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# INTERACTIONS OF YEAST EXTRACTS AND THEIR CONSTITUENTS WITH MONOAMINE OXIDASE INHIBITORS

BY

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Attacks of hypertension and headache have occurred in patients taking monoamine oxidase inhibitors and a yeast extract Marmite (Blackwell, Marley & Ryle, 1964). The attacks were very similar to those in patients taking monoamine oxidase inhibitors who eat cheese (Blackwell, 1963) or broad beans (Hodge, Nye & Emerson, 1964). These foods contain sympathomimetic amines or their precursors.

In experiments with animals treated with amine oxidase inhibitors there were marked differences between the effects of cheese and of yeast extracts. This was due to the presence of a substance with histamine-like properties as well as one with sympathomimetic activity in the extracts. The sympathomimetic rather than the histamine-like effects were potentiated by amine oxidase inhibition. However, in the cat the absorption of histamine from the yeast extract in the intestine appeared to be facilitated by amine oxidase inhibition so that large quantities of a histamine-like substance reached the systemic circulation. In addition to other histamine-like effects those due to the yeast extract on the spinal cord reflexes and electromyogram proved to be hitherto undescribed actions of histamine and are to be presented separately. A preliminary account of some of the experiments has been published (Blackwell, Marley & Mabbitt, 1965) and the results have also been communicated to the British Pharmacological Society (Blackwell & Marley, July, 1964).

## METHODS

The methods for anaesthetizing and pithing the rat and for anaesthetizing the cat in acute and in recovery experiments after removal of the superior cervical and nodose (vagal) ganglia, the methods for making spinal cats, for implanting cannulae, for intraduodenal injections, for superfusion experiments and for assay of tyramine have been described previously (Blackwell & Marley, 1966). The following additional methods were used.

### *Guinea-pig*

Guinea-pigs weighing 400 to 800 g were prepared for recording resistance of the lungs to inflation *in vivo* by the method of Konzett & Rössler (1940). The animals were anaesthetized with urethane (10 ml./kg of 25% solution, intraperitoneally), and artificially ventilated by a pump after insertion of a tracheal cannula. Rectal temperature was maintained at 35 to 40°C. A cannula was tied into a jugular vein for intravenous injections and a polyvinyl tube was tied into the second part of the duodenum for intraduodenal injections.

*Cat*

*Gastric secretion.* Cats were deprived overnight of food but not water. The abdomen was opened in the midline, the pyloro-duodenal junction occluded, preserving the pancreatico-duodenal arteries, and a cannula was tied into the greater curvature of the stomach. The oesophagus was tied at its junction with the stomach, and the vagi cut in the neck. After washing out the stomach with warm saline, the abdomen was closed round the cannula and the animal was turned on its side. Gastric juice was collected in graduated centrifuge tubes. For estimation of free and total hydrochloric acid, the specimen was titrated with 0.1 N-sodium hydroxide after the addition of Töpfers reagent, and later alcoholic phenolphthalein. In these experiments, the drug or yeast extract was injected into the duodenum distal to the occluded pyloro-duodenal junction.

*Reflex anterior tibialis twitch.* After fixing the leg by a drill through the lower end of the femur, the reflex was elicited by stimulating the central end of the divided posterior tibial nerve with supramaximal pulses fo 0.5 msec duration at rates of 8 to 12 shocks min. The resulting twitch of the tibialis anterior was recorded with a Brown-Schuster myograph writing on smoked paper. In these experiments the spinal cord was transected at the thoracico-lumbar junction and the nerves to the contralateral limb were divided.

*Limb volume.* This was measured by enclosing the shaved limb in a cylinder connected to a spirometer writing on a smoked drum. The system was made airtight by sealing the cylinder to the limb with celloidin.

*Electrocardiogram and electromyogram.* The recording electrodes were made from 50 cm lengths of Diamel-coated silver wire, 0.3 mm in diameter, prepared as described by Key & Marley (1961). They were inserted into the precordial region and into the adductor muscles of the thigh for recording electrocardiac and electromyographic activity respectively on an eight-channel Kaiser electroencephalograph.

*Haematocrit.* Blood from heparinized cats was pipetted up to the 100 mm mark in Wintrobe haematocrit tubes and centrifuged at 3,000 rev/min for 30 min and the volume of packed red cells read directly from the tube.

*Yeast extracts.* These were obtained locally except for some samples of Marmite (Salt Marmite) and Salt-free Marmite given by Bovril Ltd. The yeast and meat extract, B-V, was obtained in Boston, Massachusetts. Special preparation was not crucial since effects were obtained with extracts made up in distilled water, saline or acidified with 0.1 N-hydrochloric acid; preparation for intravenous injection is described in the text. Marmite was the yeast extract used in most experiments. In the text Marmite refers to Salt Marmite unless otherwise specified.

*Drugs*

These (with molecular weights of salts in parentheses) were the hydrochlorides of cocaine (340), α-methylbenzylhydrazine (170), nialamide (329), phenoxybenzamine (340) and tyramine (174). Also used were Compound 48/80, (−)-adrenaline bitartrate (333), bradykinin, chlorpheniramine dimaleate (391), hexamethonium bromide (362), histamine acid phosphate (307), Hydergine (the methonesulphonate of the dihydro derivative of ergotoxine), hyoscine, hydrobromide (438), (−)-isoprenaline sulphate (556), mepyramine (401), (±)-propranolol (280) and (±)-tranylcypromine (360). The doses are given in μmoles/kg except for bradykinin, Compound 48/80 and Hydergine.

## RESULTS

### *Rat*

*Intravenous injection of yeast extract*

Yeast extract was prepared by mixing with saline and centrifuging to remove particles. As shown in Fig. 1,*a* intravenous injection of the supernatant fluid (Salt Marmite, 80 mg/kg) produced a rise of blood pressure preceded by a brief depressor and followed by a longer depressor component. The pressor activity of the yeast extract (30 mg/kg) was abolished by phenoxybenzamine (3 μmoles/kg). The fall of blood pressure elicited by the yeast extract or by histamine (1 μmole/kg) was still obtained after phenoxybenzamine and was unaffected by a dose of propranolol (2 μmoles/kg), an antagonist at β-receptors, which abolished the depressor effect of isoprenaline (0.12 μmole/kg). All these injections were

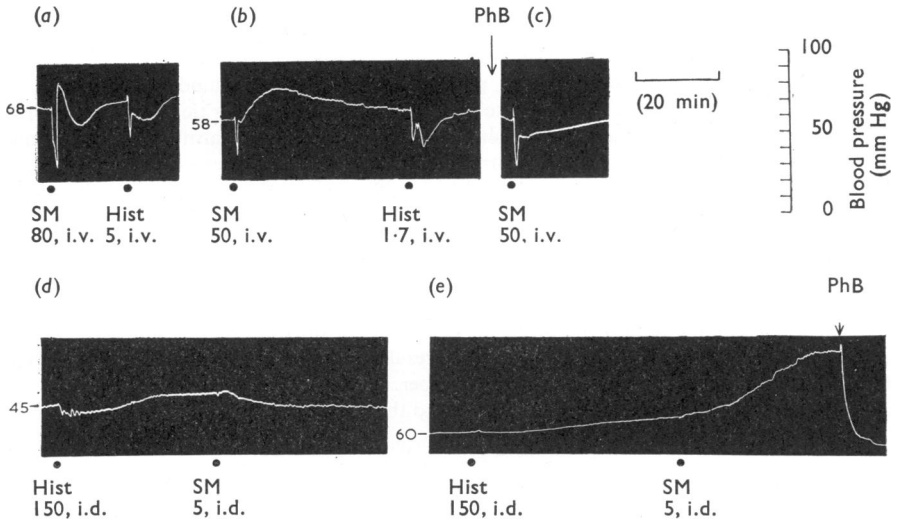


Fig. 1. Blood pressure responses in pithed rats. (*a*) Pithed rat. Blood presssure effects of the yeast extract Marmite (SM, doses in mg/kg) and of histamine (Hist, doses in μmoles/kg) injected intravenously. (*b*) and (*c*) Pithed rat previously treated with α-methylbenzylhydrazine (2 μmoles/kg, intraperitoneally for 7 days). The pressor response to yeast extract injected intravenously was much prolonged, and later (*c*) was antagonized by phenoxybenzamine (PhB 20 μmoles/kg, intravenously), whereas histamine lowered the blood pressure. (*d*) Pithed rat. Histamine or the yeast extract Marmite injected intraduodenally each produced a small fall in blood pressure. (*e*) Pithed rat treated with α-methylbenzylhydrazine (30 μmoles/kg, intraperitoneally 18 hr and 30 μmoles/kg, intraperitoneally 90 min previously). Histamine injected intraduodenally produced a small, and yeast extract a large, rise in blood pressure completely antagonized by phenoxybenzamine (20 μmoles/kg, intravenously). I.v. = intravenous; i.d. = intraduodenal.

intravenous. These results suggested that the yeast extract contained a pressor substance active on cardiovascular α-receptors and a histamine-like substance which lowered the blood pressure.

