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Periodico quadrimestrale inviato gratuitamente ai soci della European Society for Pigment Cell Research (Associazione Europea per la Ricerca sulla Cellula Pigmentaria) dalla Fondazione Pro Ricerca Dermatologica (Presidente: Prof. F. Serri). Direttore Responsabile: Prof. Giuseppe Prota, Presidente ESPCR, Dpt. di Chimica Organica e Biologica, Università di Napoli, Via Mezzocannone 16, 80134 Napoli.

LETTER TO THE EDITOR OF

PIGMENT CELL BULLETIN

REVIEW

Melanophore regulating effects of the melanin-concentrating hormone

During the past decade, studies on colour change mechanisms in teleost fish have revealed the existence of a second potent melanotropin, the melanin-concentrating hormone MCH. This is an hypothalamo-neurohypophysal peptide which is stored in high concentrations in the neural lobe of fish pituitaries and is released when fish adapt to a pale-coloured environment (Baker, 1988a; Kishida & Baker, 1989). Although an homologous ir. peptide is found in hypothalamic neurones of all vertebrates so far investigated, including man, its distribution in animals other than the teleost is restricted mainly to the brain and only small amounts are found in the posterior pituitary gland. Moreover, with the exception of the holostean fish which are ancestral to the teleosts (Sherbrooke & Hadley, 1988), the melanophores of other vertebrates appear to lack receptors to MCH and do not respond to the peptide by melanin aggregation. Thus the use of this peptide as a colour-change hormone would seem to be an evolutionary peculiarity of certain bony fish. Indeed, in some fish such as the trout, the titre of MCH in the blood changes much more rapidly than does the α-MSH concentration (Baker, 1988b; Kishida & Baker, 1989) suggesting that MCH may have become the more important hormone for regulating physiological colour change in this species. The interest of MCH for pigment cell biologists lies in its mode of action on the melanophore, and its other involvements in pigmentation. it is these roles which have been studied most up till now and which are reviewed briefly below. Its interest for comparative physiologists, however, is its function in the brain and how this pre-adapted it to the a role in pigmentary regulation. Our knowledge on this point is rather slight although it may well turn out to be more important than the pigmentary effects of the hormone.

Recent studies on MCH sprang from the finding that melanin-concentrating hormone, which could not be attributed to catecholamines, occurred in both the trout hypothalamus and pituitary gland, and that its abundance in both sites

varied with the chromatic status of the fish (Rance and Baker, 1979; Baker & Rance, 1983). The molecule from Chum salmon pituitaries was then purified by Kawauchi et al., (1983) who showed it to be a cyclic heptadecapeptide (Fig. 1). Subsequently, it wa synthetized by several groups (Okamoto et al., 1984; Wilkes et al., 1984b; Eberle et al., 1986) and it is now available commercially from Peninsula Laboratories.

The multiple effects of MCH in colour change were first apparent when it was administrated to trout over several weeks in Alzet minipumps (Baker et al., 1986). In these experiments it initially induced pallor through melanin concentration and in the long term inhibited melanogenesis. This effect on melanin synthesis could be due to a direct action of MCH on the melanophores and/or to its ability to depress the release of α-MSH from the pituitary gland, which it does by a paracrine effect in the pituitary neurointermediate lobe (Barber et al., 1987). The initial rapid paling response reflects the ability of MCH to antagonize the melanin dispersing effect of α-MSH. This antagonism can be demonstrated most easily in vitro, by incubating fragments of skin or individual scales in medium containing different concentrations of MCH and α-MSH (Baker, 1988b). Such experiments show that fish species differ in their relative sensitivity to the two hormones. Thus, melanophores from the grass carp Ctenopharyngodon idellus are very responsive to low concentrations of MCH but its aggregating effect is readily overridden by equimolar concentrations of α-MSH. In contrast, although MCH is less potent on trout melanophores, it has the dominant effect when both hormones are presented together at high doses. It is possible that these species differences reflect the relative numbers of MCH and α-MSH receptors on the melanophores. Whatever the explanation, the observations explain why it is that some fish repond to injection of fish pituitary extracts (containing both MCH and α-MSH) by melanin concentration while others respond by melanin dispersion (Pickford & Atz, 1957).

MCH appears to act on specific receptors which, in contrast to the α-MSH receptors, can be activated in the absence of extracellular calcium (Hadley et al., 1988). It is likely that α-MSH uses cAMP as its second messenger but the second messenger system of MCH is as yet unknown. MCH is able to override both the effects of exogenous dbcAMP and the melanin dispersing effect of forskolin which increases intracellular cAMP by increasing adenyl cyclase activity (Baker, unpublished observations). Nor-adrenalin from the sympathetic nervous system is also involved in causing pallor in many fish, and MCH and nor-adrenalin act synergistically on isolated trout scales (Green & Baker, in preparation). This suggests that they cause melanin aggregation through different second messenger systems.

The active site within the MCH molecule has been studied

by several groups. When fragments of salmonid MCH were tested on skin from the amazonian eel, Synbranchus, Castrucci et al., (1987) found an approximate potency of MCH_{1-17} (100%) = MCH_{5-17} > MCH_{1-14} (10%) > MCH_{5-14} (1%). These experiments reveal the importance of the C-terminal residues for receptor binding/activation, but the fact that neither MCH_{5-17} nor MCH_{5-14} appear to induce complete melanin aggregation suggests that the N-terminal sequence may also be important for full intrinsic activity in this species. Other species may show a different relative sensitivity to the fragments however, indicating species differences in receptor structure (Hadley et al., 1987; Kawazoe et al., 1987). Thus, MCH_{5-14} exhibits 100% potency when tested on melanophores from Tilapia mossambica (Kawazoe et al., 1987), while MCH_{5-17} has only about 1% potency but full intrinsic activity when tested on pigment cells of the grass carp Ctenopharyngodon (Brown et al., 1989). These studies have all used fragments of the non-homologous salmonid MCH and further studies are needed to determine whether the hormone itself has also undergone mutation in different species.

MCH causes melanin dispersion rather than aggregation when tested at high concentrations on melanophores of amphibians and reptiles (Wilkes et al., 1984a, Baker et al., 1985; Ide et al., 1985), and it also has this effect in vitro on skin of the amazonian eel (Castrucci et al., 1987) low doses of the peptide causing melanin aggregation and high doses melanin dispersion. The dispersive effect is not observed if calcium is absent from the extracellular medium, nor is it exhibited by the fragments MCH_{5-17} and MCH_{5-14} (Hadley et al., 1988) which, as noted above, exhibit melanin concentrating activity. Hadley and co-workers have therefore concluded that melanin dispersion results from an interaction between the N-terminal region of MCH with the α-MSH receptors, even, though there is no apparent similarity between the primary structures of α-MSH and MCH (Fig. 1). Such an interpretation could explain why the melanin aggregating potency of MCH is enhanced in the absence of extracellular calcium (Hadley et al., 1988a; Baker, unpublished). MCH has a similar MSH-like activity on mouse B-16 melanoma cells, inducing tyrosinase activity when added to the culture medium at a concentration of 10^{-6}M (Baker et al., 1985a).

The non-pigmentary effects of MCH are still poorly understood. Besides depressing the release of α-MSH from the pars intermedia, MCH will also inhibit the release of ACTH from the corticotrophs so that fish kept in white tanks become less responsive to moderate stresses (Gilham & Baker, 1985). MCH delivered by Alzet minipump has the same effect on ACTH release (Baker et al., 1986) and this is partly due to a direct action on the pituitary pars distalis (Baker et al., 1985b) although effects at the hypothalamic level are also possible. Other effects of MCH in the brain remain to be explored but recent studies in rats show that it is able to partially antagonize certain behavioural effects induced

by iv injections of α-MSH (dee Graan et al., 1989). It seems likely that the pigmentary role of MCH evolved either from its inhibitory interaction with α-MSH in the brain or from its ability to depress the release of α-MSH from the pituitary gland.

