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THE EFFECT OF TAURINE ON HIGH POTASSIUM- AND NORADRENALINE-INDUCED CONTRACTION IN RABBIT EAR ARTERY

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1 Intraluminal administration of taurine (40 mM) did not affect the contractile tone of rabbit isolated ear artery.

2 Taurine (10–80 mM) exerted a powerful concentration-dependent, vasodilator action in arteries contracted with high potassium medium.

3 In the same experimental conditions, the taurine analogues β-alanine and homotaurine, had no effect.

4 Taurine (40–80 mM) did not affect in a significant manner the tonic component of the noradrenaline (5×10^{-6} M)-induced contraction.

5 When noradrenaline (5×10^{-6} M) was followed by the administration of high potassium medium a further increase in intraluminal pressure was observed. Under these conditions taurine (40 mM) reversed specifically the component due to the high potassium medium.

Introduction

Taurine is a sulphonic amino acid the biological roles of which are uncertain (Blaschko, 1980) apart from its actions in biliary salt formation (Jacobsen & Smith, 1968), in cat retina neurones (Berson, Hayes, Rabin, Schmidt & Watson, 1976; Sturman, Rassin, Hayes & Gaull, 1978; Schmidt & Berson, 1978) and in epilepsy (Van Gelder, 1972; Perry, Hansen & Kennedy, 1975).

Taurine has been extensively studied for its action on the cardiovascular system, but attention has been focused chiefly on its effect on cardiac contractility (Dietrich & Diacono, 1971; Guidotti, Badiani & Giotti, 1971; Bandinelli, Franconi, Giotti, Martini, Monetti, Stendardi & Zilletti, 1981). The positive inotropic effect of taurine seems to depend on a variation in the calcium available for contraction (Schaffer, Kramer & Chovan, 1980). In some strains of rat, taurine administration also produces a highly significant reduction in the development of hypertension (Nara, Yamori & Lovenberg, 1978), and it has in fact been suggested as a possible new treatment in this disease (Schaffer & Kocsis, 1979). Moreover, taurine has been proposed for the therapy of arterial spastic diseases (Becattini, 1967); but information as to its effect on vascular smooth muscle is not yet available. We therefore decided to study both the action of taurine as such and its interference with noradrenaline- and/or high potassium-induced contraction, on preparations of rabbit isolated ear artery.

Methods

Preparation of rabbit ear artery

Male New Zealand rabbits, weighing 2.5–3.0 kg, were anaesthetized with urethane (1.5 g/kg, i.p.) and heparinized (1000 iu, i.v.). A 3 cm segment of central ear artery was dissected, cleaned of its periarterial connective tissue and transferred immediately to an oxygenated salt solution. The arterial segment was cannulated at both ends with polyethylene tubing so that the intraluminal perfusate did not mix with the extraluminal fluid. The preparation was placed in a 15 ml organ bath through which an extraluminal bathing solution flowed continuously at a rate of 8 ml/min and a temperature of 37°C; constant bath volume was maintained by overflow drainage. The artery was perfused internally with a physiological salt solution delivered by a De Saga 131900 peristaltic pump at a constant rate of 5 ml/min.

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Recording of mechanical response

The contractile tone of the artery was measured indirectly as change in intraluminal perfusion pressure by a Statham T/1/1A pressure transducer connected with a preamplifier and a Battaglia-Rangoni PFP/2400/A recorder. At basal conditions the intraluminal pressure was 23.6 ± 1.7 mmHg ($n = 70$).

Experimental procedure

An equilibration period of 60 min was allowed before starting the experiments. Then the intraluminal perfusion fluid was replaced by one containing noradrenaline (5×10^{-6} M) or with KCl (54 mM) (Figure 1). When the tonic component of contraction was stable (usually after less than 10 min of perfusion with noradrenaline or high potassium) the drugs under study were administered intraluminally (Figure 1). Usually their effects were followed for at least 30 min, a period sufficient to reach a steady state.

