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THE ACTION OF ENTERAMINE ON THE HEART OF MOLLUSCS

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Enteramine is a biological amine, probably an indolalkylamine (Erspamer, unpublished data), which shows several characteristic colour reactions and peculiar biological effects which make it distinguishable from all other known tissue products.

The main colour reactions are the coupling reaction in acid and alkaline medium with the diazonium salts of *p*-nitroaniline or sulphanilic acid, the Folin reaction, the iodine reaction and similar oxidation reactions, the fluorescence reaction in Wood's light. These colour reactions have recently been further established on the basis of paper chromatographic work (Erspamer & Boretti, 1950, 1951).

The main characteristic biological actions of enteramine are as follows: a stimulating effect on the isolated atropinized uterus of the rat and mouse in oestrus, and stimulation of the isolated atropinized duodenum of the rat and the urinary bladder of the dog both *in vitro* and *in vivo*; hypotensive action in the rabbit (Erspamer, 1940*b*); anti-diuretic action in hydrated rats (Erspamer & Ottolenghi, 1950, 1951).

The presence of enteramine has so far been demonstrated by means of the above-mentioned colour reactions and biological reactions, as well as by means of paper chromatography, in the following extracts: acetone and alcohol extracts of posterior salivary glands of *Octopus vulgaris* and *Eledone moschata* (the corresponding extracts of *Octopus macropus* contain no enteramine) (Vialli & Erspamer, 1940; Erspamer, 1940*a*, 1948*a*), of the hypobranchial body of *Murex trunculus* and *M. brandaris* (Erspamer, 1948*c*,*d*), of the intestine of *Ciona intestinalis* and *Tethium plicatum* (Erspamer, 1946), of mammalian gastro-intestinal mucosa and spleen (Erspamer, 1946), and of amphibian skin (Erspamer & Vialli, 1951). Chromatographic evidence suggests that in all these extracts enteramine is an identical and unitary substance (Erspamer & Boretti, 1951).

Enteramine may be present in acetone or alcohol extracts in two forms: 'form A' (=active), which shows the characteristic chemical and biological reactions mentioned above and which is easily attacked and inactivated by aminoxidase; 'form I' (=inactive), which gives the same colour reactions as 'form A' but is biologically inactive in all the tests hitherto tried and is also resistant to aminoxidase (Erspamer, 1942*a*, 1943). 'Form I' may be converted into the active 'form A' by heating at pH 7–10 in a boiling water-bath (Erspamer, 1942*b*). The existence of 'form I', and its convertibility to 'form A', has recently been confirmed in a particularly convincing manner by means of paper chromatography (Erspamer, unpublished data).

Extracts of the salivary glands of Octopoda contain a number of pharmacologically active substances, such as histamine, acetylcholine, tyramine, moschatine, octopamine and enteramine (Erspamer, 1948*b*; Erspamer & Boretti, 1951). Hypobranchial extracts of Muricidae also contain at least two active substances, namely murexine and enteramine. Amongst these, enteramine has attracted our particular attention because of its marked action on the heart of several species of molluscs, especially the heart of *Helix pomatia*. The study of these cardiac actions seems to us particularly interesting because of its connexion with the problem of humoral control (neuro-humoral or hormonal) of cardiovascular functions in molluscs—a problem which hitherto has received insufficient attention.

In the first part of this paper we describe the actions of extracts of the salivary glands of *Octopus vulgaris* and *Eledone* and of other extracts on the isolated heart of *Helix*, *Octopus vulgaris*, and a number of other species. In the second part of the paper, evidence is presented to show that enteramine is the substance mainly responsible for the cardiac effects produced.

METHODS AND MATERIALS

The isolated heart (ventricle) of *Helix pomatia*, *Murex trunculus*, *Murex brandaris*, *Dolium galea*, *Octopus vulgaris*, *O. macropus*, *Eledone moschata*, *Ostrea edulis* and *Aplysia limacina* was used.