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Fig. 1

The primary structures of MCH and α-MSH

MCH H-Asp-Thr-Met-Arg-Cys-Met-Val-Gly-Arg-Val-Tyr-Arg-Pro-Cys-Trp-Glu-Val-OH

MSH Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

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SHORT COMMUNICATION

Melanoma-associated gangliosides in Xiphophorus

Gangliosides from benign and malignant melanomas and from normal skin of the fish genus Xiphophorus were isolated and analyzed by thinlayer chromatography. Individual ganglioside components were characterized by mapping according to their sialic acid contents and by cleavage with neuroaminidases. In all three tissues examined, sulfatide and the gangliosides NeuAc-GalCer (GM_4), II^3NeuAc-LacCer (GM_3), II^3NeuAcGg$_3$Cer (GM_2) and II_3(NeuAc)$_2$-LacCer (GD_3) were found. Ganglioside GD_3 yielded a positive reaction, following immunoadsorption with mouse monoclonal antibody R24 on thin-layer plates. Two alkali-labile disialoganglioside species were specifically recognized by mouse monoclonal antibody D1.1, thus indicating the presence of O-acetyl-GD_3, since it could be converted to the R24 positive GD_3 ganglioside after alkaline saponification. The other one appears to be restricted to the malignant tumor and represents a novel melanoma-associated ganglioside derivative. It was characterized as O-acetyl-(NeuAc)$_2$-nLc$_4$Cer by exoglycosidase cleavage, by proving its neutral carbohydrate backbone as type II-chain lacto-series oligosaccharide using mouse monoclonal antibody 1B2, and by its cross-reaction with antibody R24 following alkaline treatment. Using antibody R24 and cryopreserved tissue sections of both benign and malignant amelanotic melanomas from albino fishes, it was demonstrated that one of the main melanoma-associated gangliosides, GD_3, was exposed predominantly in the malignant tumor. Thus, the chemical nature and even the immunohistochemical localization of the gangliosides in fish melanomas proved to be very similar to those of the known gangliosides in the phylogenetically distant human melanomas.

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CURRENT LITERATURE IN

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PIGMENT CELL RESEARCH

1. MELANINS, AND OTHER PIGMENTS CHEMISTRY

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Abstract : PAGE was used to identify an enzyme that catalyzed the dehydration of scytalone to 1,3,8-trihydroxynaphthalene, the next sequential component of the pentaketide melanin pathway. The dehydratase, extd. from the pentaketide melanin-producing black yeast Phaeococcomyces species, was partially purified by gel filtration and preparative electrophoresis. Enzyme activity was indicated by the formation of a single orange band on polyacrylamide gels after scytalone was added as substrate. The enzyme has a mol. mass of .apprx.60,000-65,000 and an isoelec. point of 5.2. The pH optimum for activity with scytalone under aerobic conditions was 7.5. Anaerobic reactions resulted in the accumulation of 1,3,8-trihydroxynaphthalene, and aerobic reactions produced 2-hydroxyjuglone, which is an orange-colored autoxidn. product of 1,3,8-trihydroxynaphthalene. Reduced nucleotides were not required for the dehydratase reaction. When the pentaketide pathway intermediate vermelone was used as a substrate it was converted to 1,8-dihydroxynaphthalene and an unknown hydroxynaphthalene. Exts. of the plant pathogenic pentaketide melanin-producing fungi Verticillium dahliae, V. albo-atrum, Alternaria solani, and Cladosporium cucumerinum were also shown to have the dehydratase activity on polyacrylamide electrophoresis gels. The dehydratase activity did not occur with exts. of yeasts that do not form pentaketide melanins or with exts. from V. dahliae and V. albo-atrum that had not yet formed melanin.

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Biomimetic synthesis of 5,6-dihydroxyindole-2-carboxylic acid and of its benzyl ester. Synth. Commun. 17:1815-1821, 1987.
Abstract : The title compds. I (R = H, CH2Ph) were prepd. from dopa benzyl ester (II) via a simple biomimetic synthesis. Thus, the oxidative cyclization of II with ceric ammonium nitrate gave dopachrome III, which underwent an in situ rearrangement in the presence of Zn(OAc) to give I (R = CH2Ph). Hydrogenolysis of the latter gave I (R = H). I (R = H) are intermediates in the biosynthesis of melanins.

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Limitations of the quantitative cytochemical assay of catechol oxidase in melanoma cells. Histochem J 20:595-602, 1988.
Abstract : The cytochemical quantification of catechol oxidase activity in fixed B16 melanoma cells was investigated using dopa as the substrate. Inhibitors showed that peroxidases do not significantly interfere. The kinetics of melanin formation were studied initially in solution with purified catechol oxidase. Two key parameters were identified : lag-time and the rate of melanin formation. The lag-time was taken as the time required by intermediates to reach a critical concentration at which the polymerization process starts and melanin production becomes measurable (at 640 nm). In solution, the lag-time decreases as the enzyme activity increases, particularly when the activity is very low. The rate at which melanin is formed by pure enzyme in solution is independent of dopa concentration when its activity is low but increases linearly with dopa concentration when the activity is comparatively high. In fixed melanoma cells, the lag-time decreases linearly with increases of dopa concentrations up to 20 mM; at concentrations higher than this, the lag decreases more slowly. In contrast, the rate of melanin production is unaffected by changes in dopa concentration. The lag-times of different cells lines incubated at the same substrate concentration decrease as the enzyme activity of the cells increases. The rate of melanin production seems to be affected by factors other than catechol oxidase activity, such as the intracellular organization and distribution of the enzyme.

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Abstract : Static and dynamic light scattering were used to study the dynamics of aggregation of polymeric synthetic melanin (prepd. by autoxidn. of an aq. l-dopa soln.) in low pH aq. solns. Depending on the final pH value of the solns., there existed 2 regimes of aggregation kinetics, one corresponding to diffusion-limited aggregation (DLA) and the other corresponding to reaction-limited aggregation (RLA). The ppts. formed in these 2 regimes could be characterized by fractal structures. Fractal dimensions of df = 1.8 for the DLA clusters and df = 2.2 for the RLA clusters were found.

2. BIOLOGY OF PIGMENT CELLS AND PIGMENTARY DISORDERS

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Skin-lightening compositions containing hinokitiol and (homo)cysteine (esters) and/or ascorbic acid (esters). 1988.
Abstract : The title compns., which inhibit melanin formation and have good storage stability, contain hinokitiol and .gtoreq.1 compd. chosen from homocysteine, cysteine, ascorbic acid, and their esters. A compn. comprising 80 .mu.mol/L homocysteine and 80 .mu.mol/L hinokitiol had excellent skin-lightening effect and was stable for .gtoreq.1 mo.

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Lesions in Brangus cattle with Chediak-Higashi syndrome. Vet Pathol 25:432-436, 1988.
Abstract : Hair, peripheral blood leukocytes, and other tissues from two related Brangus calves with phenotypic characteristics of Chediak-Higashi syndrome were examined by light and electron microscopy. Enlarged, pleomorphic, cytoplasmic granules, morphologically compatible with lysosomes, were seen in several neutrophils, many eosinophils, renal tubular epithelial cells, and Kupffer cells. Hair shafts of the calves showed irregular distribution and clumping of melanin granules. Severe infection and a possible hemorrhagic tendency were recognized. These Brangus calves represent the third breed of cattle affected with this genetic disease.

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Mutants of Rhizobium phaseoli HM Mel- obtained by means of elevated temperatures. Zentralbl. Mikrobiol. 143:529-532, 1988.
Abstract : Treatment of the strain HM of R. phaseoli (a melanin producer) at 35.degree. gave 9% Mel- colonies and treatment at 37.degree. gave 15% Mel- colonies. A high

frequency of Mel- mutants that were Nod- was obsd. Thirty percent of the Mel- colonies obtained by treatment at 35.degree., and 50% obtained at 37.degree., were also Nod-. This indicates that the loss of plasmid DNA implicated in the synthesis of melanin is related to the loss of symbiotic properties of these colonies. A change was obsd. only in 1 Mel- colony with the loss of the 230 Md or, perhaps, of both large plasmids; plasmids of 230, 195, 175 and 115 Md appeared in the remainder of the studied colonies.