In a second set of experiments, the intraluminal administration of noradrenaline (5×10^{-6} M) was followed by perfusion with a solution containing noradrenaline plus KCl (54 mM) and then the activity of taurine was tested (Figure 1).

At the end of each experiment the artery was perfused with the standard solution.

The integrity of the artery was checked by an intraluminal perfusion with Trypan blue solution (0.01%) at the end of washing, and the presence of this compound in the extraluminal compartment was checked by spectrophotometry.

Solutions

Krebs solution of the following composition was used (mM): NaCl 119, KCl 4.7, $MgSO_4$ 1.5, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25 and glucose 11. The solution was gassed with 95% (v/v) O_2 and 5% (v/v) CO_2, its pH was 7.3–7.4 and its temperature 37°C ± 0.7.

Isotonic high potassium (54 mM) solution was obtained by replacement of NaCl with an equimolar amount of KCl. In order to avoid any change in osmolarity the standard solution contained sucrose at the same concentration as the tested drug.

Ascorbic acid (0.05 mg/ml) was added to the solutions containing noradrenaline.

Drugs

The sources of drugs used were as follows: (−)-noradrenaline bitartrate (Fluka AG. Buchs S.G., Switzerland), β-alanine, taurine, $NaNO_2$ (E. Merck; Darmstedt, Germany); verapamil hydrochloride was a kind gift from Knoll AG., Ludwigshafen, Germany and homotaurine from Prof. A. Adembri.

Statistical methods

All results are expressed as the difference between intraluminal pressure measured and relative basal pressure. Mean values are given ± s.e.mean. Statistical evaluation of results was by Student's t test for paired samples for determining the statistical significance of difference between mean values. The 0.05 level of probability was regarded as significant.

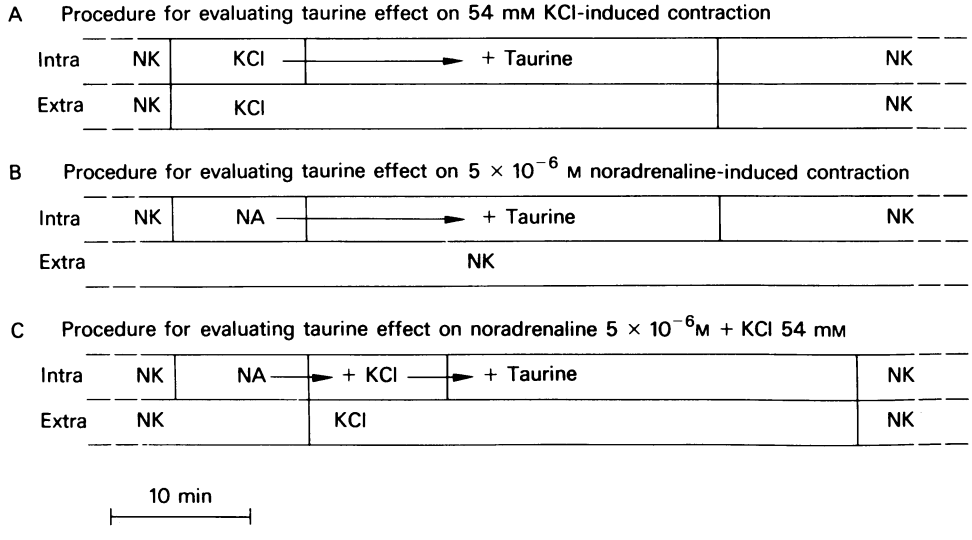

Figure 1 Experimental procedure for different experiments. Note that intraluminal (Intra) perfusion of noradrenaline, KCl (54 mM) or taurine once started was continued through the remainder of the experiment until the wash with normal Krebs. NK = normal Krebs solution, NA = noradrenaline.