Tests were next made in a rat which had been treated with α-methylbenzylhydrazine (2 μmoles/kg, intraperitoneally daily for 7 days). As shown in Fig. 1,*b* a prolonged rise of blood pressure was obtained on intravenous injection of the extract (Salt Marmite, 50 mg/kg) although histamine remained depressor. The blood pressure was restored to normal by phenoxybenzamine (20 μmoles/kg, intravenously) following which intravenous injections of the extract elicited only a fall in blood pressure (Fig. 1,*c*).

*Intraduodenal injection of yeast extract*

As illustrated in Fig. 1,*d*, histamine (150 μmoles/kg) or the yeast extract (5 g/kg) injected intraduodenally elicited small depressor responses. After treatment with α-methylbenzylhydrazine (30 μmoles/kg, 18 hr previously and 30 μmoles/kg, intraperitoneally 90 min previously) the same dose of histamine given intraduodenally produced a sustained but small rise in blood pressure (Fig. 1,*e*) whereas the yeast extract elicited a rise in blood pressure of 60 mm Hg. The blood pressure was restored to normal by phenoxybenzamine (20 μmoles/kg, intravenously).

*Cat*

*Intravenous injection of yeast extract*

As shown in Fig. 2, histamine or the yeast extract (Salt-Free Marmite) injected intravenously into an acutely adrenalectomized cat produced an immediate fall in arterial blood pressure and a rise in jugular venous pressure. In contrast, tyramine had pressor activity but was ineffective on the jugular venous pressure.

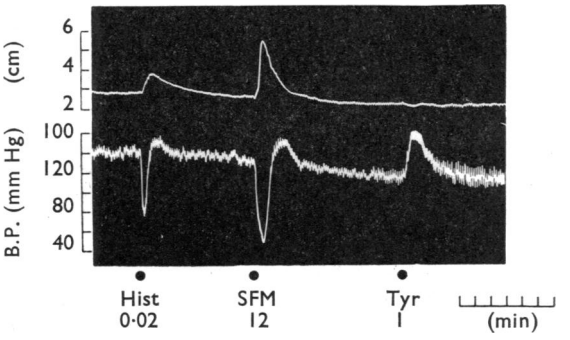


Fig. 2. Effect of intravenous injections of histamine, yeast extract and tyramine on jugular venous pressure and arterial blood presssure. Cat 4.2 kg; chloralose anathesia. Both adrenal glands were excluded from the circulation by ligatures. Upper trace, jugular venous pressure; lower trace, arterial blood pressure. Histamine (Hist, in μmoles/kg) and yeast extract (SFM, salt-free Marmite, in mg/kg) produced an immediate fall of arterial blood pressure accompanied by an increase in jugular venous pressure. Tyramine (Tyr, in μmoles/kg) raised the arterial blood pressure but was without effect on the jugular venous pressure.

In a cat treated with α-methylbenzylhydrazine (60 μmoles/kg, intraperitoneally 24 hr previously and 60 μmoles/kg, intraperitoneally 90 min beforehand) the yeast extract injected intravenously contracted the nictitating membrane, but the fall of blood pressure was now followed by a rise (Fig. 3,*a*) which was greater with Salt Marmite than with salt-free Marmite. Histamine injected intravenously evoked only a fall in blood pressure and a contraction of the nictitating membrane. With repeated intravenous injections of the salt yeast extract, the rise in blood pressure became progressively smaller, although the fall in blood pressure was still observed. The effects on the blood pressure of the third and seventh intravenous injections are shown in Fig. 3,*b* and *c*. The effect on the nictitating membrane were also smaller with the seventh injection and of similar magnitude to that obtained with the only dose of the salt-free extract (compare Fig. 3,*c* and *a*).

The waning pressor effects and diminishing contraction of the nictitating membrane which occurred on repeated injection of the extract suggested tachyphylaxis to a sympathomimetic substance, whilst the residual fall in blood pressure and persistent smaller contraction of the nictitating membrane were compatible with the presence of a histamine-like substance.

*Intraduodenal injection of yeast extract*

In six control cats, the yeast extract Marmite (2.5, 5.0 or 10 g/kg) injected intraduodenally was ineffective on the nictitating membrane although transient 20 mm Hg changes in blood

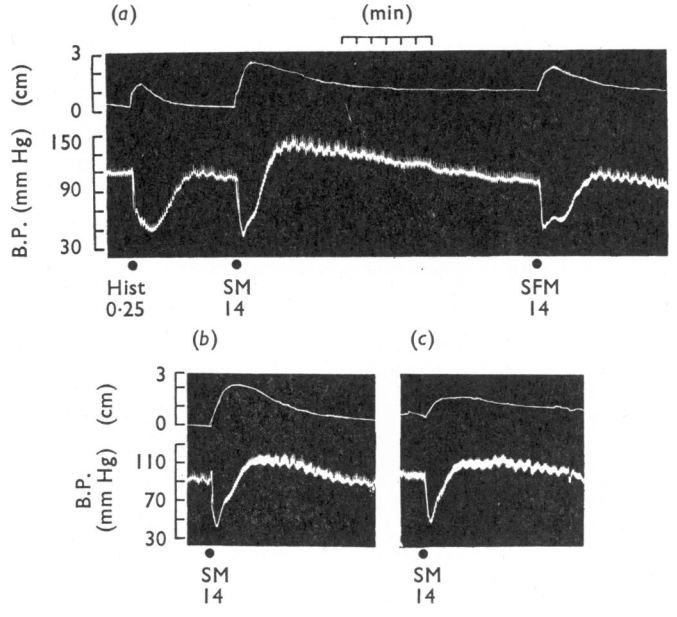


Fig. 3. Responses of the nictitating membrane and blood pressure in a 3.6 kg cat, anaesthetized with chloralose and treated with α-methylbenzylhydrazine 60 μmoles/kg intraperitoneally 24 hr and 60 μmoles/kg intraperitoneally 90 min previously. (*a*) Responses to histamine (Hist, in μmoles/kg), and the yeast extracts Marmite (SM, in mg/kg) and salt-free Marmite (SFM, in mg/kg) injected intravenously. (*b*) and (*c*) Third and seventh intravenous injections of Marmite respectively. The contraction of the nictitating membrane and the pressor component of the blood pressure response were progressively reduced; the depressor component was little affected.

pressure occurred. However, after giving α-methylbenzylhydrazine (60 or 120 μmoles/kg), nialamide (76 or 132 μmoles/kg) or tranylcypromine (5.6 μmoles/kg) intraduodenally, the intraduodenal injection of yeast extract (2.5, 5.0 or 10 g/kg), 60 to 120 min later, had considerable effects.

*Blood pressure.* The changes in blood pressure developed within 10 min of injecting the extract. In seven of sixteen cats tested, there was an average blood pressure fall of 35 mm Hg, lasting over 60 min. In three of the sixteen experiments, there was a fall lasting 3 to 10 min followed by a rise in blood pressure lasting over 60 min. In another four cats there was no initial fall and the blood pressure rose between 30 and 70 mm Hg (Fig. 8). In two cats there was no change in blood pressure.

*Electrocardiogram.* The electrocardiogram was recorded in seven cats. The usual electrocardiographic changes elicited by the intraduodenal injection of Marmite in cats previously treated with an amine oxidase inhibitor consisted of moderate bradycardia, or tachycardia accompanying the rise of blood pressure. In one cat given α-methylbenzylhydrazine (120 μmoles/kg 120 min previously) 3 min after injecting the yeast extract Marmite (5 g/kg, intraduodenally) the heart rate slowed from 228 to 157 per min with diminution of the QRS complexes and deepening of the T waves; atrioventricular conduction was normal. In this cat, however, at 9 min the rhythm became grossly abnormal. There was now no clear relation between the auricular (P wave) and ventricular (QRS)

complexes and there were frequent ventricular extrasystoles. At 20 min the rhythm and rate were again normal although the QRS complexes were reduced in amplitude.