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The presence of beta-lactamase-producing bacteria as a guideline in the management of children with recurrent tonsillitis. Am J Otolaryngol 5:382-386, 1984.
Abstract : Thirty-eight children who had recurrent tonsillitis and who were chronic carriers of group A beta-hemolytic streptococci (GABHS) were treated with oral clindamycin. Surface tonsillar cultures, obtained prior to therapy and two weeks after the termination of therapy, were processed for aerobic and anaerobic microorganisms. Mixed aerobic and anaerobic flora were obtained from all cultures. Prior to therapy, the average yield was 9.3 isolates (5.2 aerobes and 4.1 anaerobes) per specimen; after the completion of therapy, the average yield was 5.5 isolates (3.0 aerobes and 2.5 anaerobes). The GABHS were completely eliminated after clindamycin therapy, and the numbers of isolates of Bacteroides spp and Staphylococcus aureus were reduced. Beta-lactamase production was detected prior to therapy in 57 isolates recovered from all tonsillar surfaces. This group included all isolates of S. aureus (15) and Bacteroides fragilis (eight), 19 of 34 Bacteroides melaninogenicus isolates (56 per cent), and seven of 12 Bacteroides oralis isolates (58 per cent). Only four isolates of beta-lactamase-producing bacterial strains were recovered after the conclusion of therapy. Follow-up study of 33 children for eight to 16 months (average, 13 months) showed no recurrence of GABHS in 31.

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Progressive macular hypomelanosis of the trunk: primary acquired hypopigmentation. J Cutan Pathol 15:286-289, 1988.
Abstract : Dermatological practice in Martinique frequently encounters a bizarre skin condition presenting as a progressive and extensive hypomelanosis on the back. The course of this disorder is highly characteristic: it occurs mainly in females from 18-25 years of age, with a progressive development of round, pale, coalescent macules on the back and sometimes on the abdomen. This disease, which does not respond to therapy, spontaneously regresses

within 3 to 4 years. Decreased epidermal melanin is the only histological feature. Ultrastructural examination of two cases found that the macular lesions were characterized by a switch from Stage IV single melanosomes (negroid) to small Type I-III aggregated melanosomes (caucasoid). It may thus be stated that the variation in skin coloration in these patients was due to a variation in melanosome size and distribution.

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Abstract : The title compns., which remove melamin from the skin, inhibit melamin formation, and are not irritating to the skin, contain hopantenate Ca (I) and .gtoreq.1 compd. chosen from RO2C(CH2)nCO2R1 (R = C1-8 linear alkyl or alkenyl; R1 = H, C1-8 linear alkyl or alkenyl). A lotion was prepd. from I 0.05, monoethyl adipate 0.05, olive oil 15.0, iso-Pr myristate 5.0, poly(oxyethylene) nonylphenyl ether 0.5, glycerin 5.0, methylparaben 0.1, EtOH 7.0, and H2O to 100%.

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Topical melanine-biosynthesis inhibitors containing placental extracts and kojic acid or its derivatives. 1988.
Abstract : Pharmaceuticals contg. placental exts. and kojic acid (I) or its derivs. are prepd. for treating chromatopathy. An ointment was formulated contg. polyethylene glycol monostearate 2.00, autoemulsifiable glycerol monostearate 5.0, stearic acid 5.00 behenyl alc. 1.00, liq. paraffin 10.00, glyceryl trioctanoate 10.00, p-HOC6H4CO2He 0.20, 1.3-butylene glycol 5.00, H2O 48.80, I 3.0, and human placental exts. 10.0 g. Clin. tests indicated that the ointment was effective in treating chloasma.

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Volume fraction and ultrastructure of age pigment in the saccular epithelium of old mice. Hear Res 37:171-177, 1989.
Abstract : Age pigment in the sensory and supporting cells was a prominent characteristic distinguishing old saccules from young. However, the pigment was not distributed uniformly throughout the sensory epithelium but displayed cell-specific patterns of accumulation. The highest cytoplasmic volume density was in the old supporting cells followed by type I hair cells and then type II hair cells. The most common form of pigmented inclusion seen in old type I hair cells was a cluster of granules resembling melanin. This form was never seen in type II hair cells or supporting cells where a form containing a lipid-like droplet was prevalent. The differences in the amount of age pigment and the forms accumulated probably reflects

metabolic differences between the three cell types.

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  Piebaldism-Waardenburg syndrome: histopathologic evidence for a neural crest syndrome. Am J Med Genet 31:679-688, 1988.
  Abstract : Piebaldism, an autosomal dominant trait, is characterized by patchy hypopigmentation of the face, anterior chest, abdomen, and limbs, heterochromia/bicolored irises, congenital megacolon, and deafness. A 4-month-old Inuit (Eskimo) boy with these manifestations also had left pulmonic artery stenosis, ocular ptosis, and unilateral duplication of the renal collecting system. Evidence is presented for both qualitative and quantitative derangement of neural crest derivatives in this syndrome. Histologically, hypoganglionosis, hyperganglionosis, and ectopic ganglia in lamina propria (neuronal colonic dysplasia [NCD]) were documented in the rectum. The appendix, proximal to the clinical transition zone, showed similar dysplasia. In the hypopigmented skin, multiple microscopic sections were devoid of melanocytes, with no melanin in adjacent basal cells. The hyperpigmented skin contained melanin throughout the basal layer, but the melanocytes were unevenly distributed. Most tissues affected in this boy are of neural crest origin; pathogenesis could be due to faulty migration along the established pathways involving either the borders (basal laminae) or the components of the extracellular matrix (fibronectin, cytotactin, laminin, glycosaminoglycans, and collagen). The similarities between piebaldism and the Waardenburg syndromes are discussed.

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  Skin lightening cosmetics containing 5-hydroxy-2-styryl-4-pyrone esters. 1988.
  Abstract : The title compds. I (R1 = C1-26 alkoxy, chain or alicyclic hydrocarbyl, H; R2 = C2-26 acyl; n = 1-5), which inhibit melanin formation and are stable, not irritating to

the skin, and useful for skin lightening cosmetics, are prepd. Treatment of 2 g (5-hydroxy-4-pyron-2-yl)-methyltriphenylphosphonium chloride and 0.77 g 4-methoxybenzaldehyde with EtONa/EtOH in EtOH under N at room temp. for .apprx.16 h gave 400 mg I (R1 = 4-OMe, R2 = H, n = 1), which (350 mg) was treated with 2-ethylhexanoyl chloride in pyridine at room temp. for 12 h to afford 330 mg I (R1 = 4-OMe, R2 = 2-ethylhexanoyl, n = 1) (II). A skin prepn. was prepd. from stearic acid 10.0, stearyl alc. 4.0, Bu stearate 8.0, glycerin monostearate 2.0, II 0.5, propylene glycol 10.0, glycerin 4.0, KOH 0.4, perfume, sterilizer, and H2O to 100% by wt.

- Mimura M, Shimai Y.
Skin lightening cosmetics containing 5-hydroxy-2-styryl-4-pyrones. 1988
Abstract : Skin lightening cosmetics, which inhibit melanin formation and are stable and not irritating to the skin, contain the title compds. I (R = C1-26 alkoxy, chain or alicyclic hydrocarbyl, H; n = 1-5) as active ingredients. Treatment of 2 g (5-hydroxy-4-pyron-2-yl)-methyltriphenylphosphonium chloride and 0.47 g benzaldehyde with EtONa/EtOH in EtOH under N at room temp. for .apprx.16 h gave 180 mg I (R = H). A skin prepn. was prepd. consisting of stearic acid 10.0, stearyl alc. 4.0, Bu stearate 8.0, glycerin monostearate 2.0, I [R = 4-OMe, 3-(2-ethylhexyloxy), n = 2] 0.5, propylene glycol 10.0, glycerin 4.0, KOH 0.4, perfume, sterilizer, and H2O to 100% by wt.

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Pigmentation in aging and melanogenic inhibitors. Fragrance J. 17:25-33, 1989.
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Dysdifferentiation of neural crest cells by temperature in newborn mice. Anat Anz 167:165-169, 1988.
Abstract : Multiple neural crest tumors, hyperplasia, excessive cell proliferation, the cell death of neural crest cells and melanin pigmentation occurred in newborn mice injected intraperitoneally with heated deionized water. It is thought that these phenomena may not only be associated with the protein denaturation of the membrane structure in the neural crest cells, but also with temperature dependent changes of lipid-lipid and lipid-protein interactions, particularly changes of the mobility of proteins, and that may be a reflection of thermodynamic decrease in entropy that occurs during differentiation.

- Sakai T, Sakai H, Hashimoto N, Hirayasu R.