Treated and control arteries were considered paired because they were removed from the same animals. Linear regression was calculated by the method of least squares.

Results

Effect of taurine

Intraluminal perfusion of taurine (40 mM) for up to 45 min did not produce any change in the resting tone of rabbit ear artery. During taurine perfusion the intraluminal pressure varied less than 3% ($n = 6$).

Effects of noradrenaline, high potassium, verapamil and $NaNO_2$

Preliminary experiments showed that the maximal mechanical response of the artery occurred at noradrenaline 10^{-6} M. In the later experiments a supramaximal dose of noradrenaline was used (5×10^{-6} M). This catecholamine produced typical phasic and tonic contraction of rabbit ear artery (Figure 2). A steady state of intraluminal pressure was reached in about 5 min (mean increase of 203 ± 6.7 mmHg, $n = 17$) and remained quite stable ($\pm 7.45\%$). The exposure to KCl (54 mM) induced a bimodal response the tonic phase of which remained stable for at least 2 h (Figure 2), the observed increase in vascular tone being 176.7 ± 6.2 mmHg ($n = 45$).

In order to ascertain that our experimental conditions were suitable for studying vasodilator agents, two known vasodilators, verapamil (Weiss, 1977) and $NaNO_2$ (Kukovetz, Holzmann, Wurar & Poch, 1979) were studied. In the presence of verapamil (5×10^{-6} M), both the high potassium- and noradrenaline-induced contractions were markedly reduced. $NaNO_2$ (3×10^{-2} M) also produced a significant decrease in intraluminal pressure in high potassium-treated preparations as shown in Figure 3. Despite the common vasodilator activity of these two compounds there were kinetic differences in their actions. The action of verapamil was rapid, reaching its maximum in a few minutes; while the effect of $NaNO_2$ was slower to appear, as shown in Figure 3.

Effect of taurine, homotaurine and β-alanine on high potassium-induced contraction

After 10 min of exposure to 54 mM KCl and in its continuing presence, arteries were intraluminally perfused with taurine at various concentrations. A typical response of the artery to taurine is shown in Figure 4. The vasodilator action of this compound was rapid in onset and after 5 min reached a steady