*Nictitating membrane.* The nictitating membrane contracted vigorously in all sixteen experiments, the mean contraction (on the drum) being 7 cm. Although the effects on the blood pressure preceded those on the nictitating membrane, contraction of the membrane was the more sustained (Fig. 8).

*Localization of the site of action of the substances in yeast extracts*

These sympathomimetic effects of the yeast extract were obtained in cats previously treated with amine oxidase inhibitors and with the brain destroyed or the cervical sympathetic preganglionic trunks divided, and so were not due to an action on the brain or spinal cord. Tests were next made to see whether the effects were due to an action on ganglia or on sympathetic postganglionic nerves.

*Nictitating membrane.* Experiments were made in cats with the superior cervical ganglion acutely excised on one side but intact on the other. The adrenal glands were also removed. As shown in Fig. 4,*a*, both nictitating membranes contracted to tyramine or adrenaline injected intravenously. Histamine or the yeast injected intravenously contracted the membrane with its superior cervical ganglion *in situ* but not that with its ganglion removed. This observation was compatible with the yeast extract containing histamine, which contracts the nictitating membrane in the adrenalectomized cat by an action on the

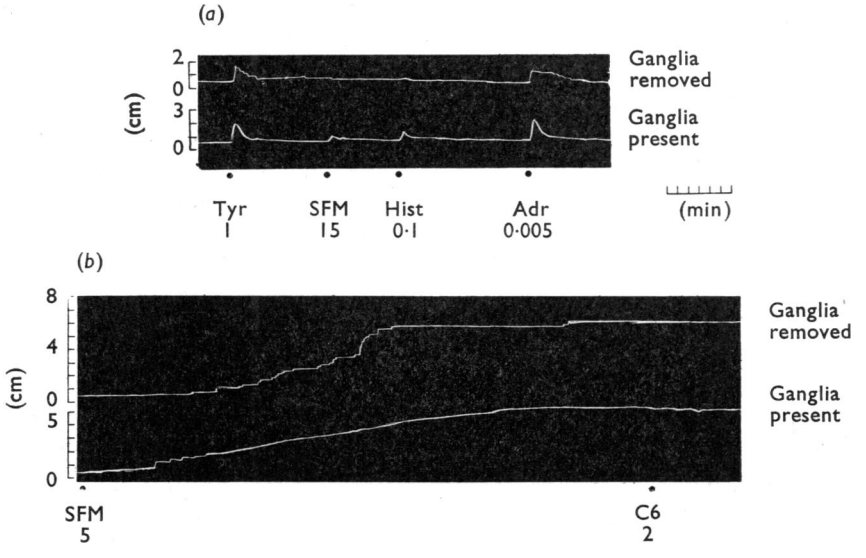


Fig. 4. Responses of the nictitating membranes with the superior cervical and nodose ganglia removed (upper trace) and with the ganglia intact (lower trace) in a 3.5 kg cat anaesthetized with chloralose. (*a*) Contractions of the membrane with the ganglia intact to intravenous injections of tyramine (Tyr, in μmoles/kg), to the yeast extract salt-free Marmite (SFM, in mg/kg) to histamine (Hist, in μmoles/kg) and to adrenaline (Adr, in μmoles/kg), but contraction of the membrane with the ganglia removed only to tyramine and to adrenaline. (*b*) Contraction of both membranes to salt-free Marmite (5 g/kg) injected intraduodenally 120 min after α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally). Finally, hexamethonium (C6, in μmoles/kg) was injected intravenously.

superior cervical ganglion (Trendelenburg, 1954). After injecting this cat with α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally 120 min previously) the sympathomimetic rather than the histamine-like effects of the yeast extract were evident. On giving the salt-free yeast extract (5 g/kg) intraduodenally (Fig. 4,*b*) sustained contraction of both membranes developed in the ensuing 6 to 12 min, but more strongly on the side without the superior cervical ganglion.

*Iris.* Tests were made in a cat in which the superior cervical ganglion had been excised 16 days previously. Both adrenal glands were removed. Nialamide (76 μmoles/kg) was given intraduodenally 120 min before the yeast extract. At 30 min after injecting the yeast extract (2 g/kg, intraduodenally) the blood pressure had risen 30 mm Hg, and the innervated iris had dilated, but the denervated iris remained constricted.

*Absorption of tyramine from the yeast extract*

In a cat given α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally) 120 min previously, tyramine was not detected in the plasma. When the yeast extract Marmite (10 g/kg) was injected intraduodenally and its effects on the blood pressure and nictitating membrane had developed, the plasma contained tyramine (0.008 μmoles/ml.).

*Experiments with drug antagonists*

If the sympathomimetic effects of the yeast extract were due to tyramine, they would be abolished by antagonists at α-receptors. Large doses of antagonists were required and the effects on the blood pressure were easier to antagonize than those on the nictitating membrane. Thus the rise in blood pressure was antagonized by phenoxybenzamine (16 μmoles/kg) but not by small doses (4 or 6 μmoles/kg). Phenoxybenzamine (15 μmoles/kg) only partly reduced the contraction of the nictitating membrane. Hydergine (4.0 mg/kg) and chlorpromazine (4 μmoles/kg) also restored the blood pressure to normal. Cocaine (8 μmoles/kg), chlorpheniramine (8 μmoles/kg), hexamethonium (2 μmoles/kg) and hyoscine (4 μmoles/kg) were ineffective. All these drugs were injected intravenously.

*Histamine-like effects*

The histamine-like effects of the yeast extracts were now studied in greater detail.

*Gastric secretion.* As shown in Fig. 5,*b*, *c* and *d*, within 10 to 25 min of giving the yeast extract Marmite (2 to 10.0 g/kg) intraduodenally to cats treated with an amine oxidase inhibitor, the volume of gastric secretion increased two- to tenfold, with an increase in total acid and the appearance of and subsequent increase in free acid. For example, in the experiment Fig. 5,*b*, the free acid which had been undetectable in the control secretion rose to between 0.4 and 0.5 g of hydrochloric acid per 100 ml. 100 min after giving the extract. The secretion, which was initially mucous and sticky, became a pale amber watery fluid. These histamine-like effects were observed in cats anaesthetized with chloralose (Fig. 5,*b* and *d*) and in a spinal cat (Fig. 5,*c*). In a control cat given only the yeast extract, the secretion was unaffected until α-methylbenzylhydrazine was injected into the duodenum when, as illustrated in Fig. 5,*a*, the volume secreted increased and free acid appeared.

These tests strongly suggested that, after an amine oxidase inhibitor, a histamine-like substance was absorbed from the yeast extract. The volume of gastric juice secreted

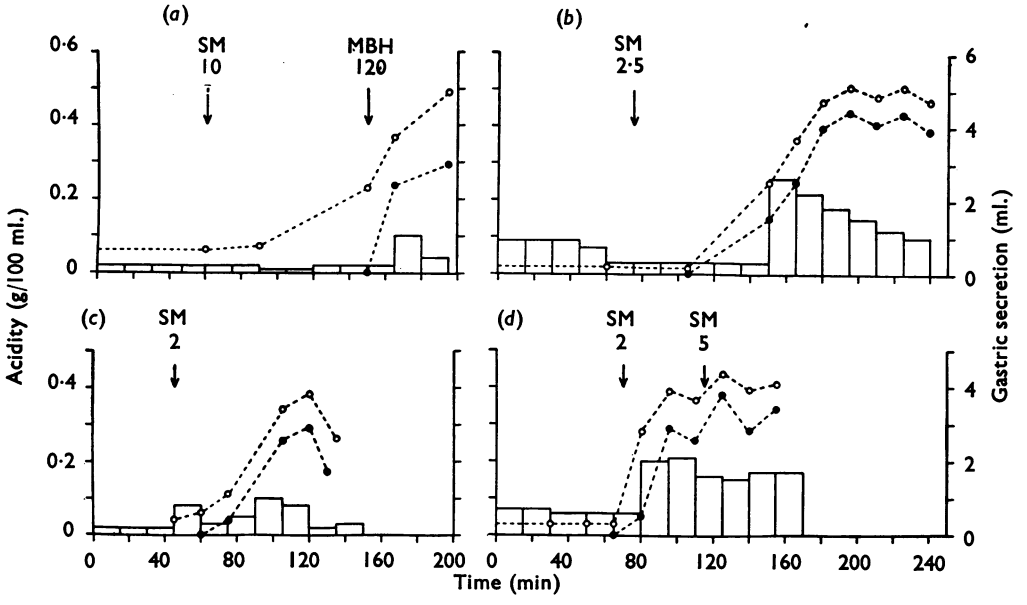


Fig. 5. Histograms of gastric secretion and graphs of free and total acidity produced by the yeast extract Marmite in a spinal cat of 2.2 kg (*c*) and in anaesthetized (chloralose) cats of 2.0 kg (*a*), 2.5 kg (*b*) and 2.1 kg (*d*) respectively. Gastric secretion is expressed as ml. on the right of each graph; free acidity (filled circles) and total acidity (empty circles) are expressed as g of hydrochloric acid per 100 ml. on the left of each graph. In (*a*), the yeast extract (SM, doses in g/kg) was given 90 min before α-methylbenzylhydrazine (MBH, 120 μmoles/kg, intraduodenally); in (*e*) and (*c*), the yeast extract was given 120 min after α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally); and in (*d*) 120 min after nialamide (76 μmoles/kg, intraduodenally).

