Obesity and Stress: The Melanocortin Connection

11

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The role of the melanocortin system in energy homeostasis, feeding behavior, and metabolism has been a focus of intense study since its discovery in 1979 (Crine et al. 1979). The ability of melanocortins to suppress feeding and increase energy expenditure has made melanocortin receptors (MCRs) a major target of anti-obesity drugs in development (Fani et al. 2014). In addition, the melanocortin system's influence on circulating glucose levels suggests it could also be targeted to treat obesity-related type 2 diabetes (Morgan et al. 2015; Parton et al. 2007). While very promising in theory, problematic side effects have plagued pharmaceutical trials for such medications, preventing FDA approval (Ericson et al. 2017). These adverse effects are due to other systemic and central functions of the melanocortin system. To understand and overcome these challenges, a more comprehensive understanding is needed of the role melanocortin peptides play and how they perform their diverse functions.

The melanocortin system can coordinate a wide variety of behavioral and physiological responses to internal and environmental cues. The number of known roles that melanocortins play continues to proliferate, ranging from the control of adrenal function, pain, and inflammation to surprising behavioral outputs such as grooming. As we will see, an organism's need to respond to stressors may be the most useful context for understanding the actions of this system. The ability to rank-order threats is critical to survival. Melanocortins play a critical role in enabling "fight or flight" responses to immediate danger. Later, endogenous opioids, AgRP/NPY circuitry, and other systems permit animals to focus on recovery, obtaining food to restore energy reserves, and activities of lesser importance. The interplay between these systems allows the animal to deal successfully with most stressors and return to physiological equilibrium.

This chapter will review the variety of roles played by melanocortins in the response to stress using insights from evolutionary development to understand their integration. Finally, we will discuss the lessons for obesity prevention and treatment arising from a holistic view of the actions of melanocortins.

11.1 The Melanocortin System: Proopiomelanocortin

Melanocortin peptides are generated from the polypeptide proopiomelanocortin (POMC) via successive posttranslational cleavage events. POMC is abundantly expressed in the pituitary and hypothalamus but also in other sites; its processing varies between tissues (Chen et al. 1986;

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Smith and Funder 1988; Mechanick et al. 1992; Forman and Bagasra 1992; Hummel and Zuhlke 1994; Ottaviani et al. 1997; Tsatmali et al. 2000; Iqbal et al. 2010; Alam et al. 2012). Generally, POMC is cleaved to form β-LPH and pro-ACTH, which prohormone convertase (PC)1/3 cleaves to form ACTH1–39. ACTH1–39 is the main product of corticotrophs in the pituitary, but in the hypothalamus, PC2 cleaves it to form ACTH1–17. Carboxypeptidase E (CPE) then removes the C-terminal basic residues to produce ACTH1–13. The C-terminus of ACTH1–13 is then amidated by peptidyl α-amidating monooxygenase (PAM) to create ACTH(1–3)NH2, also known as desacetyl α-MSH. In humans, an additional N-terminal cleavage site results in production of β-MSH, γ –MSH, and α-MSH (Pritchard et al. 2002). PC2 also cleaves β-LPH to form the endogenous opioid β-endorphin1–31. This posttranslational processing of the POMC preprohormone has been remarkably well conserved (Vallarino et al. 2012).

The genetic sequence for POMC appears across many species, from the earliest vertebrates such as lampreys to mammals. All the sequences have shown the same structural organization, suggesting that POMC was present in common ancestors 5–700 million years ago (Heinig et al. 1995). In the sea lamprey, separate genes named proopiocortin (POC) and proopiomelanotropin (POM) produce ACTH and MSH, respectively. Even invertebrates such as the leech have POMC-related sequences possessing over 80% homology in its melanocortin domain (Duvaux-Miret and Capron 1992; Salzet et al. 1997; Stefano et al. 1999). Indeed, tetrapods, mussel, and leech have the same sequentially arranged hormonal segments of this gene (Kawauchi and Sower 2006). It appears that α-, β-, and γ-MSH arose during the early evolution of invertebrates from intramolecular duplication of an ancestral MSH.

In the rodent brain, there are two recognized neuronal populations expressing POMC, although low levels of POMC mRNA have been reported in other CNS regions (Zhou et al. 2013). The largest population resides in the arcuate nucleus of the hypothalamus (ARC) and co-expresses the cocaine amphetamine-related transcript (CART) peptide (Elias et al. 1998). A second smaller population is located in the brain stem, in the nucleus of the solitary tract (NTS) (Khachaturian et al. 1986).

The melanocortin receptor family is unique in having its activity regulated by both agonists and antagonists. Two naturally occurring antagonists to MCRs exist, agouti and AgRP. Mice express agouti protein primarily in the skin where it influences pigmentation (Bultman et al. 1992). The human homolog, agouti signaling protein (ASIP), may also regulate pigmentation (Voisey et al. 2003). ASIP expression has been found in the skin and other tissues including the heart, ovary, testis, foreskin, adipose tissue, liver, and kidney (Wilson et al. 1995).

AgRP was discovered based on its sequence homology to agouti (Ollmann et al. 1997; Shutter et al. 1997). In contrast to that protein, AgRP is mainly expressed in the adrenal gland and arcuate nucleus of the hypothalamus (ARC). AgRP-producing neurons co-express two generally inhibitory neurotransmitters: neuropeptide Y (NPY) (Broberger et al. 1998; Hahn et al. 1998) and γ-aminobutyric acid (GABA) (Wu and Palmiter 2011). POMC neurons receive direct input from these NPY/AgRP neurons (Cowley et al. 2001; Atasoy et al. 2012; Tong et al. 2008; Smith et al. 2007) and other neurons inhibited by AgRP (Corander et al. 2011; Tolle and Low 2008). The mammalian central melanocortin system is defined as the neurons expressing POMC, AgRP neurons, which antagonize the effects of POMC neurons, and the downstream CNS circuits they collectively influence via MCRs.

As detailed below, POMC and AgRP neurons send and receive projections from many CNS regions (Broberger et al. 1998; Tsou et al. 1986; Palkovits et al. 1987; Zheng et al. 2005a; Haskell-Luevano et al. 1999; Bagnol et al. 1999; Schwartz 2000; Odonohue and Dorsa 1982; Cone 2005; Rinaman 2010; Magoul et al. 1993). ARC POMC neurons project most heavily throughout the hypothalamus, including to the anterior hypothalamus, medial preoptic area, medial preoptic nucleus (MPON), lateral hypothalamus, dorsomedial hypothalamus (DMH), ventromedial hypothalamic nucleus (VMH), paraventricular

nucleus of the hypothalamus (PVH), parasubthalamic nucleus (PSThN), and the posterior hypothalamus (PH). Projections to the forebrain target the bed nucleus of the stria terminalis (BNST), lateral septum (LS), nucleus of the diagonal band, medial amygdala (MeA), and the nucleus accumbens (NAc). In the brain stem, the periaqueductal gray (PAG), superior colliculus, deep mesencephalic nucleus, NTS, medial lemniscus, substantia nigra, dorsal raphe, and locus coeruleus receive projections. Finally, the spinal cord also receives input from ARC POMC neurons.

Overall, ARC POMC and AgRP neurons have similar connectivity. However, AgRP neuron projections appear to be sparser, with fewer synapses. This population projects heavily to areas from which it receives the most incoming connections. Robust projections exist to the PVH, DMH, LH, MPON, septal areas of the anterior commissure, paraventricular nucleus of the thalamus, and the LS. These neurons also send axons to the BNST, the organum vasculosum of the lamina terminalis, and the perifornical nucleus. One might expect that AgRP release directly opposes melanocortins released at these sites, but the microcircuitry involves a complex summation of both inputs. In the PVH, AgRP synapses contact cell bodies, while POMC synapses contact distal dendrites (Atasoy et al. 2012; Bouyer and Simerly 2013). Areas of volume release of AgRP and POMC, however, are likely to overlap. Finally, AgRP projections are notably absent to the brain stem, hippocampus, amygdala, corpus striatum, and olfactory cortical tract, all of which have dense POMC innervation (Palkovits et al. 1987; Bagnol et al. 1999; Watson et al. 1978; Jacobowitz and Odonohue 1978; Nilaver et al. 1979; Joseph et al. 1983).

POMC fibers of the NTS have less widespread connections, projecting sparsely to the PVH and PSThN, but more strongly within the brain stem. Targeted regions include the subcoeruleus nucleus, parvicellular reticular nucleus, medullary reticular nucleus (both dorsal and ventral), magnocellular reticular nucleus, pontine reticular nucleus, intermediate reticular nucleus, supratrigeminal nucleus, and the lateral parabrachial nucleus. Interestingly, ARC and NTS POMC neurons have reciprocal projections to each other.

11.2 Melanocortin Receptors

Five MCRs have been identified in humans, named in the order they were cloned: MC1R, MC2R, MC3R, MC4R, and MC5R (Girardet and Butler 2014). The MCRs coevolved with the POMC gene early in chordate evolution. During the multiplication of the chordates, genome duplications occurred that resulted in the ancestral MCR differentiating into an MC1/2 receptor precursor and an MC3/4 receptor precursor. (The origin of the MC5R is still debated (Cortes et al. 2014)). Evidence suggests that all MCRs responded to ACTH (and MSH) and caused release of glucocorticoids. For example, a primitive CRH-ACTH-corticosterone axis exists in the jawless hagfish (Amano et al. 2016).

