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Review

Alternative G protein coupling and biased agonism: New insights into melanocortin-4 receptor signalling

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ABSTRACT

The melanocortin-4 receptor (MC4R) is a prototypical G protein-coupled receptor (GPCR) that plays a considerable role in controlling appetite and energy homeostasis. Signalling initiated by MC4R is orchestrated by multiple agonists, inverse agonism and by interactions with accessory proteins. The exact molecular events translating MC4R signalling into its physiological role, however, are not fully understood. This review is an attempt to summarize new aspects of MC4R signalling in the context of its recently discovered alternative G protein coupling, and to give a perspective on how future research could improve our knowledge about the intertwining molecular mechanisms that are responsible for the regulation of energy homeostasis by the melanocortin system.

Contents

1. The melanocortin system

1.1. Agonists, receptors and physiological role

The melanocortin precursor molecule proopiomelanocortin (POMC) gives rise to at least 4 different melanocortins: the melanocyte-stimulating hormones (MSH) which are named α-, β- or γ-MSH and the adrenocorticotropic hormone (ACTH) (Pritchard et al., 2003; Pritchard et al., 2002). Melanocortins are small peptide hormones that bind with different affinities to 5 distinct melanocortin receptors (MCR), which belong to the super family of G protein-coupled receptors (GPCR) (Table 1). Melanocortins regu-

Abbreviations: ACTH, adrenocorticotropic hormone; cAMP, cyclic 3′,5′-adenosine monophosphate; AGRP, agouti-related protein; CTX, *cholera* toxin; ER, endoplasmic reticulum; ERK-1/2, extracellular signal-regulated kinases; FSK, forskolin; GPCR, G protein-coupled receptors; GTPγS^{35}, guanosine 5′-(3-O-thio)triphosphate; IRS, insulin receptor substrate; MGRN-1, mahogunin ring finger-1; MC4R, melanocortin-4 receptor; MRAPs, melanocortin receptor accessory proteins; MSH, melanocyte-stimulating hormones; PKA, protein kinase A; PKC, protein kinase C; PI3K, phosphatidylinositol-3-kinase; PLC, phospholipase C; POMC, proopiomelanocortin; PTX, *pertussis* toxin; RAMPs, receptor-activity-modifying proteins.

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Table 1
Melanocortins and their receptors.

Receptor subtype	Rank order of potency	Antagonists	Central effects	Peripheral effects
MC1R	α-MSH = β-MSH = ACTH > γ-MSH	Agouti	–	Pigmentation
MC2R	ACTH	Agouti	–	Glucocorticoid production
MC3R	α-MSH = β-MSH = ACTH = γ-MSH	Agouti and AGRP	Control of body weight	Release of cytokins
MC4R	α-MSH = β-MSH > ACTH > γ-MSH	Agouti and AGRP	Control of body weight and appetite regulation of blood pressure	Inhibition of inflammation
MC5R	α-MSH = β-MSH > ACTH > γ-MSH	Agouti	–	Sebum production

Data from two different sources (MacNeil et al., 2002; Schioth et al., 2005) were compiled.

late pigmentation, adrenal hormone secretion, immune functions, lipid metabolism and feeding behaviors (Brzoska et al., 2008). The MC1R is expressed in many different tissues such as skeletal muscle, brain and lung, but its most established scene of action is the skin, where MC1R signalling is responsible for pigmentation (Suzuki et al., 1996). The MC2R is the receptor for ACTH and, thus, a strong stimulator of glucocorticoid production in vertebrates (Chida et al., 2007). MC3R and MC4R are abundantly found in the brain, where they exert catabolic effects by decreasing food intake and increasing energy expenditure (Cone, 1999). Both MCR subtypes bind α- and β-MSH with similar affinity (Biebermann et al., 2006; Huszar et al., 1997; Lee et al., 2006), whereas, γ-MSH binds to the MC4R with a considerably lower affinity (by two orders of magnitude) compared to α-MSH (Voisey et al., 2003). Given the higher affinity of γ-MSH to the MC3R, it is assumed that this peptide induces its physiological effects mainly through the latter subtype. Interestingly, a newly discovered GPCR family, termed "mas-related GPCR" (Mrg), binds γ-MSH and its derivatives with similar high affinity, suggesting, that this peptide interacts with members of two unrelated GPCR families. The focus of γ-MSH research might turn to this novel aspect of melanocortin signalling in upcoming years (Han et al., 2002; Lembo et al., 2002).

