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EDITORIAL

HISTAMINE

Histamine has certain outstanding pharmacological properties, but its exact role in many physiological and pathological processes remains to be determined.

There is hardly an organ in the body which does not contain histamine; two tissues alone, namely bone and cartilage, appear not to have been examined for the presence of histamine. Histamine is also found in many physiological and pathological fluids; but it has not been found in pancreatic juice and is usually absent from saliva. It is also present in various plants, sometimes in high concentration.[1] The distribution of histamine varies in different species of animals, and it will require more complete knowledge of the physiological and pathological function of histamine before the meaning of the differences in different tissues in different species, and in the same species, becomes clear.

There is now convincing evidence that the mast cells are the storehouse for most of the histamine in the body.[2] Much of the histamine in the blood appears to be in its mast cells—the basophils or mast leucocytes;[7] and in many organs the total histamine content is in the mast cells. These cells set histamine free when they are injured by chemical agents, e.g. certain polypeptides, many basic organic compounds, and antigen-antibody reactions. The mechanism of release of bound histamine is unknown; its elucidation will be of importance in our understanding of the reaction of cells to injurious agents. The evidence at present suggests that heparin as well as histamine is contained in the granules (mitochondria) of the mast cells; both substances may be preformed in the granules. It would seem that certain basic histamine liberators accumulate in the mast cells and form a complex with heparin, as a result of which the permeability of the granules is increased and histamine then diffuses out.[3] It has long been known that tissues may contain much histamine—enough to produce marked effects if it were set free. The forces which keep histamine in the mitochondria are not powerful; little is known about them. In recent years many different ways of causing the release of histamine have been introduced. One theory

VAN DIE REDAKSIE

HISTAMIEN

Histamien besit sekere duidelike farmakologiese hoedanighede, maar sy juiste rol in verskeie fisiologiese en patologiese prosesse moet nog vasgestel word.

Byna al die organe van die liggaam bevat histamien; dit blyk dat slegs twee weefselsoorte, nl. been en kraakbeen, nog nie op die aanwesigheid van histamien ondersoek is nie. Ook word histamien in baie fisiologiese en patologiese vloeistowwe gevind; dit is egter nog nie in die sap van die alvleesklier gevind nie, en kom gewoonlik nie in die speeksel voor nie. Dit is ook, soms sterk gekonsentreer, in verskeie plante aanwesig.[1] Histamien is verskillend in die verskillende dieresoorte versprei, en deegliker kennis van die fisiologiese en patologiese rol van histamien is nodig voordat die betekenis van die verskille in die verskillende weefsels van verskillende dieresoorte, sowel as in dieselfde dieresoort, duidelik vertolk kan word.

Daar is nou oortuigende bewyse dat die liggaam se histamien hoofsaaklik in die mastselle gebêre word.[2] Die meeste van die histamien in die bloed blyk in die bloed-mastselle te wees, d.w.s. in die basofiele of mast-leukosiete;[7] en baie van die organe dra hulle totale histamien-inhoud in die mastselle. Hierdie selle stel histamien vry wanneer hul beskadig word deur chemiese stowwe, soos bv. sekere polipeptiede, baie van die basiese organiese verbindings, en reaksies tussen antigene en teenliggaampies. Dit is nie bekend hoe histamien uit verbinding bevry word nie; die verduideliking van hierdie meganisme sal van belang wees by ons begrip van selreaksies teen beskadigende stowwe. Op die oomblik dui vasgestelde feite daarop dat die mastsel-korreltjies of protoplasmadrade (mitochondria) heparien sowel as histamien bevat; moontlik word beide stowwe in die korreltjies vóórgevorm. Daar word gemeen dat sekere basiese histamien-vrystellers in die mastselle ophoop en 'n komplekse verbinding met heparien aangaan, met die gevolg dat die korreltjies meer deurdringbaar word en die histamien dan uitsyfer.[3] Dit is reeds lankal bekend dat die weefsels baie histamien kan bevat—genoeg om aansienlike effekte te bewerkstellig as dit moes vrygestel word. Die kragte wat die histamien binne die mitochondria hou is nie sterk nie; ons kennis van hulle is maar gering. In die afgelope jare is baie verskillende metodes om die histamien vry te stel ingevoer. Een van die teorieë wat ter verduideliking van die meganisme voorgestel is, is gebaseer op die beginsel van ione-uitruiling;[4, 5] histamien as basis, chemies verbind met 'n weefselsuur, sal deur enige basis met 'n groter affiniteit vir daardie suur vrygestel

put forward to explain the mode of action is based on the idea of ion exchange;[4,5] histamine as a base combined with a tissue acid will be set free by any base with a greater affinity for that acid. Among the many compounds which release histamine are well-known drugs such as morphine, atropine, tubocurarine and amphetamine. Natural and synthetic polymers can cause the release of histamine in certain animal species, depending on the molecular size of the polymer;[6] ovomucoid (egg white), dextran, polividone, and the surface active agents known as tweens have been used in studies on the release of histamine.