Comparisons of the elephant shark, Japanese sting ray, and bony fish suggest that the MC2R gradually lost its ability to act without the melanocortin receptor 2 accessory protein (MRAP1) (Takahashi et al. 2016; Reinick et al. 2012). However, once paired with MRAP1, MC2R became the most efficient ACTH receptor, allowing the other MCRs to develop differing affinities to melanocortins and differing expression levels in tissues (Schiöth et al. 2005; Dores et al. 2014). These processes allowed unique roles for MCRs to develop without disturbing glucocorticoid production (Cone 2006; Kobayashi et al. 2012). In the lamprey, MCRs appear in the skin, liver, heart, and skeletal muscle, but not in the brain (Young 1935; Eddy and Strahan 1968). Some cartilaginous fish, which arose 450 million years ago, express α-MSH and β-endorphin in the brain and melanocortin (MC) receptors in the hypothalamus, brain stem, and telencephalon (Vallarino et al. 1988, 1989; Chiba 2001; Klovins et al. 2004). These findings suggest the period when POMC products ceased to act in the periphery alone and became neurotransmitters or neuromodulators. In mammals, melanocortins acting through MC3R

and MC4Rs in the hypothalamus, telencephalon, brain stem, and olfactory bulb came to reinforce the endocrine control of stress hormones (Liang et al. 2013; Haitina et al. 2007).

While MRAP1 is strongly expressed in the adrenal, gonadal, and adipose tissue, a related protein named MRAP2 is highly expressed in the hypothalamus, including the PVN (Chan et al. 2009). Interestingly, MRAP2 interacts with other MCRs in mammals. MRAP2 knockout mice and humans with MRAP2 mutations display severe obesity, changes in cholesterol metabolism, and Sim1 deficiency without hyperphagia or reduced energy expenditure (Novoselova et al. 2016; Asai et al. 2013). These effects suggest MC4Rs and other hypothalamic receptors interact with the MRAP2 protein (Clark and Chan 2017).

In humans, the MC1R melanocyte receptor regulates melanogenesis and pigmentation of the skin and hair. Upon activation, this receptor functions by promoting eumelanin and downregulating pheomelanin (Cone 2006). Sun sensitivity and risk of skin cancer increase with mutations in the MC1R gene (Rees 2000). Many immune cells also express MC1R, suggesting that the MC1R also has an anti-inflammatory role (Catania et al. 2010).

The ACTH receptor, MC2R, is primarily expressed in the adrenal cortex (Mountjoy et al. 1992). The major role of MC2R is to regulate steroidogenesis in the adrenal gland. Gene mutations of MC2R contribute to 25% of familial glucocorticoid deficiency cases, a rare autosomal recessive disorder. MC2R knockout mice (Chida et al. 2007) share characteristics of these patients, including severe glucocorticoid deficiency and failure of the adrenal gland to respond to ACTH (Thistlethwaite et al. 1975; Chung et al. 2008; Clark and Weber 1998). Human skin cells (Slominski et al. 1996) and mouse adipocytes (Norman et al. 2003; Boston and Cone 1996; Cho et al. 2005; Moller et al. 2011) express the MC2R receptor, suggesting it may have a role in lipolysis regulation (Boston 1999). In adipocytes, ACTH and α-MSH are strong inhibitors of expression of the adipokine leptin (Norman et al. 2003).

The MC5R receptor, the newest member of this receptor family, has the most diverse expression pattern of all the MCRs (Chen et al. 1997). It is involved with exocrine gland secretion, immunomodulation in B and T cells, and adipocyte cytokine release (Chen et al. 1997; Zhang et al. 2011; Lee and Taylor 2011; Taylor and Lee 2010; Taylor and Namba 2001; Buggy 1998; Jun et al. 2010). It also alters fatty acid oxidation control in skeletal muscle, enhances lipolysis, and suppresses fatty acid reesterification (Moller et al. 2011; An et al. 2007; Rodrigues et al. 2013). Recently, the MC5R has been implicated in regulating glucose uptake by skeletal muscle and thermogenesis (Enriori et al. 2016). These results suggest that MC5R agonists may offer a new target for obesity treatment in the periphery.

The primary regulators of energy homeostasis, MC3R and MC4R, are called neural MCRs due to their high expression in the CNS (Mountjoy 2010). Both receptors interact with melanocortins and are antagonized by AgRP. MC3Rs have an expression pattern limited primarily to hypothalamic and limbic structures, with highest expression in the ARC, VMH, ventral tegmental area (VTA), and the medial habenula (MHb) (Rosellirehfuss et al. 1993). MC3Rs promote body weight regulation and sensitize NPY/AgRP neurons to the metabolic state of the animal (Butler et al. 2017). Indeed, fasted *Mc3r*−/− mice fail to increase lipolysis or activate the HPA axis (Renquist et al. 2012). MC3Rs also have roles in the periphery. MC3Rs expressed on macrophages have anti-inflammatory immune functions (Getting et al. 1999a; Getting et al. 1999b). Renal MC3Rs promote urinary excretion of sodium, reducing blood pressure on high sodium diets (Mayan et al. 1996; Ni et al. 2003, 2006; Chandramohan et al. 2009).

MC4Rs play critical roles in metabolic regulation, pain, and reproduction, including erectile function and sexual behavior in both sexes (Starowicz and Przewlocka 2003; Starowicz et al. 2009; Pfaus et al. 2004; Martin and MacIntyre 2004; Wikberg and Mutulis 2008). MC4Rs have a wide distribution in the CNS, existing in over one hundred brain nuclei. MC4Rs are most concentrated in the brain stem and the hypothalamus. Importantly, MC4Rs are found in

neurons of the PVH that produce corticotrophin-releasing hormone (CRH), oxytocin, and thyrotropin-releasing hormone (TRH) (Liu et al. 2003; Lu et al. 2003). Preganglionic neurons in the intermediolateral cell column (IML) of the spinal cord also show MC4R expression and receive direct inputs from POMC fibers (Elias et al. 1998).

The MCR family is a member of the G-protein-coupled receptor (GPCR) superfamily that maintains a high level of constitutive activity (Srinivasan et al. 2004). These receptors generally couple to Gαs proteins, which activate adenylate cyclase, increase intracellular cyclic 3′,5′-adenosine monophosphate (cAMP), and activate protein kinase A (PKA). These signaling molecules can increase neuronal excitability, facilitate neurotransmitter release, regulate how neurons integrate synaptic input, and alter synaptic strength and connectivity (Grueter et al. 2012; Kreitzer and Malenka 2008; Russo et al. 2010). That melanocortins can alter synaptic strength has implications for their downstream functions, including their influence on body weight and reward pathways (Caruso et al. 2014). However, under continuous stimulation, the MC4R undergoes desensitization and internalization (Shinyama et al. 2003).

AgRP inhibits the basal activity of MC3Rs (Tao et al. 2010) and MC4Rs (Haskell-Luevano and Monck 2001; Nijenhuis et al. 2001) and acts as a competitive antagonist that prevents the binding of melanocortins. In contrast to α-MSH, AgRP stimulates the coupling of the MC4R receptor to the Gαi/o subunit, which inhibits adenylate cyclase and decreases intracellular cAMP levels (Büch et al. 2009; Fu and van den Pol 2008). Recently, it has also been shown that AgRP can hyperpolarize neurons by binding to MC4R and opening Kir7.1, an inwardly rectifying potassium channel, independently of its inhibition of α-MSH binding (Ghamari-Langroudi et al. 2015).

The MC3R appears to be the only melanocortin receptor expressed by ARC POMC neurons (Bagnol et al. 1999; Jegou et al. 2000; Mounien et al. 2005). In contrast, AgRP/NPY neurons express both MC3Rs and MC4Rs (Bagnol et al. 1999; Mounien et al. 2005). The activation of MCRs on AgRP neurons may allow these neurons to sense the level of POMC activity and regulate AgRP release in a short feedback loop. In addition, MC3R activation of AgRP neurons increases their release of inhibitory neurotransmitters onto POMC neurons and POMC projection sites (Cowley et al. 2001). Indeed, electrophysiological, immunohistochemical, and behavioral evidence shows activation of MC3Rs diminishes POMC neuronal activity and suppresses POMC mRNA expression (Cowley et al. 2001; Lee et al. 2008; Marks et al. 2006). More research is needed to understand the role of these regulatory mechanisms.

11.3 Beta-Endorphin

The production of an opioid peptide, β-endorphin, from the POMC gene adds complexity to this neuronal system. In all chordates, POMC encodes a core melanocortin sequence and a core opioid sequence for β-endorphin. β-endorphin$_{1–31}$ is the sole opioid sequence encoded in the POMC gene in humans and rodents, although some ancient species process it into smaller opioids (Takahashi et al. 1995, 2001, 2006; Shoureshi et al. 2007). Further cleavage of β-endorphin$_{1–31}$ by PC2 and CPE to form β-endorphin$_{1–27}$ and β-endorphin$_{1–26}$ abolishes its ability to bind to opioid receptors. This effect shifts the balance in favor of MSH-related actions (Wardlaw 2011).