and the content of free acid usually remained high until the end of the experiment 110 to 140 min after giving the yeast extract, indicating that the histamine-like substance was being continuously absorbed from the duodenum into the circulation or that its effect was prolonged, or both. The amine oxidase inhibitor itself did not cause increased secretion, since in experiments Fig. 5,*b*, *c* and *d* (in which the inhibitor had been injected 40 to 75 min) secretion was minimal for the following 45 to 80 min and did not contain free acid until the yeast extract was given. The increased secretion produced by the yeast extract was obtained after treating the cat with the hydrazide, nialamid (Fig. 5,*d*), the hydrazine, α-methylbenzylhydrazine (Fig. 5,*b* and *c*) and the amine, tranylcypromine (not shown in the Fig. 5). Although, in most experiments, the yeast extract was acidified with 0.1N-hydrochloric acid, the increased secretion was as readily obtained with the extract dissolved in saline or distilled water. Nor was the salt content of the extract contributory, for the effects on gastric secretion were obtained with a salt-free yeast extract in a cat treated with α-methylbenzylhydrazine.

The effects on gastric secretion were unaffected by intravenous injections of hyoscine (2 μmoles/kg), hexamethonium (3 μmoles/kg) or mepyramine (2 μmoles/kg).

*Haematocrit and limb volume.* Dale & Laidlaw (1919) showed that histamine given intravenously caused a rise in the haematocrit. As seen in Fig 6,*c*, from a cat treated with

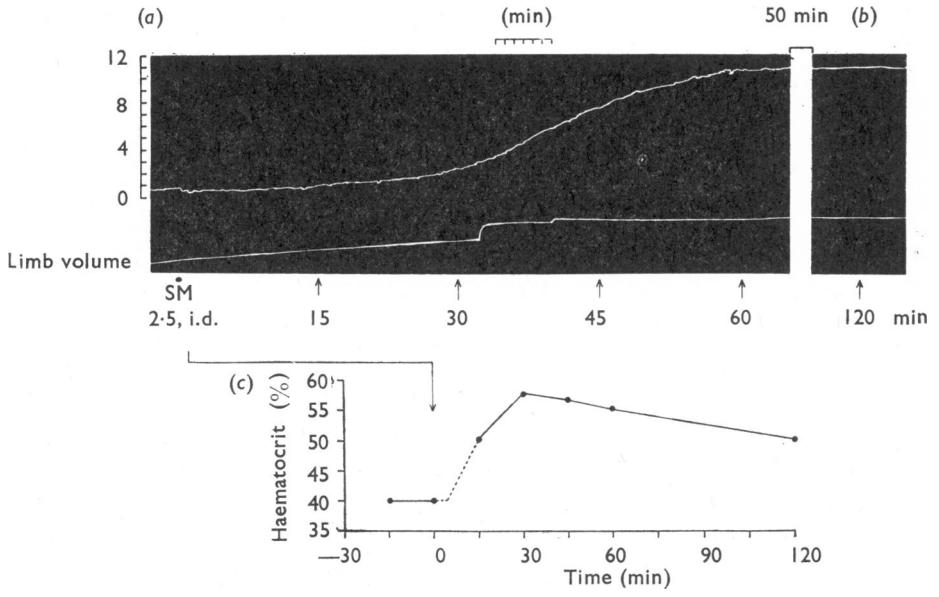


Fig. 6. Responses of the nictitating membrane and limb volume (*a*, *b*) and haematocrit (*c*) to the yeast extract Marmite (SM, 2.5 g/kg) injected intraduodenally into a 2.0 kg anaesthetized (chloralose) cat given α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally) 120 min previously. Upstroke on limb volume record indicates increase in volume. There was a 50 min interval between (*a*) and (*b*).

α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally 120 min previously), after intraduodenal injection of the yeast extract Marmite (2.5 g/kg) the haematocrit rose from a control value of 40 to 50% by 15 min and to 57% by 30 min. The rise in haematocrit preceded any marked change in the limb volume or in the tone of the nictitating membrane. The limb volume showed a small increase 38 min after giving the yeast extract (Fig. 6,*b*), and the nictitating membrane was maximally contracted at 60 min. The effects on the nictitating membrane and limb volume were still as marked at 120 min (Fig. 6,*b*), but the haematocrit had fallen to 50% (Fig. 6,*c*). Similar effects of the yeast extract on the haematocrit were obtained in another cat treated with nialamide (76 μmoles/kg, intraduodenally).

The effects of the extract on the haematocrit were not obtained without an amine oxidase inhibitor. Thus a large dose of the yeast extract Marmite (10 g/kg) was given intraduodenally but the haematocrit remained in the control range from 38 to 40% over the ensuing 60 min. Within 15 min of injecting α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally) the haematocrit rose to 65% and the nictitating membrane contracted.

*Spinal reflex and electromyogram.* The yeast extract Marmite was tested on the polysynaptic anterior tibialis twitch in spinal cats. In two control experiments, the yeast extract, α-methylbenzylhydrazine or nialamide alone was ineffective on the reflex or the electromyogram. However, 14 min after injecting the yeast extract Marmite (2.0 g/kg) intraduodenally into a cat treated with nialamide (76 μmoles/kg, intraduodenally 120 min previously) instead of eliciting a brief twitch a single shock produced a twitch with rhythmic oscillations as the twitch decayed (Fig. 7,*d*). Basal and peak tensions were unaltered. Next, extensor-flexor movements of the limbs developed, superimposed on the reflex twitch (Fig. 7,*e*). The limb movements were not evoked by the stimulus to the posterior tibial

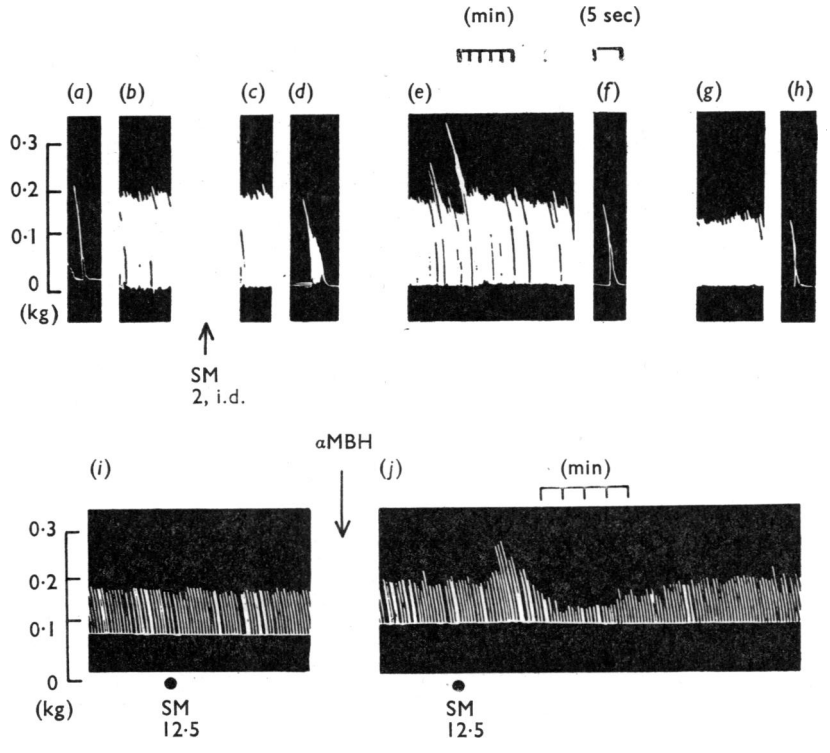


**Fig. 7.** Responses of the tibialis anterior to electrical stimulation of the central end of the divided ipselateral posterior tibial nerve; in (*a*) to (*h*) a spinal cat of 2.2 kg, and in (*i*) to (*j*) a spinal cat of 4.1 kg. In both cats there was additional spinal cord transection at the thoracico-lumbar junction and division of the contralateral femoral and sciatic nerves. (*a,b*) Control responses on a fast and slow moving drum respectively 120 min after nialamide. (*c,d*) Responses 14 min after Marmite (SM, 2g/kg intraduodenally). (*d*) Twitch duration to single shock was prolonged with oscillations as twitch decays. (*e,f*) 23 min after Marmite. (*e*) Intermittent increases in peak tension are associated with body movements. (*f*) Twitch duration was still slightly increased. (*g,h*) Diminished peak tension, with twitch duration normal at 85 min. (*i*) Yeast extract Marmite (12.5 mg/kg) given intravenously was ineffective on twitch. (*j*) 100 min after α-methylbenzylhydrazine (αMBH, 120 μmoles/kg, intraduodenally), the yeast extract produced an increase followed by a decrease in peak tension.

