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THE ACTION OF TABERNANTHINE ON NORADRENALINE-STIMULATED CONTRACTIONS AND ^{45}Ca MOVEMENTS IN RAT ISOLATED VASCULAR SMOOTH MUSCLE

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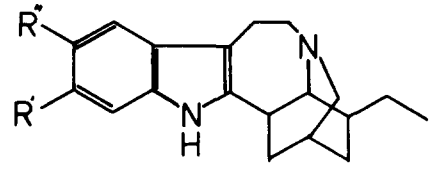
The iboga alkaloid tabernanthine inhibited depolarization (100 mM K^+)-induced contractions in aorta and mesenteric arteries in an concentration-dependent manner with the respective IC_{50} values being about 21 and 7 μM. Contractions elicited by noradrenaline in the mesenteric artery were potentiated by lower concentrations (0.1 and 1.0 μM) of tabernanthine while they were inhibited by higher concentrations (10-100 μM). Tabernanthine produced only inhibition of noradrenaline-elicited responses in aorta and portal vein, the vein being the most sensitive of the vessels to the inhibitory effects of the compound. The magnitude of the spontaneous contractions of the portal vein, the aortic intracellular calcium fraction releasable by noradrenaline and the turnover of calcium in unstimulated aorta were enhanced by tabernanthine. Depolarization-stimulated ^{45}Ca influx and contractions in the aorta were inhibited to a similar extent by tabernanthine and 100 μM virtually abolished the ^{45}Ca influx stimulated by noradrenaline and depolarization. It is concluded that tabernanthine has a calcium entry blocking action but also has other actions related to the turnover of intracellular calcium releasable by noradrenaline.

Tabernanthine Iboga alkaloids Calcium entry blockade

1. Introduction

Tabernanthine is a tremor-producing alkaloid extracted from the plant Tabernanthine Iboga and shows structural similarities to the harmala alkaloid harmine. The structures of three iboga alkaloids are shown in fig. 1. Tabernanthine exerts negative chronotropic and inotropic effects in the dog and negative chronotropic effects in the rat in vivo, and a negative chronotropic effect in rat isolated hearts (Hajo et al., 1981). Both the iboga and harmala alkaloids have been shown to exhibit negative chronotropic and inotropic effects on guinea-pig atria by a non-cholinergic, non-adrenergic mechanism while tabernanthine also antagonizes the positive chronotropic but not the inotropic actions of noradrenaline (Zetler and Singbartl, 1970; Zetler and Lessau, 1972; Hajo-Tello et



	R'	R''
IBOGAMINE	H	H
IBOGAINE	H	OCH_3
TABERNANTHINE	OCH_3	H

Fig. 1. Structure of tabernanthine Iboga alkaloids ibogamine ibogaine and tabernanthine.

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al., 1981). Tabernanthine and ibogaine have also been shown to sensitize rat duodenal smooth muscle to the effects of exogenous calcium (Valette and Leclair, 1977a,b) and to potentiate the relaxation of a rat duodenal preparation when it was exposed to a calcium-free solution. Similar effects are seen with mescaline and lysergic acid diethylamide (Valette and Leclair, 1978). In view of these apparent effects of tabernanthine on calcium availability in cardiac and smooth muscle it was thought of interest to extend the investigation of its effects in vascular smooth muscle of the rat. This is a tissue in which agonist-induced uptake and release of calcium and the effects of calcium entry blocking compounds have been closely studied (Godfraind and Miller, 1982; Godfraind and Dieu, 1981; Godfraind, 1983; Godfraind and Kaba, 1969).

2. Materials and methods

Ten to fifteen week-old male Wistar rats (240-350 g) were killed by decapitation and the thoracic aorta, superior mesenteric artery and portal vein removed as required and cleaned of all loosely adhering tissue.