In many, but not all cases, melanocortins and endorphins produce opposing physiological and behavioral effects that ensure a coordinated and balanced response to changing environmental demands and stressors (Table 11.1, modified from (Bertolini and Ferrari 1982)). The result is a form of functional reciprocity. For instance, melanocortins upregulate attention and pain sensitivity, promoting arousal and adaptation to external challenges, while simultaneous release of opioids favor de-arousal and shifting to self-directed behavior (Bertolini and Ferrari 1982; De Wied and Jolles 1982; Sandman and Kastin 1981).

The primordial role of opioids is the control of protective reactions. Even in protozoa, opiate

Table 11.1 A comparison of the effects of opioids and melanocortins

	Function	Melanocortins	Opioids
HPA and stress response	Physiological stress response	↑ ACTH, cortisone/corticosterone	↓ CRH release ↓ Development of stress adaptation ↑ Suppression of HPA axis Anti-stress via kappa receptor pathway
	Shock Hypotensive, hypovolemia	↓	↑
	Stress-induced anxious/ depressive behavior	↑ Via MC4R MC4R KO and antagonists = reduced anxiety/ depression behaviors	↓ Attenuates anxious behaviors Reduced hypercorticosterone response
CNS actions	CNS activity Neuronal firing Adenylate cyclase/ cAMP Ca2+ uptake at synapse	↑	↓
	Neurotransmitter release Norepinephrine (stress) Dopamine (behavior) Acetylcholine (immunity)	↑	↓
	Neurotransmitter turnover Serotonin (behavior-depression anxiety)	↓	↑
	POMC neurons	↓ Autoinhibition via MC3R Inhibition via MC3R/AgRP/NPY pathway	↓/↑ ↓ At high concentration Presynaptic via low sensitivity receptor on POMC neurons ↑ At low concentration Via disinhibition Postsynaptic via high sensitivity receptor near GABA synapses
	Glial expression	Express MCRs	N/A
Pain	Pain threshold	↓ Increase hypersensitivity Antagonize opioid-induced analgesia Reduce opioid tolerance *MC4R antagonism synergizes with opioid pain reduction	↑

(continued)

Table 11.1 (continued)

	Function	Melanocortins	Opioids
Immunity and inflammation	Inflammation (general)	↓ Anti-inflammatory Immune suppressive Central immune modulation (via vagus nerve-cholinergic AND glucocorticoid release) Neuroprotective	↓ Anti-inflammatory Immune suppressive
	Temperature regulation	↓ Antipyretic	↑
	Neuroinflammation	↓ Neuroinflammation ↓ Excitotoxicity	N/A
	Neuroprotection	↑ Via Oligodendrocyte development Activate astrocyte-/microglia-mediated protection	N/A
	Immune cell expression	MCR expressed on: Macrophages, B and T lymphocytes	N/A
Behavior	Arousal	↑	↓
	Attention	↑	↓
	Motivation	↑	↓
	Learning/memory	↑	↓
	Yawning/stretching	↑	↓
	Grooming	↑ Induces all components	↑ Increase/instigate duration Prolong sensitivity of grooming

ligands suppress a protective contractile response and reduce growth and motility (Dyakonova 2001; Zagon and Mclaughlin 1992), although the receptors responsible for such actions are unclear (Lesouhaitier et al. 2009; Stefano and Kream 2008). In invertebrates like mollusks and arthropods, many functions of opioids (e.g., stress-induced analgesia, deactivating immune responses, and regulation of feeding, mating, and social behavior) resemble those in vertebrate species (Dyakonova 2001). A single ancestral opioid receptor duplicated itself twice early in vertebrate evolution to create the four known opioid receptor types (Sundstrom et al. 2010; Larhammar et al. 2009). The addition of an opioid sequence to the POMC gene likely occurred around this time (Duvaux-Miret and Capron 1992; Salzet et al. 1997; Stefano et al. 1999).

Opioid receptors are found throughout the central and peripheral nervous system and the immune system (Stein and Machelska 2011; Zollner and Stein 2007). These receptors use the Gi/o signaling cascade; so, like AgRP and in opposition to melanocortins, opioid receptors inhibit adenylate cyclase activity and lower cAMP levels (Collier 1980; Tao 2010; Rene et al. 1998). β-endorphin binds to mu (μ), delta (δ), and kappa (κ) opioid receptors, with highest affinity for mu and δ types (Katritch et al. 2013; Cox 2013). Opioids may interact with ion channels as well (Luscher and Slesinger 2010; Tedford and Zamponi 2006).

β-endorphin regulates POMC neuronal activity and gene transcription through a complex feedback mechanism. Hyperpolarization of POMC neurons occurs when hypothalamic explants are treated with opioid agonists (Kelly et al. 1990), while antagonists increase secretion of both β-endorphin and γ-MSH (Jaffe et al. 1994; Nikolarakis et al. 1987). By binding to the

μ-opioid receptors they express, β-endorphin inhibits POMC activity and gene expression (Kelly et al. 1990; Zheng et al. 2005b; Markowitz et al. 1992; Pennock and Hentges 2011). This mechanism serves as a form of autoinhibition of POMC neurons (Bouret et al. 1999). In addition, opioid receptors exist on the numerous GABAergic terminals that synapse onto POMC neurons. The sensitivity to opioids is much greater at the presynaptic μ-opioid receptors than the postsynaptic μ-opioid receptors (Pennock and Hentges 2011). So, at low concentrations, β-endorphin may inhibit the presynaptic release of GABA, disinhibiting POMC neurons (Pennock and Hentges 2011, 2016). The interplay between these mechanisms likely provides fine-tuning of melanocortin and endorphin release by POMC neurons.

Optogenetic experiments suggest that the differential release of β-endorphin and α-MSH may be key to POMC neuronal actions (Yang et al. 2011; Aponte et al. 2011). Under default conditions, AgRP inhibits POMC neuron activity to promote feeding in mice. However, if leptin release by adipocytes rises in response to a long-term energy surplus, POMC neurons release β-endorphin, shutting off this inhibitory circuit. At the same time, activation of POMC neurons reduces food intake in an MCR-dependent manner. So, by simultaneously releasing melanopeptides and opioid peptides in variable ratios, the POMC system may respond to physiological or external changes with a variety of tailored responses.

Several mechanisms may underlie this differential release. Differential enzymatic inactivation of α-MSH or β-endorphin can modify the action of POMC products (Dutia et al. 2012). The enzymes which process POMC products can alter the ratio of various forms of β-endorphin and melanocortins in response to different neuronal, hormonal, environmental, and pharmacological stimuli (Wilkinson and Dorsa 1986; Cangemi et al. 1995; Young et al. 1993). Also, because POMC is posttranslationally processed to ACTH and MSH peptides in secretory vesicles, packaging of POMC in secretory granules controls the extent of POMC cleavage. Alternative methods of sorting POMC products may produce heterogeneity in secretory granule content (Pritchard and White 2007). As hinted at by earlier work (Perello et al. 2007, 2008; Petervari et al. 2011; Mercer et al. 2014), Koch and colleagues recently used electron microscopy to show that β-endorphin and α-MSH exist in separate vesicles within individual neurons of the PVH (Koch et al. 2015). In a third of POMC synaptic boutons in the PVH, β-endorphin and α-MSH did not overlap. The authors also identified hypothalamic UCP2 as being crucial for the switch from α-MSH to β-endorphin release triggered by endocannabinoids. As we shall see, the flexibility inherent in the ability of POMC neurons to release either a melanocortin or an opioid has large repercussions for the CNS response to stress.

11.4 The Stress Response: Overview

Stress is the experience of coping with a physical or emotional threat. Common physical stressors include visceral or somatic pain, hemorrhage, respiratory distress, and inflammation from illness or injury. Psychological or emotional stress may result from circumstances the individual perceives as negative or threatening, such as interpersonal conflict or financial problems. Afferent sensory information from peripheral receptors alert the CNS to physical stressors. Forebrain limbic structures like the prefrontal cortex (PFC), hippocampus, and amygdala receive input about psychogenic and emotional stressors (Ulrich-Lai and Herman 2009; Ulrich-Lai and Ryan 2014). The physical and psychological signals of the brain stem and limbic system converge at the paraventricular nucleus of the hypothalamus (PVH). Here, they integrate to engage effector mechanisms to regulate the body's physiological response (Ulrich-Lai and Herman 2009).

Two systems regulate the stress response. First, the sympathetic nervous system (SNS) releases the catecholamines epinephrine and norepinephrine. Activation of the SNS during

acute stress elicits a rapid physiological response by two mechanisms: direct innervation of peripheral organs and the systemic release of catecholamines by the adrenal medulla (Ulrich-Lai and Herman 2009; Ulrich-Lai and Engeland 2002). This system mobilizes energetic stores of both glucose and free fatty acids, increases blood pressure and heart rate, and downregulates physiological processes unnecessary in the short term, such as digestion and reproduction (Bartness and Song 2007; Yamaguchi 1992). Therefore, the sympathetic "fight or flight" system (countered by the parasympathetic "rest and digest" system) allows fast modulation of energy allocation to respond to an immediate threat to survival.

