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The effect of oxytocin on contractile responses and ^{45}Ca movements in rat isolated aortic strips

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1 The effects of oxytocin (Oxt) on contractile responses and transmembrane Ca fluxes were studied in rat isolated aortic strips.

2 Oxt (50–1000 mu ml^{-1}) induced a dose-dependent contractile response and spontaneous myogenic activity.

3 The Oxt-induced contractile response was not inhibited by pretreatment of aortic strips with phentolamine plus practolol, atropine, diphenhydramine plus cimetidine or indomethacin, but was significantly reduced by verapamil or deamino-ethyl-Oxt.

4 The dose-response curve for Oxt was shifted upwards and to the left by increasing the Ca concentration of the medium from 1.8 to 4 mM.

5 Oxt also shifted upwards the dose-response curve to Ca (1 to 5 mM) in aortic strips incubated in K depolarizing Ca-free media.

6 Oxt increased the La^{3+}-resistant ^{45}Ca content without altering ^{45}Ca efflux.

7 The present results suggest that in rat isolated aortic strips Oxt produces a contractile response which, as previously found with other neurotransmitters, can be partly attributed to an increase of Ca influx through receptor-operated channels and to the release of Ca from intracellular stores.

Introduction

The mechanical, biochemical and electrophysiological actions of oxytocin (Oxt) on uterine smooth muscle have been extensively studied (Kleinhaus & Kao, 1969; Bolton, 1979). By contrast, the actions of Oxt on vascular smooth muscle are less well understood (Nakano, 1974). In fact, Oxt contracts rat aortic strips (Altura, 1975; Altura & Altura, 1984), and in some vascular beds, such as pulmonary arterial smooth muscle of chickens (Somylo *et al.*, 1967) and human umbilical vessels (Altura *et al.*, 1972) Oxt has a higher potency than vasopressin. In other mammalian vascular strips Oxt induces relaxation (Somlyo *et al.*, 1967; Altura & Hershey, 1967). Furthermore, Oxt usually induces a hypertensive effect in the rat (Krejci *et al.*, 1970) which has been attributed to an increase in vascular peripheral resistance with no change in cardiac output (Nakano, 1974). However, Oxt produces a hypotensive response in the rabbit, dog, monkey, birds and man (Nakano, 1974). The mechanisms underlying the differences in potency between Oxt and vasopressin in contracting different smooth muscles within the same animal species, as well as the diverse responses (contraction/relaxation) to Oxt in various species have not been elucidated.

It has been known for some time that Oxt produces a contractile response in rat isolated aortic strips (Altura, 1975), but this contractile response has not been extensively studied. The present work was undertaken to characterize further the contractile effect of Oxt in this vascular preparation. The possible role of Ca influx and/or release of intracellular Ca in the contractile response to Oxt has also been evaluated.

Methods

Experimental procedure

Helically cut strips from the thoracic aorta of male Sprague-Dawley (250–350 g) rats were prepared and mounted as described by Furchgott & Bhadrakon (1953). In some experiments, thoracic aortic strips from the rabbit and guinea-pig were used. Strips were suspended in 10 ml organ baths containing Krebs-bicarbonate solution (KBS) of the following composition (mM): NaCl 118, KCl 4.75, $CaCl_2$ 1.8, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11. For Ca-free KBS, calcium chloride was omitted and 0.1 mM Na_2

EDTA was added. Solutions were gassed with 95% O_2 and 5% CO_2 and maintained at 34°C. Contractile responses were measured isometrically by means of force-displacement transducers (Grass FT03) and recorded on a linear recorder (Rinken-Denshi F43) coupled to a Grass polygraph. Each preparation was allowed to equilibrate under 2 g tension for 2 h prior to initiation of experimental procedures. After equilibration the following experiments were performed.

(1) To determine whether Oxt affected basal tension and/or was able to induce spontaneous mechanical activity, cumulative dose-response curves were obtained by a stepwise increase in the concentration of Oxt as soon as a steady-state response had been obtained to the preceding dose.

