1986).

In conclusion, the present experiments demonstrate that ET-1- and histamine-induced contractions are endothelium independent and chronic sympathectomy does not affect the sensitivity to exogenous ET-1 and histamine of the vascular smooth muscle. These findings, observed after sympathectomy in arterial rings in vitro, justify a more critical approach to cervical or periarterial sympathectomy.

References


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