The mesenteric artery was cut spirally according to the method of Furchgott (1960) and rings of thoracic aorta 2 mm wide were cut close to the aortic arch (Godfraind, 1979). Artery preparations were suspended in 50 ml organ baths under a tension of 2 g. The portal vein was suspended in the organ bath as a single longitudinal preparation under 1 g tension. The physiological solution (composition mM: NaCl 112, KCl 5 $NaHCO_3$ 25, KH_2PO_4 1, $MgSO_4$ 1.2, $CaCl_2$ 1.25, glucose 11.5) was maintained at 37°C and aerated with a gas mixture of 95% O_2 and 5% CO_2.

Contractile responses were measured using an isometric transducer coupled to a potentiometric pen recorder. After an equilibration period of 60 min the artery preparations were contracted maximally in a depolarizing medium (mM: NaCl 17, KCl 100, $NaHCO_3$ 25, KH_2PO_4 1, $MgSO_4$ 1.2, $CaCl_2$ 1.25, glucose 11.5), washed in normal physiological solution and allowed a further 60 min period of equilibration. Cumulative concentration-effect curves with noradrenaline (0.1 nM to 1 μM for aorta, 0.1 nM to 10 μM for mesenteric artery and 1 nM to 3 μM for portal vein) were obtained by approximately tripling the bath concentration in successive steps. After a maximal response had been obtained, the preparations were washed until baseline tension was regained and allowed a further 30 min rest period. The tissues were then incubated with various concentrations of tabernanthine for 60 min after which time a second cumulative concentration-effect curve with noradrenaline was obtained. The same procedure was followed to produce a third concentration-effect curve in the presence of second larger concentration of tabernanthine in some preparations. Control experiments were performed using the same protocol but omitting tabernanthine. In other experiments single maximal contractions of the tissues were produced by noradrenaline (10 μM) or by the depolarizing medium in place of the cumulative additions of noradrenaline.

2.1. Measurement of ^{45}Ca influx and efflux

The depolarization- or noradrenaline (10 μM)-induced influx of ^{45}Ca into the smooth muscle cells of the aorta in the absence and presence of tabernanthine was estimated by measuring the changes induced in the specific activity of the calcium fraction resistant to displacement by lanthanum. The method of Godfraind (1976) was used.

The artery was cut open longitudinally to form a flat strip weighing about 6-11 mg and equilibrated for at least 60 min in physiological solution (composition mM: NaCl 122, KCl 5.9, $NaHCO_3$ 15, $MgCl_2$ 1.25, $CaCl_2$ 1.25, glucose 11) maintained at 37°C and aerated with a gas mixture of 95% O_2 and 5% CO_2. After a preincubation period of 60 min in physiological solution containing tabernanthine (30-100 μM), the artery strips were further incubated for 5 min in 10 ml of physiological solution containing ^{45}Ca (1 μCi/ml) as well as tabernanthine, then for another 2 min in the same solution with the addition of noradrenaline 10 μM. The depolarization-dependent ^{45}Ca influx was studied by exposing the artery strips to ^{45}Ca (1 μCi/ml) in a depolarizing medium (mM

NaCl 27.9, KCl 100, $NaHCO_3$ 15, $MgCl_2$ 1.25; $CaCl_2$ 1.25, glucose 11).

Thereafter the preparations were washed for 5 min in 500 ml of a La^{3+} solution [composition mM: NaCl 122, KCl 5.9, $MgCl_2$ 1.5 $LaCl_3$ 50, glucose 11, tris maleate 15 (pH 6.8)] to remove extracellular Ca^{2+} from the tissue. Parallel control experiments in the absence of tabernanthine were always performed at the same time. After the La^{3+} wash the artery strips were placed between two sheets of filter paper and pressed three times with a roller weighing 350 g. Each strip was weighed then dissolved in 0.1 ml of a solution composed of equal parts of perchloric acid (37% w/v) and H_2O_2 (30 vol) by heating for 15 min at 75°C. After cooling, 5 ml of Aqualuma (Lumac) was added and the radioactivity of the samples counted in a liquid scintillation counter as usual, with appropriate controls. The results of each determination were converted to the apparent tissue content of ^{45}Ca (mmol/kg wet wt).