The second system regulating the stress response, the hypothalamic-pituitary-adrenal (HPA) axis, releases glucocorticoids such as cortisol. Activation of the HPA axis yields a slower, sustained, and amplified physiological response to acute stress. The HPA axis becomes activated when stress-related internal and external sensory input converges on corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus (PVH) (Dent et al. 2000; Ma et al. 1997). CRH stimulates synthesis and release of melanocortin peptides by the anterior pituitary, specifically adrenocorticotropic hormone (ACTH) from corticotrophs and MSH from melanotrophs (Gagner and Drouin 1985; Gagner and Drouin 1987; Eberwine et al. 1987). ACTH, produced from POMC, then stimulates the adrenal cortex to produce glucocorticoids (cortisol in humans or corticosterone in rodents). Once released, glucocorticoids mediate many systemic and neurological effects. Transcription of the POMC gene in corticotrophs undergoes feedback repression by glucocorticoids via the glucocorticoid receptors (GR) (Gagner and Drouin 1985). This negative feedback loop is essential for the HPA axis to maintain homeostasis. During long-term stress, however, the HPA axis can become chronically activated (Ulrich-Lai and Herman 2009; Ulrich-Lai and Ryan 2014).

CRH also has other mechanisms to trigger a stress response. It influences the sympathetic stress response by acting on the locus ceruleus, adrenal medulla, and the peripheral SNS (Valentino et al. 1993; Brown et al. 1982). In addition, CRH directly affects behavioral states of anxiety (Bale and Vale 2004; Reul and Holsboer 2002). Many brain areas involved in stress perception and response express CRH, including the amygdala (Roozendaal et al. 2002; Gallagher et al. 2008; Regev et al. 2012), hippocampus (Lee et al. 1993; Chen et al. 2001, 2013; Refojo et al. 2011), inferior olive (Chang et al. 1996), locus ceruleus (Valentino and Van Bockstaele 2008), bed nucleus of the stria terminalis (Dabrowska et al. 2011), and the cortex (De Souza et al. 1986; Behan et al. 1995; Gallopin et al. 2006). Central overexpression of CRH induces an anxious behavioral phenotype in rodents (Dunn and Berridge 1990; Dautzenberg et al. 2004; van Gaalen et al. 2002), while suppressing CRH expression has anxiolytic effects under both stressed and unstressed conditions (Skutella et al. 1994a, b). CRH can also suppress GnRH release (Sirinathsinghji 1987; Traslavina and Franci 2012), sleep (Romanowski et al. 2010), and appetite (Glowa et al. 1992).

The evolution of CRH in chordate ancestors played an essential role in the success of vertebrates and ultimately mammals and humans (Endsin et al. 2017) by permitting a robust stress response. In fish, hypothalamic CRH released during stress triggers pituitary ACTH release, which stimulates the interrenal tissue to secrete glucocorticoids. The pituitary-interrenal axis is also responsible for other biological processes such as metabolism of carbohydrates, amino acids, and free fatty acids; mineral balance; immune function; and growth (Wendelaar Bonga 1997). The multiple roles for glucocorticoids in this distant relative highlight the relationship between energy use and the stress response. The stress axis seems to have diverged from the reproductive axis around the time of the evolution of jawless fish, the most ancient of vertebrates; in the lamprey, GnRH and CRH cause release of 11-deoxycortisol, a putative stress steroid (Roberts et al. 2014). Likewise, GRs diverged from estrogen receptors (Thornton 2001). So, the

trade-off between stressor survival and fertility predates and shaped the development of mammalian systems.

Once the HPA axis is activated, glucocorticoids levels rise. Glucocorticoids raise blood glucose levels to meet elevated energy needs under stressful conditions. To do this, glucocorticoids promote gluconeogenesis by increasing protein catabolism and lipolysis while decreasing glucose use and insulin sensitivity of adipose tissue. At the same time, they suppress the immune system and aid metabolism of macronutrients. They increase blood pressure by promoting the sensitivity of the vasculature to epinephrine and norepinephrine (Smart et al. 2007; Pavlov and Tracey 2006). Glucocorticoids also impair liver sensitivity to growth hormone, leading to low levels of circulating insulin-like growth factor 1 (IGF-1), which may cause a decrease in neural plasticity (Mechanick et al. 1992), hippocampal learning (Lutter and Nestler 2009), neuroprotection, and neuronal replacement (Lutter and Nestler 2009; Fletcher and Kim 2017).

Glucocorticoids also have a direct impact on the brain and spinal cord. Glucocorticoids cross the blood-brain barrier and bind to glucocorticoid (GR) and mineralocorticoid receptors (MR) on both neurons and glial cells. In the brain, MRs show high affinity for glucocorticoids (de Kloet and Sarabdjitsingh 2008; De Kloet et al. 1998). Therefore, they may sense basal glucocorticoid levels and mediate physiological responses to low glucocorticoid levels (de Kloet et al. 2005). In contrast, GR remains unbound at low glucocorticoid levels due to its lower binding affinity; it therefore mediates responses to elevated levels of glucocorticoids (de Kloet et al. 2005; Reul and Dekloet 1985). The expression patterns of these receptors reflect their roles. GR is abundantly expressed throughout the brain, including in key sites for stress regulation like the medial prefrontal cortex (mPFC), hippocampus, amygdala, BNST, hypothalamus, and the hindbrain (Reul and Dekloet 1986; Meaney et al. 1985; Fuxe et al. 1987)). MR expression, in contrast, is more limited. Interestingly, MR and GR co-localize in several areas important to the behavioral response to stress, including the hippocampus, amygdala, and the mPFC (Reul and Dekloet 1985; Dekloet and Reul 1987).

Alterations of the HPA axis are associated with anxiety (Pego et al. 2010). The chronic actions of glucocorticoids in the mPFC increase the use of habitual strategies over goal-oriented decision-making (Dias-Ferreira et al. 2009). This reversion to habitual strategies during chronic stress may improve efficiency in predictable tasks by creating an instinctual response instead of wasting resources on the appraisal process (Dias-Ferreira et al. 2009; Schwabe et al. 2013). The amygdala underlies anxiety and fear responses (Davis et al. 2010; LeDoux 2012). When administered to the central amygdala, glucocorticoids enhance anxious behavior in rodents (Shepard et al. 2000). Application of GR and MR antagonists to the central amygdala abolishes this behavior (Myers and Greenwood-Van Meerveld 2007).

By acting on the hippocampus and amygdala, glucocorticoids enhance memory consolidation but impair working memory (Barsegyan et al. 2010; Roozendaal et al. 2004; Mizoguchi et al. 2000). In the hippocampus, glucocorticoids help form emotionally powerful short-term memories (de Kloet et al. 1999; Smeets et al. 2009) but cause memory retrieval disruption for already assimilated items (Roozendaal 2002). Chronic stress conditions weaken performance on hippocampal-dependent tasks (Conrad et al. 1996; Kleen et al. 2006) and cause spatial reference memory deficits (Oliveira et al. 2013). Glucocorticoids acting in the basolateral amygdalar complex (BLA) affect the learning and memory of aversive stimuli (Roozendaal et al. 1996). They also alter the reconsolidation of auditory fear-based conditioning and memory consolidation (Jin et al. 2007). These mechanisms allow consolidation of emotionally prominent events while diminishing input from competing information.

Glucocorticoids also have direct actions on neuroendocrine functions of the hypothalamus, including mimicking the negative feedback effects of sex hormones. They inhibit GnRH release and may, as a result, impair fertility and

delay the onset of puberty during chronic stress (Calogero et al. 1999; Gore et al. 2006). In addition, high glucocorticoid levels directly impede male sexual behavior (Rivier and Vale 1984; Pednekar et al. 1993; Retana-Marquez et al. 2009). Glucocorticoids also suppress the secretion of other hypothalamic hormones, such as thyrotropin-releasing hormone (TRH) (Brabant et al. 1987), leading to decreased metabolic demands during stress and contributing to weight gain.

While excess glucocorticoids are harmful, levels that are too low also lead to physiological dysfunction (de Kloet et al. 1999; Herman 2013; Myers et al. 2014). The psychological and physiological adaptations induced by glucocorticoids allow an organism to survive and regain normal equilibrium. Specifically, when energy availability is low, restriction of growth, reproduction, immune processes, and other vegetative functions become the "biological cost" of adapting to the stressor (Moberg 2000). Whether these trade-offs prove to be helpful or damaging depends on the organism's environmental context and on how long they last (Sinha 2008; McEwen 2007).

11.5 Melanocortins and the Physiologic Stress Response

A unifying function underlying the actions of the melanocortin system and its doppelgänger, the opioid system, is to produce a suitable response to acute stress. Melanocortins promote pain sensing, the energy releasing powers of glucocorticoids, and anxious behavior while inhibiting inflammation so that the individual can combat a threat to survival. These functions complement those of the ACTH-CORT endocrine axis from which the melanocortin system evolved. The role that POMC products play in this aspect of the stress response is under-recognized.

Three main stages to the stress response have been identified: alarm, resistance, and compensation (Schreck 2000). To handle a stressor effectively, the threat must first be perceived. This alarm stage involves the induction of the secretion of glucocorticoids and catecholamines to make energy available for resistance strategies, such as fighting or flight. During the resistance stage, the organism rations energy and attention in such a way that disease resistance, reproduction, growth, learning, and other functions are impaired. Compensation or recovery consists of adaptive changes to restore homeostasis and physiological equilibrium.