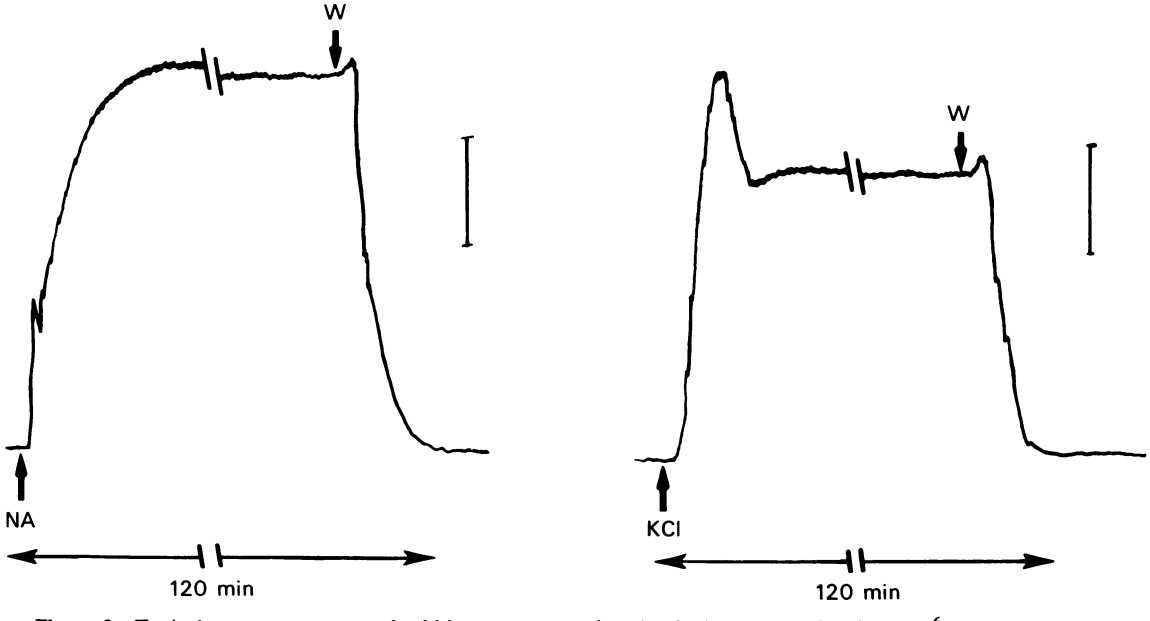

Figure 2 Typical pressor response of rabbit ear artery to intraluminal noradrenaline (5×10^{-6} M) and to both intraluminal and extraluminal administration of KCl (54 mM) for 120 min. The artery was intraluminally perfused at a constant rate (5 ml/min) and changes in vascular tone were measured by recording intraluminal pressure. Vertical scale = 50 mmHg; W = wash with normal Krebs solution, NA = noradrenaline.

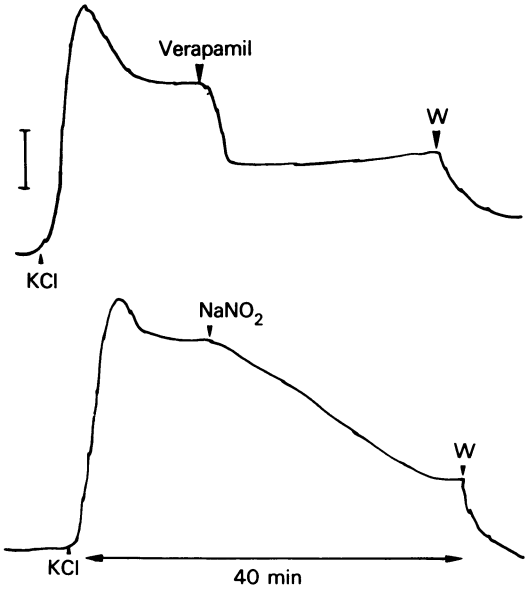

Figure 3 Effect of verapamil (5×10^{-5} M) and $NaNO_2$ (3×10^{-2} M) on the contraction induced by both intra- and extraluminal administration of KCl (54 mM). Each segment of artery was exposed to KCl and after 10 min vasodilator drugs were added intraluminally. The artery was perfused at a constant rate and changes in vascular tone were measured by recording intraluminal pressure. Vertical scale = 50 mmHg; W = wash with normal Krebs solution.

Table 1 Effect of taurine on high potassium-induced contraction in rabbit ear artery

Taurine (mM)	*Control* (mmHg)	*Treated* (mmHg)	P *value*
10	143.2 ± 11.3 (9)	109.1 ± 8.8 (9)	0.01
20	174.2 ± 14.9 (7)	107.4 ± 11.6 (7)	0.01
40	153.5 ± 10.9 (7)	82.6 ± 12.8 (7)	0.001
80	110.7 ± 14.8 (5)	23.0 ± 5.4 (5)	0.001

The arteries were perfused with 54 mM KCl for 10 min (control) and for 30 min with taurine in addition. Each value is mean ± s.e.mean. The number of experiments is given in parentheses.

state. The taurine action was rapidly reversed when it was removed and the tissue still exposed to a high-potassium medium. This taurine action was concentration-dependent (Table 1) and analysis of the data showed a linear response with a regression coefficient of 0.99 (Figure 5). β-Alanine and homotaurine (both 40 mM) had no effect (Table 2), while in contrast taurine (40 mM) produced a decrease of about 50% in intraluminal pressure (Figure 5).