The noradrenaline-dependent ^{45}Ca efflux was estimated in artery strips after they had been preincubated in ^{45}Ca (2 μCi/ml)-containing physiological solution for 2 h, tabernanthine being present for the last 1 h. The artery strips were rinsed in non-radioactive solution for 5 min then transferred to non-radioactive solution containing noradrenaline 10 μM for a further 2 min, both of these solutions containing tabernanthine. After this the strips were placed in the lantanum solution and treated as described for the ^{45}Ca influx experiments.

Control experiments were performed by omitting noradrenaline and rinsing in a solution containing non-radioactive tabernanthine for 7 min and also by following an identical procedure but omitting tabernanthine. The total tissue content of ^{45}Ca was estimated at the end of the initial 2 h preincubation period by placing artery strips directly into the lanthanum solution. In all the ^{45}Ca efflux experiments equal numbers of appropriate control and agonist treated preparations were always processed at the same time.

2.2. Measurement of Na, K, Mg and Ca content

Strips of aorta were equilibrated for 2 h in 50 ml of physiological solution as used in the ^{45}Ca experiments, or for 1 h in physiological solution then for a second hour in the same solution containing tabernanthine 100 μM. At the end of the incubation period the strips were removed and blotted on filter paper as described above. After weighing they were dried overnight at 100°C and reweighed. To remove organic material the strips were placed in an oven at 500°C for 18 h. The residue was dissolved in 1 ml HCl 0.01 M, diluted in an appropriate solution and assayed for Na, K, Mg and Ca by atomic absorption spectroscopy (Perkin-Elmer 303).

2.3. Drugs

Noradrenaline bitartrate (Flucker) was dissolved in distilled water containing 7.9 mM Na_2SO_4 and 35 mM HCl as a stock solution of 10 mM and diluted in saline prior to use. Tabernanthine HCl, purified by Dr. F. Potier, CNPS Gif sur Yvette, France, was dissolved in distilled water as required.

2.4. Statistical analysis

The data are expressed as means $\pm$S.E.M. Student's t-test was used to assess significance. P values smaller than 0.05 were considered significant. The concentrations of tabernanthine producing 50% inhibition of the maximal contractile response induced by depolarization (IC_{50}) were estimated from concentration-effect curves.

3. Results

3.1. Aorta

Consecutive cumulative noradrenaline concentration-effect curves were reproducible when separated by 90 min and were unaffected by tabernanthine 1 μM. A 10 fold higher concentration produced a small but significant parallel 2 fold shift to the right to the concentration-effect curves while 50 μM produced a 7.4 fold shift to the right and inhibited the maximal response by about 12.4% (table 1).

Single supra-maximal concentrations of norad-

TABLE 1

Effect of tabernanthine on the maximal contractions (%) produced by noradrenaline (10 μM) and depolarization (100 mM K^+) in aorta and mesenteric arteries.

Tabernanthine (μM)	Aorta		Mesenteric artery	
	Noradrenaline	Depolarization	Noradrenaline	Depolarization
0	100	100	100	100
0.1			104.9 ± 3.9 (4)	
1.0	100 ± 5.0 (4)		106.7 ± 4.6 (5) [a]	93.2 ± 0.6 (3)
10	100 ± 3.5 (8)	78.4 ± 4.2 (3)	88.3 ± 4.0 (8) [a]	42.8 ± 4.1 (4)
50	88.6 ± 3.6 (5)	18.6 ± 3.2 (3)	60.3 (2)	
100	74.0 ± 3.1 (6) [a]	0 (3)	34.7 ± 4.4 (3) [a]	0 (3)

[a] Denotes experiments involving single concentrations of noradrenaline. Numbers in parentheses represent number of experiments.