The heart of *Helix*, *Murex*, *Dolium* and *Aplysia* was isolated by the method described by Jullien (1936) and suspended in a small nutritive bath (4–5 ml.) of Carnot's liquid (*Helix*) or sea water (the others). The heart of Octopoda was, on the contrary, suspended by a method analogous to that used for the frog heart: a Straub's cannula was introduced through one of the atria, all the vessels which open into the ventricle having been ligatured first. The bath was oxygenated by bubbling air through it. Procedures for differentiating the various active substances contained in these extracts have been described elsewhere (Erspamer, 1948*a*, *d*). Before use, the solvent was evaporated under reduced pressure and the residue taken up with the nutrient liquid.

The following acetone extracts were tested: *Octopus vulgaris* and *O. macropus*: posterior salivary glands; *Eledone moschata*: posterior salivary glands, testis, gut, gills, kidney, hepatopancreas, musculature; *Murex trunculus*: hypobranchial body (medial, branchial and rectal zones), hepatopancreas, gonads, musculature of foot; *Murex brandaris*, *Euthria cornea*, *Vulgocerithium vulgatum*: hypobranchial body; *Helix pomatia*: lung; *Ostrea edulis* and *Mytilus galloprovincialis*: hepatopancreas, gills musculature; rabbit: mucosa of the undus portion of the stomach; ox: spleen.

RESULTS

Extracts of salivary glands of Octopus vulgaris *and* Eledone

Action on the isolated heart of Helix

Introduction of small quantities of these extracts into the bath in which the isolated heart of *Helix* is suspended causes a marked increase in the amplitude of systolic contractions, an increased frequency, and a rise of tonus (Fig. 1).

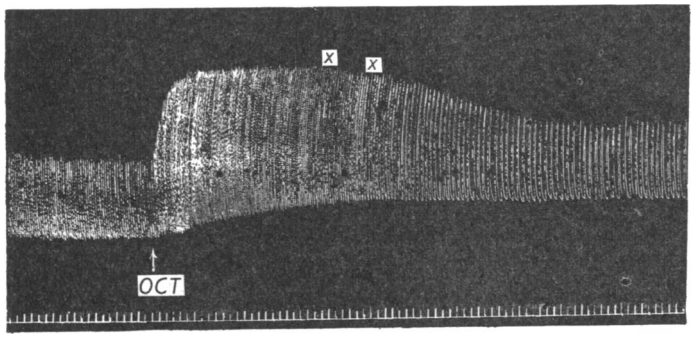

Fig. 1. Isolated *Helix* heart. At *OCT*, the extract obtained from 10 mg. fresh salivary tissue of *Octopus vulgaris*. At *x* washing out. Time marking, 10 sec.

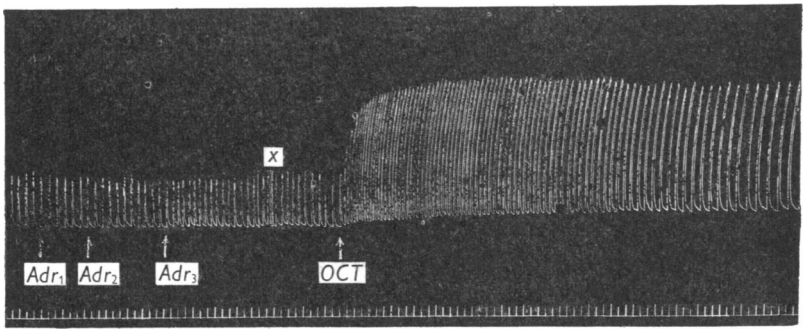

Fig. 2. Isolated *Helix* heart. At Adr_1, 2 μg. adrenaline; at Adr_2, 5 μg. adrenaline; at Adr_3, 15 μg adrenaline; at *OCT*, the *Vulgaris* extract obtained from 0·5 mg. fresh salivary tissue. At *x*, washing out. Time marking 10 sec.