nerve, as they occurred when the nerve was not stimulated. Spinal cord excitability was increased, for stimulus irradiation also occurred. Thus, in two cats with intact nerves to the contralateral lower limb, a marked crossed extensor thrust not present before injecting the yeast extract developed with each stimulus to the ipsilateral posterior tibial nerve. The yeast extract injected intravenously into another cat was ineffective on the reflex twitch (Fig. 7,*i*) but the same dose 100 min after α-methylbenzylhydrazine (120 μmoles/kg, intravenously) produced an increase followed by a decrease in peak tension (Fig. 7,*j*).

The limb movements were preceded and accompanied by electromyographic potentials. The effects on the electromyogram, blood pressure and nictitating membrane are illustrated in Fig. 8. The electromyograms were taken from the thigh adductor muscles of a spinal cat given nialamide (76 μmoles/kg, intraduodenally) 150 min previously. The control record (at A) shows minimal electromyographic activity. After giving the yeast extract

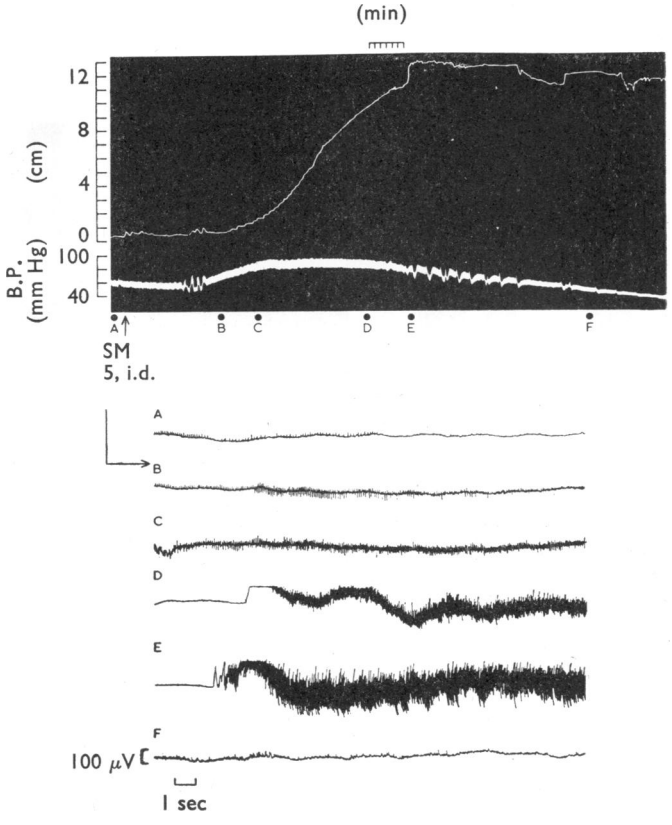


Fig. 8. Responses of the acutely denervated nictitating membrane, the blood pressure and electromyogram in a spinal cat, 3.5 kg, to the yeast extract Marmite (SM, 5 g/kg) given intraduodenally 150 min after the intraduodenal injection of nialamide (76 μmoles/kg). Contraction of the nictitating membrane (uppermost trace) develops 18 min after the injection of Marmite, and is sustained with superimposed fluctuations in tone due to limb movements. Blood pressure (middle trace) rises 30 mm Hg. Electromyographic records (lower traces). A, Control: alternating phases of minimal electromyographic activity and quiescence. B and C, Progressive increase in amplitude and quantity of muscle potentials 17 and 24 min after Marmite. D and E, Large electromyographic potentials accompanying limb movements at 43 and 51 min. F, Electromyographic activity abating at 82 min.

Marmite (5 g/kg, intraduodenally) a small blood pressure rise and large contraction of the nictitating membrane ensued; 24 min later (at C) the electromyographic potentials were more marked and continuous although limb movements had not yet appeared. Subsequently, limb movements developed accompanied by huge electromyographic potentials (at D and E). The periods between limb movements were accompanied by electromyographic silence. The limb movements and electromyographic potentials ultimately waned (at F).

*Release of endogenous histamine or histamine absorption?* The question arose whether or not the histamine-like effects were due to histamine release following absorption of mono- and di-basic substances in the yeast extract Marmite, or to the absorption of a histamine-like substance from the yeast extract in the gut.

The yeast extract was tested in a cat which had been injected with compound 48/80

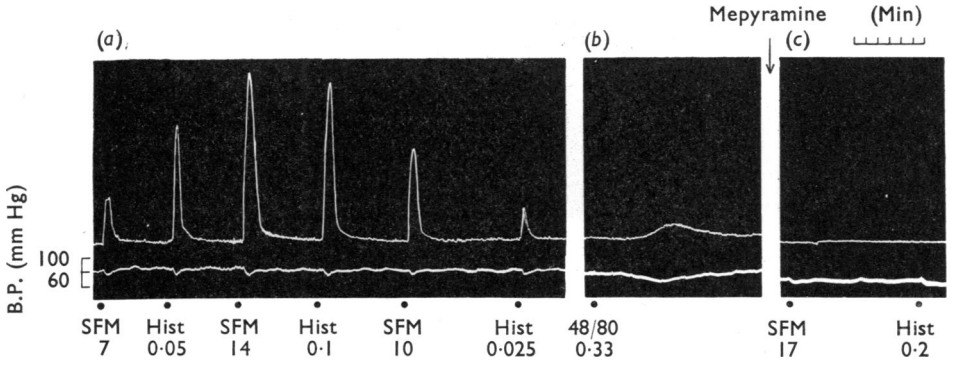


Fig. 9. Responses of a guinea-pig ileum preparation to superfused blood from a carotid artery and of the blood pressure in a 3.0 kg cat anaesthetized with chloralose and treated with Compound 48/80 (total of 130 mg, intraperitoneally over the preceeding 25 days). (*a*) Contractions of the superfused guinea-pig ileum and falls of blood pressure produced by yeast extract (SFM, salt-free Marmite, in mg/kg) or histamine (Hist, in μmoles/kg) injected intravenously. (*b*) Minimal response of ileum and blood pressure to Compound 48/80 (in mg/kg) injected intravenously. (*c*) Effects of yeast extract and of histamine on the superfused guinea-pig ileum preparation are abolished by intravenous injection of mepyramine (1 μmole/kg).

(130 mg in divided doses, intraperitoneally over 25 days). Ultimately the daily injection of compound 48/80 (6 mg, intraperitoneally) produced no signs of histamine release. The cat was then anaesthetized with chloralose and a guinea-pig ileum preparation was arranged in an extracorporeal circuit so as to be superfused by the cat's carotid arterial blood. As shown in Fig. 9,*a*, the yeast extract or histamine injected intravenously contracted the superfused guinea-pig ileum, effects which were later abolished by mepyramine (Fig. 9,*c*). The cat had been adequately depleted of histamine, for an injection of compound 48/80 (0.33 mg/kg, intravenously) which would have produced sustained maximal contraction of the superfused guinea-pig ileum in an untreated cat elicited a small response (Fig. 9,*b*). The contraction of the superfused ileum by the yeast extract could, therefore, be explained by the presence of histamine in the extract.