Once histamine is released it appears in the tissue fluids and the circulation. In the blood stream it is transported, with 5-hydroxytryptamine and the catechol amines, in the platelets. The eosinophil cells have been shown to contain histamine.[9] In human beings there is a decrease in the number of eosinophils and basophils after administration of cortisone, and this is associated with a fall in the concentration of histamine in the blood.[10] Both the basophils and the eosinophils appear to carry histamine in the blood.

Histamine exerts its biological actions by being bound again at specific receptors on the effector cells. All the amines mentioned above are inactivated by oxidative de-amination but, whereas the site of inactivation for the catechol amines and 5-hydroxytryptamine seems to be mainly intracellular, for histamine there appears to be both intracellular and extracellular inactivation; the relative amounts inactivated in these sites remain to be determined. A modern view is that the eosinophil cells are concerned with the detoxication and disposal of histamine.[8] The mechanisms by which histamine is believed to be inactivated include (1) the acetylation of histamine and (2) the oxidative de-amination of histamine. After the administration of histamine acetylhistamine has been isolated from the urine, and this has been confirmed by studies with radio-active histamine. The exact site of the acetylation has not yet been demonstrated. As regards the enzymology of histamine oxidation, it would appear that histaminase and diamine oxidase are not identical,[11] and the nomenclature may one day be revised. Until the experts settle this question of correct nomenclature the term histaminase may continue to be used. This enzyme appears to be in the cytoplasm of the cell; perhaps the long life of histamine in cells may be due to the fact that it is protected by being enclosed in the mitochondria.

1. Werle, E. and Raub, A. (1948): Biochem. Z., **318,** 538.
2. Riley, J. F. (1954): Lancet, **1,** 841.
3. Grossberg, A. L. and Garcia-Arocha, H. (1954): Science, **120,** 762.
4. Eldridge, E. and Paton, W. D. M. (1954): J. Physiol., **124,** 27 P.
5. Riley, J. F. and West, G. B. (1954): *Ibid.*, **125,** 47 P.
6. Halpern, B. N. and Briot, M. (1950): Arch. Int. Pharmacodyn., **82,** 247.
7. Valentine, W. N. *et al.* (1955): Blood, **10,** 154.
8. Vaughn, J. (1953): *Ibid.*, **8,** 1.
9. Code, C. F. and Mitchell, R. G. (1954): J. Clin. Invest., **33,** 924.
10. Code, C. F. *et al.* (1954): Proc. Mayo Clin., **29,** 200.
11. Schayer, R. W. *et al.* (1954): J. Biol. Chem., **206,** 461.

word. Welbekende middels soos morfien, atropien, tubukurarien en amfetamien tel onder die baie verbindings wat in staat is om histamien te bevry. Natuurlike en sintetiese polimere kan die vrystelling van histamien by sekere dieresoorte teweegbring mits die molekulêre gewig van die polimeer dit toelaat;[6] ovomukoïede (wit van eier), *dextran*, *polyvidone*, en die kapillêr-aktiewe agente wat bekend is as *tweens* is reeds gebruik by navorsing op die vrystelling van histamien.

Sodra histamien vrygestel word, kom dit in die weefselvloeistowwe en in die bloedsomloop. Dit word tesame met 5-hidroksitriptamien en die katesjolamiene langs die bloedbaan in die bloedplaatjies vervoer.

Dit is reeds bewys dat die eosinofielselle histamien bevat.[9] By die mens verminder die aantal eosinofiele en basofiele ná die toediening van kortisoon, en hierdie feit staan in verband met 'n daling in die konsentrasie van histamien in die bloed.[10] Beide die basofiele en die eosinofiele dra blykbaar die histamien in die bloed.

Histamien oefen sy biologiese aksies uit deur weer 'n verbinding aan te gaan by bepaalde reseptore op die effektorselle. Al die bogenoemde amiene word buite werking gestel deur deaminering weens oksidering, maar blykbaar vind die onaktivering van die katesjol-amiene en 5-hidroksitriptamien hoofsaaklik *binne* die selle plaas, terwyl histamien egter *binne* sowel as *buite* die selle onwerksaam gemaak word—die relatiewe hoeveelhede wat in hierdie plekke onaktiveer word moet nog bepaal word.

Die moderne denke is dat die eosinofielselle betrokke is by die onskadelik maak en die verwydering van histamien.[8] Die meganismes waardeur histamien vermoedelik onwerksaam gemaak word sluit die volgende prosesse in: (1) die asetilasie daarvan, en (2) die deaminering van die histamien deur oksidering. Asetielhistamien is reeds in die urine afgesonder ná die toediening van histamien en dit is bevestig deur studies van radioaktiewe histamien. Dit is nog nie vasgestel presies *waar* die asetilasie plaasvind nie. Wat die ensiemeverband van die oksidering van histamien betref, is histaminase en diamien-oksidase blykbaar nie dieselfde stof nie[11]—die benaming sal moontlik eendag hersien word. Totdat die gesaghebbendes oor hierdie saak van juiste benaming beslis, mag die woord histaminase nog gebruik word. Blykbaar kom hierdie ensiem in die sitoplasma van die sel voor; moontlik het histamien sy lang bestaan in die selle te danke aan die feit dat dit beskerm word deurdat dit deur die protoplasmadrade omring is.

1. Werle, E. en Raub, A. (1948): Biochem. Z., **318,** 538.
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