THE PLACE OF HISTAMINE IN NEUROHUMORAL TRANSMISSION

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Histamine is one of the local hormones which have been claimed to play a role in neurohumoral transmission. It is a normal constituent of nervous tissue, as are histidine decarboxylase and histaminase. These facts were shown by Kwiatkowski (18), by von Euler (5, 6) and by Werle and co-workers (34, 35). Von Euler and Aström (7) showed that a histamine-like substance is released in Tyrode solution when an excised nerve of cattle is stimulated. The question thus arises whether under physiological conditions histamine plays a role in neurohumoral transmission (see a recent review, 1).

The humoral transmission of posterior root vasodilator fibres. The vasodilatation by stimulation of the posterior spinal roots is the first phenomenon which suggested neurohumoral transmission: the reasons are its slowness to appear and disappear, and the fact that it can be postponed by interruption of the circulation.

(a) Evidence of humoral transport was given by the experiments of Kibjakow (17), Bain (4), and chiefly Ungar and co-workers (29, 30, 31). But there was no evidence that the substance was histamine itself, and Ungar spoke of histamine-like substances defined as compounds increasing gastric secretion in the atropinized dog at low doses. This was a pharmacological, not a chemical definition, and, in this sense, Ungar suggested that these nerves should be called histaminergic.

When Ungar and I (32) studied in the dog the substance released in the venous plasma by peripheral stimulation of lumbar dorsal roots, we found that its chemical and pharmacological properties were not those of histamine. Its properties were similar to those of a compound obtainable from epinephrine (33). Its action on isolated guinea pig's ileum is inhibited by atropine sulfate at 5×10^{-7}, a concentration ten times higher than that required to inhibit the action of acetylcholine.

The histamine-like mediator found by Kwiatkowski (18) in chloralosed cats and by Ibrahim, Stella and Talaat (15) in chloralosed dogs may be identical with the above substance. In the nervous vasodilatation of the urethanized rabbit's ear histamine seems to be excluded as a mediator (14).

(b) On the other hand, antihistaminic compounds seem without influence on nervous vasodilatation. After intravenous injection of antergan (10 mg./kg.) in the chloralosed dog, Lefebvre and I (26) showed in 1943 that the peripheral stimulation of the first sacral posterior root gives rise to about the same degree of vasodilatation as previously. However, the dose of histamine which previously elicited a vasodilatation of about the same range as nervous stimulation was no longer effective, In man, after ingestion of antergan (0.40 g), the reflex component of the triple response to histamine was prevented; however, the vasodilatation produced in the skin by electric stimulation of nerves had still the same effect

(26). In rabbit ear, Holton and Perry (14) found that the nervous vasodilatation persisted when histamine vasodilatation was abolished by neo-antergan. In the dog, the dorsal root vasodilator response is not inhibited by pyribenzamine, as shown in 1953 by Frumin and co-workers (10); thus the positive results of Ibrahim, Stella and Talaat (15) in chloralosed dogs have not been confirmed.

(c) The chemical nature of the mediator is not known, although according to recent work of Holton and Holton (13a), it might be ATP or ADP; it may be said that it is less stable than histamine and more so than acetylcholine (32). Atropine sulfate, at a dose of 0.1 to 1 mg./kg., abolishes cholinergic (8), but not posterior root vasodilatation; at doses of 3 to 5 mg./kg., given intravenously, it can block the posterior root vasodilatation transiently and incompletely, without altering vasodilatation elicited by intra-arterial histamine (10). Eserine does not potentiate posterior root vasodilatation in the dog (10) or in the rabbit (14), and the opposite results of Wybauw (36) in the cat are open to question.

Humoral transmission in the spinal cord. Hellauer and Umrath (13) assumed that the substance causing so-called antidromic vasodilatation was identical with the central synaptic transmitter of sensory nerves; and, in fact, Häusler and Sterz (12) claimed that the stimulation of sensory nerves releases a histamine-like substance in the perfused spinal cord of the frog and that injection of histamine in this preparation produces stimulation of motor nerves. But the chemical nature of the histamine-like substance released seems still uncertain.

Histamine and the vasodilator axon reflex. Another question is whether histamine is involved in the vasodilator axon reflex, which takes place after irritation of the skin. Injected histamine can stimulate the peripheral end of these fibres and elicit a vasodilator axon reflex. On the other hand, local irritation of the skin is followed by such a response, and injured cells release histamine-like substances, as shown by Lewis (20 and 21).

In man, I could show (24) that the surrounding flare which appears after skin injury is prevented by ingestion of antergan (0.40 g). Therefore it seems that the histamine-like substance involved is histamine itself. Furthermore, since the vasodilator nerves are still effective on direct stimulation, it is apparent that histamine acts not as mediator at the end of the axon reflex but as the stimulus at its origin. I suggested elsewhere (23) that the stimulated fibres are not sensory but centrifugal fibres, just as in all other known types of axon reflexes.

