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Review

Brain effects of melanocortins☆

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ABSTRACT

The melanocortins (α, β and γ-melanocyte-stimulating hormones: MSHs; adrenocorticotrophic hormone: ACTH), a family of pro-opiomelanocortin (POMC)-derived peptides having in common the tetrapeptide sequence His-Phe-Arg-Trp, have progressively revealed an incredibly wide range of extra-hormonal effects, so to become one of the most promising source of innovative drugs for many, important and widespread pathological conditions.

The discovery of their effects on some brain functions, independently made by William Ferrari and David De Wied about half a century ago, led to the formulation of the term "neuropeptide" at a time when no demonstration of the actual production of peptide molecules by neurons, in the brain, was still available, and there were no receptors characterized for these molecules.

In the course of the subsequent decades it came out that melanocortins, besides inducing one of the most complex and bizarre behavioural syndromes (excessive grooming, crises of stretchings and yawnings, repeated episodes of spontaneous penile erection and ejaculation, increased sexual receptivity), play a key role in functions of fundamental physiological importance as well as impressive therapeutic effects in different pathological conditions.

If serendipity had been an important determinant in the discovery of the above-mentioned first-noticed extra-hormonal effects of melanocortins, many of the subsequent discoveries in the pharmacology of these peptides (feeding inhibition, shock reversal, role in opiate tolerance/withdrawal, etc.) have been the result of a planned research, aimed at testing the "pro-nociceptive/anti-nociceptive homeostatic system" hypothesis.

The discovery of melanocortin receptors, and the ensuing synthesis of selective ligands with agonist or antagonist activity, is generating completely innovative drugs for the treatment of a potentially very long list of important and widespread pathological conditions: sexual impotence, frigidity, overweight/obesity, anorexia, cachexia, haemorrhagic shock, other forms of shock, myocardial infarction, ischemia/reperfusion-induced brain damage, neuropathic pain, rheumathoid arthritis, inflammatory bowel disease, nerve injury, toxic neuropathies, diabetic neuropathy, etc.

This review recalls the history of these researches and outlines the pharmacology of the extra-hormonal effects of melanocortins which are produced by an action at the brain level (or mainly at the brain level). In our opinion the picture is still incomplete, in spite of being already so incredibly vast and complex. So, for example, several of their effects and preliminary animal data suggest that melanocortins might be of concrete effectiveness in one of the areas of most increasing concern, i.e., that of neurodegenerative diseases.

Contents

☆ Dedicated to my unforgettable Teacher, Professor William Ferrari.

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1. Introduction

Melanocortins (melanotropins, melanopeptides) (α, β and γ-melanocyte-stimulating hormones: MSHs; adrenocorticotrophic hormone: ACTH; their fragments and fragment analogues), or, more comprehensively (after the discovery and characterization of melanocortin receptors), both agonists and antagonists at melanocortin receptors, are rapidly becoming one of the most interesting and promising matters in pharmacology, mainly for their innovative therapeutic potential in various pathological conditions. For many years melanocortins have been thought to have as their sole function the control of endocrine and metabolic processes. The finding that a sequence of only a few aminoacids of the ACTH molecule was required for the behavioural effects of this pituitary hormone led to the concept that besides their classical endocrine effects, pituitary hormones had a central nervous system (CNS) activity not mediated by the peripheral endocrine organs [1,2].

Such peptides with CNS activity were originally designated as "neurogenic peptides" or "neurotrophic peptides" [1], or "neurohormones" [3]. The term "neuropeptides" [4] was in the end universally agreed.

It is now well evident that the extra-hormonal effects of melanocortins, in part discovered and studied at first by very few people [essentially the groups of Ferrari and associates, De Wied and associates, and Kastin and associates], are indeed various and important, and often concern functions whose upset is the cause of many morbid conditions (sexual dysfunctions, anorexia, cachexia, hyperphagia, obesity, pain, inflammation, shock, ischemia- and ischemia/reperfusion-induced injuries, neurodegenerative diseases). The natural melanocortin able to induce practically all the extra-hormonal effects so far observed with the administration of these peptides, of their fragments and fragment analogues, is α-MSH. This molecule, that appeared during the Paleozoic, gives to several species of the animal kingdom the remarkable capacity to become invisible thanks to camouflage: one of the most extraordinary forms of passive defence, a life-saving mechanism against ever-imminent aggressions from a basically hostile environment. In this connection it is worth noting that the animal species endowed with the camouflage capacity are the same that can regenerate parts of the body (tail, limbs).

The precursor protein of melanocortins, pro-opiomelanocortin (POMC), is comprised of three main domains: the N-terminal pro-γ-MSH, the central ACTH, and the C-terminal β-lipotropin. Each domain contains one form of MSH, i.e., γ-MSH in pro-γ-MSH, α-MSH as N-terminal sequence of ACTH, and β-MSH in β-lipotropin domain. The latter domain further includes the C-terminal β-endorphin peptide. The posttranslational processing of POMC occurs in a tissue-specific manner. In neurons of the arcuate nucleus of the hypothalamus, POMC is processed by the prohormone convertases 1 and 2 (PC1 and PC2) (and perhaps others) and by carboxypeptidase E to the main end products α-MSH (=C-terminally amidated and α-*N*-acetylated $ACTH_{1-13}$), $ACTH_{18-39}$ (=CLIP, corticotropin-like intermediate lobe peptide), and several forms of β-endorphin. In melanotrophs of the intermediate lobe of the pituitary, the proteolytic processing of POMC is similar. In the corticotrophs of the anterior pituitary, POMC is processed to β-lipotropin (β-LPH), $ACTH_{1-39}$, and 16 k peptide; PC2 cleaves in part β-LPH to form γ-LPH and β-endorphin, and further cleave γ-LPH to generate β-MSH (the 18 C-terminal amino acid residue of γ-LPH). The 16 k peptide is cleaved by PC1 to *N*-POC (=N-terminal POMC, or pro-γ-MSH), joining peptide (JP) and ACTH. Three forms of γ-MSH are produced by additional cleavage of *N*-POC: γ_1-MSH contains 11 amino acids and is C-terminally amidated; γ_2-MSH has an additional C-terminal glycine and is not amidated; γ_3-MSH is C-terminally extended and contains 25 amino acid residues. Two discrete groups of neurons placed between the hypothalamus and the medulla also produce POMC, which is mainly processed to α-MSH and β-endorphin.

Just as amazingly wide and varied is the overall range of effects of melanocortins, alike amazing is the fact that so diverse effects are anyway all produced by an action in the brain (Table 1).

The discovery, in the eighties, that melanocortins are contained in a precursor protein (POMC) that also contains the most important opioid peptides (endorphins); the distribution of POMC system in the body, such that it controls nervous, behavioural, endocrine and immune functions; the usually opposite influence of melanocortins and opioids on target cells; all these facts led to the hypothesis of a regulatory, homeostatic role of the POMC system under both physiological and pathological conditions. The subsequent experimental testing of such hypothesis produced the discovery of several unfore-