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The Highly Efficient Genome

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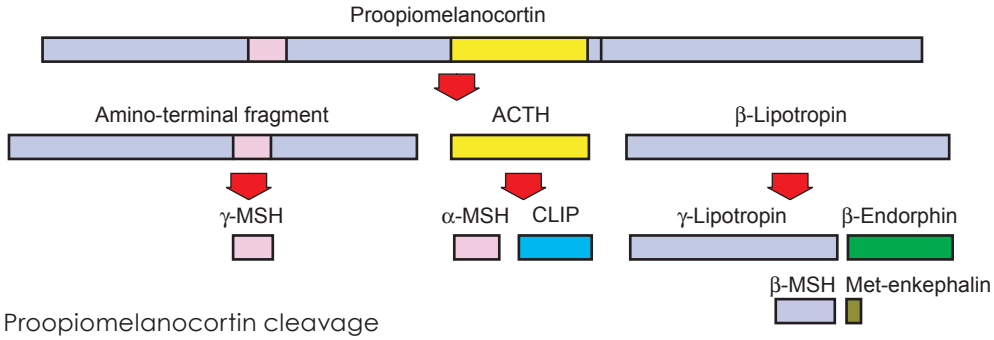

Proopiomelanocortin cleavage

When the human genome project began, it had been estimated that around 100,000 genes would be found. To the surprise of scientists, less than 25,000 have been found despite the fact that the human body is known to have the ability to produce several times this many proteins.[1] A number of genes are now known to be polycistronic; that is, they produce more than one protein. One interesting example is the proopiomelanocortin (POMC) gene which gives rise to a prohormone which may be cut into a number of different hormone proteins. The pro prefix refers to the fact that further processing is necessary for the final product, opio refers to the opiate peptide β-endorphin, and melanocortin refers to four related peptides: α-melanocyte stimulating hormone (MSH), β-MSH, γ-MSH, and adrenocorticotropic hormone (ACTH).[2]

Hormone Formation

After translation, the POMC prohormone may be enzymatically cleaved to form γ-MSH, ACTH, and β-lipotropin. A different enzyme is used to cleave ACTH to form α-MSH and corticotrophin-like intermediate lobe peptide (CLIP). Additionally, β-lipotropin may be cleaved to form γ-lipotropin and β-endorphin. Further cleavage of γ-lipotropin yields β-MSH. Each of these hormones must undergo further processing to reach their biologically active form.[3] Currently there are 10 known products of this gene. The products formed are tissue specific and are controlled by available enzymes.[4]

Melanocortins and Pigmentation

The melanocortins are the most studied products of this gene. They are similar in that all contain the amino acid sequence Histadine-Phenylalanine-Arginine-Tryptophan and they have some overlap in their activity. In fur-bearing mammals α-MSH has been shown to stimulate melanocyte (pigment cell) differentiation and eumelanin (a dark brown to black pigment) synthesis. Without this stimulation these cells produce pheomelanin (a yellow to red pigment).

Studies in humans reveal that exposure to ultraviolet (UV) radiation causes an increase in ACTH and α-MSH production in keratinocytes (skin cells). This, in turn, causes an increase in eumelanin production and a darkening of the skin. This response depends on a functional melanocortin 1 receptor (MC1R). Some people have a mutation in the MC1R gene which makes the receptor unresponsive to these hormones. These people have red hair (from pheomelanin), fair skin, and burn easily when exposed to UV light.[5]

Melanocortins and Body Weight Regulation

Pigmentation is not the only thing affected by these hormones. ACTH is an important hormone produced in the pituitary gland of the brain which signals the adrenal glands to produce glucocorticoids. In patients with

pituitary disease where ACTH is not secreted normally, anorexia and weight loss occur.