Under conditions of stress, ARC POMC neurons show rapid activation. For example, acute restraint and forced-swim treatments in rodents cause increased activity of ARC POMC neurons projecting to the PVH (Liu et al. 2007). In addition, rats subjected to foot shock showed increased POMC mRNA in the hypothalamus, increased CRH mRNA in the amygdala, and increased MC4R mRNA in both locations (Yamano et al. 2004). Another study found that psychological stress increases expression of MC4R mRNA in the ARC of rats in a glucocorticoid-independent manner (Ryan et al. 2014). Intracerebroventricular (ICV) injection of an MC4R agonist produces a dose-dependent increase in renal and lumbar sympathetic nerve activity, which is reversed by an MC3R/MC4R antagonist (Haynes et al. 1999). This SNS activation exacerbates the response to stress; sympathetic innervation of the adrenal cortex enhances sensitivity to ACTH, which promotes glucocorticoid secretion (Engeland and Arnhold 2005; Edwards and Jones 1993).

Tonic suppression by neuronal POMC peptides keeps CRH levels within physiological limits. In the hypothalamus, the ARC POMC neuron population has abundant synaptic projections to PVH CRH neurons (Lu et al. 2003), many of which express MC4R (Lu et al. 2003; Dhillo et al. 2002; Sarkar et al. 2002). A chronic reduction or absence of hypothalamic POMC leads to elevated CRH specifically in the PVH, elevated basal but attenuated stress-induced ACTH secretion, and elevated basal plasma corticosterone (Smart et al. 2007). Whether suppression of CRH levels by POMC peptides occurs via direct actions in the PVH remains to be determined.

Some evidence suggests β-endorphin suppresses CRH levels in vivo as well (Plotsky 1986), but selective loss of β-endorphin beginning during development does not alter CRH mRNA or glucocorticoid levels (Smart et al. 2007; Rubinstein et al. 1996).

α-MSH release by POMC neurons may also act via the MC4R to augment CRH release during a psychological or physiological challenge. Short-term ICV infusion of α-MSH can increase CRH expression, ACTH, and corticosterone levels after a stressful event (Lu et al. 2003; Dhillo et al. 2002; Kas et al. 2005). Loss of MC4R signaling prevents stress-induced activation of neurons in the PVH and MeA and lowers ACTH and corticosterone release (Ryan et al. 2014; Karami Kheirabad et al. 2015). Pharmacological stimulation of MC4R in the PVH also increases CRH mRNA expression, circulating ACTH, and corticosterone (Lu et al. 2003; Dhillo et al. 2002). In contrast, the MC3R influences the response of the HPA axis to fasting but no other stressors (Renquist et al. 2012).

Glucocorticoids, the final products of HPA axis activation, regulate the HPA axis through negative feedback. They suppress ACTH release at the level of the pituitary and CRH synthesis and release in the PVH (Lim et al. 2000). ACTH may also exert a regional form of feedback control of the HPA axis. ACTH suppresses CRH expression in the medial amygdala and hippocampus, but these effects are not seen in the hypothalamus (Brunson et al. 2001; Wang et al. 2012).

Glucocorticoids appear to exert feedback control of the melanocortin system in a similarly region-specific manner (Beaulieu et al. 1988; Wardlaw et al. 1998). Glucocorticoids downregulate POMC gene expression in the pituitary (Pritchard et al. 2002; Krude and Gruters 2000). While most POMC neurons in the ARC also contain GR, glucocorticoids seem to upregulate POMC gene expression in the hypothalamus of rats. ARC POMC gene expression falls after adrenalectomy and returns to normal after replacing glucocorticoids at physiological concentrations (Wardlaw et al. 1998; Pelletier 1993). The number of inhibitory synaptic inputs onto POMC neuron cell bodies also fell in adrenalectomized animals; replacement of corticosterone reversed this effect (Gyengesi et al. 2010). These mechanisms allow regulation of the melanocortin response to stress.

These studies show that melanocortins have powerful and integrative effects on both systems that mediate classic stress responses, the SAM system and the HPA axis. However, stressors often involve pain, immune reactions, and psychological challenges; melanocortins have a foundational role reestablishing homeostatic balance in each of these situations as well.

11.6 Melanocortins and Immune Function

Illness is a classic condition of physiological stress. As described below, the melanocortin system acts to inhibit inflammatory processes both centrally and peripherally. In addition, it combats fever and the cardiovascular processes related to shock. These functions play an essential role in appropriately calibrating the physiological response to illness. Indeed, melanocortin agonists are an underexploited anti-inflammatory therapy that holds great promise for treatment of immune disorders (Montero-Melendez 2015).

The systemic effects of melanocortins include direct action by circulating or local melanocortins on their receptors. The MC1R has an anti-inflammatory role in a wide variety of immune cells (Catania et al. 2004, 2010). In addition, the MC5R plays a role in lymphocyte modulation, specifically the activation of regulatory T-cell lymphocytes in ocular immunity (Taylor and Lee 2010; Taylor et al. 2006) and B-lymphocyte immunomodulation (Buggy 1998). In adipocytes, the MC5R stimulates cytokine secretion (Jun et al. 2010).

The central melanocortin system also has suppressive effects on the systemic immune response. ICV α-MSH inhibits transcription factor nuclear factor kappa B (NF-κB) activation at peripheral inflammatory sites (Ceriani et al. 1994; Ichiyama et al. 1999a; Lipton et al. 1991). By directly sensing cytokines at the circumven-

tricular organs, highly vascularized areas of the brain with a leaky blood-brain barrier, the CNS can detect peripheral inflammation. The ARC, NTS, and dorsal motor nucleus of the vagus (DMX) are near circumventricular organs. Acute inflammation such as that caused by bacterial lipopolysaccharide (LPS) activates TNF-α, IL-1β, and IL-6 and induces Pomc expression (Kariagina et al. 2004). Under these conditions, NF-κB activation directly promotes Pomc transcription independent of STAT3 activation (Shi et al. 2013). (Chronic inflammatory conditions, however, can impair the direct activation of Pomc promoter (Shi et al. 2013).) The CNS also receives information on the systemic inflammatory status via ascending sensory pathways from affected tissues through the vagus nerve and pain afferent fibers (Goehler et al. 1997, 2000; Watkins et al. 1995). By promoting glucocorticoid release in response to sensory input, the melanocortin system suppresses immune responses in the periphery (Besedovsky et al. 1986; Hu et al. 1991).

If augmented pharmacologically, the anti-inflammatory effects of α-MSH can counter the life-threatening vasodilatory actions of endogenous opioids and histamine that are massively released during shock (Bernton et al. 1985; Carmignani et al. 2005; Chernow et al. 1986; Elam et al. 1984; Schadt 1989; Guarini et al. 1997, 2004; Bertolini et al. 1986a, 1986b; Giuliani et al. 2007; Bitto et al. 2011). Melanocortins can reverse this immune response by acting on parasympathetic preganglionic neurons of the DMV that produce acetylcholine and express MC4Rs (Catania et al. 2004; Sohn et al. 2013). These neurons form part of the efferent arm of the cholinergic anti-inflammatory pathway (Guarini et al. 1989; Bertolini et al. 2009). The vagus nerve can induce rapid release of acetylcholine to inhibit pro-inflammatory cytokine release from macrophages in target organs (especially in the liver, spleen, gastrointestinal tract, and heart) (Guarini et al. 2004; Pavlov and Tracey 2006; Tracey 2002, 2007). The release of anti-inflammatory cytokines is unaffected (Borovikova et al. 2000). Bilateral injury or dissection of the vagus nerve or inhibition of primary afferent nociceptive nerve fibers compromises the ability of melanocortins to inhibit harmful and unnecessary inflammatory responses to hypoxic conditions, such as during hemorrhagic shock (Bertolini et al. 1989, 2009).

Melanocortins also combat fever and have a broad, suppressive effect on body temperature. ICV α-MSH inhibits systemic inflammatory reactions, including fever (Delgado Hernandez et al. 1999; Murphy et al. 1983). Melanocortins reduce body temperature acutely (reaching a nadir at 40 minutes) through several mechanisms, including reducing brown adipose tissue thermogenesis, lessening vasodilation, promoting active seeking of a cool environment, reducing physical activity, and suppressing compensatory shivering (Lute et al. 2014).

Melanocortins also induce stretching and yawning (Wessells et al. 2000, 2003; Vergoni et al. 1998), which we suggest are part of this program of body temperature reduction. Strong evidence from humans and other warm-blooded animals shows that both stretching and yawning are part of a coordinated physiological program to alter brain and body temperature (Gallup and Eldakar 2013; Eguibar et al. 2017). When body temperature is both excessive and higher than air temperature, yawning and stretching increase to allow increased airflow within the mouth and around the limbs to cool circulating blood. Co-injection of an MC4R antagonist inhibits yawning produced by microinjection of ACTH into the PVH (Argiolas et al. 2000), although other target areas may also be involved (Argiolas et al. 1987). In contrast, opioids suppress yawning and stretching; for example, β-endorphin inhibits ACTH-induced yawning (Fratta et al. 1981; Vergoni et al. 1989; Himmelsbach 1939; Seevers 1936; Zharkovsky et al. 1993). ACTH- and α-MSH-induced yawning correspond to an increase in the turnover rate of acetylcholine in the hippocampus; central cholinergic antagonists impede yawns (Ferrari et al. 1963; Fujikawa et al. 1995; Wood et al. 1978). The circuit underlying these behaviors may include α-MSH-activated neurons in the PVH that project to medial septum cholinergic neurons that, in turn, project to the hippocampus (Collins and Eguibar 2010).