*Absorption of histamine from the intestine*

If the effects of the yeast extract were due to absorption of histamine, then the next problem was the extent to which histamine was absorbed from the intestine and whether absorption was affected by amine oxidase inhibition. The method of Vane (1958) was again used in which a length of guinea-pig ileum was superfused with carotid arterial blood in a cat's extracorporeal circuit. The adrenal glands were removed.

*Intraduodenal injection of histamine.* In three control cats, histamine (55 μmoles/kg) was injected intraduodenally. In two, the histamine was ineffective on the superfused guinea-pig ileum, although the preparation contracted to histamine (0.01 μmole/kg) injected intravenously. In the third experiment, shown in Fig. 10,*a*, absorption of histamine from the gut was evident by contraction of the superfused ileum beginning 12 min after the injection although the blood pressure was elevated. In one cat in which histamine was not absorbed from the gut, the injection of histamine (0.02 μmole/kg) into the splenic vein contracted the superfused ileum. These findings point to the variability of absorption of histamine

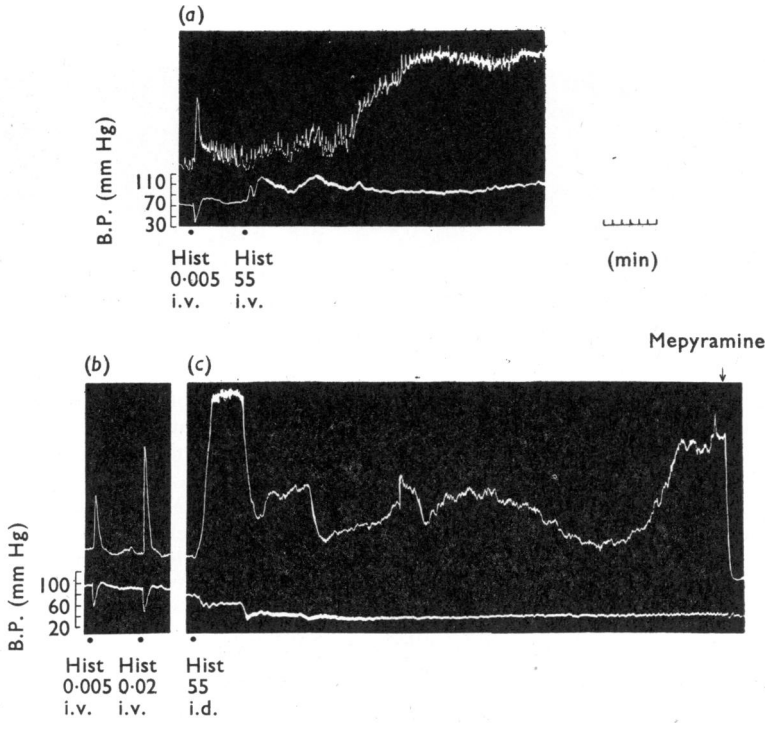


Fig. 10. Responses of a guinea-pig ileum preparation to superfused blood from a carotid artery and of the blood pressure in anaesthetized (chloralose) cats (*a*) of 3.0 kg and (*b*,*c*) of 3.2 kg. Adrenal glands were removed in both cats. (*a*) Contraction of the superfused guinea-pig ileum beginning 12 min after the intraduodenal injection of histamine (Hist, in $\mu$moles/kg). (*b*) Control responses of the superfused ileum and of the blood pressure to histamine injected intravenously. (*c*) Immediate contraction of the superfused ileum and fall of blood pressure produced by histamine injected intraduodenally 60 min after the intraduodenal injection of $\alpha$-methylbenzylhydrazine (120 $\mu$moles/kg). Contraction of the superfused ileum was abolished by mepyramine (2 $\mu$moles/kg, intravenously). I.v. = intravenous; i.d. = intraduodenal.

from the gut in different cats, and to the intestinal wall rather than the liver as the site of histamine inactivation.

The response of two cats treated with $\alpha$-methylbenzylhydrazine (120 $\mu$moles/kg, intraduodenally 60 min previously) was quite different. As shown in Fig. 10,*c*, the superfused guinea-pig ileum contracted immediately and maximally after injecting histamine (55 $\mu$moles/kg) intraduodenally, and there was a fall in blood pressure. The contraction of the superfused ileum was not sustained and, as shown in Fig. 10, after 4 min it became less marked, although the blood pressure fell further. The partial loss of tone seemed to be due to deoxygenation of the superfusing blood possibly caused by the effect of histamine on the pulmonary circulation. Thus, in both the experiments, and although the cats were artificially ventilated with pure oxygen, within 4 to 10 min of the superfused ileum contracting maximally the oxygenated superfusing blood became dark blue, followed immediately by the partial loss of tone in the ileum. The loss of tone was not caused by catechol amines liberated from the adrenal medullae by histamine as the glands had been removed. The residual contraction of the superfused ileum was abolished by mepyramine (Fig. 10,*c*).

The difference in response to intraduodenal histamine between cats which had received α-methylbenzylhydrazine, and those which had not, was not due to enhanced sensitivity of the superfused ileum since its sensitivity to intravenously injected histamine declined slightly after the amine oxidase inhibitor. The amine oxidase inhibitor obviously influenced absorption of histamine from the gut. For example, in an untreated cat in which histamine (55 μmoles/kg) injected intraduodenally had been ineffective, this dose of histamine given 30 min after α-methylbenzylhydrazine in the same cat (120 μmoles/kg, intraduodenally) led to contraction of the superfused ileum. Absorption of histamine was not facilitated if it was given simultaneously with the amine oxidase inhibitor, and at least 30 min were required for adequate inhibition of the deaminating enzyme in the gut wall.

*Intraduodenal injection of yeast extract.* The yeast extract salt-free Marmite was tested in two control cats after it had been assayed on the guinea-pig isolated ileum and found to contain 15 μmoles/g of a histamine-like substance. In one cat, a small contraction of the superfused guinea-pig ileum developed 40 min after intraduodenal injection of the extract (5 g/kg). In the other, as shown in Fig. 11,*a*, the superfused ileum began to contract 12 min after giving the extract intraduodenally (5 g/kg) and was maximally contracted at 14 min. The blood pressure, which was elevated after the injection, fell to the control level as the strip contracted.

The response in two cats treated with α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally 90 min previously) differed. As illustrated in Fig. 11,*b*, the guinea-pig ileum contracted immediately and maximally on placing the yeast extract (5 g/kg) into the duodenum and the blood pressure fell from 75 to 35 mm Hg. The contraction of the superfused ileum was abolished by mepyramine (1 μmole/kg, intravenously) which effectively antagonized a subsequent intravenous injection of histamine (1 μmole/kg).

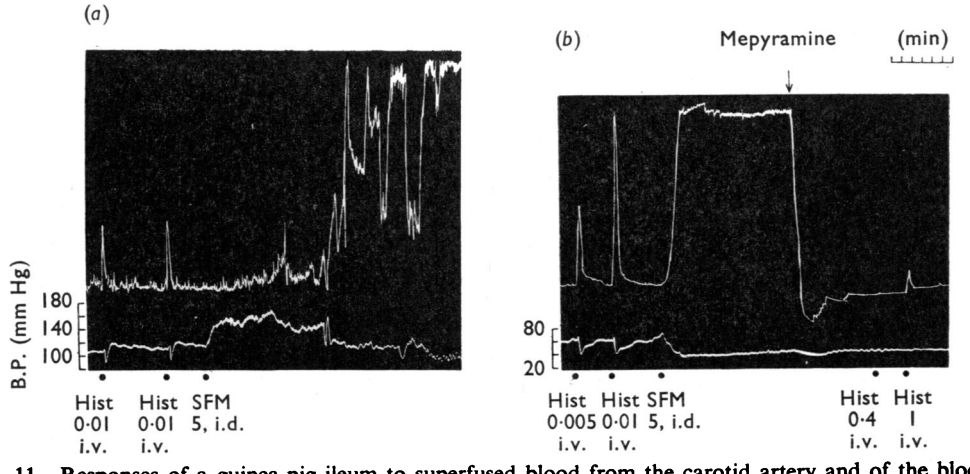


Fig. 11. Responses of a guinea-pig ileum to superfused blood from the carotid artery and of the blood pressure in anaesthetized (chloralose) cats (*a*) of 3.4 kg and (*b*) of 3.0 kg. Adrenal glands were excluded from the circulation by ligatures in both cats. (*a*) Contraction of the superfused guinea-pig ileum beginning 12 min after the intraduodenal injection of the yeast extract, salt-free Marmite (SFM, in g/kg) with initial rise and then fall in blood pressure. (*b*) Immediate contraction of the superfused ileum and fall of blood pressure produced by the yeast extract, salt-free Marmite injected intraduodenally 90 min after the intraduodenal injection of α-methylbenzylhydrazine (120 μmoles/kg). Contraction of the superfused ileum was abolished by mepyramine. (1 μmole/kg, intravenously) I.v. = intravenous; i.d. = intraduodenal. Histamine (Hist, in μmoles/kg) was injected intravenously.