Gingival pigmentation beneath a metallic crown : light and electron microscopic observations and energy dispersive X-ray analysis. J Oral Pathol 17:409-415, 1988.
Abstract : Light and electron microscopic studies and energy dispersive X-ray analysis disclosed that the essential cause of gingival discoloration following the placement of a metallic crown, was marked deposition of melanin pigment. Deposition of melanin pigment was observed in epithelial cells, on basement membranes, and in fibroblasts, macrophages and among intercellular ground substance of the proprial layer. Brown or dark brown colored granules were observed in the deep portion of the proprial layer. Some metallic elements as silver and sulfur were detected. It was presumed that these materials were dental metals accidentally implanted in gingival tissues during the therapeutic procedure. The deposition of melanin pigment closely corresponded with mucosal tissue where these materials were present in the deep portion of the proprial layer. These findings suggested that these materials influenced the physiological metabolism of melanin and induced its pathological deposition in the proprial tissue.

- Sato T, Niino Y.
Manufacture of skin lightening compositions containing ascorbic acid derivatives. 1988.
Abstract : The title derivs. I (R = C1-6 alkyl), useful for storage-stable skin lightening compns., are prepd. by treating 5,6-acetal (or -ketal) of ascorbic acid with corresponding .alpha.-haloacetic acid alkyl esters in the presence of alkali inorg. bases in non-hydroxy solvents. Skin prepns. contg. I inhibit melanin formation in the skin. 5,6-O-Isopropylidene-L-ascorbic acid (21.6 g) was treated with 8.4 g NaHCO3 in DMSO at room temp. for 0.5 h, then with 12.5 g ClCH2CO2Et for 20 h to give 7.9 g 3-O-(ethoxycarbonylmethyl)-5,6-O-isopropylidene-L-ascorbic acid, which (3.0 g) was treated with 0.1N HCl in EtOH at 60.degree. for 15 min to afford 2.5 g I (R = Et) (II). A cream was prepd. from II 1.5, micorcryst. wax 11.0, beeswax 4.0, vaseline 5.0, hydrogenated lanolin 7.0, squalane 34.0, hexadecyl adipate 10.0, glycerin monooleate 3.0, poly(oxyethylene) sorbitan nonooleate 1.0, propylene glycol 2.5, H2O 20.5, flavoring material 0.5%, and others (antioxidant and sterilizer).

- Sprott MS, Kearns AM.
Metronidazole-resistant Bacteroides melaninogenicus. J. Antimicrob. Chemother. 22:951-952, 1988.
Abstract : A strain of metronidazole-resistant B. melaninogenicus was isolated from a patient with vaginal trichomoniasis. Sensitivity testing showed no zone of inhibition to a 5-.mu.g metronidazole disk, and the min. inhibitory concn. of metronidazole was 32 .mu.g/mL. The organism retained its resistance following passage on metronidazole-free medium for >30 subcultures.

3. MSH, MCH, OTHER HORMONES, DIFFERENTIATION

- Bird DJ, Baker BI.
An immunological study of the secretory activity of neurons producing melanin-concentrating hormone in a teleost. Neuroscience (Oxford) 28:245-251, 1989.
Abstract : The melanin-concg. hormone is a general vertebrate neurosecretory peptide which, in bony fish, serves as a neurohypophyseal hormone influencing pigmentary changes in response to background color. Young carp were reared for 6 mo in white- or black-colored tanks to det. how this would influence the development of the neurons producing the peptide. Cytol. criteria and RIA of tissue exts. showed that the background markedly influenced the synthetic activity of these neurons.,. In carp reared in black tanks, the perikarya were small and poorly granulated, with small nuclei and often undetectable nucleoli. Transfer of such fish to a white tank for 6 days caused no significant change in hormone content but cytol. criteria suggested an increased activity of some of the neurons. In fish reared on a white background, over 50% of these neurons showed a greatly enhanced synthetic activity, whereas RIAs showed higher concns. of immunoreactive peptide in their hypothalami but not in their pituitary glands. After such fish were moved to black tanks for 6 days, the neuropeptide content of the hypothalamus and pituitary gland was significantly increased. Histol., this was reflected in the amt. of immunostainable granulation in both sites, but cell nuclear size was not decreased. These changes are interpreted in terms of changes of hormone synthesis and release. The observations provide evidence that the activity of many but not necessarily all of the neurons producing melanin-concg. hormone in the carp hypothalamus is controlled by background color.

- Kameyama K, Tanaka S, Ishida Y, Hearing VJ.
Interferons modulate the expression of hormone receptors on the surface of murine melanoma cells. J Clin Invest 83:213-221, 1989.
Abstract : The effects of IFN-alpha, IFN-beta, and IFN-gamma on the differentiation of murine melanoma cells has been studied, in the presence and absence of melanocyte-stimulating hormone (MSH); the cells were highly responsive to treatment with MSH, which increased the rate of melanin production 25-fold and tyrosinase activity 6-fold within 4 d. Treatment of melanoma cells with IFN-alpha, IFN-beta, or IFN-gamma alone had no stimulatory effect on melanin production, but when the cells were cultured with IFN in the presence of MSH, pigment production was significantly and synergistically increased relative to cells cultured with MSH only. Flow cytometric analysis revealed that levels of tyrosinase in the cells were not affected by MSH or by IFN, which suggests that stimulation of melanogenic activity occurred by activation

of a preexisting cellular enzyme. Scatchard analyses showed that the number of MSH receptors on IFN-treated cells was significantly increased (approximately 2.5-fold) relative to untreated cells (approximately 61,000/cell). These findings demonstrate that IFN stimulate differentiation (that is, pigmentation) of melanocytes by increasing the expression of surface MSH receptors; this in turn suggests that such a mechanism may in part be responsible for postinflammatory skin pigmentation, and provides an additional basis for action in the clinical responses of melanoma to IFN treatment.

- Kishida M, Baker BI, Bird DJ.
Localisation and identification of melanocyte-stimulating hormones in the fish brain. Gen Comp Endocrinol 71:229-242, 1988.
Abstract : The existence of melanocyte-stimulating hormone (MSH) in fish brains was investigated by a range of techniques: radioimmunoassay, HPLC, bioassay, and immunocytochemistry. Immunoreactive alpha MSH (ir alpha MSH) was detected by radioimmunoassay in all regions of carp and trout brains, with the highest concentration in the basal hypothalamus. In trout, ir alpha MSH cell bodies were located by immunocytochemistry only periventricularly, in the medial basal hypothalamus near the third ventricle, whereas in the carp ir alpha MSH staining was seen both in periventricular cells and also in some of the magnocellular neurones in the lateral hypothalamus. When white-adapted fish were transferred to a black tank for 6 days, the melanin-concentrating hormone (MCH) content of the basal hypothalamus of both carp and trout increased 2- and 4.6-fold, respectively, but the alpha MSH content did not change in either species. Analysis by HPLC of pituitary gland, hypothalamic, and optic tectal extracts revealed that the pituitary contains desacetyl, monoacetyl, and diacetyl alpha MSH, although the ratio of these forms differed in the two species. The hypothalamus and optic tectum, however, contained predominantly the desacetyl form of alpha MSH. Bioassays for MSH in the HPLC fractions revealed the existence of presumptive beta MSH in both the pituitary and hypothalamus. An argument is advanced that the periventricular ir alpha MSH neurones are homologous with the proopiomelanocortin cells of the arcuate nucleus in mammals, and that the immunocytochemical alpha MSH-like activity in the MCH neurones may not be authentic alpha MSH.

- Moons L, Cambre M, Ollevier F, Vandesande F.
Immunocytochemical demonstration of close relationships between neuropeptidergic nerve fibers and hormone-producing cell types in the adenohypophysis of the sea bass (Dicentrarchus labrax). Gen. Comp. Endocrinol. 73:270-283, 1989.
Abstract : Light microscopic double immunocytochem. stainings, performed on sea bass hypothalamohypophyseal sections, revealed the projection of different

neuropeptide-immunoreactive neurons innervating the hormone-producing cell populations in the pituitary gland. In the rostral pars distalis (PD) ACTH cells were found in close proximity to fibers immunoreactive for somatostatin (SRIF), growth hormone-releasing hormone (GRF), ACTH-releasing hormone (CRF), vasotocin (VT), isotocin (IT), substance P (SP), neurotensin, and galanin (GAL), whereas the PRL cell zone seemed only innervated by nerve fibers immunopos. for GAL. In the proximal PD, fibers immunoreactive for SRIF, GRF, VT, IT, cholecystokinin, SP, neuropeptide Y, and GAL formed a close relationship with the growth hormone cells. The gonadotrophs were obsd. near nerve fibers immunostained for LH-RH, IT, and less obviously GRF and VT, whereas fibers pos. for GRF, CRF, VT, IT, SP, and GAL penetrated between and formed a close assocn. with the thyrotrophs. In the pars intermedia the MSH cells and the PAS-pos. (PAS+) cells seemed both innervated by sep. nerve fibers immunoreactive for GRF, CRF, melanin-concg. hormone, VT, IT, and SP. All these results suggest a functional role of the neuropeptides in the adenohypophysis of the sea bass, possibly in the synthesis and/or release of hypophyseal hormones from the different cell types.