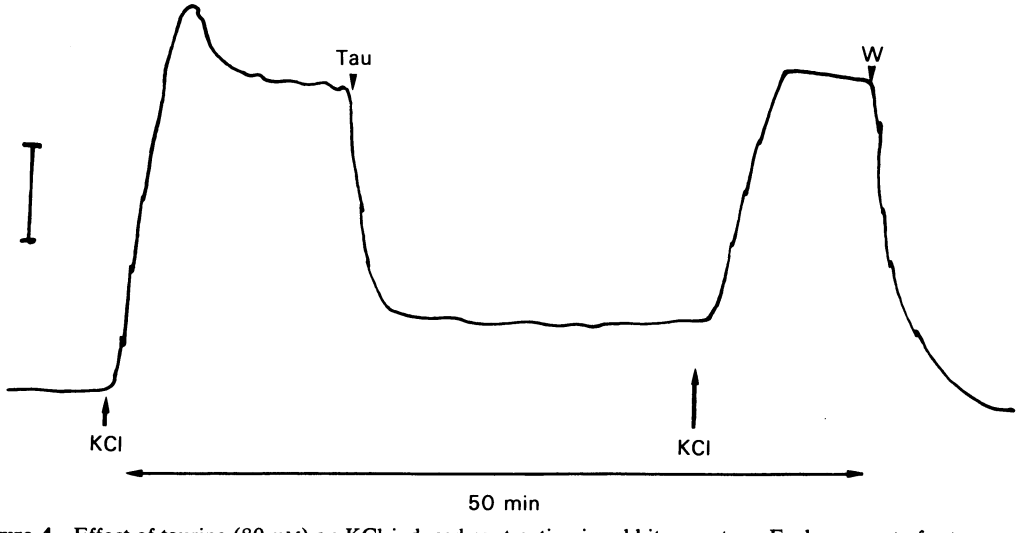

Figure 4 Effect of taurine (80 mM) on KCl-induced contraction in rabbit ear artery. Each segment of artery was contracted by 54 mM KCl given both intra- and extraluminally and after 10 min taurine (80 mM) was administered intraluminally. On its removal, the taurine effect was reversed by continuing the contact with 54 mM KCl. The artery was perfused at a constant rate and changes in vascular tone were measured by recording intraluminal pressure. Vertical scale = 50 mmHg; W = wash with standard solution; Tau = taurine.

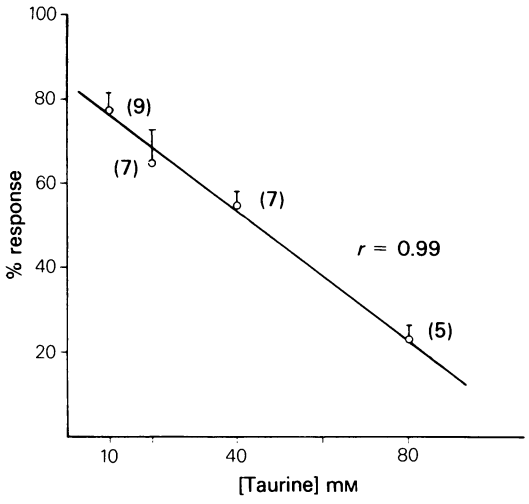

Figure 5 Concentration-response relationship between taurine concentration and % reduction of vasoconstriction induced by KCl (54 mM) in rabbit ear artery. The straight line was generated by linear regression analysis; r = correlation coefficient. The vertical bars indicate s.e.mean and each point represents mean of 5 to 9 determinations.

Table 2 Effect of taurine analogues on high potassium-induced contraction in rabbit ear artery

Drugs (40 mM)	*Control* (mmHg)	*Treated* (mmHg)	P
β-Alanine	176.4 ± 29.6 (4)	205.2 ± 25.7 (4)	NS
Homotaurine	145.3 ± 9.4 (4)	155.6 ± 12.4 (4)	NS

The artery was perfused with 54 mM KCl for 10 min (control) and then with each drug in addition. Each value is mean ± s.e.mean. The number of experiments is given in parentheses.