renaline (10 μM) produced sustained contractions of the aorta which reached a plateau after 20 min. In the presence of tabernanthine 100 μM these contractions were still sustained but significantly reduced to 74.0 ± 3.1% (n = 6) of the control (table 1). In 100 mM K^+ containing physiological solution, sustained contractions were also produced which were significantly inhibited in a concentration-dependent manner by tabernanthine 10-100 μM. Complete inhibition of these 100 mM

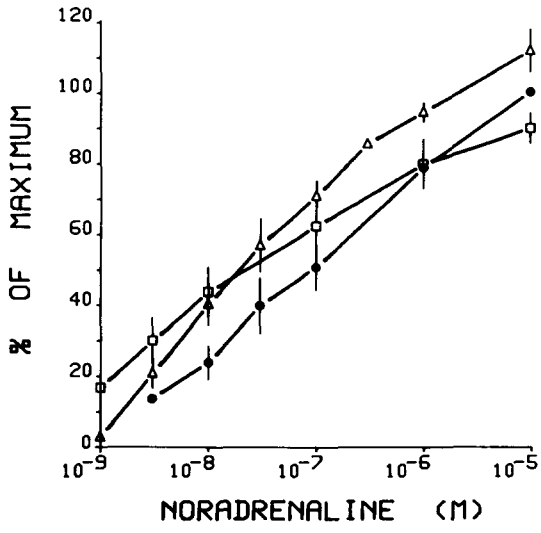

Fig. 2. Concentration-effect curves with noradrenaline in rat mesenteric artery in the absence (●) and presence of tabernanthine 1 μM (△) and 10 μM (□). Responses are expressed as a percent of maximal control responses to noradrenaline. Each point is the mean of at least 3 observations. Vertical bars represent the S.E.M. when it exceeds symbol size.

K^+-induced contractions occurred with 100 μM tabernanthine (table 1) and the IC_{50} value was about 21 μM.

3.2. *Mesenteric artery*

Cumulative noradrenaline concentration-effect curves were reproducible when separated by 90 min and not significantly affected by tabernanthine 0.1 μM. At 1 μM, tabernanthine produced a significant 4.47 fold leftward shift of the concentration-effect curve and a significant increase in the maximal response to 111.7 ± 6.2% of control ($0.05 < P < 0.02$, n = 3). Tabernanthine 10 μM did not increase the leftward shift of the curve but significantly depressed the maximum response to 89.7 ± 4.4% of control ($0.02 < P < 0.01$, n = 3) (fig. 2).

Contractions produced by single maximal concentrations of noradrenaline (10 μM) reached a plateau after 10-15 min which was then sustained. This contraction was also sustained but significantly reduced in magnitude in the presence of tabernanthine 10 μM to 88.3 ± 4.0% of control ($0.05 < P < 0.025$, n = 8) and was further depressed by tabernanthine 100 μM to 34.7 ± 4.4% (n = 3) of the control (table 1). These depressant effects of tabernanthine could be reversed by washing the preparations for 2 h.

Contractions induced by high potassium-containing physiological solution were also sustained for at least 30 min. Tabernanthine (1 and 10 μM) produced a concentration-related inhibition of the

sustained response and 100 μM tabernanthine abolished the 100 mM K^+-induced contraction (table 1). The IC_{50} value was about 7.2 μM.

3.3. *Portal vein*

The isolated portal vein preparation of the rat exhibits regular spontaneous contractile activity. Noradrenaline 10 nM to 1.0 μM increased the amplitude of these spontaneous contractions in a concentration-dependent manner, the maximal effect being apparent at about 0.3 to 1 μM. Concentrations greater than 1 μM caused a decrease in the amplitude (fig. 3, 4). The basal tone of the portal vein also increased in the presence of noradrenaline 0.1 μM to 10 μM (fig. 3, 4). Tabernanthine at concentrations up to 30 μM had no effect on the basal tone of the vein while concentrations greater than 1 μM always increased the amplitude and decreased the frequency of spontaneous activity (fig. 5). In the presence of tabernanthine 10-30 μM the frequency of contraction usually decreased from 9-12 to 1-2 contractions per min and the amplitude was increased 4-11 fold.