The effect is usually protracted, depending somewhat on the condition of the organ and on the quantity of extract added. After washing with a fresh solution the original activity is not completely restored. As a rule the beat becomes slower and in some cases a transitory diastolic arrest occurs. It would seem that the heart has been exhausted by the previous administration of the extract. In view of this lack of reversibility of action, it is difficult to perform a quantitative

assay. This would only be possible by working with very small doses and can, in any case, give only approximate values.

Very small doses of extracts of salivary glands of *Octopus vulgaris* and *Eledone* produce only a positive inotropic action. Bigger doses also produce a positive chronotropic and tonotropic effect. If the heart is in good condition it will respond to a dose of extract corresponding to 10 μg. of fresh salivary gland tissue.

Comparison with adrenaline and tyramine. According to Boyer (1927), the isolated heart of *Helix* is inhibited by adrenaline. In our experiments adrenaline produced altogether a negligible effect. As Fig. 2 shows, a salivary extract of *Octopus vulgaris* obtained from 0·5 mg. fresh tissue has a much more powerful effect than 10–15 μg. adrenaline. Tyramine produces a positive chronotropic and inotropic action. Minimum effective concentrations are of the order of 10^{-6}. A dose of 100μg. tyramine produces an effect which is about equivalent to that of the extract from 1000 to 1500 μg. fresh tissue, the latter corresponding to a dry residue of approximately 50–75 μg.

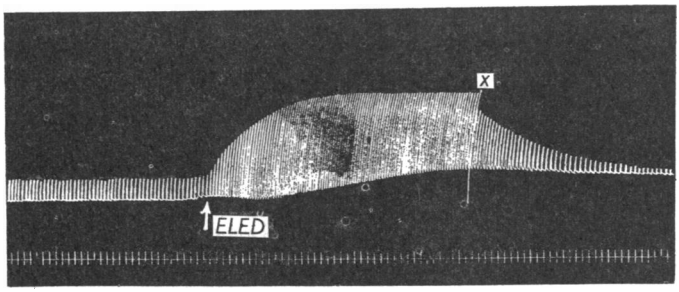

Fig. 3. Isolated heart of *Octopus macropus*. At *ELED*, the extract from 2 mg. fresh salivary tissue of *Eledone moschata*. At *x*, washing out. Time marking, 10 sec.

Action on the isolated heart of Octopus vulgaris, Octopus macropus *and* Eledone moschata.

These hearts all react alike to extracts of salivary glands of *Octopus vulgaris* or *Eledone*, the heart of *Octopus vulgaris* being probably the most sensitive. If a small quantity of extract is introduced into the Straub cannula it produces a small increase of systolic contractions, or else it may induce contractions if these have previously been absent. They also cause an increase in frequency and, in high doses, an increase in tone (Fig. 3). Solutions containing the equivalent of 1 μg. of tissue in 1 ml. usually produce a marked response. Solutions containing the equivalent of 2–20 mg. tissue/ml. produce a powerful action on the heart leading finally to the arrest of the organ in systole. When the active solution is replaced by sea water, there occurs an immediate loss of tone and a reduction of the amplitude of contractions. Frequently the heart will stop for a period in diastole. Repeated introduction of the extract as a rule causes

a progressive reduction in the sensitivity of the organ, and the higher the dose the more marked is this reduction and the sooner it occurs.

If the heart is left in contact with a suitable dose of extract corresponding, for example, to 0·3–1 mg. fresh tissue/ml., the heart continues to beat, apparently until its energy is exhausted. The stoppage is preceded by a progressive reduction of frequency of contractions and by irregularities of rhythm. Even more prolonged effects may be produced by perfusing hearts in which the little genital artery has not been ligated and which therefore continues to drip.