(2) In other experiments the effects of various blocking agents, such as phentolamine, practolol, cimetidine, diphenhydramine, atropine and indomethacin, on the contractile responses to Oxt were determined. All the pharmacological antagonists were used in concentrations that inhibit $ED_{50}-ED_{60}$ doses of their respective agonists (Altura *et al.*, 1978). In these experiments the aorta was bisected and one half was used as the control and the other half as the experimental preparation. The effect of verapamil and deamino-ethyl-oxytocin on the Oxt-induced contractile response was also studied following a similar experimental design.

(3) In aortic strips contracted by high-potassium (80 mM) depolarizing KBS, Oxt was added to the bath either when the contractile effect of KCl reached the maximum or after mechanical restoration of the KCl-induced contractile response to control tension values (2 g) had been performed.

(4) In additional experiments, aortae were bisected and both halves equilibrated in Ca-free KBS for 2 h with successive washings every 20 min. Control halves were exposed to cumulative concentrations of calcium (1 to 5 mM) and when the contractile response reached steady-state values, Oxt (200 mu ml^{-1}) was added. In the experimental preparation Oxt was added and when its contractile response reached the maximum then calcium (1 to 5 mM) was added to the bath in a stepwise fashion.

(5) To study the effects of external calcium concentration on Oxt-induced contractile responses, cumulative dose-response curves to Oxt were obtained in aortic strips preincubated in KBS containing various concentrations of calcium (0.45, 1.80 or 4.00 mM).

Effect of oxytocin on ^{45}Ca movements

Measurements of ^{45}Ca influx and ^{45}Ca efflux were also undertaken in this study using techniques described previously by Godfraind (1976). To determine ^{45}Ca influx the aortae were bisected and in each experiment, half of the aorta served as control and the other half as an experimental preparation. Both halves were mounted in separate organ baths containing Tris-buffered solution of the following composition (mM): NaCl 160, KCl 4.6, $CaCl_2$ 1.5, $MgCl_2$ 1.0, glucose 11 and Tris ((hydroxymethyl)-amino-methane) 6.0. The solutions were adjusted to pH 7.4 with 4 N HCl and aerated with 100% O_2. After equilibration they were exposed to ^{45}Ca Tris solution (specific activity 0.4 $\mu Ci\ ml^{-1}$) for 5 min. Then they were transferred to ^{45}Ca Tris solution containing Oxt (600 mu ml^{-1}) in the experimental half. After 7 min, both control and experimental preparations were washed in 50 mM La^{3+}-Ca-free solution for 5 min in order to remove extracellular bound calcium. Then the strips were removed and the radioactivity of the samples counted in a liquid scintillation counter as previously described (Barrigón *et al.*, 1982; 1985). To determine ^{45}Ca efflux, aortic strips were incubated in ^{45}Ca-labelled Tris solution (specific activity 2 $\mu Ci\ ml^{-1}$) for 2 h. Tissues were then rinsed in non-radioactive Tris solution before being placed in successive tubes containing 2 ml of Ca-free Tris solution every minute for the duration of the washout (25 min). In some vials and from 15 min to 25 min, Oxt (200–600 mu ml^{-1}) was added to Ca-free Tris solution. Radioactivity lost into the tubes and present in the tissues at the end of the experiment was measured as described for ^{45}Ca influx experiments. The data obtained were plotted as desaturation curves which illustrate the decline of tissue ^{45}Ca with time (Barrigón *et al.*, 1983).

Chemicals and drugs

The following drugs were used: oxytocin grade III and IV (Sigma), deamino-ethyl-oxytocin (Ferro AG, Malmo, Sweden), noradrenaline bitartrate (NA, Sigma), verapamil hydrochloride (Knoll), indomethacin (Merck), practolol (ICI), reserpine phosphate (Serpasol, Ciba Geigy), phentolamine hydrochloride (Ciba Geigy) atropine sulphate (Sigma), cimetidine (SKF), diphenhydramine hydrochloride (Parke Davis), potassium chloride (Merck), calcium chloride (Merck) and $^{45}CaCl_2$ (sp. act. 23 mCi mg^{-1}; The Radiochemical Centre, Amersham). All drugs were dissolved in distilled water with the exception of indomethacin which was dissolved in a 10% w/v sodium bicarbonate solution. The concentrations for each chemical or drug are expressed as final concentrations in the bath. Ascorbic acid was added to each daily prepared solution of NA.