Tabernanthine 10 μM depressed the stimulant effect of noradrenaline on the spontaneous contractions (fig. 3, 4). The degree of inhibition was not significant at 10-30 nM noradrenaline but amounted to about 75% at 0.1 μM and about 86% at 0.3 μM noradrenaline and the responses elicited by 3 μM noradrenaline were abolished (fig. 3, 4).

Increases in the basal tone induced in the portal vein by noradrenaline 0.1-1 μM were not significantly affected by tabernanthine 10 μM but the responses elicited by 3 and 10 μM noradrenaline were inhibited significantly by about 59 and 51% respectively (fig. 3).

3.4. *^{45}Ca uptake in rat aorta*

The uptake of ^{45}Ca after a 7 min incubation period in ^{45}Ca-containing physiological solution was 98.1 ± 3.5 μM calcium/kg wet wt (n = 34). Tabernanthine 50 μM increased the uptake slightly but significantly by about 14.9 ± 4.8 μM/kg (n =

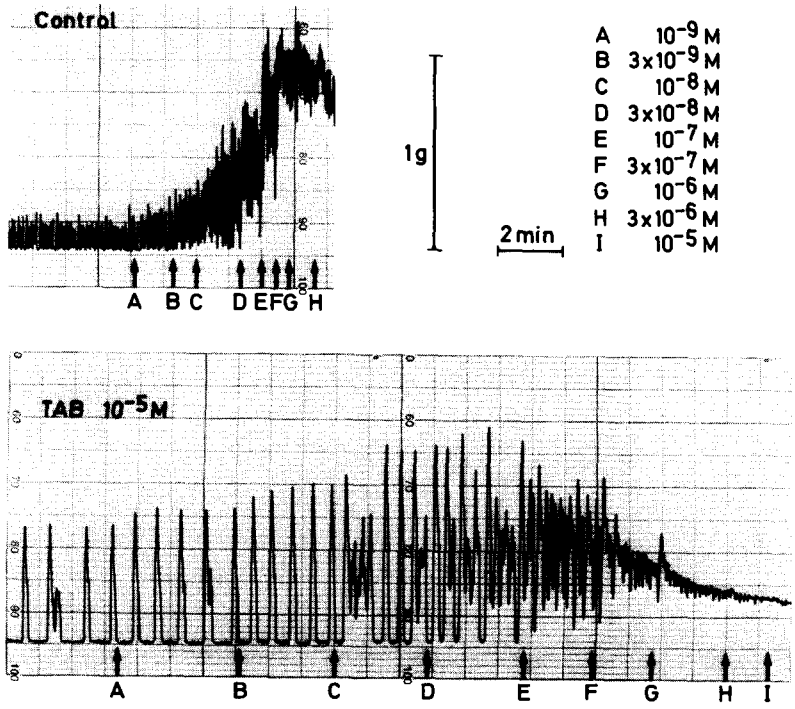

Fig. 3. Typical responses induced by noradrenaline in a rat portal vein in the absence and presence of tabernanthine 10 μM.

