Proopiomelanocortin (POMC) is a polyprotein found mainly in the pituitary gland [1], although it is also present in brain, placenta and intestine [2]. While POMC itself has little biological activity, adrenocorticotropin (ACTH) and beta-endorphin, opioid peptides within the structure of the POMC molecule, are physiologically important hormones [3]. ACTH and beta-endorphin are freed from POMC by a series of proteolytic cleavage steps. This processing has been investigated most extensively in the anterior and intermediate lobes of the pituitary where some of the peptidases involved in POMC processing have been characterized [4, 5]. The degradation of POMC in these two lobes is different since ACTH is converted to alpha melanocyte stimulating hormone (alpha-MSH) in the intermediate but not the anterior pituitary. As a result, the main biologically active secreted POMC products from the intermediate lobe are alpha-MSH and beta-endorphin, whereas ACTH and beta-endorphin are released from the adenohypophysis. Differential expression of processing enzymes, therefore, is the crucial determinant for the tissue-selective appearance of various POMC-derived peptides.

ACTH and beta-endorphin have numerous physiological actions including mediating the response of the body to stress, regulation of pain mechanisms, and modification of the immune system. While the expression of different POMC peptides varies according to the presence of the processing enzymes, the levels of these opioids are directly dependent on the activity of the POMC gene. Within the last decade, the structure of the POMC gene has been identified, and many of the regulatory and molecular factors regulating its activity have been elucidated. This commentary will discuss recent advances in our knowledge of the control of the POMC gene and how modifications in its activity may have important physiological consequences.

POMC gene

The human POMC gene consists of three exons separated by two non-coding intervening sequences [6]. The biologically active POMC peptides, beta-endorphin and ACTH, are exclusively coded by exon 3, whereas the signal peptide and amino terminal region of the precursor protein results from expression of exon 2 [7]. Exon 1 is not known to code for any proteins. The structure of the POMC gene has many similarities to that of the gene for preproenkephalin, another opioid peptide [2]. Furthermore, human preproenkephalin, the precursor of met- and leu-enkephalin, and POMC have the same number of amino acid residues and the biologically active peptides in each precursor polypeptide are flanked by dibasic amino acid residues. These similarities may allow the opioid peptide precursor molecules to be processed to mature hormone by common proteolytic mechanisms [2].

Glucocorticoid regulation

The synthesis of POMC-derived peptides in the pituitary is regulated by hormones both of peripheral and central origin. Glucocorticoids, whose production and release from the adrenal cortex is stimulated by ACTH [8], inhibits POMC gene activity in the anterior pituitary [9–12]. In a series of studies that examined the mechanisms by which glucocorticoids regulate POMC expression, it was shown that removal of the adrenal gland, the major source of glucocorticoids in the body, raised POMC mRNA levels and the transcription rate of the POMC gene in the adenohypophysis [11, 12]. Injection of glucocorticoid analogues such as dexamethasone into adrenalectomized animals returned POMC gene transcriptional activity back to normal levels. As a result, it was suggested that glucocorticoids tonically inhibit POMC gene activity in anterior pituitary.

Glucocorticoids suppress POMC gene expression through at least two mechanisms. By modifying the synthesis and release of corticotropin releasing factor (CRF), a potent central stimulant of ACTH and beta-endorphin secretion and production, glucocorticoid could indirectly control POMC expression [11, 12]. In support of this proposal, adrenalectomy was shown to raise the levels of CRF immuno-reactivity in the paraventricular nucleus of the hypothalamus [13, 14]. Glucocorticoids can also act directly on corticophils to block POMC gene