Histamine as a peripheral mediator of pain. A stimulus begins to be painful just when it begins to be injurious for cells. On the other hand, injured cells may release histamine and intracutaneous histamine injection can elicit a painful sensation. Therefore, histamine was considered as the specific mediator for pain by Rosenthal and co-workers (19, 27, 29). One of their numerous and well-known observations was the inhibition by high dosages of compound 929 F of pupillary reflexes evoked in the dog by pinching, pricking, cutting or faradically stimulating the skin.

I was unable (25) to confirm these results on vasomotor reflexes with a more specific antihistamine: antergan (10 mg./kg.). But for two other painful sensa-

tions, perhaps burning, and very likely itching, histamine may be the mediator. The evidence is as follows: a. Histamine induces itching when superficially, and burning when more deeply injected in the skin. b. Histamine is released by itching or burning stimuli. c. Antihistaminics are very effective against itching, and I saw that antergan is able to weaken the burning sensation produced by hot water (25). Using the terminology recently proposed, it may be possible to assume the existence of "histaminoceptive" fibres; other substances, however, especially acetylcholine, may participate in the stimulation of these fibres. The analgesia developing during histamine desensitization (16) may also indicate some complex connection between histamine and pain.

Histamine and gastric secretion. An early theory proposed that histamine may be gastrin, but Komarov (17a) was able to obtain a gastrin preparation which was apparently free of histamine. Then Babkin (2) and MacIntosh (22) suggested that histamine acts as a final common agent released in response to all kinds of stimuli, and, amongst them, to nerve stimulation. In fact, autonomic nerve stimulation does not provoke acid secretion in those species where histamine is also ineffective (3, 9); and histaminase is capable of reducing greatly or abolishing the gastric secretory response to histamine, as well as to food and to other drugs (11).

Conclusions. 1. The mediator of the vasodilator fibres of the posterior roots seems to be neither histamine nor acetylcholine. 2. After irritation of the skin, histamine released by injured cells is able to stimulate peripheral endings of the vasodilator fibres and elicit a vasodilator axon reflex. 3. In the same way, histamine released from the skin by certain aggressions can stimulate the peripheral origin of certain sensory nerves and elicit painful sensations such as, possibly, burning and, very probably, itching.

REFERENCES

1. Ambrus, J. L. and Ambrus, C. M.: The role of histamine in the function of sensory nerves. Ztschr. Vitamin-Hormon- u. Fermentforsch., 5: 45–49, 1952.
2. Babkin, B. P.: The abnormal functioning of the gastric secretory mechanism as a possible factor in the pathogenesis of peptic ulcer. Canad. M. A. J., 38: 421–429, 1938.
3. Babkin, B. P., Chaisson, A. F. and Friedman, M. H. F.: Factors determining the course of the gastric secretion in elasmobranchs. J. Biol. Board Canad., 1 (4): 251–259, 1935.
4. Bain, W. A.: The mode of action of vaso-dilator and vaso-constrictor nerves. Quart. J. Exper. Physiol., 23: 381–389, 1933.
5. Euler, U. S. von: Sympathin, histamine and acetylcholine in mammalian nerves. J. Physiol., 107: 10P, 1948.
6. Euler, U. S. von.: Histamine as a specific constituent of certain autonomic nerve fibres. Acta physiol. scandinav., 19: 85–93, 1949.
7. Euler, U. S von and Åström, A.: 1948 quoted after U. S. von Euler 1949.
8. Folkow, B. and Uvnäs, B.: Do adrenergic vasodilator nerves exist? Acta. physiol. scandinav., 20: 329–337, 1950.
9. Friedman, M. H. F.: Gastric secretion in Necturus. J. Cell. & Comp. Physiol., 20: 379–384, 1942.
10. Frumin, M. J., Ngai, S. H. and Wang, S. C.: Evaluation of vasodilator mechanisms in the canine hind leg; question of dorsal root participation. Am. J. Physiol., 173: 428–438, 1953.
11. Grossman, M. I. and Robertson, C. R.: Inhibition by histamine of gastric secretion in dogs. Am. J. Physiol., 153: 447–453, 1948.
12. Häusler, H. F. and Stertz, H.: Zur Frage der Übertragung sensibler Impulse im Rückenmark des Frosches J. Mt. Sinai Hosp., 19: 121–130, 1952.
13. Hellauer, H. F. and Umrath, K.: Über die Aktionssubstanz der sensiblen Nerven. Arch. ges. Physiol., 249: 619–630, 1948.
13a. Holton, F. A. and Holton, P.: The possibility that ATP is a transmitter of sensory nerve endings. J. Physiol., 119: 50P, 1953.
14. Holton, P. and Perry, W. L. M.: On the transmitter responsible for antidromic vasodilatation in the rabbit's ear. J. Physiol., 114: 240–251, 1951.