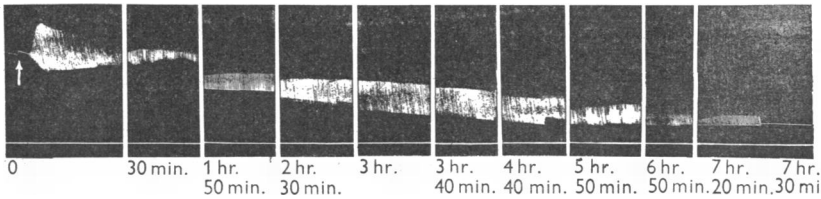

Fig. 4. Isolated heart of *Octopus vulgaris* perfused (arrow) with sea water containing, per ml., the extract from 0·5 mg. fresh salivary tissue of *O. vulgaris*.

In these cases the heart may continue beating in sea water containing salivary extract (1–2 mg. fresh tissue/ml.) for 7–10 hr. (Fig. 4). Also hearts which are left *in situ* for 10–12 hr. at 3° C. in animals removed from water, may begin to beat again if perfused with sea water containing 0·1–0·3 mg./ml. salivary extract.

The action of extracts of the salivary glands of *O. macropus* on the heart of *Octopus* is 50–200 times weaker than that of extracts from *O. vulgaris*.

Comparison with adrenaline and noradrenaline. Whilst adrenaline, as shown above, has relatively little action on the heart of *Helix*, it produces a marked effect in the heart of *Octopus*. Concentrations of the order of 10^{-9} adrenaline or noradrenaline produce a marked stimulation. 0·1 μg. adrenaline has a positive inotropic and chronotropic action about equivalent to that of an extract obtained from 30–50 μg. fresh salivary tissue. Larger doses of adrenaline and noradrenaline injure the heart and may damage it irreparably. Extracts of salivary glands do not produce this irreparable damage.

Action on the isolated hearts of other molluscs

The hearts of *Murex trunculus*, *M. brandaris* and *Dolium galea* are less sensitive than the heart of *Helix*. *Murex trunculus*, however, will respond to an extract from 0·5 mg. of tissue, the response being about equivalent to that given by 100 μg. tyramine and greater than that given by 100 μg. adrenaline. *Dolium* is relatively insensitive, and will respond only to a dose of extract corresponding to 1–5 mg. fresh tissue. The isolated heart of *Aplysia limacina* and the heart *in situ* of *Ostrea edulis* also responded to the extract of salivary glands of *Octopus vulgaris*.

Action on arterioles

Extracts of the salivary glands of *O. vulgaris* and *Eledone* act also on the arterioles of the viscera (e.g. those of the kidney and gills); these are powerfully stimulated with reinforcement of contractions, or, if the arterial rhythmic activity has weakened or disappeared through keeping the animals out of water, the extracts cause a renewal of rhythmic contractions.

Effect of chemical treatment

The stimulant action on the heart of these extracts is completely destroyed by treatment with formalin, potassium iodate, nitrous acid, diazonium salts and benzoyl chloride; it is also abolished by enzymes of the amine oxidase type.

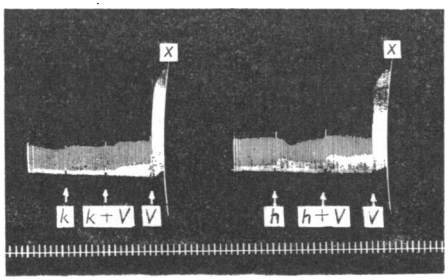

Fig. 5. Isolated heart of *Octopus vulgaris*. At *V*, untreated salivary extract of *O. vulgaris* (= 1 mg. fresh tissue); at *k* and *h*, 0·5 ml. of a sea-water extract of kidney (*k*) or hepatopancreas (*h*) of *Sepia*; at *kV* and *hV* salivary extract of *O. vulgaris* (the same quantity as at *V*) after treatment with kidney or hepatopancreas extracts of *Sepia*. At *x*, washing out. Time marking, 7 sec.

