CHAPTER 2

Melanocortins and Pigmentation

Aaron B. Lerner

It all began in 1916, the story not only for the melanocortins and pigmentation but also for the entire field of pituitary endocrinology. Two independent papers appeared in Science by two young biologists, Philip E. Smith in California (1) and Bennett M. Allen in Kansas (2). They described a way to ablate the pituitary glands of tadpoles without killing the animals, and they observed that the tadpoles so treated were light in color. Soon after these reports it was found that injections of pituitary extracts into tadpoles and frogs would turn them dark (3). Before this apparently simple achievement, it was thought that the pituitary gland was necessary for life. No investigator had been able to destroy or remove that gland from any animal and keep it alive. Ten years later Smith (4), in another major success, reported his procedure for the ablation of the hypophysis in rats. He opened the door for intense research on the role of the pituitary gland in mammalian systems. It should not be a surprise that a change in color of tadpoles marked the beginning of pituitary endocrinology. It was essential that one be able to see and measure a change with visible light. There were no spectrophotometers or other equipment to monitor the metabolic processes that occurred outside the visible range after the destruction or removal of a gland or the injection of extracts from glands into animals.

While impressive advances were being made in the basic biologic and medical sciences, there were numerous questions in clinical medicine regarding disorders of pigmentation. Some people had defects from birth—albinism, piebaldism, large nevi, and so on. Others had conditions that were acquired—local or generalized hyperpigmentation or hypopigmentation, or both. Both acquired conditions occur in adrenal insufficiency or Addison’s disease. In this paper I will be concerned mostly with the darkening that occurs in patients with loss of adrenal function from any cause (idiopathic atrophy, tuberculosis, metastatic cancer, removal of the adrenals, etc.). In this disorder there is hyperpigmentation of the exposed areas (face, hands, arms) the body folds and
creases (axillae, groin, palms), pigmented nevi, the oral cavity, and sites of recent scars. People of medium dark color and who tan well can become extremely dark. Replacement therapy with relatively low doses of cortisone, 37.5 mg daily, is usually sufficient to get the patient back to his or her original color.

What caused the darkening? It was generally assumed that the darkening that occurred in tadpoles and frogs minutes after the injection of pituitary extracts was totally unrelated to what happens in human beings. It was assumed—wrongly—that it takes days or weeks for human being to darken following adrenalectomy. It should have been realized that under the proper conditions human beings do have the capacity to darken quickly. For example, some people of medium dark complexion can darken within 24 hours after exposure to strong sunlight. Injection of melanocyte-stimulating hormone (MSH) can darken someone in 2 or 3 days.

In the early 1950s efforts were being made to isolate MSH from the pituitary gland. Smith had also previously identified an adrenocorticotropic principle when he demonstrated that adrenal atrophy following hypophysectomy could be reversed by implantation of pituitaries. At about the same time the Armour Laboratories began to market adrenocorticotropic hormone (ACTH) for clinical use. It was found that Armour ACTH was a potent darkening agent for tadpoles and frogs. In addition, patients receiving ACTH for several weeks were turning dark. Some investigators were beginning to conclude that ACTH was the major darkening peptide in the pituitary. But when α- and β-MSH were isolated, they proved to be more potent than ACTH in darkening frog skin, with no ability to stimulate the adrenal glands. Armour produced their ACTH from whole bovine pituitary glands while we isolated MSH from bovine posterior pituitary glands, which we knew included cells of the intermediate lobe. Armour changed their method and began to separate physically the anterior lobes from the posterointermediate lobes. When their commercial ACTH came only from the anterior lobes the darkening stopped. Something other than ACTH caused the darkening. Their first ACTH product was contaminated with MSH and it was the MSH that was the offending agent. Injections of MSH into human subjects made them dark (5–9).

The five peptides α-, β-, and γ-MSH, ACTH, and β-lipotropin that are part of the precursor molecule proopiomelanocortin (POMC) are referred to as melanocortins. They are peptide hormones and neuropeptides that together with their receptors participate in the control of an amazing array of processes, including pigmentation, adrenocortical steroidogenesis, energy homeostasis, inflammation, and others. Most is known about α-MSH and ACTH and their receptors. It appears that γ-MSH has no role in pigmentation. We do not know whether β-MSH can be processed from its parent peptide β-lipotropin or from