- Naito N.
Melanin-concentrating hormone - fish to rat. Jikken Igaku 6:654-656, 1988.
Abstract : A review, with 10 refs., on the structure, function, and distribution in brain of chum salmon melanin-concg. hormone (MCH), and its counterpart in rats.

- Ono M, Wada C, Oikawa I, Kawazoe I, Kawauchi H.
Structures of two kinds of mRNA encoding the chum salmon melanin-concentrating hormone. Gene 71:433-438, 1988.
Abstract : The structures of two kinds of melanin-concentrating hormone (MCH) cDNA clones isolated from a chum salmon hypothalamus cDNA library were described. The MCH heptadecapeptide was present at the C terminus of a putative MCH precursor consisting of 132 amino acid residues. The two clones were 80% homologous with each other at the amino acid sequence level. Two genes, each directing one of the mRNAs was noted at about a single copy per haploid salmon genome. MCH genes were efficiently expressed as 0.9-kb poly(A)+RNA in salmon hypothalamus, and sequences hybridizable with salmon MCH cDNA were found in rat hypothalamus.

- Prasad KC.
Induction of differentiated phenotypes in melanoma cells by a combination of an adenosine 3',5'-cyclic monophosphate stimulating agent and D-alpha tocopheryl succinate. Cancer Lett 44:17-22, 1989.
Abstract : The purpose of this investigation was to identify those agents and combinations of agents that help convert murine melanoma cells to cells of differentiated (normal-like) phenotype in culture. The agents used were

4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (R020-1724), which is an adenosine 3',5'-cyclic monophosphate (cAMP) phosphodiesterase inhibitor that has never been tested on melanoma cells in culture, and d-alpha tocopheryl succinate (vitamin E succinate), which has previously been shown to inhibit growth and induce morphological differentiation in melanoma cells. The results indicated that R020-1724 by itself inhibited growth, reduced survival, caused morphological differentiation and increased the melanin content (one of the biochemical differentiated functions) in melanoma cells. Vitamin E succinate had a similar effect on the melanoma cells, which supports past research on this vitamin. A combination of R20-1724 and vitamin E succinate had a significantly greater effect on the melanoma cells than either of the agents by themselves. The agents identified in this study may provide useful tools for studying the mechanisms of differentiation in melanoma cells.

4. PHOTOBIOLOGY AND PHOTOCHEMISTRY

- Barr L.
  Hypersensitivity to light of the iris (Sphincter pupillae) of the albino axolotl (Ambystoma mexicanum). J Exp Biol 137:589-596, 1988.
  Abstract : As is common for amphibians, the sphincter pupillae of the axolotl contracts in vitro in response to illumination with visible light. 1. In a comparison of photomechanical responses of albino and normally pigmented axolotls, similar time courses and maxima of force development were found. 2. The dependence of isometric active force development on the length of the sphincter pupillae is similar to that of other smooth muscles. 3. The action spectrum of the axolotl is similar to the absorption spectrum of frog rhodopsin. 4. At low stimulus strengths, the increase of normalized, isometric, active force with increasing stimulus strength is approximately seven times as great in albino axolotls as in normally pigmented ones. 5. Melanin appears to decrease the light sensitivity of the irises of normally pigmented animals by acting as a simple light shield.

- Dover JS, Margolis RJ, Polla LL, Watanabe S, Hruza GJ, Parrish JA, Anderson RR.
  Pigmented guinea pig skin irradiated with Q-switched ruby laser pulses. Morphologic and histologic findings. Arch Dermatol 125:43-49, 1989.
  Abstract : Q-switched ruby laser pulses cause selective damage to cutaneous pigmented cells. Repair of this selective damage has not been well described. Therefore, using epilated pigmented and albino guinea pig skin, we studied the acute injury and tissue repair caused by 40-ns, Q-switched ruby laser pulses. Gross observation and light

and electron microscopy were performed. No specific changes were evident in the albino guinea pigs. In pigmented animals, with radiant exposures of 0.4 J/cm2 or greater, white spots confined to the 2.5-mm exposure sites developed immediately and faded over 20 minutes. Delayed depigmentation occurred at seven to ten days, followed by full repigmentation by four to eight weeks. Regrowing hairs in sites irradiated at and above 0.4 J/cm2 remained white for at least four months. Histologically, vacuolation of pigment-laden cells was seen immediately in the epidermis and the follicular epithelium at exposures of 0.3 J/cm2 and greater. Melanosomal disruption was seen immediately by electron microscopy at and above 0.3 J/cm2. Over the next seven days, epidermal necrosis was followed by regeneration of a depigmented epidermis. By four months, melanosomes and melanin pigmentation had returned; however, hair follicles remained depigmented and devoid of melanocytes. This study demonstrates that selective melanosomal disruption caused by Q-switched ruby laser pulses leads to transient cutaneous depigmentation and persistent follicular depigmentation. Potential exists for selective treatment of pigmented epidermal and dermal lesions with this modality.

- Friedl KE, Hannan CJ, Mader TH, Patience TH, Schadler PW. Effect of eye color on heart rate response to intramuscular administration of atropine. J Auton Nerv Syst 24:51-56, 1988.
Abstract : Melanin has been previously shown to modify the mydriatic response to atropine instillation. Skin and iris pigmentation has also been shown to modify aspects of the heart rate response to injected atropine, although these observations have been generally overlooked. In this study, 20 healthy non-smoker male subjects, ages 20-30 years, were injected by two different automatic injector devices and the mydriatic and heart rate responses in the first 90 min were reported. The group included 8 brown-eyed, 4 hazel-eyed, and 8 blue-eyed subjects. Although there were differences in the rate of atropine delivery between the two injection devices, the heart rate responses were independently modified by eye color to a magnitude of difference as great as the differences between injectors. Subjects with more pigmented irides (brown-eyed) showed a more rapid rise in heart rate compared to less pigmented irides (hazel-eyed and blue-eyed subjects). Following injection by the device with a slower atropine absorption rate, these differences were particularly enhanced and an abbreviated bradycardic phase of the heart rate response was observed for the brown-eyed subjects. This observation confirms earlier reports and suggests the possibility of an interference by melanin (in the iris or elsewhere) in atropine accessibility to selected muscarinic target sites.

- Ionescu P, Begnescu R, Vasiliu V.
Experimental studies regarding the influence of laser

radiation with helium-neon on a peripheral lymph nodes subjected to indirect irradiation. Stud. Cercet. Fiz. 40:591-597 7, 1988.
Abstract : The effect of laser radiation (He-Ne laser; 32-63 mW/cm2) on peripheral lymph nodes was studied in rabbits. Laser irradn. induced lymph node hyperplasia as illustrated by an enhancement of blastic elements, i.e., lymphoblasts and young lymphocytic cells. Irradn. also induced hyperplasia of the capillary endothelium, edema of the superficial derma, and an increase in melanin pigmentation in the Unna layer of the dermis.

- Land EJ.
Pulsed irradiation studies of some reactive intermediates of melanogenesis. Rev. Chem. Intermed. 10:219-240, 1988.
Abstract : A review, with 32 refs., describing the use of the pulsed radiation techniques of pulse radiolysis and flash photolysis as novel means of very rapidly producing the short-lived semiquinone, quinone and subsequent intermediates of melanogenesis, derived from various precursors including dopa, cysteinyldopa and dihydroxyindole, and the false precursor 4-hydroxyanisole, with the aim of providing a detailed kinetic understanding of the chem. involved.

- Porges SB, Kaidbey KH, Grove GL.
Quantification of visible light-induced melanogenesis in human skin. Photodermatol 5:197-200, 1988.
Abstract : Exposure of normal skin to visible light (400-700 nm) resulted in the induction of immediate pigment darkening (IPD), immediate erythema and a persistent (delayed) tanning reaction. The intensity of pigmentation and time course of the reaction were monitored by measuring chromaticity coordinates. Both IPD and immediate erythema faded over a 24-h period but, unlike erythema, the pigmentation did not totally disappear and the residual tanning response remained unchanged for the rest of the 10-day observation period. The threshold dose for IPD with visible light was between 40 and 80 J/cm2, while the threshold dose for "persistent" pigmentation was greater than or equal to 80 J/cm2.