Throughout the paper results are expressed as mean ± s.e.mean. Statistical significance was evaluated by Student's t test for paired or unpaired data and differences were considered significant when $P < 0.05$.

Results

Effects on basal tension and spontaneous mechanical activity

The effects of Oxt (50 to 1000 mu ml^{-1}; 10^{-7} M to 2×10^{-6} M) on basal tension and spontaneous activity were studied on rat isolated aortic strips. Figure 1 shows that Oxt produced a dose-dependent increase in contractile force ($ED_{50} = 125 \pm 10.6$ mu ml^{-1}). The development of contractile force was rapid in onset and developed slowly taking 7 to 10 min to reach maximum effect. On repeated exposure to Oxt tachyphylaxis developed, diminishing the maximum contractile response (E_{max}) of the second exposure by 33.5% ($P < 0.01$). Therefore, in each preparation, only one dose-response curve to Oxt was performed and in paired experiments aortae were bisected; one half serving as control and the other as the experimental preparation. No significant differences were found between the increase of contractile force induced by Oxt grade III (aqueous solution) and that induced by Oxt grade IV (lyophilized powder), therefore, Oxt grade III was used in all the experiments described in this paper. The increase in contractile force induced by Oxt was rapidly reversed when it was washed out and it seemed to be species-dependent since it could not be demonstrated in rabbit or guinea-pig isolated aortic strips (unpublished observations). The maximum contractile response induced by Oxt 1000 mu ml^{-1} (0.656 ± 0.055 g; $n = 22$) was similar to that produced by 80 mM KCl (0.645 ± 0.045; $n = 12$) but 30.2% lower than the response to 1 μM noradrenaline (0.875 ± 0.0825 g; $n = 12$. $P < 0.05$). Furthermore, Oxt, 50–200 mu ml^{-1}, induced not only an increase in contractile force but as shown in Figure 1 it also induced spontaneous myogenic activity in some aortic strips (17 out of 53 preparations), which was suppressed by verapamil, 5×10^{-5} M. In order to determine whether the increase in contractile force induced by Oxt on aortic strips was mediated by effects on specific receptors, the effects of Oxt were studied in the presence and in the absence of different antagonists. The contractile response induced by Oxt was not affected by pretreatment with phentolamine (10^{-6} M) plus practolol (3.3×10^{-6} M), diphenhydramine

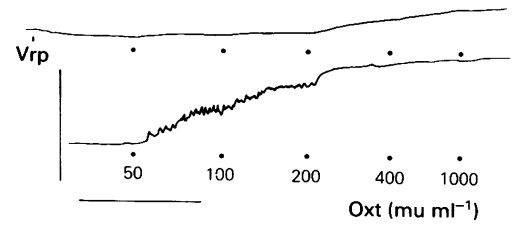

Figure 1 Typical experiment showing the contractile response to oxytocin (Oxt) on bisected isolated aortic strips of the rat. Lower trace shows the spontaneous mechanical activity induced by Oxt under control conditions. Upper trace shows the effect of Oxt after 4 min incubation with verapamil (Vrp, 5×10^{-5} M) on the experimental half. Calibrations 0.5 g and 5 min.