Effect of taurine on noradrenaline-induced contraction

The administration of noradrenaline (5×10^{-6} M) produced a typical response as shown in Figure 2. After 10 min, taurine was added to the perfusion fluid, 40 mM producing a slight decrease from 187.2 ± 13 to 162.4 ± 15.3 mmHg ($n = 6$); 80 mM taurine behaved in the same way, reducing vascular tone from 214 ± 10 to 184 ± 8 mmHg ($n = 6$). The statistical analysis revealed that these differences were not significant.

Effect of taurine (40 mM) on contractions produced by noradrenaline plus high potassium

The experimental procedure followed is shown in Figure 1, row C. The intraluminal administration of noradrenaline produced a typical response (Figure 6), and the subsequent administration of 54 mM KCl caused a further increase in intraluminal pressure (Table 3, Figure 6). Then, the addition of 40 mM taurine eliminated that component of vascular tone which appeared to be due to the high potassium (Table 3, Figure 6).

Discussion

This is the first account of interference by taurine with excitation–contraction coupling in vascular smooth muscle. Taurine exhibited a vasodilator effect against KCl-induced pressor responses in rabbit ear artery. The taurine concentration (about 40 mM) that produced a decrease of 50% in vascular tone (Figure 5) is similar to the serum taurine level (Jacobsen & Smith, 1968). In addition to the fact that high blood levels of taurine can be obtained by its release from ischaemic cardiac muscle and during acute human myocardial infarction (Paasonen, Pentiila, Himberg & Solatunturi, 1980), the reversibility of

Table 3 Effect of taurine on contraction induced by noradrenaline (NA) plus KCl in rabbit ear artery

Drugs	*Increase in pressure* (mmHg)	*Increase* (%)	P *value*
NA 5×10^{-6} M	183.8 ± 10.6	100	-----
NA 5×10^{-6} M + KCl 54 mM	239.0 ± 14.1	130.0 ± 3.1	0.001[1]
NA 5×10^{-6} M + KCl 54 mM + taurine 40 mM	198.7 ± 13.8	107.9 ± 2.2	0.001[2]

Each value represents the mean ± s.e.mean ($n = 6$).
The same ear artery was exposed for 10 min to noradrenaline, then for 10 min to high-potassium medium and finally to taurine.
P values: [1]compared to response obtained with noradrenaline 5×10^{-6} M; [2]compared to response obtained with noradrenaline 5×10^{-6} M + KCl 54 mM.