- Smith-Kappus SD.
Effects of ultraviolet radiation on the survival and metabolic end products of Bacteroides melaninogenicus. 1987.

- Vasilevskii VK, Zherebtsov LD, Spichak AD, Feoktistov SM.
Color and morphological characteristics of the skin in people of different racial groups. Biull Eksp Biol Med 106:495-498, 1988.
Abstract : A complex colorimetric, spectrometric and morphological research of race-dependent differences in skin colour and structure has been carried out. Certain regularities in the quantity, distribution and morphological composition of melanin-containing structures

and Hb pigment have been revealed in the Russians, Vietnamese, Angolans and Mulattoes. The study has shown that sex differences in skin color depend on hemoglobin concentration--in people of the Caucasian race; both on melanin and hemoglobin concentration--in people of the Mongolian race and only on melanin concentration--in people of the Negroid race.

5. NEUROMELANINS

- Iizuka H, Nakamura T, Kadoya S.
Spinal melanotic schwannoma: report of a case. No Shinkei Geka 16:1199-1205, 1988.
Abstract : A case of spinal dumbbell shaped melanotic schwannoma was reported. A 58-year-old housewife had a 3-months history of progressive gait disturbance. She also complained of mild backache and numbness in both legs. Her family history was not remarkable. When examined on admission, October 10, 1982, mild weakness of both legs with spasticity and sensory impairment below the level of T10 dermatome without sacral sparing were evident. Her deep tendon reflexes were hyperactive on both sides and plantar responses were extensor bilaterally. Sphincteric disturbance was not significant. The function of her cranial nerves was intact. She had neither cutaneous lesions, abdominal mass nor organomegaly. Thoracic plain X-rays revealed erosion of the right side vertebral body and pedicle of the 10th thoracic vertebra. Myelography disclosed a complete block at the same level by an epidural mass. On CT-myelogram, soft tissue density mass compressing the thoracic cord was apparent in the right epidural space of the spinal canal which extended to the paravertebral region through the right intervertebral foramen. Partial destruction of the body and the right side pedicle was easily recognized. Laminectomy from T9 to T11 exposed a large extradural mass which was encapsulated, elastic soft and pigmented in nature. The tumor was dumbbell shaped and extended to the right paravertebral region through the intervertebral foramen. Costotransversectomy was performed to excise the mass entirely. Following the total removal of the tumor, internal fixation was carried out by means of Harrington instrumentation with methylmethacrylate.

- Lindquist NG, Larsson BS, Lyden-Sokolowski A.
Autoradiography of [14C]paraquat or [14C]diquat in frogs and mice: accumulation in neuromelanin. Neurosci Lett 93:1-6, 1988.
The herbicide paraquat has been suggested as a causative agent for Parkinson's disease because of its structural similarity to a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which may induce a parkinsonism-like condition. MPTP as well as

its metabolite 1-methyl-4-phenylpyridine have melanin affinity, and the parkinsonism-inducing potency of MPTP is much stronger in species with melanin in the nerve cells. Autoradiography of [3H]MPTP in experimental animals has shown accumulation in melanin-containing tissues, including pigmented neurons. In the present whole body autoradiographic study accumulation and retention was seen in neuromelanin in frogs after i.p. injection of [14C]paraquat or [14C]diquat. By means of whole body autoradiography of [14C]diquat in mice (a species with no or very limited amounts of neuromelanin) a low, relatively uniformly distributed level of radioactivity was observed in brain tissue. Accumulation of toxic chemical compounds, such as paraquat, in neuromelanin may ultimately cause lesions in the pigmented nerve cells, leading to Parkinson's disease.

- Scheck O, Ruck P, Harms D, Kaiserling E.
Melanotic neuroectodermal tumor of infancy occurring in the left thigh of a 6-month-old female infant. Ultrastruct Pathol 13:23-33, 1989.
Abstract : We report an exceptional case of melanotic neuroectodermal tumor of infancy (MNTI) occurring in the soft tissue of the left thigh of a 6-month-old female infant. The tumor consisted mainly of small round cells (neuroblasts) arranged in cords and nests that were separated by broad fibrovascular areas. In addition, there were a few medium-sized tumor cells containing melanin pigment (melanocytic cells) that in electron microscopy contained melanosomes as well as tonofilaments. Both tumor cell types immunostained for neuron-specific enolase (NSE) and vimentin, and the melanocytic cells reacted additionally with the antikeratin antibody KL1. Within the tumor stroma, neurofilament- and S-100-protein-positive neural cells and vimentin- and desmin-positive myofibroblasts were seen. Although dense-core granules were demonstrated ultrastructurally in some neuroblasts, no immunostaining for chromogranin A, Leu-7, serotonin, or regulatory peptides was found. MNTI located in an extremity can be confused with malignant small round and blue cell tumors of childhood. The distinction between MNTI and these tumors is of clinical significance because MNTI, in most cases, is a benign tumor that, in contrast to the latter, can be cured by complete excision. The presence of a biphasic cell population with neuroblasts and melanocytic cells must be considered the main diagnostic feature of MNTI.

6. GENETICS

- Barton DE, Kwon BS, Francke U.
Human tyrosinase gene, mapped to chromosome 11 (q14----q21), defines second region of homology with mouse

chromosome 7. Genomics 3:17-24, 1988.
Abstract : The enzyme tyrosinase (monophenol,L-dopa:oxygen oxidoreductase; EC 1.14.18.1) catalyzes the first two steps in the conversion of tyrosine to melanin, the major pigment found in melanocytes. Some forms of oculocutaneous albinism, characterized by the absence of melanin in skin and eyes and by a deficiency of tyrosinase activity, may result from mutations in the tyrosinase structural gene. A recently isolated human tyrosinase cDNA was used to map the human tyrosinase locus (TYR) to chromosome 11, region q14----q21, by Southern blot analysis of somatic cell hybrid DNA and by in situ chromosomal hybridization. A second site of tyrosinase-related sequences was detected on the short arm of chromosome 11 near the centromere (p11.2----cen). Furthermore, we have confirmed the localization of the tyrosinase gene in the mouse at or near the c locus on chromosome 7. Comparison of the genetic maps of human chromosome 11 and mouse chromosome 7 leads to hypotheses regarding the evolution of human chromosome 11.

- Jimenez M, Maloy WL, Hearing VJ.
Specific identification of an authentic clone for mammalian tyrosinase. J Biol Chem 264:3397-3403, 1989.
Abstract : Tyrosinase, the critical enzyme to melanin pigmentation in mammals, occurs as a series of isozymic forms, which have been previously regarded as different stages in processing of a single precursor form. Recently, three different cDNA clones have been identified which may encode tyrosinase, they share extensive sequence homology but are distinct; two of them have been mapped to genetic loci which regulate different aspects of melanogenesis. Since direct confirmation of the authentic tyrosinase sequence has proven impossible by conventional protein sequencing strategies, we have approached the identification of the tyrosinase gene by synthesizing peptides encoded by the putative genes and preparing antibodies to those peptides. By use of pulse-chase labeling and immunoprecipitation analyses, and by enzymatic determinations, pMT4 (which maps to the brown b locus in mice) is shown to encode a molecule with tyrosinase catalytic activity which is biochemically identical with authentic tyrosinase. However, our results raise the possibility that other gene products may contribute to melanogenesis by one or more melanogenic activities.

- Kwon BS.
Cloning, sequencing, and use of human tyrosinase cDNA. 1988
Abstract : The cDNA for human tyrosinase is cloned and sequenced. This DNA is useful for genetic anal. of human albinism, prenatal diagnosis of albinism, diagnosis of melanotic and/or amelanotic melanoma, and study of melanin prodn. Clone .lambda.mel34 of a cDNA library of human melanocytes was found to encode tyrosinase: no bands were apparent upon Southern blotting of the genomic DNA of c3H/c3Hmice (albino locus deleted) with this cDNA. Another clone, .lambda.mel17-1, hybridized to melanocyte mRNA

regardless of the presence or absence of the albino locus. It was concluded that this clone contained a melanin biosynthetic enzyme cDNA.