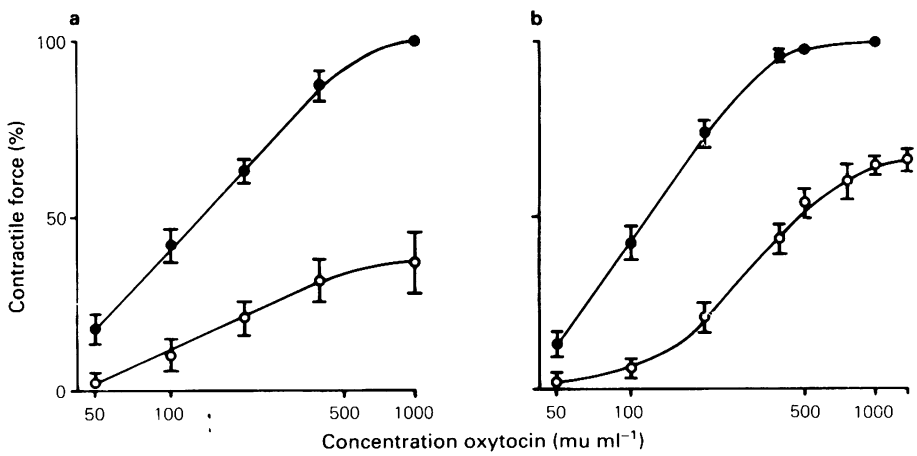

Figure 2 Effect of different antagonists on the contractile response elicited in bisected isolated aortic strips of the rat. (a) Effect of verapamil, (○) 10^{-5} M, on the control dose-response curve to oxytocin (Oxt) (●). (b) Effect of pretreatment (5 min) with deamino-ethyl-Oxt (5×10^{-7} M) on the contractile responses to Oxt. (●) Control Strips; (○) antagonist (deamino-ethyl-Oxt) pretreated aortic strips. $P < 0.01$ for all concentrations tested. Each point is the mean of 6 paired experiments; vertical lines show s.e.mean.

(5×10^{-5} M) plus cimetidine (5×10^{-5} M), atropine (10^{-6} M) or indomethacin (2×10^{-5} M) when these antagonists were added 20 min before the addition of Oxt to the bathing media. Pretreatment with verapamil (10^{-5} M) for 5 min shifted the dose-response curve to Oxt downwards and significantly reduced ($P < 0.001$) the maximal contractile response induced by addition of any dose of Oxt tested (Figure 2a). In contrast (as is shown in Figure 3), in aortic strips obtained from reserpine-treated animals (10 mg kg^{-1}, i.p., 24 h; $n = 6$) the E_{max} induced by Oxt was significantly increased by 34.0% (879.0 ± 60.2 mg as compared to 656.0 ± 55.4 mg; $P < 0.05$). Figure 2b shows concentration-response curves for Oxt (50 to 1000 mu ml^{-1}) obtained under control condition and in the presence of deamino-ethyl-Oxt, a competitive antagonist of Oxt in uterine smooth muscle (Melin *et al.*, 1981). Deamino-ethyl-Oxt, 5×10^{-7} M, had no effect on basal tension but shifted the concentration-response curveto Oxt downwards and to the right, decreasing the maximal contractile response induced by 1000 mu ml^{-1} Oxt by 35.1 ± 3.9% ($n = 6$; $P < 0.001$). The relaxant ability of deamino-ethyl-Oxt was also studied in 6 strips previously contracted with 1000 mu ml^{-1} Oxt. Under these conditions the antagonist relaxed the Oxt-induced contractile response by 73.3 ± 6.6%. In another group of experiments the strips were contracted with a submaximal concentration of KCl (80 mM). When the K^+-induced contractile response reached steady-state values, Oxt (400–1000 mu ml^{-1}) was applied cumulatively to the bath. Figure 4a illustrates one of those experiments. As is shown, under these conditions, Oxt still produced a slight concentration-dependent increase in contractile force. Moreover, Oxt (50 to 1000 mu ml^{-1}) also induced a dose-dependent contractile response in KCl-depolarized aortic strips when added after mechanical restoration of developed tension to resting values had been performed (2 g) (Figure 4b). In contrast, when aortic strips were contracted with 1 μM NA, increasing concentrations of Oxt (50–1000 mu ml^{-1}) did not significantly increased the developed contractile force.