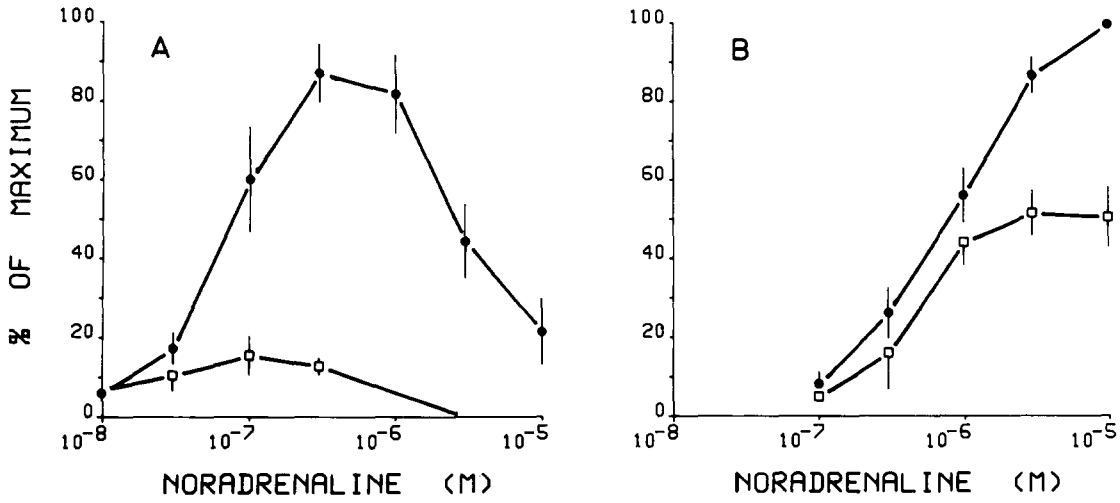

Fig. 4. Concentration-effect curves with noradrenaline in the absence (●) and presence of tabernanthine 10 μM (□) in rat portal vein. (A) Increase in amplitude of spontaneous activity. (B) Increase in basal tension. In each case the response is expressed as a percent of the maximal response attained in the absence of tabernanthine. Each curve is the mean of 4 observations. Vertical bars represent S.E.M.

6). A higher concentration of tabernanthine (100 μM) produced no further increase in unstimulated influx. Both noradrenaline 10 μM and high potassium solution elicited large increases in the uptake of ^{45}Ca. The increased uptake due to high potassium solution was significantly greater than the increase in uptake due to noradrenaline (table 2).

Tabernanthine 50 μM inhibited 100 mM K^+-

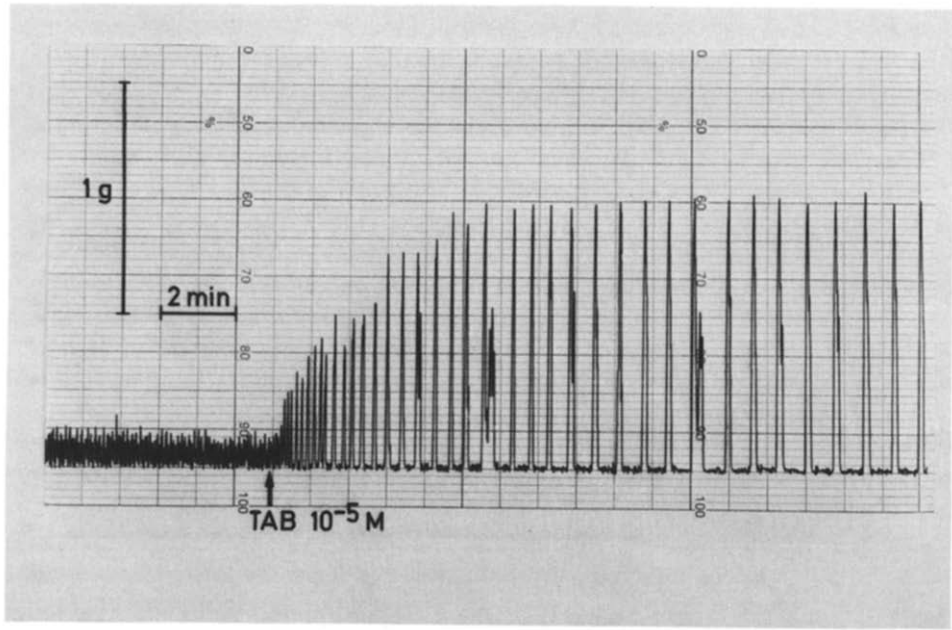

Fig. 5. Effect of tabernanthine 10 μM on the spontaneous activity of a rat poretal vein.

stimulated ^{45}Ca uptake by about 66.0% and 100 μM produced about 100% inhibition (table 2). When measured after the same time interval (2 min), the contractions were depressed by 69.8 ± 3.6% and 100% respectively. The ^{45}Ca uptake stimulated by noradrenaline (10 μM) was not significantly affected by 10 μM tabernanthine (nor was the noradrenaline-mediated contraction) but was abolished by 100 μM (table 2). This latter concentration of tabernanthine depressed the effect of noradrenaline by only 34.5 ± 1.5% after 2 min.