Melanocortins may have direct anti-inflammatory and neuroprotective actions within the brain. For example, in a traumatic brain injury mouse model, a single application of α-MSH (Hummel and Zuhlke 1994; Ottaviani et al. 1997; Tsatmali et al. 2000) reduced inflammation, apoptosis, and brain damage (Schaible et al. 2013). Similarly, MC4R activation had anti-apoptotic effects during cerebral ischemia (Giuliani et al. 2006) and in the hippocampus where excitotoxicity induced neuronal cell death (Forslin Aronsson et al. 2007).

Evidence suggests that these neuroprotective effects may result from melanocortin actions in glial cells. Multiple types of glial cells show MCR expression. Human microglia express MCRs (MC1R, MC3R, MC4R, and MC5R) (Lindberg et al. 2005). Melanocortins can directly suppress the activation of nuclear factor kappa B (NF-κB), tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS) expression in activated microglia (Catania et al. 2004; Delgado et al. 1998; Galimberti et al. 1999). Oligodendrocytes, the CNS glial cells responsible for myelination, also express MC4R (Arnason et al. 2013; Selkirk et al. 2007; Lisak et al. 2016; Benjamins et al. 2014). $ACTH_{1–39}$ increases proliferation, differentiation, and maturation of oligodendrocyte progenitor cells. It also reduces apoptosis in both progenitor and mature oligodendrocytes. At the same time, $ACTH_{1–39}$ protects against excitotoxicity and inflammation (Lisak et al. 2016; Benjamins et al. 2014). In multiple sclerosis, $ACTH_{1–39}$ has been used clinically to treat immune system-induced myelin damage. Finally, astrocytes express MC4Rs (but not MC3Rs) in rats (Selkirk et al. 2007; Caruso et al. 2007). In reaction to hypoxia or other stressors, reactive astrocytes produce nitric oxide (NO) and pro-inflammatory cytokines and chemokines (Dong and Benveniste 2001). MC4R activation blocks apoptosis of astrocytes (Giuliani et al. 2006), reduces their secretion of NO and prostaglandin G2 (PEG2), and inhibits their expression of iNOS and COX-2 (Giuliani et al. 2006; Caruso et al. 2007). Although not involved in anti-inflammatory responses of α-MSH, the MC1R is expressed in astrocytes as well (Ichiyama et al. 1999b). The activation of astrocytes plays a role in the pathology of many neurodegenerative conditions, so controlling astrocyte activation through melanocortin receptor activation may be an effective avenue for decreasing the severity of such diseases.

11.7 Melanocortins and Pain Pathways

Pain is a potent stressor. Pain is a noxious sensory or emotional experience caused by actual or potential tissue damage (Leeson et al. 2014). The ability of an organism to sense noxious stimuli is essential for preventing physical injury. Afferent fibers in the spinal cord carry nociceptive signals to higher brain centers through spinothalamic, spinobulbar, spinopontine, and spinomesencephalic tracts (Al-Chaer 2013; Boadas-Vaello et al. 2016). Sensory-discriminative signals mediating pain localization propagate through the dorsal root of the spinal cord to thalamic nuclei and the PAG in the midbrain. The brain stem reticular formation, thalamus, and hypothalamus contribute the affective-motivational components of pain (Ab Aziz and Ahmad 2006). At the level of the thalamus, third-order neurons that receive both sensory and affective information ascend to terminate in the somatosensory cortex.

A diffuse, multisynaptic descending pathway produces analgesia. It originates from higher brain centers, such as the cerebral cortex, hypothalamus, and amygdala, and projects to the PAG. From here, projections synapse at the rostral ventromedial medulla (RVM) and locus ceruleus. They then project down the spinal cord and terminate on the initial pain sensing spinal dorsal root to inhibit incoming signals (Fardin et al. 1984; Pagano et al. 2012; Kerman et al. 2006). This PAG-RVM system plays a key role in pain sensation and modulation. These pathways use predominantly catecholaminergic, serotonergic, and opioid systems. The PAG was the first brain area where activation of an endogenous pain inhibition system was described; electrical stimulation and opioid injections into

the PAG produce analgesia, which is reversible by application of naloxone (Reynolds 1969; Hosobuchi et al. 1977; Lewis and Gebhart 1977). The RVM is the final common relay point in the modulation of the descending pain pathway. It can both enhance and lessen pain (Heinricher et al. 2009).

The melanocortin system can modulate pain sensitivity. For example, MC4R signaling amplifies neuropathic pain in rats (Vrinten et al. 2001; Nijenhuis et al. 2003). MC4R expression is extensive throughout both ascending and descending nociceptive circuits. As well as being found in primary afferent neurons, MC4Rs are located in the reticular formation, somatosensory and motor cortex, PAG, RVM, and dorsal horn of the spinal cord (Kishi et al. 2003; Gautron et al. 2012; Ye et al. 2014). The MC4R-positive neurons of the RVM are 10% catecholaminergic and 50–75% serotonergic, suggesting that MC4R signaling modulates nociceptive serotonergic sympathetic outflow (Pan et al. 2013).

MCRs share a neuroanatomical distribution pattern with μ-opioid receptors (Arvidsson et al. 1995; Kalyuzhny et al. 1996; Matthes et al. 1996). Anatomically, α-MSH and β-endorphin are both released in response to painful stimuli at the same site (Adan and Gispen 2000). As mentioned before, melanocortins and endorphins generally produce opposing responses in their common targets (Bertolini et al. 1979; Amir and Amit 1979). This effect applies in the modulation of pain through interaction at the level of the brain and spinal cord. For example, ICV injection of α-MSH in rodents induces hypersensitivity to pain, reversing the analgesia produced by endogenous opioids and morphine (Sandman and Kastin 1981; Contreras and Takemori 1984; Kalange et al. 2007). MC4R agonists enhance hypersensitivity in a neuropathic pain model (Starowicz et al. 2002; Vrinten et al. 2000).

Melanocortin antagonists work synergistically with opioids, enhancing the analgesic effect produced by opioid agonists (Kalange et al. 2007; Vrinten et al. 2000; Ercil et al. 2005). For example, the opioid antagonist naloxone lessened the analgesic effects of a melanocortin antagonist administered to the spinal theca in a model of pain hypersensitivity (Vrinten et al. 2000). Also, targeted delivery of an MC4R antagonist to the PAG diminished neuropathic hyperalgesia (Chu et al. 2012), to an even greater extent than morphine (Starowicz et al. 2002; Chu et al. 2012). MC4R and POMC mRNA expression rises in the PAG along with heightened sensitivity in a rat model of neuropathic pain (Chu et al. 2012). Consistent with this, morphine downregulated MC4R mRNA expression in various brain areas, including the PAG, NuA, and striatum, in a time-dependent manner (Alvaro et al. 1996). This response may be, in part, an adaptive mechanism of opioids to cause tolerance and dependency. MC4R antagonists also prevent opioid tolerance when administered to the brain or spinal cord (Kalange et al. 2007; Niu et al. 2012). In morphine-tolerant rats, a single administration of melanocortin antagonists restored the analgesic potency of morphine (Starowicz et al. 2005). If MC4Rs participate in opioid tolerance, they make a logical target for its prevention. Developing pharmacological treatments targeting MCRs may improve pain management by preventing tolerance and dependency.

11.8 Melanocortins and the Behavioral Responses to Stress

Along with increasing sensitivity to pain, the melanocortin system, and particularly MC4R signaling, promotes stress, anxiety, and depression-related behaviors. In mice, chronic social defeat results in social avoidance associated with reduced expression of POMC in the hypothalamus (Chuang et al. 2010). Administration of an MC3R/MC4R agonist increased this avoidance. Conversely, MC4R-null mice showed less anxiety and depression and more social behaviors (Chuang et al. 2010). Similarly, the ICV administration of a selective MC4R antagonist to rats before stressful restraint reduces depressive behavior (Goyal et al. 2006; Chaki and Okubo 2007) and stress-elicited anorexia (Chaki et al. 2003; Vergoni et al. 1999a). An intranasal MC4R antagonist,

HS014, also prevented anxious and depressive behavior in rats (Serova et al. 2013). Further, the intranasal MC4R agonist, HS014, led to improved resilience in rats after traumatic stress (Serova et al. 2013). These behavioral responses involve the medial amygdala (MeA), which receives ARC POMC projections and expresses high levels of MC4R. Acute restraint activates MC4R-expressing neurons in the MeA in rats as shown by c-fos induction (Liu et al. 2013). Pharmacological stimulation of MC4Rs in the MeA before restraint stress test induced anxiety-associated behaviors, increased plasma corticosterone, and reduced food intake. Conversely, MC4R loss or inhibition abolished these stress-induced responses (Ryan et al. 2014; Liu et al. 2013). Taken together, these data show that MC4R signaling in a POMC-MeA circuit strongly regulates behavioral responses to stress in rodents. Strategies targeting this melanocortin pathway could therefore lead to treatments in humans suffering from post-traumatic stress disorders.