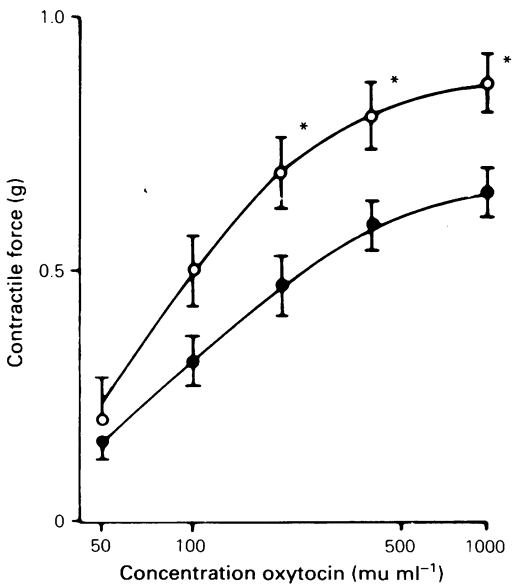

Figure 3 Contractile dose-response curves to oxytocin on isolated aortic strips of the rat under control conditions (●; $n = 22$) and 24 h after (10 mg kg^{-1}, i.p.) reserpine treatment (○; $n = 6$). * $P < 0.05$. Vertical lines show s.e.mean.

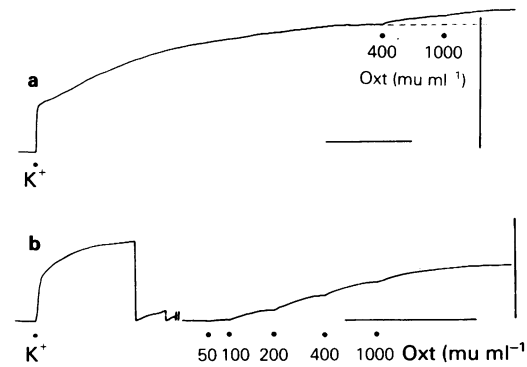

Figure 4 Effect of oxytocin (Oxt) on 80 mM K^+-depolarized rat aortic strips. (a) Effect of Oxt (400–1000 mu ml^{-1}) on K^+-depolarized strips after contractile tension has reached the maximum. (b) Effect of increasing concentrations of Oxt on K^+-depolarized strips after mechanical restoration of K^+-induced contractile responses to tension control values (2 g). Calibrations 1 g and 10 min.

Effect of different calcium concentrations on contractile responses induced by oxytocin

These experiments were designed to evaluate the effect of Ca concentration in the bathing media on the contractile response to Oxt. Concentration-response curves to Oxt (50 to 1000 mu ml^{-1}) were also obtained in the presence of low (0.45 mM), normal (1.8 mM) and high (4.0 mM) Ca media. In bisected aortic strips incubated in normal KBS, Oxt (50 to 1000 mu ml^{-1}) increased contractile force by 270.0 ± 18.4 mg (Figure 5a). Raising the Ca concentration from 1.8 to 4.0 mM shifted the control concentration-response curve for Oxt upward and to the left and the maximal contractile tension induced by 1000 mu ml^{-1} increased by 58.7 ± 4.28% (429.5 ± 20.2 mg; $n = 6$. $P < 0.001$). A reduction of Ca in the bathing media from 1.8 to

