received food and water ad libitum. 2 weeks later the experiment was repeated once in a crossed-over-design.

All score values refering to a certain injection time and a certain treatment condition were averaged for each animal separately and the mean values obtained under either saline or naltrexone treatment were compared to one another, using the Wilcoxon test for paired samples.

Naltrexone had no influence on the sleeping behaviour during the adaptation period (days 1-3 of hibernation conditions). Thereafter, naltrexone decreased the score for sleeping behaviour at the observation period prior to and after the midnight injection by an average of 46% ($p < 0.05$; figure 2), as compared to saline treatment. At the other 3 observation periods, no statistically significant changes were observed.

These preliminary results seem to indicate an involvement of endogenous opioids in the control of hibernation, possibly dependent upon regular endogenous fluctuations over time. Endorphins are known to modulate neurotransmitter systems. For example, they inhibit the release of noradrenaline[4], whose turnover is changed during hibernation in the same direction, i.e. depressed[5]. Thus, opiate receptor blockade may cause disturbances of neurotransmitter systems participating in the control of hibernation. However, the endorphins seem to have only a partial influence upon neuronal mechanisms involved in the control of hibernation, which may explain why no effect of naltrexone could be seen in a few animals.

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Action of histamine on phasic and tonic components of vascular smooth muscle contraction[1]

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Summary. The isometric contractile response of rabbit aortic strips in response to histamine was studied. Biphasic dose-dependent contractions reflecting release of internal Ca^{2+} (phasic component) and simultaneous mobilization of external Ca^{2+} stores (tonic component) were produced.

Vascular smooth muscle constitutes an important effector system permitting appropriate adjustment of vascular tone to the existing physiological state. Hence, functional properties and effects of drugs acting on this tissue have been widely studied. Recently, it has been appreciated that activation of vascular smooth muscle may involve mobilization of internal and/or external Ca^{2+} stores depending upon the agonist used. Biphasic contractions of vascular smooth muscle in response to catecholamines have been described as consisting of an initial rapid rise in tension (fast component) reflecting release of intracellular Ca^{2+} followed by a slower (slow component) phase dependent on extracellular calcium[3-15]. The endogenous vasoconstrictor, angiotensin, activates arterial smooth muscle by a process independent of extracellular calcium while histamine produces a biphasic response similar to that elicited by norepinephrine[3,4,13]. The above findings have led to the concept of phasic and tonic components of contraction as being functional properties of vascular smooth muscle. However, those descriptions relate only to maximal effective agonist concentrations and do not provide quantitative information about these functional properties of vascular smooth muscle. Recently, we have developed a new approach for studying the effects of drugs on the phasic and tonic components of vascular smooth muscle contraction which affords detailed information about the functional properties of vascular smooth muscle[16,17]. The purpose of the present study was to examine the actions of histamine on phasic and tonic components of vascular smooth muscle contraction.

Materials and methods. Aortic strips were prepared from 2-3 kg New Zealand White rabbits according to the method of Furchgott[18]. Strips were mounted isometrically in isolated organ baths containing 28 ml of Krebs-Henseleit bicarbonate solution[19] (KHB, 37±1 °C) equilibrated with a 95% O_2 5% CO_2 gas mixture (pH=7.4). Isometric contractions were recorded with Grass FTO3 linear force displacement transducers and were displayed on a Grass Model 7 polygraph. For experiments using Ca^{2+}-free KHB, Ca^{2+} was

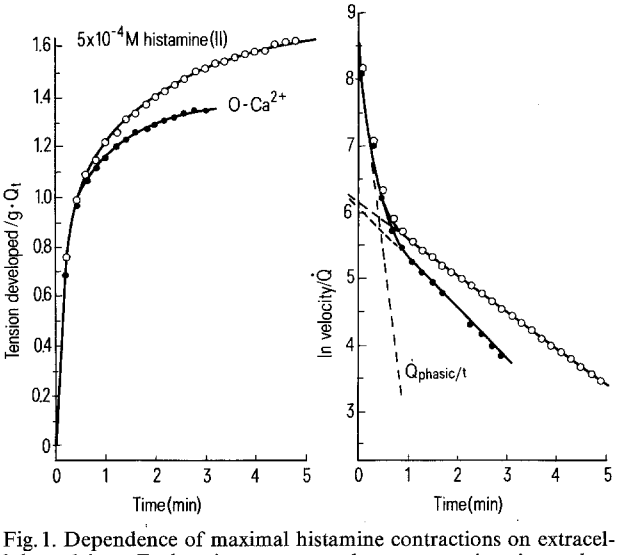

Fig. 1. Dependence of maximal histamine contractions on extracellular calcium. Each point represents the mean tension-time values for control ○ and calcium-free ● contractions. ( )=number of rabbit aortas. Dashed lines indicate resolved components of contraction.