3.5. ^{45}Ca efflux

Tabernanthine 100 μM produced a significant increase in the tissue ^{45}Ca content after a 2 h incubation in ^{45}Ca-containing solution as compared to control tissues. When, after 2 h loading with ^{45}Ca, the pieces of aortic tissue were rinsed in normal physiological solution for 7 min both the tabernanthine-treated and the control tissues showed a marked decrease in residual ^{45}Ca content, the net loss in 7 min being about 114.4 μM calcium/kg wet wt in the controls and significantly greater, i.e. about 212.7 μM/kg wet wt in the tabernanthine-treated tissues. When noradrenaline 10 μM was included in the rinsing solution for last 2 min the control tissues showed a further marked decrease in residual ^{45}Ca content while this procedure produced little further loss of ^{45}Ca from the tabernanthine-treated tissues (table 3).

3.6. Na, K, Mg and Ca content

The total tissue content of Na^+, K^+, Mg^{2+} and Ca^{2+} was unchanged after a 60 min equilibration period in the presence of tabernanthine 100 μM. The values (mmol/kg) were: Na^+ 74.1 ± 1.6 (78.5 ± 1.9 in presence of tabernanthine), K^+ 39.4 ± 1.1 (37.0 ± 1.3), Ca^{2+} 3.6 ± 0.3 (3.8 ± 0.2) and Mg^{2+} 3.4 ± 0.1 (3.4 ± 0.1).

4. Discussion

Calcium entry blockers have been defined as compounds that inhibit the stimulated influx of calcium into cells and the consequent response in an identical manner (Godfraind, 1981). Contractions of vascular smooth muscle induced by high potassium solution are entirely dependent on extracellular calcium (Godfraind and Kaba, 1969; Bolton, 1979), and have been used to provide a

TABLE 2

Effect of tabernanthine on the tissue content of calcium in the lanthanum resistant calcium fraction of rat aorta measured as ^{45}Ca uptake (μmol Ca/kg wet wt ± S.E.M.) after 7 min exposure to ^{45}Ca containing physiological solution (control), or after 5 min exposure to ^{45}Ca containing physiological solution followed by a 2 min exposure to ^{45}Ca-containing physiological solution in the presence of either 10 μM noradrenaline or 100 mM K^+ (depolarization). Numbers in parentheses represent number of tissue samples.

Tabernanthine (μM)	Control	Noradrenaline	Depolarization
0	98.1 ± 3.5 (34)	157.6 ± 7.3 (14)	183.9 ± 6.0 (12)
50	113.0 ± 4.0 (6)		142.2 ± 6.4 (6)
100	117.1 ± 3.7 (23)	117.1 ± 5.7 (14)	128.7 ± 1.1 (6)

TABLE 3

Tissue content of Ca in the lanthanum resistant Ca fraction of rat aorta, measured as ^{45}Ca after 2 h incubation in ^{45}Ca-containing physiological solution (μM Ca/kg wet wt ± S.E.M.).

Tabernanthine (μM)	Time 0	7 min wash	5 min wash 2 min noradrenaline 10 μM
0	303.0 ± 20.7 (8)	188.6 ± 7.7 (14)	121.1 ± 10.8 (8)
100	371.2 ± 17.5 (8) [a]	159.8 ± 7.8 (15) [b]	152.5 ± 9.7 (10) [a]

[a] ($0.05 < P < 0.02$) and [b] ($0.02 < P < 0.01$) significantly different from respective control values. Numbers in parenthesis represent number of experiments.

simple means of studying compounds with possible calcium entry blocking properties (Godfraind and Polster, 1968; Godfraind and Dieu, 1981; Van Breemen et al., 1972).