15. Ibrahim, F. O., Stella, G. and Talaat, M.: The mechanism of antidromic vasodilatation. Quart. J. Exper. Physiol., 36: 189–198, 1951.
16. Jacob, J., Ambrus, J. and Ambrus, C.: Effets analgesiques des administrations répétées de bichlorhydrate d'histamine chez le rat. Ann. Inst. Pasteur, 81: 281–291, 1951.
17. Kibjakow, A. W.: Zur Frage des Vasodilatationsmechanismus bei der Reizung antidromer Nerven. I. Ueber die gefässerweiterden Eigenschaften des Blutes beim Reiz der hinteren sensiblen Wurseln. Arch. ges. Physiol., 228: 30–39. 1931.
17a. Komarov, S. A.: Gastrin. Proc. Soc. Exper. Biol. & Med., 38: 514–516, 1938.
18. Kwiatkowski, H.: Histamine in nervous tissue. J. Physiol., 102: 32–41, 1943.
19. Lambert, E. and Rosenthal, S. R.: Study of skin histamine (with some results of splanchnic nerve stimulation). Proc. Soc. Exper. Biol. & Med., 52: 302–304, 1943.
20. Lewis, Th. and Grant, R. T.: Vascular reactions of the skin to injury. Heart., 11: 119–209, 1924.
21. Lewis, Th. and Marvin, H. M.: Observations relating to vasodilatation arising from antidromic impulses to herpes zoster and trophic effects. Heart., 14: 27–47, 1927.
22. MacIntosh, F. C.: Histamine as a normal stimulant of gastric secretion. Quart. J. Exper. Physiol., 28: 87–98, 1938.
23. Parrot, J.-L.: Hypothèse sur la nature des fibres nerveuses qui interviennent dans le reflexe d'axone vasodilatateur. Comm. soc. Anat., Paris, 1-3, 1943.
24. Parrot, J.-L.: Les modifications apportées par un antagoniste de l'histamine (2339 RP) à la réaction vasculaire locale de la peau. Compt. rend. Soc. biol., 136: 715–716, 1942.
25. Parrot, J.-L.: Sur le mécanisme peripherique de la douleur. Intervention de l'histamine dans la brûlure et le prurit. Compt. rend. Soc. biol., 137: 620, 1943.
26. Parrot, J.-L. and Lefebvre, J.: Analyse de la triple réaction cutanée au moyen d'un antagoniste de l'histamine. Compt. rend. Soc. biol., 137: 316–317, 1943.
27. Rosenthal, S. R.: Histamine as possible chemical mediator for cutaneous pain. Dual pain response to histamine. Proc. Soc. Exper. Biol. & Med., 74: 167–170, 1950.
28. Rosenthal, S. R. and Minard, D.: Experiments on histamine as the chemical mediator for cutaneous pain. J. Exper. Med., 70: 415–426, 1939.
29. Ungar, G.: Effet de l'excitation du bout périphérique des nerfs sensitifs sur la sécrétion gastrique. Transmission neuro-humorale histaminique. Compt. rend. Soc. biol., 118: 630–631, 1935.
30. Ungar, G.: Demonstration de la mise en liberté de substances histaminiques. Transmission neuro-humorale histaminergique. J. Physiol. Path. gén., 34: 77–91, 1936.
31. Ungar, G.: *Les substances histaminiques et la transmission chimique de l'influx nerveux. L'histaminergie normale et pathologique.* Hermann et Cie, Paris. 1937.
32. Ungar, G. and Parrot, J.-L.: Sur la nature de la substance libérée au cours de la vasodilatation dite antidromique. Compt. rend. Soc. biol., 129: 753–755, 1938.
33. Ungar, G. and Parrot, J.-L.: Sur les rapports entre la substance libérée au cours de la vasodilatation antidromique et le corps hypotenseur produit par la transformation enzymatique de l'adrenaline. Compt. rend. Soc. biol., 131: 1165–1166, 1939.
34. Werle, E. and Palm, D.: Histamin in Nerven II. Biochem. Ztschr., 320: 323–334, 1950.
35. Werle, E. and Wecken, G.: Über das Vorkommen von Histamin in Nerven. Biochem. Ztschr., 319: 457–462, 1949.
36. Wybauw, L.: Contribution à l'étude du rôle vasomoteur et trophique des nerfs sensitifs. Arch. internat. physiol., 46: 293–388; 334–344, 1938.