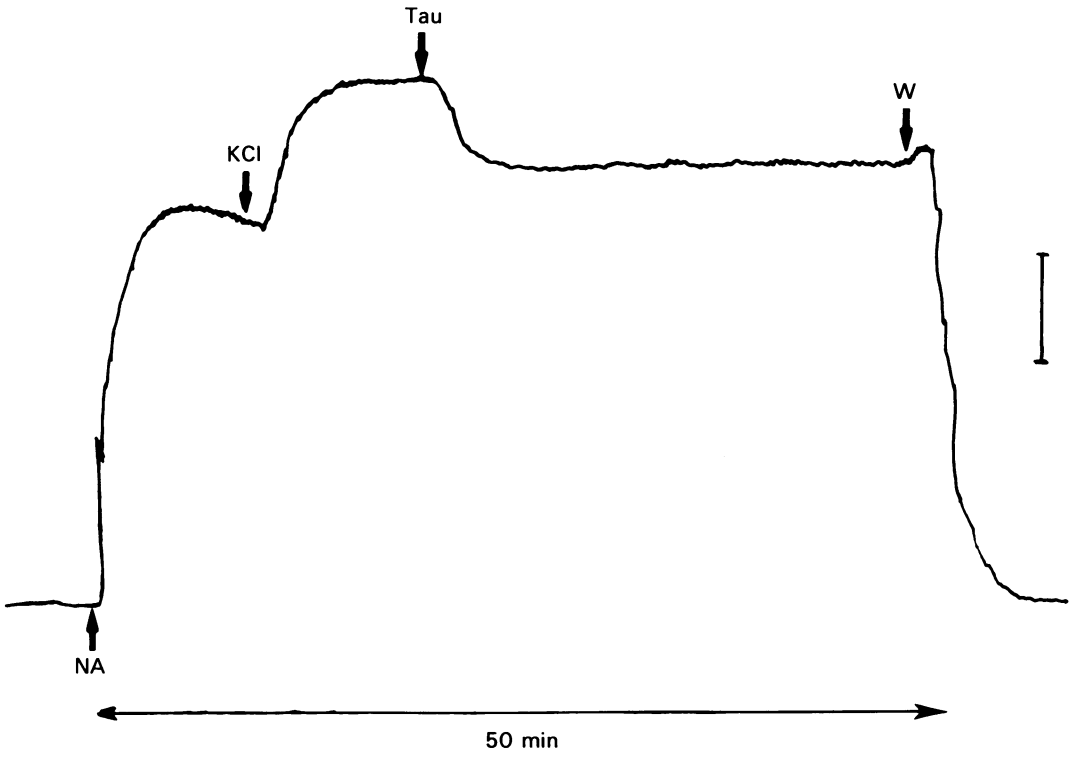

Figure 6 The effect of taurine (40 mM) on the response to intraluminal administration of noradrenaline (5×10^{-6} M) plus intra- and extraluminal administration of KCl 54 mM) in rabbit ear artery. Each artery was initially perfused with noradrenaline and then exposed additionally to a high-potassium medium. When the steady state tension level was obtained taurine (40 mM) was also administered intraluminally. The artery was perfused at a constant rate and changes in vascular tone were measured by recording intraluminal pressure. Vertical scale = 50 mmHg; NA = noradrenaline; Tau = taurine; W = wash with normal Krebs solution.

the taurine effect in the present study also suggests a possible role for this compound in vascular smooth muscle. The vasodilator effect of taurine was rapid, reaching a steady state in a few minutes; a similar action is observed with verapamil but not with $NaNO_2$. To study the effect of verapamil and $NaNO_2$ in our preparation a dose was chosen which has been shown markedly to reduce vascular tone (Fleckenstein, 1977; Kukovetz *et al.*, 1979).

The action of taurine was specific, in that two taurine analogues, β-alanine and homotaurine, had no effect in our preparation when used at 40 mM. From this we conclude that the sulphonic group is essential for the activity, and also that the carbon chain length is important.

Taurine decreased the contraction induced by 54 mM KCl in rabbit ear artery in a concentration-dependent manner (Figure 5), while it had no effect on the contraction induced by 5×10^{-6} M noradrenaline. When the two vasoconstrictor agents were administered together with the procedure shown in Figure 1, row C, taurine appeared to antagonize specifically the high potassium component of contraction.

Vascular smooth muscle contraction induced by high potassium is due to an increased influx of Ca^{2+} through voltage-dependent channels in the depolarized cell membrane (electromechanical coupling) (Van Breeman & McNaughton, 1970; Weiss, 1977; Casteel, 1980). High potassium contraction also involves a sensitive pool of Ca^{2+} ions, loosely bound to the plasma membranes (Weiss, 1977). Noradrenaline, on the other hand brings about vascular contractions either by increasing transmembranal Ca^{2+} influx through a receptor-operated channel (Casteel, 1980) or by releasing tightly-bound intracellular sequestered calcium (Hiraoka, Yamagishi & Samo, 1968; Bevan, Garstka, Su & Su, 1973; Steinsland, Furchgott & Kirpekar, 1973; Karaki, Kubota & Urakawa, 1979). Moreover, in rabbit ear artery, noradrenaline can induce contraction without or with only limited depolarization of the plasma membrane (pharmacomechanical coupling) (Somlyo & Somlyo, 1968; Droogmans, Kaeymaekers & Cas-