Thus, phosphate extracts of mammalian liver or intestine, and sea-water extracts of hepatopancreas and kidney of *Octopus* and *Sepia* cause inactivation of the extracts (Fig. 5). The enzyme activity is cyanide resistant, but is blocked by methylene blue and amphetamine. Ultra-violet irradiation destroys activity. The extracts are relatively resistant to treatment with N-NaOH (10–20 min. at 100° C.) and to a lesser degree to treatment with N-HCl.

Action of other extracts on the heart of molluscs

The following also have a remarkable action on the heart of *Helix*: extracts of the hypobranchial body of *Murex trunculus* and *M. brandaris* and extracts of rabbit gastric mucosa and ox spleen. Compared with extracts of the salivary glands of *Octopus vulgaris* and *Eledone*, the activity of these four extracts (in terms of fresh tissue) is roughly 30–40, 5–10, 1–3, and 1–3%. Extracts of hepatopancreas and ovary, as well as all other non-salivary tissue extracts of *Eledone* have a negligible action on *Helix* heart. This action is, moreover, completely unspecific, sometimes depressive, at others stimulating. In this latter case it is at least 300–500 times weaker than that of *Octopus vulgaris* salivary extracts (Fig. 6).

The stimulating action of the *Murex* extracts becomes apparent after destruction, by alkali treatment, of murexine, a choline derivative with curariform and nicotinic properties (Erspamer, 1948*d*). Extracts from the median zone of the hypobranchial body of *M. trunculus* are at least 20 times as active as those of the lateral, branchial and rectal, zones.

Posterior salivary gland extracts of *Octopus macropus* possess only a moderate stimulant action (less than 1% of that of *O. vulgaris*) which is also qualitatively different from that just described, i.e. it is of a prevalently tyraminic type.

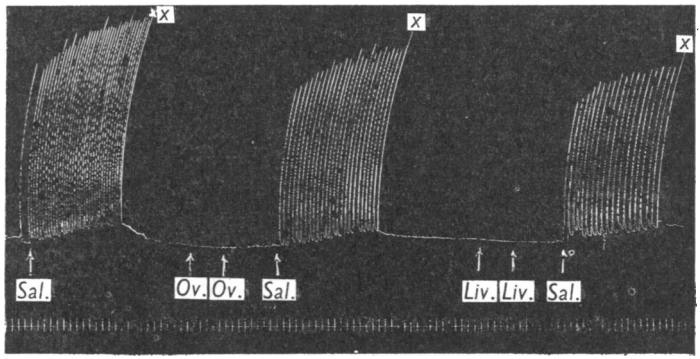

Fig. 6. Isolated *Helix* heart. At *Sal.* the extract obtained from 2 mg. fresh salivary tissue; at *Ov.* the extract from 100 and 200 mg. fresh ovary tissue; at *Liv.* the extract from 100 and 200 mg. fresh hepatopancreas tissue of *Eledone moschata*. At *x*, washing out. Time marking, 10 sec.

Extracts of the hypobranchial body of *Murex trunculus* and *M. brandaris* possess a stimulant action also on the isolated heart of *Octopus*. A similar effect is produced by extracts of rabbit gastric muscosa and ox spleen.

Identification of enteramine

The following experimental data suggest that the active principle which stimulates the heart of molluscs, is enteramine:

(1) The field of distribution of the cardiostimulating principle is strikingly similar to that of enteramine, both in different animal species and in different organs of an individual animal. Indeed, not only extracts of salivary glands of *Octopus vulgaris* and *Eledone moschata* possess cardiostimulating activity, but also extracts of the hypobranchial body of *Murex trunculus* and *M. brandaris*; as well as, although to a lesser extent, extracts from ox spleen and rabbit gastric mucosa. These extracts all contain enteramine (Erspamer, 1940*a*, *b*, 1948*a*, *c*; Erspamer & Boretti, 1950, 1951). All other extracts are quite ineffective on the molluscan heart, and all are completely free of enteramine, including the extract of posterior salivary glands of *Octopus macropus*, rich in all other active sub-

stances present in the salivary extracts of *O. vulgaris* (tyramine, octopamine, histamine)..