Contraction velocity analysis for histamine-induced contraction in the presence and absence of extracellular calcium and different histamine concentrations

	Contraction velocity parameters ± SE of estimate[b]				Tension (mg)			
	Phasic		Tonic		Q_{phasic}	Q_{tonic}	Q_{tot}	$Q_{experimental}$ ± SEM
	ϕ_1 mg/min	ϕ_2 min^{-1}	θ_1 mg/min	θ_2 min^{-1}				
Calcium present 2.55 mM								
Yes[a] (11)	6313 ± 1.09	6.93 ± 0.01	467 ± 1.03	0.55 ± 0.001	911	798	1709	1633 ± 58
No[a] (11)	6531 ± 1.44	6.90 ± 0.23	448 ± 1.10	0.78 ± 0.003	947	523	1470	1348 ± 60[c]
Histamine concentration (M)								
1×10^{-6} (5)	1788 ± 1.40	5.21 ± 0.17	365 ± 1.07	0.55 ± 0.002	343	582	925	873 ± 96
1×10^{-5} (6)	1875 ± 1.18	5.14 ± 0.04	515 ± 1.03	0.55 ± 0.001	365	877	1242	1256 ± 113
1×10^{-4} (10)	3847 ± 1.08	5.33 ± 0.01	488 ± 1.03	0.52 ± 0.001	722	876	1598	1547 ± 138
1×10^{-3} (6)[d]	5101 ± 1.08	6.09 ± 0.01	262 ± 1.03	0.33 ± 0.001	838	684	1522	1463 ± 119

[a] Maximal effective concentration, 5×10^{-4} M; ( ), number of rabbit aortas. [b] Calculated from regression line[20,21]. [c] $p < 0.05$. [d] Supramaximal concentration.

simply omitted and the KHB contained 2.4×10^{-4} M EGTA. Histamine diphosphate was prepared fresh immediately before use and added to the bath in 0.1 ml volumes. The responses were examined by contraction velocity analysis, details of which may be found elsewhere[17]. Briefly, the ln velocity of contraction was plotted vs time and fitted to the expression $\dot{Q}_t$ (velocity at any time t (min)) = $\Phi_1 e^{-\Phi_2 t} + \theta_1 e^{-\theta_2 t}$ where Φ_1 and θ_1 are the velocity at time zero and Φ_2 and θ_2 are contraction velocity constants. The 2nd term was identified by experiments in Ca^{2+}-free KHB as the tonic component of contraction and hence the symbols Φ and θ refer to the phasic and tonic components of contraction, respectively.

Results and discussion. Initial experiments were carried out with histamine to determine the profile of the tension development curve and also the dependence of contraction on extracellular calcium ion (Ca^{2+}-free KHB). Figure 1 shows the tension development curve for a maximal effective concentration of histamine (5×10^{-4} M) is very similar to that of norepinephrine[3-5,16,17] insofar as a fast and a slow component of contraction are evident. Further inspection shows that in the absence of extracellular calcium, the fast component did not appear to be greatly affected; the slow component was greatly diminished and the total tension acheived was decreased from 1633 ± 58 mg in the presence of, and to 1348 ± 60 mg in the absence of extracellular calcium. The velocity of contraction plot for these histamine-induced contractions in the presence and absence of extracellular calcium is also shown. The contraction velocity constant (θ_2) of the 2nd component of contraction was significantly increased in the absence of extracellular calcium. The table shows that the calculated phasic contribution to the total contraction was essentially the same. However, the contribution of the tonic component was decreased from 798 to 523 mg by extracellular calcium deprivation. The decrease in the tonic component completely accounted for the diminished developed tension. The effect of varying concentrations of histamine on the contribution of phasic and tonic components of contraction to total tension developed was studied. For these studies, strips were contracted with increasing concentrations of histamine. Each strip was exposed only once to histamine. Figure 2 depicts the curves for the development of tension with time for 4 different histamine concentrations. The table also summarizes the results of contraction velocity analysis for the curves shown in figure 2. For each concentration, the experimental values for the velocity of contraction were fitted exceedingly well by a 2-term exponential function. This is indicated by the small SE of estimate of regression for the contraction velocity parameters and by the close correspondence of the total tension predicted by the fitted function with the actual maximal experimental tensions observed. Like norepinephrine[16,17], the contraction velocity constant (θ_2) for the tonic component did not vary with agonist concentration except at a supramaximal concentration (table). The major influence of histamine concentration was observed on the initial velocity of contraction (at zero time) which increased with concentration, particularly for the phasic component. As the table shows, the calculated contribution of the phasic component to total developed tension with increasing concentrations of histamine increased from 37% at the smallest concentration (1×10^{-6} M) to 55% at a maximal effect concentration (1×10^{-5} M). These results are quite similar to those obtained with norepinephrine and acetylcholine[16,17]. In summary, histamine contracts vascular smooth muscle by causing simultaneous activation of phasic and tonic Ca^{2+} pools. This action is common to norepinephrine and acetylcholine[16,17].