teel, 1977). The presence of two different pathways for Ca^{2+} influx is also confirmed by the fact that in rat mesenteric artery, nifedipine (an organic calcium blocker) specifically inhibits high potassium-induced contraction while it has only a slightly effect on noradrenaline-induced contraction (Kondo, Suzuki, Okuno, Suda & Saruta, 1980). Also Meisheri, Hwang & van Breemen (1981) demonstrated that contraction of rabbit aorta induced by noradrenaline and high potassium depolarization stimulated Ca^{2+} influx through two separate pathways.

Our experiments confirm that the tonic component of noradrenaline- and high potassium-induced contractions are maintained by different mechanisms. When high potassium was administered to arteries already contracted by a supramaximal dose of noradrenaline, a further significant increase in vascular tone was observed (Table 3). Since the noradrenaline concentration was supramaximal, if high potassium were to produce a cytoplasmic Ca^{2+} increase by the same mechanism no further change in intraluminal pressure would be expected.

Our findings on rabbit ear artery could be explained by at least two mechanisms: (1) a hyperpolarizing action of taurine, or (2) an interaction between taurine and low affinity calcium binding sites with a consequential inhibition of calcium influx through voltage-dependent channels.

(1) Although no electrophysiological data are available on taurine action in vascular smooth muscle, a hyperpolarizing effect is possible. With such an action, taurine ought not to inhibit noradrenaline-induced contractions which, in rabbit ear artery, are not associated with changes in membrane potential (Droogmans *et al.*, 1977; Johansson & Somlyo, 1980). Taurine is known to exert a hyperpolarizing effect in tissues such as rat extensor digitorum muscle (Gruener, Mankowitz, Huxtable & Biessler, 1975), neurones of mudpuppy retina (Cunningham & Miller, 1980), guinea-pig ventricular strips and sheep Purkinje fibres (Dolara, Ledda, Mugelli, Mantelli, Zilletti, Franconi & Giotti, 1978).

(2) The KCl-induced contractions seem to be dependent on increasing Ca^{2+} uptake in vascular smooth muscle at low affinity sites (Karaki & Weiss, 1979). The selective taurine action on high potassium-induced contraction could be explained by its interference with these low affinity calcium binding sites.

Although extrapolation of data from one tissue to another is hazardous, it is of interest that Chovan, Kulakowski, Sheakowski & Schaffer (1979) showed that taurine interacts with low affinity calcium binding sites at cardiac sarcolemma. Indeed, the action of taurine on the heart is dependent on extracellular calcium concentrations. Chovan *et al.* (1979) demonstrated that with calcium concentrations below 0.9 mM, taurine increased calcium binding. On the other hand, Azari & Huxtable (1980) observed that taurine decreased calcium binding in 2.5 mM $CaCl_2$ (the same concentration as in the present study) and at this concentration, taurine also decreased contractility and calcium levels in guinea-pig ventricular strips (Franconi, Martini, Stendardi, Zilletti & Giotti; unpublished observations).

Moreover, the time course of taurine's effect on high potassium-induced contraction resembles that obtained with verapamil. Karaki & Weiss (1979) showed that D600 inhibits the increase of ^{45}Ca uptake elicited either by high-potassium or by depolarizing concentrations of noradrenaline (10^{-4} M) in aortic smooth muscle. Kondo *et al.* (1980) also demonstrated that some organic calcium blockers selectively inhibit high potassium-induced contraction in rat mesenteric artery. The above observations suggest that taurine could interact with these low affinity calcium binding sites in the same way as certain organic calcium blockers do.

It is too early yet to draw any conclusion about the physiological and pharmacological significance of this taurine vasodilator action, but the present data suggest that taurine may play a modulatory role in the maintenance of vascular tone.

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