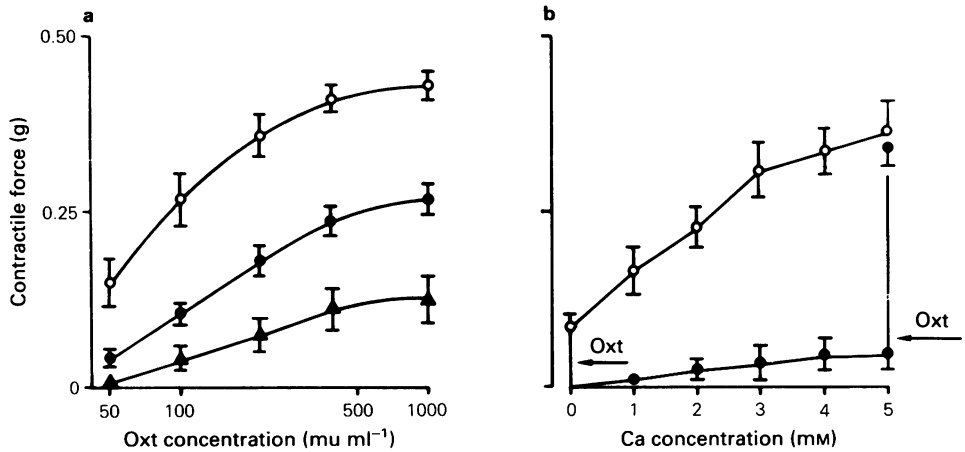

Figure 5 Calcium dependence of the contractile effect induced by oxytocin (Oxt) in bisected isolated aortic strips of the rat. (a) Dose-response curves for Oxt in strips previously equilibrated for 2 h in low, (▲) 0.45 mM, normal, (●) 1.8 mM, and high, (O) 4 mM, Ca^{2+} media. (b) Effect of cumulative addition of calcium (1–5 mM) on the contractile responses induced by Oxt in strips preincubated in Ca^{2+}-free Krebs solution for 2 h. (●) Control, (O) pretreated with Oxt, 200 mu ml^{-1}. Each point is the mean of at least 6 paired experiments; vertical lines show s.e.mean. $P < 0.05$ for all concentrations tested.

0.45 mM decreased the maximal contractile tension by 45.4 ± 5.2% (122.8 ± 42.1 mg; $n = 4$. $P < 0.01$) and shifted the control concentration-response curve to Oxt downward. Figure 5b shows that in aortic strips incubated in Ca-free KBS, Oxt (200 mu ml^{-1}) induced a significant increase in contractile force (23.2% of E_{max}) and significantly ($P < 0.001$) shifted the concentration-response curve to Ca (1 to 5 mM) upwards. When aortic strips were exposed to Ca-free KBS, cumulative addition of calcium (1 to 5 mM) to the bath of the control preparation produced a slight increase in the developed tension. The addition of Oxt, 200 mu ml^{-1}, when the maximal contractile response to 5 mM calcium chloride had been obtained, produced an increase in the developed tension which reached similar values to those obtained in Oxt-pretreated aortic strips (375.0 ± 50.8 mg compared to 371.7 ± 86.2 mg; $n = 6$. $P > 0.05$).

Effect of oxytocin on ^{45}Ca influx and ^{45}Ca efflux

The effect of Oxt on ^{45}Ca uptake into the La^{3+}-resistant fraction was estimated after 7 min in ^{45}Ca solution. After 5 min preincubation in radioactive solution, Oxt (600 mu ml^{-1}) increased the La-resistant Ca content by 34.1 ± 9.4% (0.88 ± 0.11 mmol kg^{-1} wet wt. compared to 1.19 ± 0.16 mmol kg^{-1} wet wt.; $n = 4$. $P < 0.05$). The effects of Oxt, 200 and 600 mu ml^{-1}, on ^{45}Ca efflux were also studied in 6 experiments. Aortic strips were washed in Ca-free medium during the first 15 min of the 25 min washout and then Oxt was added for the final 10 min of the washout. After exposure for 10 min to Oxt 200 or 600 mu ml^{-1} the desaturation curve was not significantly modified (Figure 6), which suggests that under these experimental conditions Oxt does not affect Ca efflux.

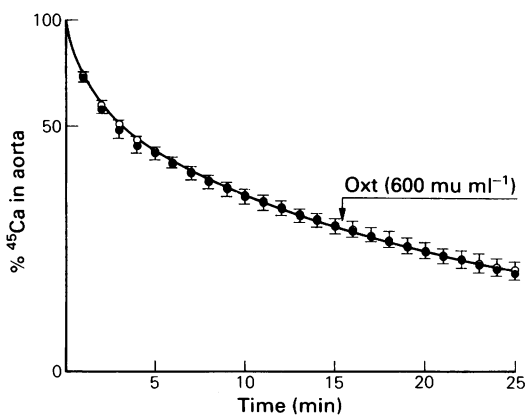

Figure 6 Effect of oxytocin (Oxt), 600 mu ml^{-1}, on ^{45}Ca efflux from rat isolated aortic strips. Muscles were incubated for 2 h in ^{45}Ca Tris (2 μCi ml^{-1}) prior to washout in Ca^{2+}-free Tris. Each point represents the mean of four to six experiments. (●) Control strips. (O) Oxt-treated strips (15 to 25 min). Vertical lines show s.e.mean.