In the present experiments tabernanthine inhibited 100 mM K^+-induced contractions of both aorta and mesenteric artery in a concentration-dependent manner and also inhibited to a similar extent the 100 mM K^+-stimulated uptake of ^{45}Ca by the aorta. Tabernanthine was about 3 fold more potent as an inhibitor of contractions in the mesenteric artery than in the aorta. Thus tabernanthine has the characteristics of calcium entry blockers such as cinnarizine, flunarizine and nifedipine (Godfraind and Dieu, 1981; Godfraind and Miller, 1983; Godfraind, 1983).

Most of the calcium entry blockers so far described are relatively more potent as inhibitors of 100 mM K^+-induced than of noradrenaline-induced contractions and this is also true of tabernanthine (table 1). However tabernanthine differs from other calcium entry blockers in that the maximal inhibition of noradrenaline-induced contractions in the aorta and mesenteric artery only amounts to about 26 and 70% respectively while the stimulated calcium influx was abolished. The maximal inhibition produced by cinnarizine and flunarizine in the same arteries (about 50-55% and 85-90% respectively) correlates well with that part of the contraction which is dependent on extracellular calcium (Godfraind and Kaba, 1969; Godfraind and Dieu, 1981). In the presence of tabernanthine there is therefore an apparently increased component of noradrenaline-mediated contraction insensitive to extracellular calcium in both arteries. This may be due to tabernanthine stimulating an increased turnover of calcium in intracellular calcium stores releasable by noradrenaline, since tabernanthine increased the unstimulated influx and efflux of ^{45}Ca in the aorta without affecting the total calcium content. Also, this might inditicate a further intracellular action of the compound.

Such an increased rate of calcium turnover might also explain the potentiation of noradrenaline-induced concentration-effect curves for mesenteric artery. However tabernanthine also differs from cinnarizine, flunarizine and nifedipine in that it produced pronounced rightward shifts of the noradrenaline concentration-effect curves for aorta, perhaps indicating additional more complex actions.

In the rat portal vein the spontaneous contractile activity is dependent on extracellular calcium (Sigurdson et al., 1975) and can be inhibited by calcium entry blockers such as nifedipine and D600 but not by flunarizine (Weston, 1977; Jetley and Weston, 1980; Van Nueten and Vanhoutte, 1981). These contractions were potentiated by tabernanthine and their frequency was reduced. Such a negative chronotropic effect has been described in heart (Zetler and Singbartle, 1970; Zetler and Lessau, 1972) and although the mechanism of action is unknown it may be related to effects of tabernanthine on membrane permeability to ions other than calcium.

Both noradrenaline-mediated enhancement of the amplitude of spontaneous contractions in the portal vein and the increase in basal tension were inhibited by tabernanthine although their sensitivities differed markedly, the spontaneous contractions being inhibited to a much greater extent than the basal contraction (fig. 4a,b). This may indicate that the calcium channels activated by noradrenaline and subserving the different effects are not identical, or that their gating mechanisms have differing affinities for tabernanthine. Such differences in sensitivity of calcium gating mechanisms activated by a particular agonist in rat arterial tissue from different vascular beds have been described (Godfraind and Dieu, 1981).

These experiments show that noradrenaline-mediated effects on the portal vein were much more sensitive to inhibition by tabernanthine than were noradrenaline-induced contractions of either the aorta or mesenteric artery, indicating that calcium gating mechanisms sensitive to noradrenaline are also not identical in arterial and venous tissue.

In conclusion, tabernanthine has been shown to exert a calcium entry blocking action in rat aorta, but also to have other effects related to the turnover of intracellular calcium releasible by noradrenaline, which may indicate additional intracellular actions unrelated to blockade of calcium entry.

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