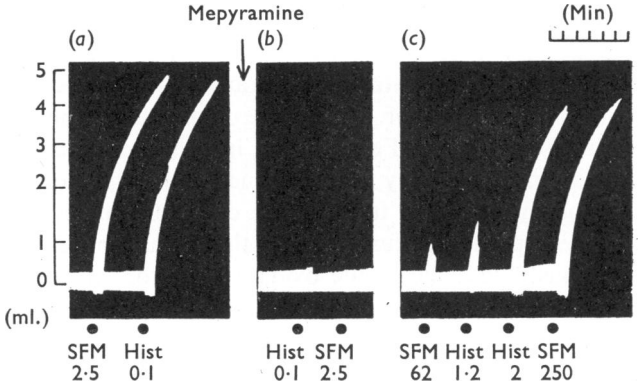


Fig. 12. Guinea-pig; resistance of lungs to inflation (*in vivo*). (*a*) Maximal resistance to inflation produced by the intravenous injection of the yeast extract salt-free Marmite (SFM, in mg/kg) and of histamine (Hist in μmoles/kg). Between (*a*) and (*b*) mepyramine (0.3 μmoles/kg) was injected intravenously. (*b*) Antagonism or the effects of histamine and of yeast extract, progressively surmounted (*c*) by increasing doses of the substances.

The results indicated that histamine in the yeast extract was absorbed more readily from the gut after amine oxidase inhibition.

*Other yeast extracts.* Baker's Yeast, Yestrel and Yex, and the yeast and meat extract, B-V, were tested in 10 to 40 mg/kg intravenous doses. All contracted the nictitating membrane. Baker's Yeast was pressor; Yex had depressor and Yestrel and B-V had mixed pressor and depressor activity. Two extracts were tested in different cats after treatment with α-methylbenzylhydrazine (120 μmoles/kg, intraduodenally 90 min previously). A rise in blood pressure and contraction of the nictitating membrane ensued after the intraduodenal injection of Yex (10 g/kg) but these were much smaller than with a similar dose of the extract Marmite. A dose of B-V (10 g/kg) was without effect.

### *Guinea-pig*

As shown in Fig. 12,*a*, intravenous injection of yeast extract (2.5 mg/kg) or histamine (0.1 μmole/kg) immediately and maximally increased resistance to inflation of the guinea-pig lungs indicating constriction of the tracheobronchial muscle. These responses were completely antagonized by mepyramine (Fig. 12,*b*) but antagonism was progressively surmountable by larger intravenous doses of histamine or the yeast extract (Fig. 12,*c*).

The effects of histamine and of the yeast extract injected intraduodenally were also tested. As shown in Fig. 13,*a*, the yeast extract (12.5 g/kg) given into the duodenum led to gradually increasing resistance to inflation of the guinea-pig lungs starting after 10 min and becoming near-maximal at 30 min. Antagonism by mepyramine (1.25 μmole/kg, intravenously) was only partly successful and in spite of injecting a larger dose of mepyramine (3 μmoles/kg, intravenously) the animal died with bronchial constriction.

In another experiment (Fig. 13,*b*), histamine (82 μmoles/kg) was injected intraduodenally. Bronchial constriction developed after 30 min as shown by the increase in overflow. This effect was cut short by the intravenous injection of mepyramine in successive doses to a total of 6 μmoles/kg. However, resistance to inflation again developed, presumably due to

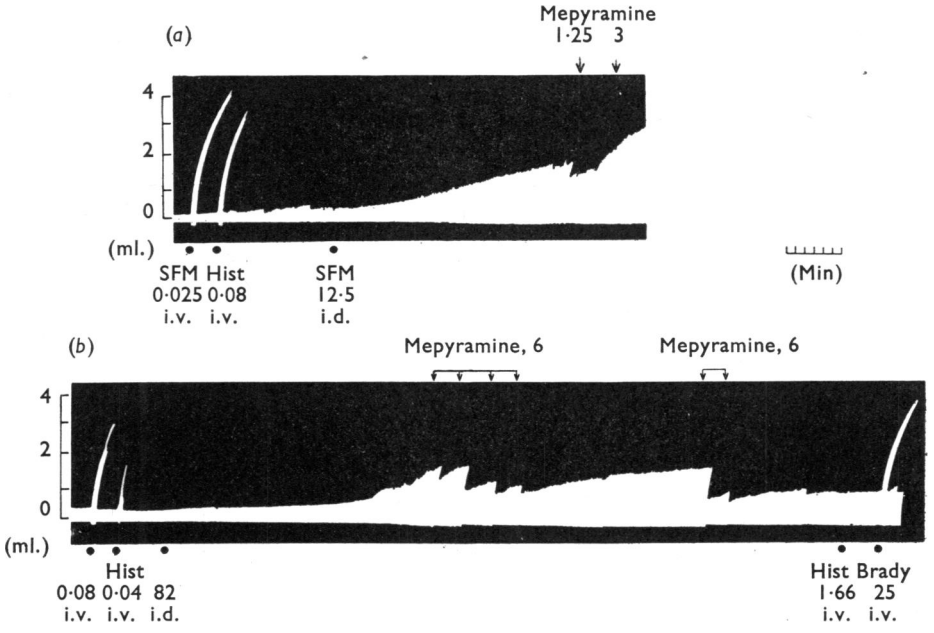


Fig. 13. Two guinea-pigs (*a* and *b*): resistance of lungs to inflation (*in vivo*). (*a*) Resistance to inflation produced initially by intravenous injections of the yeast extract salt-free Marmite (SFM, in g/kg) and by histamine (Hist, in μmoles/kg) and then by the yeast extract injected intraduodenally which produced a progressive increase in resistance to inflation unaffected by intravenous mepyramine (1.25 and 3 μmoles/kg) and with fatal termination. (*b*) Increase in resistance to inflation produced initially by intravenous injection of histamine. Progressive increase in resistance to inflation elicited by the intraduodenal injection of histamine antagonized by intravenous mepyramine (six doses of 6 μmoles/kg). An intravenous dose of histamine was now ineffective although bradykinin (Brady, in μg/kg) still elicited maximal resistance to inflation. I.v. = intravenous; i.d. = intraduodenal.

continuing absorption of histamine from the gut, and this was antagonized once more by mepyramine (total 6 μmoles/kg, intravenously). After this last dose of mepyramine, histamine injected intravenously in an amount twenty times greater than the control dose was now ineffective on overflow, whereas increased resistance to overflow was obtained by injecting bradykinin intravenously. These results were confirmed in other experiments.

Experiments were also made in guinea-pigs given α-methylbenzylhydrazine (300 μmoles/kg) into the duodenum 60 min previously. The same doses of histamine or the yeast extract as used in the previous experiments were then administered intraduodenally. Their effects on resistance to inflation of the guinea-pig lungs were not significantly different from those in tests without the amine oxidase inhibitor.

## DISCUSSION

Yeast extracts possessed various degrees of sympathomimetic and histamine-like activity, particularly marked in the extract Marmite. The effect of the extract on intravenous injection depended on whether or not the animal had been treated with an amine oxidase inhibitor. In the untreated cat, sympathomimetic and histamine-like effects were elicited on the cardiovascular system but, after amine oxidase inhibition, sympathomimetic

effects predominated. The effects also varied with the species studied. In the rat, which is relatively resistant to histamine, the sympathomimetic effects were prominent, whereas in the guinea-pig, which is particularly sensitive to histamine, the histamine-like effects were paramount.

There was strong evidence that the sympathomimetic effects were due to tyramine. Chromatographic analysis of Marmite revealed a high tyramine content (Blackwell *et al.*, 1965). Tyramine was detected in the plasma after, but not before, the intraduodenal injection of the yeast extract in a cat previously treated with an amine oxidase inhibitor and in sufficient concentration to account for the rise in blood pressure, contraction of the nictitating membrane and mydriasis. Other evidence favouring the presence of an "indirectly-acting" amine was the development of tachyphylaxis to the pressor effects on repeated injection of the extract and the loss of mydriatic action on the chronic sympathetic denervated iris. Adequate inhibition of monoamine oxidase in the gut and liver was essential for sympathomimetic effects to develop after the intraduodenal injection of the yeast extract.