(2) Provided that care has been taken to eliminate any possible interfering, materials (murexine and moschatine, for example, which are easily destroyed by brief alkaline treatment), the cardiostimulating activity of our extracts is clearly proportional to the content of enteramine, as determined colorimetrically (coupling reaction with diazonium salts in an acid medium, Ottolenghi, 1951, to be published) and biologically (oestrus-uterus of rats, urinary bladder of dogs).

The quantitative data recorded in Table 1 are referred to a standard salivary extract of *O. vulgaris* (summer 1950 extract, obtained from 14·3 kg. fresh tissue) arbitrarily considered = 100.

TABLE 1. The relative activities of various enteramine-containing extracts

	Coupling reaction in an acid medium	Action on the		
		Oestrus uterus of rats	Bladder urinary of dogs	Heart of *Helix*
Enteramine containing extracts:				
Post. sal. gl. *O. vulgaris*	100	100	100	100
Post. sal. gl. *E. moschata*	120—140	120—130	120—150	>100
Hypobr. body *M. trunculus*	30—35	30—35	30—40	30—40
Ox spleen	1—3	1—3	1—3	1—3
Rabbit gastric mucosa	1—3	1—3	1—3	1—3
Enteramine free extracts:				
Post. sal. gl. *O. macropus*	0	0	0	<1
Hypobr. body *E. cornea* and *V. vulgatum*	0	0	0	<1
Different organs and tissues of *E. moschata, M. trunculus, O. edulis, M. galloprovincialis* and *H. pomatia*	0	0	0	<1

(3) Any procedure which destroys or inactivates enteramine (treatment with formalin, with diazonium salts, with potassium iodate, benzoylation, ultraviolet irradiation) also destroys the cardiostimulating activity of the enteramine-containing extracts. Moreover, the cardioactive principle of crude extracts closely resembles enteramine in its resistance to alkali and acids when heated.

Amine oxidase of fresh phosphate extracts of mammalian liver and intestine and of sea-water extracts of hepatopancreas or kidney of *Octopus* and *Sepia* completely destroys the cardiostimulating activity of the enteramine extracts, at least so long as the enzyme is not inhibited by methylene blue or amphetamine.

(4) To these important data another was recently added, which we believe may be reasonably considered decisive for the identification of enteramine as the active principle on the molluscan heart.

Fig. 7 shows a bidimensional paper chromatogram of the standard salivary extract of *Octopus vulgaris*. The fourteen reproduced spots have been developed with the diazonium salt of *p*-nitroaniline, in an alkaline medium. The criteria of identification of the individual spots are thoroughly described in another paper (Erspamer & Boretti, 1951).

Eluates were prepared, with warm distilled water, from each spot or, better, from spots I–V, II, III, IV–VI–VIII, VII, IX, X, XI–XII, XII–XIII, XIV. All were tested on the *Octopus* heart.