In contrast, there are several mutations in the POMC gene that result in early-onset obesity and red hair along with adrenal insufficiency. These mutations result in a defective ACTH molecule which explains the adrenal insufficiency. The other symptoms relate to the loss of α-MSH activity. α-MSH is derived from ACTH and plays an important role in suppressing appetite via the melanocortin 4 receptor (MC4R) in the brain. The loss of α-MSH means there is no suppression of appetite, resulting in obesity, and no signal for eumelanin synthesis, resulting in red hair.[6]

Melanocortins and Inflammation

Recent research has revealed that melanocortins play a critical and diverse role in modulating immune function and inflammation. As mentioned above, ACTH is a hormone that is released from the pituitary. It travels via the blood stream and signals the adrenal glands to produce glucocorticoids. Glucocorticoids have a number of important functions which include a systemic anti-inflammatory effect. In addition to this endocrine pathway, melanocortins can act centrally through several neurogenic pathways. Research has shown that α-MSH within the brain can signal via the sympathetic nervous system to control acute inflammation of the skin in mice. Additionally, cholinergic pathways, specifically through the vagus nerve, have been shown to protect from hemorrhagic shock and tissue reperfusion injury.

In addition to the anti-inflammatory effects that are controlled centrally, melanocortins can exert control locally. When the anti-inflammatory effects of melanocortins were first being studied, researchers were amazed at the wide variety of effects they had. It was discovered that they exert their influence very early in the chain of events leading to inflammation. Within inflammatory cells (for example, macrophages) there is a nuclear factor (NF-κB) which is normally bound to a molecule (IκBα) inside the cell membrane. Cytokines, endotoxin, and other compounds that stimulate an inflammatory response do so by phosphorylating IκBα. This causes the molecule to break down, releasing NF-κB, which travels to the nucleus and signals the transcription of numerous genes involved in the inflammatory response.[7] Melanocortins stabilize the bond between NF-κB and IκBα which inhibits this response. Without the control of melanocortins, the inflammatory response could easily run out of control and harm the very life it was designed to protect.

Melanocortins and Sexual Function

Melanocortins have also been documented to play a role in sexual function. Both α-MSH and ACTH injected into various portions of the brain caused penile erection in rats. In men with psychogenic or organic erectile dysfunction, peripherally administered MT-II, a MCR agonist produced by a different gene, caused penile erection. Further studies implicate the MC4R as playing an important role in this response. There is an interest in developing drugs that specifically target the MC4R for treatment of sexual dysfunction. Since this receptor also plays a role in body weight regulation, as mentioned above, drugs targeting it have been considered for controlling obesity.[8] The fact that MC4R agonists can have pleiotropic effects could result in undesirable side effects.

Melanocortins also play a role in female sexual behavior. Studies in rats indicate that they can either increase or decrease sexual behavior depending on the receptivity of the female at the time. It appears there are no results from human females at present.

Other POMC Hormones and their Functions

In addition to melanocortins, the POMC gene produces lipotropins, endorphins, and several other less-well-studied peptides. Lipotropins promote the usage of fat by the body and β-lipotropin can be cleaved to form β-endorphin. Endorphins are secreted in the brain and bind opioid receptors to decrease pain, increase relaxation, and provide an overall sense of well-being.[9] Additionally, β-endorphin has been found in various immune cells responding to peripheral inflammation. Stressful stimuli signal the release of endorphin which binds peripheral opioid receptors to inhibit pain.[10]

Conclusion

Polycistronic genes such as POMC make the genome very efficient because less space is needed to code for the proteins than if each were coded by a separate gene. The fact that different enzymes are used to cleave POMC into different products allows the body to control the final product by controlling which enzymes are present. Sometimes these proteins act in diverse locations to bring about the same basic effect (for example, the anti-inflammatory effects of melanocortins both within the central nervous system and peripherally). Other times the same protein exhibits a diverse range of effects (for example, α-MSH affects pigmentation,

food intake, inflammation, etc.). From this brief overview it should be apparent that we are looking at an irreducible complex system. Both receptors and their ligands (the proteins that bind to them) need to be in the right locations for these systems to work. The proper enzymes need to be available in the proper locations too, so the POMC molecule can be cleaved to form the appropriate product. These undergo further processing to bring the protein to its final biologically active form. These are not the types of things one would expect to see as a result of random, chance processes. The complexity of interactions far exceeds what is described here. These astoundingly well integrated and complex interactions certainly inspire awe for the Creator and provide plenty of fascinating questions to be answered by scientific investigation.

Footnotes

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