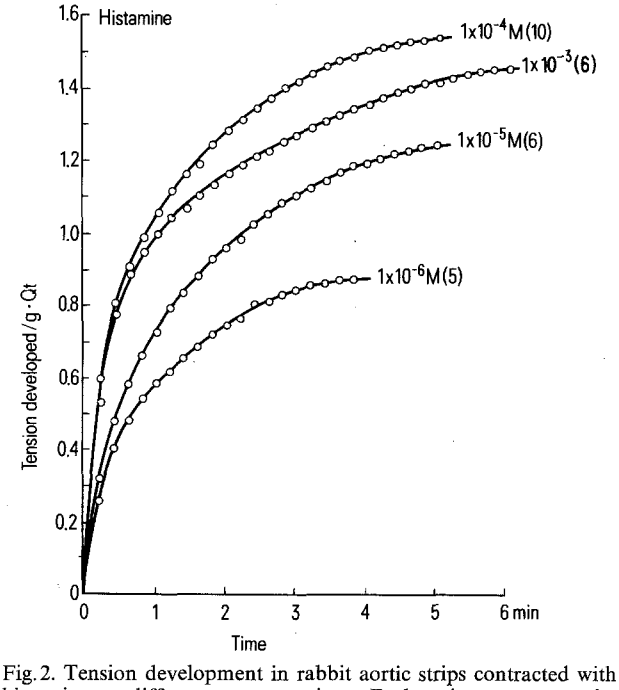

Fig. 2. Tension development in rabbit aortic strips contracted with histamine at different concentrations. Each point represents the mean tension-time value, ( ) = number of aortas.

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Effect of cyproheptadine on the octopamine-induced responses in the mammalian central nervous system[1]

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Summary. Extracellular recordings have been made from rat thalamic neurones anaesthetized with urethane, 1.5–2 g/kg i.p. Iontophoretically applied octopamine excited certain thalamic neurones in the ventral basal complex while inhibiting others. Both effects were reversibly antagonized by iontophoretically applied cyproheptadine without affecting responses to noradrenaline and dopamine.

There is now considerable evidence for a role for octopamine as a transmitter or modulator in the invertebrates[2–4]. Octopamine has been found to have an uneven distribution in the mammalian brain[5] and its levels can be manipulated following drug pretreatment[6]. Octopamine has also been shown to have actions on rat cortical neurones which would appear to be distinct from a possible effect on noradrenaline or dopamine receptors[7]. These authors reported that propranolol and α-flupenthixol specifically blocked noradrenaline and dopamine induced responses respectively on rat cortical neurones, without having an effect on octopamine responses. Metoclopramide had no effect on any of the responses to these amines. However we have found that none of these antagonists were of use in differentiating between octopamine and dopamine or noradrenaline-induced responses to rat thalamic neurones in the ventral basal complex. During an investigation to try and find a specific octopamine antagonist we have found that cyproheptadine can selectively and reversibly block the inhibitory or excitatory actions of octopamine on thalamic neurones within the ventral basal complex without affecting either noradrenaline or dopamine responses.

Materials and methods. Experiments were performed on 15 male Wistar Albino rats weighing 200 g and anaesthetized with urethane 1.5–2 g/kg i.p. Extracellular recordings were made from single neurones in the ventral basal complex of the thalamus using parallel multibarrel glass microelectrodes[8]. Cells were identified by stimulating the locus coeruleus using a concentric bipolar stimulating electrode. The position of the neurones was located by ejecting Pontamine Sky Blue from the recording barrel[9] and then preparing frozen sections. The drugs in this study were iontophoretically ejected from the multibarrel microelectrode. DL-Octopamine, dopamine, (−)-noradrenaline and 5-hydroxytryptamine, all at 0.5 M, were ejected as cations, as was cyproheptadine hydrochloride, 3 mM. L-Glutamate, 0.5 M was ejected as an anion. Current balancing was used during the ejection of all drugs[10].

Results and discussion. Cyproheptadine was tested on the responses to noradrenaline and octopamine on 18 neurones in the ventral basal complex of the thalamus. Octopamine, 30–70 nA, was reversibly blocked by cyproheptadine, 5–40 nA, on all 18 different thalamic neurones where cyproheptadine had no effect on the noradrenaline response. The table shows in 10 cases both amines inhibited the activity of the neurone under test, in 1 case octopamine inhibited the cell while noradrenaline excited, in 4 cases octopamine excited the cell while noradrenaline inhibited and in 3 cases both amines excited the neurones. The figure shows the result of an experiment where both amines inhibited cell activity. Glutamate, 10 nA, excited the cell while noradrenaline and octopamine, both at 50 nA, inhibited cell activity (figure, a). In the presence of cyproheptadine, 30 nA for a total of 5 min, there was no effect on the noradrenaline and glutamate responses while the octopamine response was completely blocked (figure, c). In the figure, d, can be seen the recovery of the octopamine response. It took 6–7 min for the octopamine response to completely recover. Note

The table shows the effects of 18 thalamic neurones in the ventral basal complex tested with both octopamine and noradrenaline. All the octopamine responses were reversibly blocked by cyproheptadine (30 nA) where cyproheptadine had no effect on the noradrenaline responses

	Noradrenaline Excitation	Inhibition
Octopamine Excitation	3	4
Inhibition	1	10