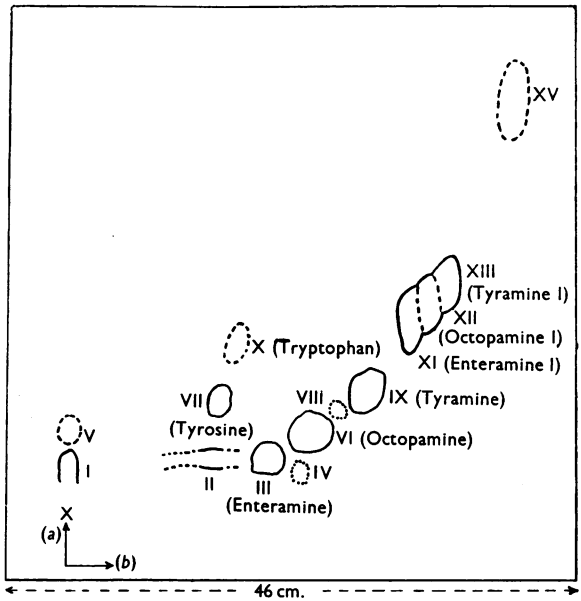

Fig. 7. Bidimensional chromatogram of a salivary extract of *Octopus vulgaris*. At *x*, 0·01 ml. of the summer 1950 extract, corresponding to 0·2 g. fresh tissue. Whatman no. 1 paper. First solvent (*a*): *n*-butanol saturated with N-HCl (48 hr.); second solvent (*b*): pyridine + amyl-alcohol + water (2:2:1) (48 hr.).

It appeared immediately clear that only the eluates of spot III (enteramine A) possessed a cardiostimulating activity. Such activity was practically identical with that manifested by the corresponding crude extract applied on paper, that is the entire activity appeared concentrated in spot III.

Moreover, eluates of spot XI (enteramine I) by themselves lacking, like all other eluates except those of spot III, any appreciable cardiostimulating action, became active after alkalinization at pH 8–9 and treatment in a boiling water-bath for 10 min. Under these conditions the activity of eluates XI was equal to that of eluates III diluted to give a coupling reaction, in an acid medium, of the same intensity; that is, the activity was proportional to the content of enteramine.

On summing the activity of eluate III with that of activated eluate XI one has values satisfactorily near to those given by the corresponding activated crude extract:

Cardiostimulating activity of untreated crude extract	100
Cardiostimulating activity of untreated eluate III	85–95
Cardiostimulating activity of untreated eluate XI	0
Cardiostimulating activity of activated crude extract	120
Cardiostimulating activity of activated eluate III	85–95
Cardiostimulating activity of activated eluate XI	15–20
Cardiostimulating activity of the other eluates, untreated and activated	0

The solvents employed in the paper chromatography of the salivary extracts were several. In every case only the eluates of enteramine spots appeared active.

The cardiostimulating activity of the salivary extracts of *Eledone moschata*, of the hypobranchial extracts of *Murex trunculus* and of the ox spleen extracts was also rigorously localized at the level of the enteramine spots.

DISCUSSION

Enteramine possesses a conspicuous stimulating action on the heart of all the molluscs studied. This is the fundamental observation in the present research. There is a relationship between the magnitude of the response and the quantity of substance put in contact with the heart. There is no evidence of damage to the organ, indeed it would seem that enteramine has a resuscitating action on the heart and on the contractile arteries.

What is the significance and the physiological importance of enteramine in the control of the cardiac activity of the molluscs in general and of the octopods in particular? By a simple calculation it appears that 1·5 g. of salivary tissue of an *Octopus vulgaris* of 500–600 g. body weight contain as much as 25,000–30,000 active doses of enteramine, admitting a dilution of each single active dose in 25–30 ml. haemolymph. At first sight it would seem conceivable that enteramine has the function of a regulating hormone of the octopod heart, but this assumption is difficult to reconcile with the fact that enteramine is absent in the posterior salivary glands of another species of octopods (*O. macropus*) although its heart is very sensitive to this substance. Enteramine is also lacking in the posterior salivary glands of *Sepia* (Ottaviano, 1942), and in the hypobranchial body of numerous prosobranch molluscs and in all the tissues of *Mytilus* and *Ostrea*.

It is thus difficult, faced with these experimental data, to attribute to this substance a general significance in the regulation of cardiovascular or other functions, unless the presence of minute quantities of the substance is postulated even in those molluscs in which it has not been possible to demonstrate it by our pharmacological methods. At all events, it cannot at this stage be

definitely affirmed that enteramine is concerned in the control of cardiac activity even in *Octopus vulgaris*, *Eledone moschata* and *Murex trunculus*.

