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EDITORIAL

PIGMENTATION AND MSH

MSH (melanocyte-stimulating hormone), also known as intermedin, melanophore-expanding hormone, and melanin-dispersing hormone, is found in the pars intermedia of the pituitary gland. It has been recognized for some 35 years to be the hormone responsible for controlling the darkening of the skin of the frog and other amphibia. Such darkening of the skin occurs in a dark environment, while in a bright environment the skin again becomes lighter. This increased pigmentation has been clearly shown to be caused locally by a dispersion of melanin within the melanocyte. The hormone is undoubtedly present in the pituitary glands of mammals also, but no such clear effect has hitherto been ascribable to it. It does appear, however, that melanin can be formed in the melanocyte of the skin of mammals (including man) and that extracts of pituitary glands containing much MSH activity can stimulate an increase in the amount of melanin in the skin.

The old teaching was that the pigmentation of Addison's disease was caused by a deviation of tyrosine from adrenalin formation (the adrenal being no longer able to elaborate adrenalin) to melanin formation, for which the adrenal gland was not necessary. This theory, however, was without any foundation in fact, so that it was natural that investigators should wonder whether MSH might not have something to do with the pigmentation. In fact, a high level of MSH activity has been found in the blood of patients suffering from Addison's disease. Similarly, MSH activity has been found to be excessive in Cushing's syndrome, in pregnant women, and in certain states of stress. In all these conditions, incidentally, an excess of circulating corticotrophin (ACTH) is also to be expected (although the relation of Cushing's syndrome to ACTH is still uncertain at the present time). In Addison's disease the low blood concentration of corticosteroids releases the inhibition to formation of ACTH in the pituitary. The demonstration of a close connection between MSH and ACTH was taken further by the fact that the most highly purified samples of ACTH still retained MSH activity. It was even suggested that ACTH and MSH might actually be the same thing.

That ACTH and MSH were distinct substances was soon shown by the almost complete separation of their activities;

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PIGMENTASIE EN MSH

MSH (melanosiet-stimulerende hormoon), ook bekend as intermedien, melanofoor-uitdyende hormoon en melanien-verspreiende hormoon, word in die pars intermedia van die skildklier gevind. Vir ongeveer 35 jaar bestaan die wete dat dit die hormoon is wat vir die beheer van die verdonkering van die vel van die padda en ander amfibieë verantwoordelik is. Sodanige verdonkering van die vel geskied in 'n donker omgewing, terwyl die vel in 'n helder omgewing weer ligter word. Dit is duidelik getoon dat hierdie toename van pigmentasie plaaslik veroorsaak word deur 'n verspreiding van melanien binne-in die melanosiet. Die hormoon is ongetwyfeld ook in die skildkliere van soogdiere aanwesig, maar geen soortgelyk duidelike uitwerking is tot nog toe daaraan toegeskryf nie. Dit skyn egter dat melanien wel in die melanosiet van die vel van soogdiere (insluitende die mens) gevorm kan word en dat uittreksels van skildkliere, wat baie MSH-werking bevat, 'n vermeerdering in die hoeveelheid van melanien in die vel kan stimuleer.

Die ou leer was dat die pigmentasie by Addision se siekte teweeggebring is deur 'n afwyking van tirosien wat veroorsaak dat melanien, waarvoor die bynier nie nodig was nie, i.p.v. adrenalien, (aangesien die bynier nie langer in staat was om adrenalien voort te bring nie), gevorm is. Hierdie teorie was egter inderdaad ongegrond, sodat dit heel natuurlik was dat navorsers sou wonder of MSH-werking nie iets met die pigmentasie te doen het nie. 'n Hoë vlak van MSH-werking is inderdaad in die bloed van pasiënte, wat aan Addison se siekte ly, gevind. Soortgelyk is dit gevind dat MSH-aktiwiteit oormatig is by Cushing se sindroom, by swanger vroue, en by sekere toestande van spanning. Toevallig kan 'n oormaat van sirkulerende kortikotrofien (ACTH) ook by al hierdie toestande verwag word (alhoewel die verwantskap van Cushing se sindroom met ACTH tans nog onseker is). By Addison se siekte bevry die lae bloedkonsentrasie van kortikosteroïede die onderdrukking van ACTH-vorming in die skildklier. Die demonstrasie van 'n noue verwantskap tussen MSH en ACTH is verder opgehelder deur die feit dat die mees-gesuiwerde monsters van ACTH nog MSH-werking oorgehou het. Dit is selfs aan die hand gedoen dat ACTH en MSH inderdaad een en dieselfde is.