Another behavior altered by stress is grooming. Self-grooming is an essential behavior present in arthropods, birds, and mammals to care for the body surface. In rodents, grooming comprises a highly stereotyped sequence of behaviors. It begins with licking the paws, then head, body, legs, genitals, and tail, interrupted occasionally by scratching and whole body shaking (Fentress 1988; Berridge et al. 2005). Humans also exhibit self-grooming behavior (Prokop et al. 2014; Cohen-Mansfield and Jensen 2007). While the brain stem initiates self-grooming movements and regulates the assembly of the sequential patterning in rodents, control of its sequencing requires the basal ganglia, particularly dopaminergic inputs to the striatum (Kalueff et al. 2016). However, in times of stress, grooming can occur at inappropriate times or with inappropriate intensity. The amygdala and other limbic regions modulate this context-specific behavior (Kalueff et al. 2016; Hong et al. 2014; Roeling et al. 1993). In rats, stressful conditions result in an excessive, aberrant form of grooming that damages the fur (Adan et al. 1999; Mul et al. 2012; Willemse et al. 1994). Under these conditions, grooming loses its precise temporal patterning (Kalueff and Tuohimaa 2004, 2005). Aberrant rodent self-grooming resembles human disorders with abnormal self-grooming and other compulsive or stereotyped behaviors that do not require sensory feedback (Kalueff et al. 2007).

In dogs, rabbits, cats, rats, mice, and monkeys, central or cerebrospinal administration of melanocortins (or CRH) potently induces behavior similar to spontaneous grooming (Vergoni et al. 1998; Argiolas et al. 2000; Ferrari et al. 1955, 1963; Ferrari 1958; Gessa et al. 1967; Aloyo et al. 1983; Spruijt et al. 1985; Gispen et al. 1975; Dunn 1988; Dunn et al. 1987). The MC4R mediates this induced and spontaneous grooming behavior (Nijenhuis et al. 2003; Adan et al. 1994, 1999); for example, melanocortin peptides did not elicit any grooming response in rats deficient for MC4R (Mul et al. 2012). Additionally, administration of an MC4R antagonist reverses excessive grooming behavior (Adan et al. 1999).

Connections between the hypothalamus, amygdala, and mesolimbic reward system may allow melanocortins to alter stress-related grooming and its patterning (Hong et al. 2014; Roeling et al. 1993; Kruk et al. 1998; Homberg et al. 2002). It is known that dopaminergic cell bodies in the VTA receive input from GABAergic neurons, and ACh input can modulate their activity. A key study showed that α-MSH administration stimulates cholinergic neurons in the VTA to cause excessive grooming. When a GABA antagonist was injected before α-MSH, excessive grooming behavior increased (De Barioglio et al. 1991), suggesting the presynaptic actions of GABA can promote these melanocortin effects (Sanchez et al. 2001; Debarioglio et al. 1991). Thus, melanocortins can promote anxiety and stress-related behaviors including disordered self-care.

Interestingly, opioids also promote grooming and lead to excessive and obsessive grooming (Willemse et al. 1994; Ayhan and Randrup 1973). In addition, opioids like β-endorphin extend grooming bouts and prolong sensitivity to the grooming-inducing effects of melanocortins (Jolles et al. 1978). α-MSH has no affinity for

opiate receptors (Terenius et al. 1975); however, naloxone, a high-affinity μ-opioid antagonist, can still block α-MSH-induced grooming (Aloyo et al. 1983; Walker et al. 1982; van Wimersma Greidanus et al. 1986), suggesting α-MSH and β-endorphin target similar neural circuits. Additional research is needed to understand the interaction of melanocortins and opioids in grooming circuits. At a conceptual level, since opioids ease the ability to cope with stress, grooming may also act as a coping mechanism through which the organism lessens arousal.

11.9 Stress and Body Weight Regulation

Melanocortins are intimately involved in the effects of stress on body weight. Three mechanisms underlie this influence. First, stressors induce a sympathetic and HPA axis stress response, in which, as we have seen, melanocortins play an integral role. Second, food stress interacts with hypothalamic circuits that include POMC neurons regulating caloric intake and expenditure. Finally, physical and psychological stressors act on mesolimbic dopaminergic pathways that express melanocortin receptors to influence hedonic feeding (Lutter and Nestler 2009). During acute stress, these mechanisms allow melanocortins to suppress feeding and promote energy expenditure. However, chronic stress can oppose and undermine these actions. In addition to these topics, two situations deserve special attention: the stress of food scarcity and the stress of obesity itself. Finally, we will discuss recent progress in investigating how sensitivity to melanocortins and their downstream effectors can be restored when adaptive responses have failed.

11.9.1 Food Insecurity and Obesity

Since most threats are difficult to anticipate, complex organisms must have a set of responses that will be appropriate for any attack, injury, or illness an animal is facing. As we have seen, melanocortins play a key role in coordinating the body's perception of and response to acute stress by releasing stored energy, increasing pain sensitivity, increasing anxious behavior, and preventing the diversion of resources for inflammation and related recuperative processes. This array of physiological processes does not require the precise nature of the threat to be identified. These reactions are generally useful regardless of the threat, although they may fail to deal adequately with chronic stressors.

Food scarcity, in contrast, is a specific and predictable threat. It might well have been the first stressor encountered by organisms. Coping mechanisms for famine predate the development of the melanocortin system, the HPA axis, and the SNS. These later systems were later incorporated into the overall response for preventing starvation.

An organism accustomed to food insecurity will often take advantage of temporary abundance by maturing and reproducing quickly. When food is scarce, two strategies are available: spending additional energy to find and digest food or suppressing the metabolic rate as much as possible to extend life span. These choices are dramatically demonstrated by the nematode *C. elegans*, where an insulin-like signaling pathway regulates reproduction, life span, and entry into a dormant state (Fletcher and Kim 2017; Ren et al. 1996; Schackwitz et al. 1996). Specifically, insulin, cGMP, and TGF-β pathways signal a favorable environment and encourage continued growth and reproduction (Riddle et al. 1981; Kenyon et al. 1993; Vowels and Thomas 1992; Gottlieb and Ruvkun 1994). When food is limited, young worms assume a nonreproductive form specialized for long-term survival instead of developing to adulthood (Riddle et al. 1981). Thus, insulin acquired an important role in energy allocation and food intake before the development of the neuronal melanocortin system.

In mammals, arcuate POMC neurons and associated circuits play an essential role in the control of food intake (Hill and Faulkner 2017). While stimulation of POMC neurons inhibits feeding behavior, stimulating AgRP/NPY neurons provokes feeding (Aponte et al. 2011;

Zhan et al. 2013; Krashes et al. 2011). The inhibition of POMC or AgRP/NPY neurons can lead to obesity or anorexia, respectively (Yaswen et al. 1999; Gropp et al. 2005; Luquet et al. 2005). Fasting activates NPY/AgRP neurons and suppresses the activity of POMC neurons. MC3Rs may reinforce this pattern of neuronal activity. MC3R knockout mice show no adjustment of circadian corticosterone secretion or orexigenic neuropeptide expression to food restriction (Girardet et al. 2017). When access to food is restricted to a brief window each day, MC3Rs are required for binge feeding, anticipatory activity, and entrainment to nutrient availability (Butler et al. 2017; Begriche et al. 2012; Girardet et al. 2017; Mavrikaki et al. 2016). Thus, while MC3Rs in the CNS have a minor impact on feeding behavior in mice when food is plentiful, they regulate the motivation to feed and possibly the discomfort of hunger during food restriction (Girardet et al. 2017).

Both POMC and AgRP/NPY neurons can sense circulating metabolic factors such as leptin and insulin, thought to allow them to regulate food intake and energy expenditure appropriately (Varela and Horvath 2012). However, the ability of insulin to regulate food intake, energy balance, and glucose homeostasis may depend primarily on its actions in a more ancient set of NPY neurons (only some of which express AgRP) in both rodents and fruit flies (Loh et al. 2017; Konner et al. 2007). If true, insulin sensing by POMC neurons may primarily regulate adipose tissue lipolysis and prevent hepatic fat storage during exposure to high-caloric diets in adult animals (Shin et al. 2017). In addition, insulin signaling in POMC neurons may reinforce the actions of leptin in this neuronal population; both contribute to systemic insulin sensitivity and the browning of white fat (Hill et al. 2010; Dodd et al. 2015). This adjustment can occur prenatally or in early infancy; hyperinsulinemia influences the formation of POMC circuits postnatally, resulting in hyperphagia and an obese phenotype in adulthood (Vogt et al. 2014).

Leptin, in contrast, took on its role in energy balance more recently. *C. elegans* has no apparent leptin ortholog; instead, it may use products of the fat metabolism pathway to regulate feeding behavior (Hyun et al. 2016). Although found in numerous vertebrate species, leptin appears to have evolved its role as an adiposity signal in tetrapods (Cui et al. 2014; Prokop et al. 2012). Mammalian leptin shows particularly high sequence conservation (Doyon et al. 2001), which we suggest is due to the critical nature of fat depot regulation in warm-blooded animals. The development of the arcuate melanocortin system and its ability to sense leptin and insulin no doubt added robustness and precision to the control of body weight and metabolic homeostasis in mammals.