The significance of tyramine and other biological amines should be considered with equal reserve. A simple demonstration of the presence of tyramine in salivary extracts of *Octopus macropus* alone (Henze, 1913) was sufficient to postulate that the substance might at the same time be not only the venom of the posterior salivary glands of Cephalopods (Henze, 1913; Baglioni, 1909), but also actually a 'normal product of the metabolism of Cephalopods' (Lelu, 1938) and the 'possible humoral mediator of the visceral nerve regulating the heart of Cephalopods'.

Nothing could be more arbitrary than such inferences and generalizations to all groups of cephalopods from the results obtained on one or few species of octopods. To remain in the field of tyramine researches, Erspamer & Boretti (1951) have been able to show, by paper chromatography, that this substance, contained in abundance in salivary extracts of *Octopus vulgaris* and *O. macropus*, is absent or present only in very minute quantities in *Eledone moschata*.

SUMMARY

1. Extracts of posterior salivary glands of *Octopus vulgaris* and *Eledone moschata*, of hypobranchial body of *Murex trunculus* and *M. brandaris*, as well as of ox spleen and rabbit gastric mucosa, show a powerful positive inotropic, chronotropic and tonotropic action on the molluscan heart, especially of *Helix* and *Octopus*.

2. The quantitative distribution of the cardiostimulant principle in various organs and tissues, its behaviour under various treatments and its localization in paper chromatograms correspond exactly to those of enteramine, permitting its certain identification with this substance. Only enteramine A is directly active on the heart; enteramine I becomes active after a suitable activating pretreatment.

3. The possible significance of enteramine in the functional control of the circulatory system of molluscs is discussed.

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REFERENCES

Baglioni, S. (1909). *Z. Biol.* **52**, 130.
Boyer, P. (1927). *C.R. Soc. Biol., Paris*, **95**, 1244.
Erspamer, V. (1940*a*). *Arch. Sci. biol., Napoli*, **26**, 295.
Erspamer, V. (1940*b*). *Arch. exp. Path. Pharmak.* **196**, 343, 366, 391.
Erspamer, V. (1942*a*). *Arch. exp. Path. Pharmak.* **200**, 43.
Erspamer, V. (1942*b*). *Arch. exp. Path. Pharmak.* **200**, 60.
Erspamer, V. (1943). *Arch. exp. Path. Pharmak.* **201**, 377.

Erspamer, V. (1946). *Experientia*, **2**, 369.
Erspamer, V. (1948*a*). *Acta pharmacol. toxicol.* **4**, 213.
Erspamer, V. (1948*b*). *Acta pharmacol. toxicol.* **4**, 224.
Erspamer, V. (1948*c*). *Arch. int. Pharmacodyn.* **76**, 308.
Erspamer, V. (1948*d*). *Experientia*, **5**, 79.
Erspamer, V. & Boretti, G. (1950). *Experientia*, **6**, 348.
Erspamer, V. & Boretti, G. (1951). *Arch. int. Pharmacodyn.* (in the Press). p. 296
Erspamer, V. & Ottolenghi, A. (1950). *Experientia*, **6**, 348.
Erspamer, V. & Ottolenghi, A. (1951). *Experientia*, **7**, 191.
Erspamer, V. & Vialli, M. (1951). *Nature, Lond.*, **167**, 1033.
Henze, M. (1913). *Hoppe-Seyl. Z.* **87**, 51.
Jullien, A. (1936). *Des réactions comparées de cœurs de Vertébrés et d'Invertébrés vis à vis des électrolytes et des drogues.* Paris: Baillière, Tindall and Cox.
Lelu, P. (1938). *Les corrélations humorales chez les Invertébrés.* Paris: Gauthier-Villars.
Ottaviano, G. (1942). *Arch. Sci. biol., Napoli*, **28**, 404.
Vialli, M. & Erspamer, V. (1940). *Arch. Fisiol.* **40**, 293.