Discussion

The results of this work demonstrated that in rat isolated aortic strips Oxt produced a dose-dependent contraction. Moreover, the effects of repeated doses of Oxt were smaller than those of the initial response. These findings confirm and extend previous evidence which demonstrated that the effects of repeated doses of Oxt were less than those of the first doses (Nakano & Fisher, 1963; Katz, 1964; Altura, 1975). Tachyphylaxis to the vasodilator and hypotensive actions of Oxt has also been described in rabbits, dog and man (Nakano & Fisher, 1963; Nakano, 1974). Unfortunately, the pharmacodynamic mechanism responsible for the genesis of tachyphylaxis remains uncertain. Moreover, the contractile response to Oxt seems to be species-dependent since this response was not observed in rabbit and guinea-pig aortic strips. This species difference is related to the different blood pressure responses to Oxt. Thus, in the rat Oxt did not modify cardiac rate and contractility but produced a hypertensive response (Lloyd, 1959; Krejci *et al.*, 1970), whereas it produced a hypotensive response in rabbit, dog, monkey, birds and man (Nakano, 1974).

The contractile response induced by Oxt in rat aorta was unaffected by pretreatment with different antagonists, i.e. phentolamine, practolol, atropine, diphenhydramine and cimetidine, which suggests that it is not mediated through stimulation of adrenoceptors, cholinoceptors or histamine receptors. Previous evidence has shown that the avian vasodepressor effect of Oxt or its vasodilator effect on canine arterial strips can be blocked by dichloroisoprenaline, a β-adrenoceptor blocking drug (Walaszek *et al.*, 1963). However, these results were obtained with synthetic Oxt, which contains chlorbutanol as a preservative, and it is well-known that chlorbutanol itself inhibits the contractile responses induced by different agonists as well as the ^{45}Ca movements in rat isolated aorta (Barrigón *et al.*, 1984). In addition, indomethacin, a potent inhibitor of prostaglandin synthesis (Vane, 1971), did not interfere with the contractile responses to Oxt. Pretreatment with the Oxt antagonist deamino-ethyl-Oxt shifted the concentration-response curve to Oxt downward decreasing its maximal contractile response. This result suggests that deamino-ethyl-Oxt behaves as a non-competitive antagonist of Oxt in the rat aortic strip. However, it has been shown previously that this antagonist caused a parallel displacement of the dose-response curve without a decrease in the maximal response to Oxt in the rat uterus, which indicates that its inhibitory effect was competitive (Melin *et al.*, 1981). Since Oxt vascular receptor binding studies are not available at present, we cannot know if this paradoxical antagonism on aortic strips, compared to the uterus, occurs at the receptor or at a site remote from the receptor by a distinct pharmacodynamic mechanism. Finally, reserpine potentiated the contractile effect of Oxt on the isolated aortic strips. The mechanism of such potentiation remains unclear. In fact, Carrier & Jurevics (1972) have suggested that tissue calcium is involved in the phenomenon of supersensitivity since they found an increased available Ca fraction for mobilization in response to NA and isoprenaline and an increased membrane permeability to extracellular Ca in response to acetylcholine and K in reserpine-treated rabbit aortic strips. However, a change in the number and/or in the affinity of the Oxt receptor in rat aortic strips after reserpine treatment cannot be excluded.

It is generally accepted that the contractile response of smooth muscle cells is triggered by an increase of the free cytoplasmic concentration of Ca ions. This increase may be due to an increased net influx of Ca ions from the extracellular medium through voltage- or receptor-operated channels (VOCs and ROCs, respectively), to a release of Ca ions from intracellular stores or a combination of the two (Bolton, 1979; Casteels, 1980).