The MC5R shows a broad expression pattern and targeted disruption of this gene results in widespread dysfunction of exocrine glands including a marked decrease in the production of sebum (Thiboutot et al., 2000). Since the complexity of signalling initiated by all 5 receptor subtypes and the melanocortins in different tissues is way beyond the scope of one review, in the following, we will concentrate on the MC4R.

The MC4R has been shown to play a pivotal role in controlling meal size and energy homeostasis. Adipose tissue-derived hormones such as leptin increase POMC expression in α-MSH-releasing neurons located in the arcuate nucleus of the hypothalamus (Shimizu et al., 2007). Secreted α-MSH activates MC4R expressing neurons of various hypothalamic nuclei, which, in turn, enhance the release of anorexigenic stimuli (e.g. thyrotropin- and corticotropin-releasing hormone) or inhibit the liberation of orexigenic peptides (e.g. orexins and melanin-concentrating hormone) (Ellacott and Cone, 2004).

The importance of MC4R signalling in the regulation of human metabolism has been highlighted by the finding that mutations in the MC4R gene are the most frequent monogenic cause of severe obesity. Accordingly, targeted disruption of the MC4R or the POMC gene in mice causes an obesity-diabetes syndrome characterized by hyperphagia, hyperinsulinemia and hyperglycemia (Balthasar et al., 2005; Huszar et al., 1997).

Besides its effects on the regulation of energy homeostasis, MC4R has also been shown to sensitise sexual sensation of

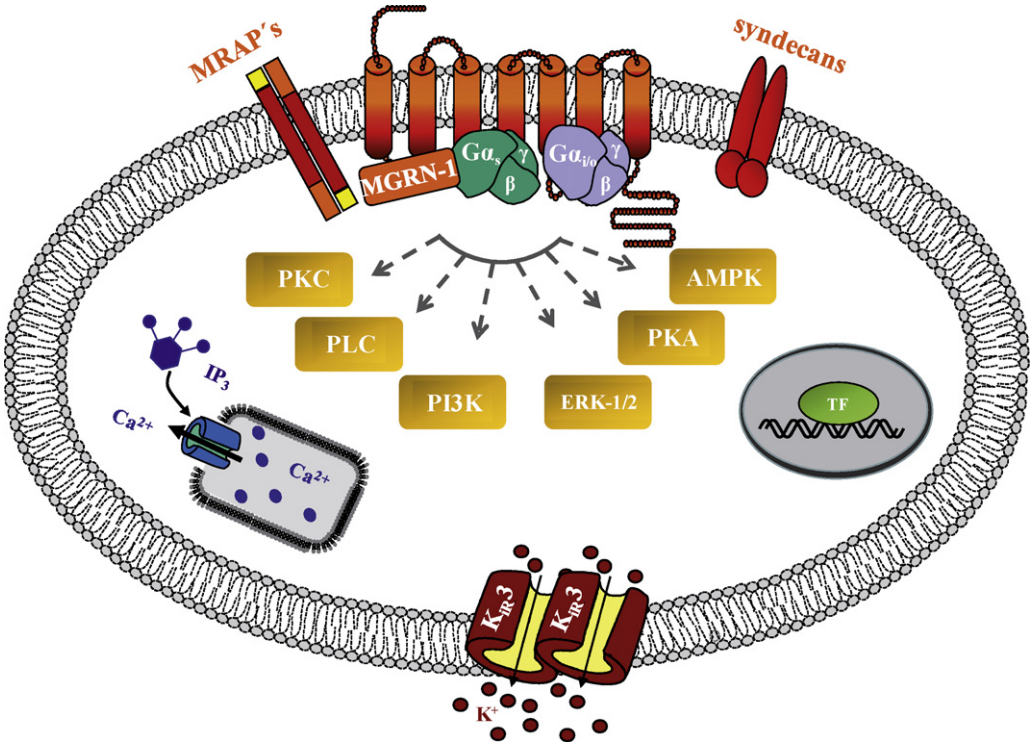

Fig. 1. Regulation of MC4R signalling by accessory proteins and alternative G protein coupling leads to the activation of numerous kinases, lipases and, in turn, to the modification of various down-stream effectors including transcription factors (TF), ion chanels and IRS-1. Data obtained in different studies and various cell models are compiled.