Dat ACTH en MSH afsonderlike stowwe is, is gou getoon deur die bykans algehele skeiding van hulle aktiwiteite; bowendien, sekere chemiese behandelings het die ACTH-aktiwiteit van die ‚hormoon' vernietig terwyl MSH-aktiwiteit

moreover, certain chemical treatments destroyed the ACTH activity of the 'hormone', while MSH activity was retained. Furthermore, different parts of the pituitary gland have very different ratios of activity of ACTH and MSH. Thus the anterior lobe is rich in corticotrophin while the posterior and intermediate lobes are rich in MSH. These differences of activity are of the order of 100 times.

Recently both ACTH and MSH (or at least, one variety of MSH) have been isolated and structurally analysed. Corticotrophin is apparently a peptide containing 30 amino acids in a long chain, while MSH contains some 18 amino acids, also in a single chain. A sequence of 7 amino acids is said to be identical in the two hormones, so that there is little wonder that their chemical properties are very similar and their separation very difficult. This similarity may even confer a basic melanocyte-stimulating property on pure ACTH, although very much weaker than that of pure MSH. Thus apparently pure corticotrophin subjected to complicated chemical alteration, and then partially regenerated, first lost and then recovered both ACTH and MSH activity—the two could not be separated. No amount of purification has been able to rid ACTH of a constant small amount of MSH activity, which really does, therefore, appear to be a property of the corticotrophin itself. Incidentally, commercial ACTH has a good deal more MSH activity than this basic amount, indicating its contamination with the MSH hormone. Now treatment of corticotrophin with periodate has been found to destroy its ACTH activity, while leaving intact the small moiety of MSH action. It is believed that this treatment attacked only the serine residue at the end of the corticotrophin peptide chain, leaving intact the 7 amino acids common to both ACTH and MSH.

We can now tentatively explain the pigmentation of Addison's disease and that following adrenalectomy as being caused by an increased production of MSH and ACTH, assuming that the output of both these hormones is regulated by the quantity of circulating corticosteroids of the cortisone type. On treatment with cortisone or hydrocortisone some depression of production of these hormones occurs and the pigmentation lightens, although it does not entirely disappear. In Cushing's syndrome, and in pregnancy, pigmentation may again be correlated with high ACTH and MSH production, this time with increased adrenal function also. In panhypopituitarism the skin colour may become paler and the patients no longer tan in sunlight. The pituitary ACTH and MSH production is here suppressed by local disease, and no change is brought about by treatment with replacement hormones. The clinical issues, however, are by no means clear cut, and we must await further elucidation along these lines.

A large number of workers have contributed to work in this field, and the interested reader is referred to the Brit. Med. J. 20 *April* 1957, *p.* 935, *for a list of references. For easily accessible reviews:*

Syndor, K. L. *et al.* (1953): J. Clin. Endocr., **13,** 891.
Shizume, K. and Lerner, A. B. (1954): *Ibid.*, **14,** 1491.
Lee, T. H. and Lerner, A. B. (1956): J. Biol. Chem., **221,** 943.

behoue gebly het. Boonop het verskillende dele van die skildklier hoogs verskillende aktiwiteitsverhoudings van ACTH en MSH. Aldus is die voorste lob ryk aan kortikotrofien terwyl die agterste en tussenlobbe ryk aan MSH is. Hierdie verskille van aktiwiteit is in die verhouding van 100-maal.

Onlangs is beide ACTH en MSH (of, ten minste, een soort van MSH) afgesonder en volgens struktuur ontleed. Kortikotrofien is blykbaar 'n peptied wat 30 aminosure in 'n lang ketting bevat, terwyl MSH ongeveer 18 aminosure, ook in 'n enkel ketting, bevat. Dit word beweer dat 7 aminosure, wat mekaar opvolg, identies by beide hormone is, sodat dit glad nie verbasend is dat hulle chemiese hoedanighede baie eenders en hulle skeiding baie moeilik is nie. Hierdie eendersheid mag selfs 'n basiese melanosiet-stimulerende hoedanigheid aan suiwer ACTH verleen, alhoewel dit baie swakker as dié van suiwer MSH sal wees. Op hierdie wyse het suiwer kortikotrofien, onderworpe aan ingewikkelde chemiese verandering en dan gedeeltelik geregenereer, blykbaar eers beide ACTH- en MSH-werking verloor en dit dan teruggewen—die twee kon nie geskei word nie. Geen mate van suiwering was daartoe in staat om ACTH van 'n konstante klein hoeveelheid van MSH-aktiwiteit te bevry nie. Dit skyn dus of dit werklik 'n hoedanigheid van die kortikotrofien self is. Terloops, handels-ACTH het heelwat meer MSH-aktiwiteit as hierdie basiese hoeveelheid, wat die vermenging daarvan met die MSH-hormoon aandui. Dit is nou gevind dat behandeling van kortikotrofien met perjodaat die ACTH-aktiwiteit daarvan vernietig, terwyl die klein mate van MSH-werking ongeskonde bly. Die mening is dat hierdie behandeling slegs die serien-oorskot aan die end van die kortikotrofien-peptiedketting aanval en die 7 aminosure, wat beide ACTH en MSH in gemeen het, onaangetas laat.