- Kwon BS, Wakulchik M, Haq AK, Halaban R, Kestler D.
Sequence analysis of mouse tyrosinase cDNA and the effect of melanotropin on its gene expression. Biochem. Biophys. Res. Commun. 153:1301-1309, 1988.
Abstract : Using human tyrosinase cDNA as a probe, a mouse tyrosinase cDNA clone representing approx. 75% of the tyrosinase coding region and a mouse genomic clone which includes the tyrosinase 5' coding sequences were isolated: nucleotide and deduced amino acid sequence of the mouse tyrosinase gene were detd. from these clones. The predicted amino acid sequence revealed that the mouse tyrosinase is composed of 533 amino acids with a mol. wt. of 60,536. The deduced protein contains 6 potential N-glycosylation sites, two cysteine- and two histidine-rich regions which may serve as copper-binding sites, a potential signal and transmembrane sequences. The mouse and human tyrosinase nucleotide and deduced amino acid sequences are .apprx.81% homologous. The level of mouse tyrosinase mRNA was elevated after stimulation of Cloudman S-91 melanoma cells with melanotropin and isobutylmethylxanthine and the level of transcript reflected that of tyrosinase activity and melanin content in the cells.

- Wilson RE, Dooley TP, Hart IR.
Induction of tumorigenicity and lack of in vitro growth requirement for 12-O-tetradecanoylphorbol-13-acetate by transfection of murine melanocytes with v-Ha-ras. Cancer Res 49:711-716, 1989.
Abstract : A nontumorigenic line of murine melanocytes, Mel-ab, has been transfected with the v-Ha-ras gene under transcriptional control of the Moloney murine leukemia virus long terminal repeat. Transfectants produced rapidly growing undifferentiated melanomas in recipient mice. The inhibition of melanin production in transformed cells, observable both in vitro and in vivo, suggests that ras may affect melanocyte cytodifferentiation. Mel-ab cells require the continual presence of 12-O-tetradecanoylphorbol-13-acetate, or other activators of protein kinase C, for in vitro growth. Transfectants expressing v-Ha-ras no longer manifested this requirement and were actually growth inhibited by the addition of protein kinase C activators. These results are consistent with the notion that ras acts via the protein kinase C pathway in conferring autonomous growth on Mel-ab cells.

7. TYROSINASE AND OTHER ENZYMES

- Abdel-Malek ZA, Swope VB, Trinkle LS, Nordlund JJ.
Stimulation of Cloudman melanoma tyrosinase activity occurs predominantly in G2 phase of the cell cycle. Exp Cell Res 180:198-208, 1989.
Abstract : A widely accepted notion is that an increasing cellular cyclic AMP (cAMP) concentration is prerequisite for increasing tyrosinase activity and melanin synthesis and for regulating proliferation of pigment cells. alpha-Melanocyte stimulating hormone (alpha-MSH) increases cAMP and tyrosinase activity in Cloudman melanoma cells. Prostaglandins (PGs) E1 and E2 increase melanoma cell tyrosinase activity and inhibit proliferation. Both PGs, but not alpha-MSH, block the progression of Cloudman melanoma cells from G2 phase of the cell cycle into M or G1. Only PGE1 and not PGE2 causes an elevation of cellular cAMP concentrations. The adenylate cyclase inhibitor 2',5'-dideoxyadenosine (DDA) at 5 x 10(-4) M effectively blocks the increased cAMP synthesis by cells treated with 10 micrograms/ml PGE1. The addition of DDA, however, enhances the melanogenic response of melanoma cells to 10 micrograms/ml PGE1 or PGE2, 10(-7) M alpha-MSH, 10(-4) M isobutylmethylxanthine, 10(-4) M dibutyryl cyclic AMP. DDA also augments the effects of PGE1 or PGE2 on the melanoma cell cycle. Moreover, when DDA is added concomitantly with alpha-MSH, more cells are recruited into G2 than observed in untreated controls. Neither alpha-MSH nor DDA alone has any effect on the cell cycle. These findings undermine the role of cAMP in the melanogenic process and suggest that blocking melanoma cells in G2 may be required for the remarkable stimulation of tyrosinase activity observed with PGE1 or PGE2 alone or in combination with DDA. The observed block in G2 may be essential for the synthesis of sufficient mRNA, which is required for stimulation of tyrosinase activity.

- Halliday GM, Li YW, Joh TH, Cotton RG, Howe PR, Geffen LB, Blessing WW.
Distribution of monoamine-synthesizing neurons in the human medulla oblongata. J Comp Neurol 273:301-317, 1988.
Abstract : We have employed immunohistochemical and morphometric procedures to study the distribution of monoamine-synthesizing neurons in the medulla oblongata of the adult human, utilizing antibodies to tyrosine hydroxylase (TH), phenylethanolamine N-methyltransferase (PNMT), and phenylalanine hydroxylase (PH8). In the human brain, the antigen with which PH8 reacts occurs within neurons that presumably synthesize serotonin (Haan et al., '87). Neurons containing these antigens were mapped and counted in successive coronal sections with the aid of a computer-assisted procedure. The results indicate that monoamine-synthesizing neurons are distributed in the human brain in patterns broadly similar to those described for other species. TH-immunoreactive cells extended

caudorostrally for approximately 32 mm commencing at the spinomedullary junction and ending 8 mm caudal to the pontomedullary junction. In coronal sections these TH-immunoreactive neurons were seen in the lateral medulla dorsal to the inferior olive extending in a continuous band to the dorsomedial medulla. Above the obex the majority of these cells apparently synthesize adrenaline since many PNMT-immunoreactive cells were also found in this region. There were few or no PNMT-immunoreactive cells caudal to the obex, indicating that the TH-immunoreactive cells in this region synthesize either noradrenaline or dopamine. Approximately 65% of these TH-immunoreactive neurons contained melanin pigment, whereas few or no PNMT-immunoreactive cells contained melanin pigment. PH8-immunoreactive cells extended throughout the rostrocaudal extent of the medulla oblongata (approximately 40 mm). In coronal sections the majority were found in the medullary raphe nuclei. However, many cells throughout the rostrocaudal extent of the medulla were found laterally intermingled with catecholamine-synthesizing neurons. Occasional neurons in the lateral medulla appeared to contain both PH8- and TH-immunoreactivity.

- Jacobsohn MK, Dobre VC, Branam C, Jacobsohn GM.
Oxidation of 2-hydroxyestradiol and its incorporation into melanin by mushroom tyrosinase. J. Steroid Biochem. 31:377-385, 1988.
Abstract : The presence of catechol in a reaction mixt. has previously been shown to promote oxidn. of 2-hydroxyestradiol by mushroom tyrosinase. Here, it is shown that the oxidized products of the catecholestrogen are incorporated into melanin under the influence of the enzyme. Whether the oxidn. is restricted to tyrosinase or to enzymes with specific steroid-oxidizing properties was examd. by sepg. tyrosinase on agarose gel followed by hydroxylapatite chromatog. The effectiveness of the sepn. was monitored electrophoretically. Two bands of enzyme activity of 127 kilodaltons was found. One of these bands could be cleanly sepd. from the other. The fraction which contained the single band, as well as the one which contained both bands, had similar apparent Km values, i.e., 1.5 .times. 10-4 and 2.1 .times. 10-4 M. They both catalyzed the oxidn. of 2-hydroxyestradiol, but only in the presence of catechol. All enzyme fractions showed the same pattern of activity toward the estrogen. HPLC anal. of reaction products of catechol indicated that not all of the substrate was consumed during the reaction. About 26% remained unreacted at an initial concn. of 100-400 .mu.M of catechol. This remaining catechol, rather than its reaction products, appeared to function as activator of the steroid reaction. The data were consistent with the presence on the enzyme of an allosteric activator site specific for catechol and an active site with a much lower structural specificity occupied by the catecholestrogen.