The histamine-like activity of yeast extracts was demonstrated by *in vivo* tests. In the cat, intravenous injection of the yeast extract elicited an immediate fall in blood pressure accompanied by a rise in jugular venous pressure similar to that obtained with histamine. On intraduodenal injection of the extract into cats previously treated with an amine oxidase inhibitor, the histamine-like effects included a raised haematocrit, an increase in limb volume and increased gastric secretion with the appearance of and increase of free acid in the secretion. The yeast extract had strong actions, after amine oxidase inhibition, on the electromyogram and a spinal cord reflex, which proved to be hitherto undescribed effects of histamine (Blackwell & Marley, unpublished). In the guinea-pig, intravenous or intraduodenal injection of the yeast extract produced an increased resistance to inflation of the lungs. This occurred whether the animal had been treated with an amine oxidase inhibitor or not, and was abolished by mepyramine.

A crucial point to establish was the absorption of histamine from the gut. Koessler & Hanke (1924) showed that large quantities of histamine introduced into the stomach elicited mild symptoms of intoxication in guinea-pigs and were without effect in dogs. They concluded that, although a small amount of histamine was absorbed from the gut, most was rendered inert in its passage through the intestinal wall. On the other hand, Meakins & Harington (1923) suggested that histamine was absorbed from the cat's small intestine. Their conclusion was based on the sharp fall in blood pressure within a few seconds of placing histamine in the gut. Contraction of the uterus *in situ* and respiratory disturbance also occurred but the time of onset was not stipulated. There are objections to using a fall of blood pressure as an index of histamine absorption. For example, fluids such as saline injected into the bowel sometimes elicited dramatic falls in blood pressure. If arterial tone is low, then, as found by Dale & Laidlaw (1919), the immediate effect of injecting a large intravenous dose of histamine is to raise the blood pressure.

Use of the superfused guinea-pig ileum offered advantages over previous methods. It was more sensitive than the blood pressure to histamine injected intravenously, large contractions being obtained with doses which had little effect on the blood pressure. Whereas proportionately larger contractions of the ileum were obtained with larger doses of histamine, this was not always reflected in a larger fall of blood pressure which was consequently less

useful for differentiating between different amounts of circulating histamine. Finally, the vasodepressor effect of histamine is not blocked so completely by antihistamines as the effect of histamine on other smooth muscles (Goodman & Gilman, 1955), so there is no verification that the observed effects are due to histamine. In contrast, the contraction of the superfused ileum to the same dose of histamine was abolished by mepyramine, an antagonism surmountable by larger doses of histamine.

In our experiments, absorption of histamine from the small intestine occurred in some cats but not in others. When there was absorption, this was delayed for 10 to 20 min after placing histamine in the intestine. After amine oxidase inhibition, however, histamine absorption occurred immediately. Similar findings were obtained for the histamine-like substance in the yeast extract. Although histamine-release was theoretically possible by constituents in the yeast extract, and would have accounted for all the histamine-like effects, it did not seem to contribute significantly to the effects observed.

There are two major enzymes which metabolize histamine (Schayer, 1956). One is diamine oxidase which is inhibited by iproniazid (Schayer, Kennedy & Smiley, 1953), and the second enzyme methylates histamine on the ring nitrogen atom remote from the side-chain (Brown, Tomchick & Axelrod, 1959). The enhanced effect of histamine on some systems was possibly due to inactivation of diamine oxidase, although, according to Schayer (1956), methylation is the principle route of histamine inactivation in cat and man. The oxidation of 1,4-methylhistamine *in vivo* is largely by monoamine oxidase (Rothschild & Schayer, 1958). However, in other experiments (Blackwell & Marley, unpublished) marked effects were obtained with histamine on spinal cord reflexes and on other systems in cats treated with amine oxidase inhibitors, whereas larger molar doses of 1,4-methyl-histamine were ineffective. It seems therefore that the histamine-like effects of yeast extracts that appeared only after amine oxidase inhibition were due to interference with the conversion of histamine to imidazoleacetaldehyde either by inactivation of diamine oxidase, of monoamine oxidase, or both.

On comparing the results previously obtained with cheese in cats treated with monoamine oxidase inhibitors (Blackwell & Marley, 1966) with those due to yeast extracts containing the same amount of tyramine per g as the cheese, the pressor effects were less marked with the yeast extracts but the contractions of the nictitating membrane were more intense. The effect of the yeast extracts on blood pressure presumably depended on the relative quantities of tyramine and histamine absorbed from the gut, and the effect of histamine would be to diminish the rise in blood pressure evoked by tyramine although this might be offset by the secretion of adrenal medullary catchechol amines evoked by histamine. The intense contraction of the nictitating membrane would presumably be due to the combined effect of tyramine on the cervical sympathetic postganglionic nerves, to the action on the membrane of catechol amines liberated by histamine from the adrenal medulla, and to the weak stimulating action of histamine on the superior cervical ganglion.

These experiments in animals can explain the reaction produced by yeast extracts in patients given monoamine oxidase inhibitors. The hypertensive crisis and the headache can be accounted for by the raised blood pressure produced by the tyramine in the extract. However, unexplained hypotensive collapse has occurred in patients taking $\alpha$-methylbenzyl-hydrazine (Cooper & Keddie, 1964). This was conceivably due to absorption of histamine from the gut after monoamine oxidase inhibition or to liberation of endogenous histamine

caused by drugs or food constituents not normally absorbed from the intestine. Some of the headaches may also have been caused or contributed to by histamine. Horwitz, Lovenberg, Engelman & Sjoerdsma (1964) reported a patient in whom cheese evoked headache without hypertension; conversely, large rises in blood pressure without headache were precipitated by broad beans in patients taking pargyline (Hodge *et al.*, 1964).

Yeast extracts are used in many foods such as canned soups, sandwich spreads, sauces, relishes, brawns, moulded meat products and meats in aspic jelly (Lyall, 1963) and allergy to baker's and brewer's yeast is well recognized. It would be reasonable to expect, because of the rapid absorption of histamine from the gut after monoamine oxidase inhibition, that precipitation or exacerbation of allergic phenomena by yeast extracts would be more frequent in susceptible persons taking monoamine oxidase inhibitors. There has as yet been no substantiation of this.

SUMMARY

1. Yeast extracts were tested in rats, cats and guinea-pigs. The yeast extracts had sympathomimetic and histamine-like properties. The extract Marmite was tested in most experiments.

2. The yeast extract injected intravenously into the untreated rat and cat produced a fall followed by a rise in blood pressure, and contracted the nictitating membrane. These sympathomimetic effects were prolonged by previous treatment with an amine oxidase inhibitor.

3. After treatment of the animal with an amine oxidase inhibitor, yeast extract injected intraduodenally produced a sustained rise in blood pressure in rats; there was a sustained fall of blood pressure in some cats, a sustained rise in others, and a brief depressor followed by a long-lasting pressor reaction in others together with electrocardiographic changes, contraction of the nictitating membrane and mydriasis.

4. Tyramine in a pharmacologically active concentration was detected in the plasma in a cat, previously treated with an amine oxidase inhibitor, after intraduodenal injection of the yeast extract.

5. The mydriatic action of the yeast extract did not occur after degeneration of the cervical sympathetic postganglionic nerve.

6. In the rat and cat, the pressor activity of the yeast extract was abolished by antagonists of adrenaline at $\alpha$-receptors. The contraction of the nictitating membrane in the cat was only partly reduced by these antagonists.

7. The histamine-like effects of the yeast extracts on intravenous injection included a rise in jugular venous pressure with a fall of blood pressure in the cat, increased tension of the reflex tibialis twitch and enhanced electromyographic activity.

8. The histamine-like effects on intraduodenal injection of the yeast extract included increased volume and acidity of gastric secretion, increase in the haematocrit and limb volume, increased tension of the reflex tibialis anterior twitch, enhanced electromyographic activity and the development of limb movements.

9. The histamine-like effects could be attributed to the absorption of a histamine-like substance from the yeast extract in the intestine which was facilitated by inhibition of monoamine oxidase.

10. In the guinea-pig the intravenous or intraduodenal injection of yeast extract increased resistance to inflation of the lungs.

11. The effects of the yeast extract on intraduodenal injection were only obtained in the rat or cat after treament with an amine oxidase inhibitor. The inhibitors used were of the amine, hydrazine and hydrazide variety.

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