Ons kan nou voorlopig die pigmentasie van Addison se siekte en dié wat op adrenalektomie volg, verklaar deur te sê dat dit deur 'n vermeerderde vervaardiging van MSH en ACTH veroorsaak word, indien ons aanneem dat die produksievermoë van beide hierdie hormone deur die hoeveelheid sirkulerende kortikosteroïede, van die kortisoon tipe, gereguleer word. By behandeling met kortisoon of hidrokortisoon vind 'n sekere mate van onderdrukking van die vervaardiging deur hierdie hormone plaas en die pigmentasie word ligter, alhoewel dit nie heeltemal verdwyn nie. By Cushing se sindroom en by swangerskap kan pigmentasie weereens met 'n hoë ACTH- en MSH-vervaardiging gekorreleer word, nou ook met vermeerderde bynierwerking. By panhipopituitarisme mag die kleur van die vel ligter word en die pasiënte brand nie meer bruin in sonlig nie. By hierdie toestand word die ACTH- en MSH-vervaardiging deur die skildklier deur plaaslike siekte onderdruk en die toestand verbeter geensins deur behandeling met verplasingshormone nie. Die kliniese beslissings is egter glad nie baie duidelik nie, en ons moet wag op verdere opheldering in hierdie rigting.

'n Groot aantal navorsers het bydraes gelewer tot werke op hierdie gebied, en die geïnteresseerde leser word verwys na die Brit. Med. J. *van* 20 *April* 1957 *vir 'n lys van verwysings. Vir maklik-bekombare oorsigte:*

Syndor, K. L. *et al.* (1953): J. Clin. Endocr., **13,** 891.
Shizume, K. en Lerner, A. B. (1954): *Ibid.*, **14,** 1491.
Lee, T. H. en Lerner, A. B. (1956): J. Biol. Chem., **221,** 943.

GLUCAGON

The name glucagon was applied as early as 1923[1] to a hyperglycaemic factor (HGF) present in certain extracts of the pancreas. Since that time, and particularly in more recent years, much work has been done in order to establish the site of origin of this substance, its role in the regulation of carbohydrate metabolism and in relation to the action of insulin, and indeed whether it is really a hormone at all. There have been conflicting reports in the literature which render the status of glucagon in some respects unsatisfactory.[2]

Glucagon has been extracted not only from the pancreas but also from other tissues such as the gastric and duodenal mucosa, and some claim to have demonstrated its presence in the urine. It can be extracted after destruction of the beta cells of the islets by alloxan. For a number of years it has been stated that glucagon comes from the alpha cells of the pancreas, and while some workers state that it is not exclusively manufactured by these cells the evidence on the whole is overwhelming in favour of this site as the place of origin for this hyperglycaemic factor.

The question whether glucagon is an antagonist or synergist of insulin has led to controversy. A number of the activities of glucagon are opposed to the metabolic actions of insulin, for example in the liver. In the peripheral tissues the situation is more complicated; some regard glucagon and insulin as synergistic in action, others have demonstrated that glucagon has anti-insulin actions at this level. One explanation put forward to account for the apparently paradoxical findings is the fact that preparations containing glucagon may contain insulin. It is clear that even more highly purified crystalline glucagon will need to be used in all studies with this compound. If glucagon is a hormone its peripheral effects are probably secondary. After leaving the pancreas it enters the liver, where it is rapidly inactivated; little will escape to act on the peripheral tissues.

The hormonal status of glucagon is still uncertain, but it presents a strong appearance of being a hormone. There is not only indirect but also direct evidence that it is secreted into the blood stream; for example, a hyperglycaemic factor has been demonstrated in the pancreatico-duodenal blood. It is a polypeptide of fairly low molecular weight like certain hormones. It is produced in the islets of Langerhans. It has powerful and specific effects on various metabolic processes, for example in the liver, in extremely low concentrations. The liver has a powerful inactivating mechanism for the substance. All these points strongly suggest that glucagon is a hormone.

While many may regard our present knowledge concerning glucagon as inconclusive, the weight of evidence appears to place it as a hormone, formed most probably in the alpha cells of the islets of the pancreas, and acting as a powerful hepatic antagonist or corrector of insulin.

1. Gibbs, C. B. F. *et al.* (1923): Quart. J. Exp. Physiol. suppl. **13,** 128.
2. Editorial (1956): Brit. Med. J., **2,** 288.