Some of the results presented in this paper suggest that the Oxt-induced contractile response is partly mediated by an increase in Ca influx through ROCs. The experimental evidence is supported by four observations which are: (a) the contractile response to Oxt was markedly influenced by the concentration of extracellular Ca. Thus, the maximum effect of Oxt was greatly enhanced by increasing the Ca concentration in the bathing media from 1.8 to 4.0 mM. On the other hand, decreasing the concentration of Ca from 1.8 to 0.45 mM provoked a significant reduction in the contractile response. Moreover, Oxt increased the contractile responses induced by cumulative addition of Ca and thus shifted upwards the dose-response curve to Ca added to strips incubated in Ca-free solution.

(b) Pretreatment with verapamil, a Ca entry blocker (Fleckenstein, 1977), or with deamino-ethyl-Oxt shifted the dose-response curve to Oxt downward and to the right and reduced its maximal contractile response. Also, deamino-ethyl-Oxt caused a relaxation of Oxt-contracted strips. These results suggest that the contractile response to Oxt is related, at least partly, to its ability to increase the influx of Ca through ROCs.

(c) Oxt induced a small contractile response in strips previously contracted with high K, which is known to increase Ca influx through VOCs. However, Oxt did not evoke a contractile response when the strips were previously contracted by NA which increases Ca influx through ROCs. This provides further evidence that Oxt produces an increase of Ca influx through ROCs.

(d) Finally, Oxt increased the La^{3+}-resistant ^{45}Ca uptake in aortic strips without altering ^{45}Ca efflux.

In uterine smooth muscle fibres it has been demonstrated that at high concentrations the effects of Oxt are accompanied by a reduction of the resting potential. A depolarization of vascular smooth muscle fibres can lead to an increase in Ca entry through VOCs. In the present experiments Oxt induced spontaneous myogenic activity superimposed on the contractile response. Such activity has been attributed to a spontaneous depolarization of the vascular smooth muscle membrane which in turn increases its permeability to Ca possibly through activation of VOCs (Somlyo & Somlyo, 1968; Golenhofen & Lammel, 1972). Moreover, Oxt-induced myogenic activity was suppressed after removal of Ca from the Krebs solution or in strips pretreated with verapamil. Since the effects of Oxt on resting potential in rat aortae are unknown, these results represent only indirect evidence that at high concentrations Oxt may increase Ca influx, not only by activation of the ROCs but also through activation of the VOCs.

However, there are some results in this paper which suggest that, as previously found with other neurotransmitters (Bolton, 1979; Cauvin *et al.*, 1983), Oxt-induced contractile responses are due not only to an increase in Ca influx but may also be mediated through the release of intracellular Ca. Such an effect is supported by the finding that Oxt was able to produce a contractile response in aortic strips incubated in Ca-free Krebs solution. In addition, the contractile response induced by Oxt was only reduced to about half of the maximal response in strips pretreated with verapamil, which indicates that it induces a contractile response to a large extent through a mechanism that is independent of extracellular Ca. Furthermore, Oxt induced a contractile response in strips previously contracted with high-K, but a response was not observed in strips previously contracted with NA. The contractile response induced in depolarized strips can be explained on the assumption that in vascular smooth muscle fibres where VOCs have been activated by membrane depolarization, Oxt may induce a further increase in Ca entry through the activation of the ROCs or an increased release of intracellular Ca, or both mechanisms. Recently, it has been demonstrated that the same intracellular Ca store is released not only by NA but also by other neurotransmitters (Deth & Van Breemen, 1974; Loutzenhizer & Van Breemen, 1981). This concept of one common intracellular store, which can be released either by NA or Oxt, may also explain why Oxt-induced contractile responses were not observed in strips previously contracted by NA.

In conclusion, this study shows that in rat isolated aortic strips Oxt produced a contractile response which, as previously found with other neurotransmitters, can be partly attributed to an increase of Ca influx through receptor-operated channels and in part to the release of Ca from intracellular stores.

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