8. MELANOMA

- Bertrand G.
  Melanotic adenocarcinoma of the uterus. Neuroendocrine tumor of the uterus. Ann Pathol 8:295-304, 1988.
  Abstract : The case reported concerns a 76-year-old woman under treatment for a previously diagnosed "poorly differentiated endocervical adenocarcinoma". New biopsies revealed an adenocarcinomatous tumor with unexpected melanotic pigmentation. The patient underwent cesium therapy followed by colpohysterectomy with lymphadenectomy. As there were no metastases, external complementary radiotherapy was not used. Four months after surgery, a large recurrence was detected; surgical excision proved impossible but revealed a grossly pigmented tumor from which several samples were taken. The patient died 11 months after the first consultation. No autopsy was performed. Morphological study was done on the initial biopsy, on the uterine tumor and on the recurrent tumor, using histological, cytological, ultrastructural and immunohistochemical techniques. Flow cytometry and biochemical study were also carried out on the recurrent tumor. All the samples studied histologically revealed uniform tumor morphology showing a poorly differentiated adenocarcinoma with an irregular distribution of melanin pigmentation (Fontana +). Electron microscopy confirmed the epithelial nature of the tumor, showing differentiated apical poles with villosities, linked by desmosomes. Basement membranes were irregularly present. Electron microscopy also demonstrated the melanotic nature of the pigmentation with melanosomes and premelanosomes. A few membrane-bound neurosecretory granules were seen. Immunohistochemistry showed that the tumor contains no S 100 protein and that no staining was obtained with monoclonal antibodies against malignant melanoma. Hormonal secretion and chromogranin were not detected. Tumor cells contained neither GFAP nor neurofilaments. Positive staining was obtained for neuron specific enolase and synaptophysin. Tumor cells contained three types of intermediate filament proteins = Vimentin, cytokeratins and peripherin (peripherin is an intermediate filament protein identified in 1984 by Portier, of the college of France, who very kindly supplied the antiserum and was good enough to do most of the biochemical study. Peripherin is considered to be characteristic of the peripheral nervous system. This case is the first example of demonstration of peripherin in a tumor). The biochemical study gave the following results: Cytosol assays for estrogen and progesterone receptors were negative. Vimentin, cytokeratins and peripherin were demonstrated by a study carried out in the College de France. No GFAP was found. A study of the metabolism of melanin derivatives showed high levels of urinary dopamine, serum and cytosol L. dopa.

- Grignon DJ, Ro JY, Ayala AG.

Malignant melanoma with metastasis to adenocarcinoma of the prostate. Cancer 63:196-198, 1989.
Abstract : Tumor-to-tumor metastases are uncommon despite the fact that the presence of two or more malignancies in a single patient is not a rare occurrence. The most frequent donor tumors are the lung, prostate, and thyroid gland, whereas renal cell carcinoma is by far the most common recipient. In this report we describe a patient dying of metastatic malignant melanoma and locally advanced prostate cancer in which the melanoma metastasized to the prostatic adenocarcinoma. The prostatic primary was well differentiated and stained positively with prostate-specific antigen and prostatic acid phosphatase, whereas the melanoma contained abundant melanin pigment and stained positively for S-100 protein. This is the second reported instance of prostatic carcinoma as the recipient in a case of tumor-to-tumor metastases and the first in the English language literature.

- Kable EP, Parsons PG.
Melanin synthesis and the action of L-dopa and 3,4-dihydroxybenzylamine in human melanoma cells. Cancer Chemother Pharmacol 23:1-7, 1989.
Abstract : The toxicity and selectivity of 3,4-dihydroxybenzylamine (DHBA), an experimental antimelanoma agent that cannot enter the melanin pathway, broadly paralleled that of L-dopa in a panel of human melanoma cell lines sensitive or resistant to the latter drug. A human retinoblastoma cell line was found to be sensitive to both compounds. The toxicity and selectivity of both catechols were associated with inhibition of DNA synthesis; DHBA was more potent yet allowed a much greater degree of recovery compared with an equitoxic level of dopa. Dopa and DHBA had similar, dose-dependent effects on the cell cycle, arresting cells in S phase at low doses and in G1 at high doses. Replication of the DNA virus adenovirus was found to be inhibited by both agents. There was no difference between sensitive and resistant cell lines in the manganese or copper/zinc forms of superoxide dismutase, or in iron content and iron-binding capacity. Catechol toxicity was inhibited by the hydrogen peroxide scavenging agents pyruvate and methaemoglobin. Sensitivity to catechols did not correlate with melanin or tyrosinase content, rate of incorporation of tyrosine or dopa, intracellular levels of phenylalanine or tyrosine, or binding of a new monoclonal antibody directed against a melanosomal protein. These results indicate that DHBA and dopa exhibit selective toxicity for neural crest tumor cells independently of the melanisation pathway and of the superoxide scavenging system.

- Kimura N, Ishioka K, Miura Y, Sasano N, Takaya K, Mouri T, Kimura T, Nakazato Y, Yamada R.
Melanin-producing medullary thyroid carcinoma with glandular differentiation. Acta Cytol 33:61-66, 1989.
Abstract : A rare case is reported of melanin-producing

medullary thyroid carcinoma in a 62-year-old man. Intraoperative imprints of the thyroid tumor revealed numerous detached tumor cells containing large amounts of brown pigment. The Fontana-Masson argentaffin reaction with bleach confirmed that those granules were melanin. Histologically, the tumor was composed of two different components--a medullary area with hyalinized stroma and a follicular area. Melanin was scattered in both areas. The tumor cells in both areas were immunoreactive to carcinoembryonic antigen, calcitonin, gastrin-releasing peptide, somatostatin, met.-enkephalin, neuron-specific enolase, chromogranin and neurofilaments, and negative for thyroglobulin and S-100 protein. The histologic diagnosis was melanin-producing medullary thyroid carcinoma with glandular differentiation. Although various kinds of peptides and amines have been reported to be produced in medullary thyroid carcinoma, melanin production is quite rare; this appears to be only the third reported case.

- Mafee MF, Barany M, Gotsis ED, Dobben GD, Puklin J, Chow JM, Wenig BL.
Potential use of in vivo proton spectroscopy for head and neck lesions. Radiol Clin North Am 27:243-254, 1989.
Abstract : Early experience with in vivo MRS has shown its potential for obtaining biochemical information, thus enhancing the diagnostic sensitivity of MRI studies. Further work on combined MRI and in vivo MRS is needed, with the goal of characterization and abnormal conditions according to their spectral patterns and for identification of tumor markers. We presented in this communication our preliminary results. It seems that the resonance from melanin can be used as a marker for melanotic tumors.

- Okihiro MS.
Chromatophoromas in two species of Hawaiian butterflyfish, Chaetodon multicinctus and C. miliaris. Vet Pathol 25:422-431, 1988.
Abstract : Chromatophoromas (cutaneous pigment cell tumors) were seen in two species of butterflyfish, Chaetodon multicinctus and Chaetodon miliaris, over an 11-year period (1976-1987) in waters off the islands of Maui, Lanai, and Molokini in the state of Hawaii. The chromatophore tumors found in the brown-barred butterflyfish, C. multicinctus, were predominantly iridophoromas (characterized by the presence of birefringent olive-green crystalline pigment), while the tumors in the lemon butterflyfish, C. miliaris, were primarily melanophoromas (characterized by the presence of melanin pigment). Mixed chromatophoromas, composed of iridophores, melanophores, and undifferentiated chromatophores, were found in both species. The prevalence of chromatophoromas in C. multicinctus off the island of Maui varied from a low of 22-25% in 1976 to a high of 50% in 1987. The estimated prevalence of chromatophoromas in C. miliaris was 2.5% off the island of Molokini in 1976, and 5.0% off Lanai in 1987. The cause or causes of chromatophoromas in these two species of butterflyfish has

not been determined.

- van Haard PM.
  Chromatography of urinary indole derivatives. J Chromatogr 429:59-94, 1988.
  Abstract : Latest strategies are discussed for the routine chromatographic analysis of clinically important indole derivatives in urine. Analysis of 5-hydroxyindoleacetic acid and, perhaps more importantly, serotonin and 5-hydroxytryptophan remains attractive in the screening for carcinoid tumours and their differentiation. Analyses of two precursors of the skin pigment eumelanin seem to be promising in the monitoring of treatment of malignant melanoma and screening for pigmentation disorders and gallstone formation. Studies on the clinical relevance of the determination of tetrahydro-beta-carbolines and melatonin-related indoles await routine application of chromatographic methods designed to take into consideration the relative instability of these compounds. Application of GC-MS, although confined to larger and/or governmental laboratories remains attractive as a way of improving the specificity of analyses and in establishing reference methods. As for HPLC, the recent development of chromatographic and detection methods for the concurrent determination of different clinically important and metabolically related compounds from the same sample, preferably by direct injection techniques, seems to be fruitful and should be continued.

9. EYE

- Fukuda M, Sasaki K.
  The influence of melanin on intraocular dynamics. Nippon Ganka Gakkai Zasshi 92:1839-1843, 1988.

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