While missing a meal is not an acute threat to a healthy individual, food scarcity or insecurity acts as a psychological stressor. Fasting increases cortisol levels (Nakamura et al. 2016). Placing mice accustomed to high-fat chow on a "diet" of low-fat food induced stress, anxiety, depression, and high motivation to consume both sucrose and fatty food (Sharma et al. 2013; Avena et al. 2008; Cottone et al. 2009). Low food security combined with plentiful high-calorie, energy-dense foods causes weight gain in humans to increase (Wilde and Peterman 2006). Remarkably, just the perception of scarcity in resources can increase the desire for calories and anxious behavior (Briers and Laporte 2013). As a result, many social solutions for addressing food insecurity do not reduce and can even increase obesity (Leroy et al. 2013; Jones and Frongillo 2006; Townsend et al. 2001). These findings suggest increased energy intake among those of low socioeconomic status may be a fundamental response to threats to food security, which persists regardless of the actual food supply (Dhurandhar 2016).

11.9.2 Acute Stress and Body Weight

The stress endocrine axis arose to divert energy from nonessential functions to life-sustaining energy conservation. Coping with an acute stress requires potentially high levels of energy expenditure. Under acute stress brought about by an imminent threat, HPA axis and

sympathetic activation serve to liberate energy into the bloodstream for use by the muscles and cardiovascular system. Thus, glucocorticoid hormones promote gluconeogenesis, lipolysis, and insulin resistance to raise circulating levels of glucose and fatty acids acutely (Ottosson et al. 2000; Bjorntorp 1996). When combined with energy use, these actions result in weight loss.

Behavioral changes accompany these hormonal effects. Attention and effort cannot be expended on restoring energy reserves until the immediate danger has passed and the compensatory stage begins. So, it is not surprising that acute and intense stressors, including illness, inhibit feeding (Krahn et al. 1990; Rybkin et al. 1997). For example, intense emotional stress suppresses appetite in humans and laboratory rodents (Valles et al. 2000; Laurent et al. 2013; De Souza et al. 2000). Anticipatory fear promotes hypophagia and anorexia in otherwise hungry rats. These effects depend on activity in the central amygdala, likely working with the ventromedial prefrontal cortex and lateral hypothalamic area (Land et al. 2014; Mena et al. 2013; Petrovich et al. 2009).

Melanocortins are very important for appetite suppression under stressful conditions. Using double immunolabeling techniques, it has been shown that most POMC neurons in the arcuate nucleus are glucocorticoid receptor positive (Cintra and Bortolotti 1992). Thirty minutes of restraint stress activates ARC POMC neurons and MC4R expressing neurons in the MeA, stimulates the HPA axis, induces anxious behavior, and reduces food intake (Ryan et al. 2014; Liu et al. 2013; Baubet et al. 1994). Anorexia and weight loss induced by stress were reversed by MC4 receptor blockade (Vergoni et al. 1999b). Similar effects were seen with infusion of an MC4R agonist to the MeA, while blockade of MC4R in this brain region attenuated restraint stress-induced anorectic effects and endocrine responses (Liu et al. 2013). Therefore, enhanced arcuate melanocortinergic input to the MeA during stress may contribute to anorexia and HPA axis activation.

Mice subjected to chronic stress, such as restraint stress, are also anhedonic as demonstrated by a loss of preference for a sucrose solution over water (Lim et al. 2012; Nestler and Hyman 2010). Reduced activation of D1 medium spiny neurons in the nucleus accumbens may underlie this effect. The loss of sucrose preference requires MC4R activation in NAc D1-MSNs, since knockdown of MC4R in the NAc or specifically in D1-MSNs prevented this loss (Lim et al. 2012). Therefore, release of α-MSH by POMC neurons can suppress activity in dopaminergic neurons in the nucleus accumbens and lead to the loss of appetite that is associated with stress and depression.

POMC neurons may also induce stress-related anorexia by acting directly or indirectly on CRH neurons. CRH neurons affect food intake (Bale et al. 2002; Menzaghi et al. 1993); chronic administration of CRH into the hypothalamus or activation of CRH-2 receptors decreases food intake and body weight gain in rats (Tempel and Leibowitz 1994; Fekete and Zorrilla 2007). Injecting a CRH-2 receptor blocker into the BNST attenuated restraint-induced anorexia (Ohata and Shibasaki 2011). The effects of CRH may be due to it suppressing NPY synthesis and release, thus reducing food intake (Tempel and Leibowitz 1994; White 1993). Melanocortin-sensitive MeA neurons project to the vicinity of the PVH where projections to CRH neurons can influence HPA output (Herman and Morrison 1996; Cullinan 2000; Miklos and Kovacs 2002). In addition, the MeA projects to BNST CRH neurons that directly innervate PVN CRH neurons (Ohata and Shibasaki 2011; Coolen and Wood 1998; Ciccocioppo et al. 2003). By increasing CRH release, melanocortins may suppress feeding.

In addition, the effect of glucocorticoids on circulating leptin levels may play a role. Glucocorticoids can directly increase leptin levels (Mostyn et al. 2001; Zakrzewska et al. 1999; Dagogo-Jack et al. 1997). In normal humans, administration of dexamethasone can increase plasma leptin almost threefold compared to controls (Miell et al. 1996). Similarly, repeated injection of dexamethasone for 4 days in rats

dramatically increased plasma leptin levels, reduced body weight, and suppressed food intake (Jahng et al. 2008). In response to increased leptin levels, POMC neuronal activity increases to promote satiety; this mechanism may contribute to the suppressive effect of acute stress on the appetite.

Acute illness is another stressor with suppressive effects on appetite. LPS stimulates insulin and leptin secretion in peripheral tissues and secretion of other pro-inflammatory cytokines in microglial cells and periphery (Grunfeld et al. 1996). Altered leptin and cytokine levels during an inflammatory challenge suppress food intake (Borges et al. 2016a). A recent study found that this effect requires activation of the PI3K/Akt pathway in hypothalamic neurons (Borges et al. 2016b). Acute inflammation, like that induced by LPS and IL-1β, leads to activation of POMC neurons (Ellacott and Cone 2006), increases expression of MC4R (Borges et al. 2011), and increases POMC expression (Jang et al. 2010; Endo et al. 2007). MC4R antagonism can prevent LPS-induced anorexia (Jang et al. 2010; Sartin et al. 2008; Huang et al. 1999). Interestingly, data from pharmacogenetically activated AgRP neurons in LPS-treated mice show that AgRP-DREADD neuronal activation does not prevent LPS hypophagia in mice (Liu et al. 2016). Thus, leptin activation of PI3K and Jak-STAT signaling after LPS administration may stimulate transcription of POMC, which inhibits food intake and promotes weight loss (Borges et al. 2016a). Even so, studies have found no detectable changes in LPS-induced c-Fos expression in POMC neurons (Liu et al. 2016; Gautron et al. 2005). The precise role of POMC neurons in LPS-induced hypophagia remains inconclusive and further studies are warranted.

The mechanism inducing cachexia in longer-term illnesses, such as cancer (Michalaki et al. 2004; Okada et al. 1998; Andersson et al. 2014), HIV (Roberts et al. 2010), heart failure (Rauchhaus et al. 2000; Pan et al. 2004), and COPD (Humbert et al. 1995), is unclear and likely to be multifactorial (Ezeoke and Morley 2015). In such cases leptin levels drop (Lopez-Soriano et al. 1999) and POMC expression decreases (Suzuki et al. 2011; Hashimoto et al. 2007; Dwarkasing et al. 2014; Wisse et al. 2003). IL-1β activates and depolarizes POMC neurons in the ARC, suggesting that this cytokine takes part in the hypophagia during these diseases (Scarlett et al. 2007). However, blocking cytokines in the presence of cancer (Arruda et al. 2010; Strassmann et al. 1992; Fujimoto-Ouchi et al. 1995; Gelin et al. 1991) or HIV (Ting and Koo 2006) only results in a partial, though significant, reduction of anorexia-cachexia. AgRP inhibits anorexia in mice carrying sarcomas (Marks et al. 2001). In addition, melanocortin antagonists increase food intake in several cancer models (Tran et al. 2007; Chen et al. 2008; Jiang et al. 2007; Markison et al. 2005; Dallmann et al. 2011; Weyermann et al. 2009; Wisse et al. 2001). Furthermore, MC4R knockout mice show no decrease in food intake when they carry lung adenocarcinoma (Wisse et al. 2001). In contrast, an MC4R antagonist did not restore feeding in rats with a methylcholanthrene-induced sarcoma (Chance et al. 2003). Therefore, the melanocortin system mediates the cachexia produced by some, but not all, cancers (Ezeoke and Morley 2015).

11.9.3 Chronic Stress and Body Weight

The stress that humans encounter on a daily basis is generally prolonged and mild, unlike the intense stressors that laboratory animals undergo to induce appetite suppression. In humans, the effect of chronic stress on feeding is highly variable. This type of stressor can induce either weight gain or anorexia (Oliver et al. 2000; Zellner et al. 2006; Pollard et al. 1995; Adam and Epel 2007; Serlachius et al. 2007). Evidence suggests that lean individuals may be more prone to weight loss, while overweight individuals tend to increase body weight in response to chronic stress (Kivimaki et al. 2006). On average, chronic psychological life stress induces weight gain

(Torres and Nowson 2007); in a meta-analysis of 13 studies, job strain positively correlated with BMI (Nyberg et al. 2012).

Chronic stress in humans (Bjorntorp and Rosmond 2000; Peeke and Chrousos 1995; Wallerius et al. 2003) and rodents (Rebuffescrive et al. 1992) increases glucocorticoid levels, adipocyte size, and abdominal fat. Greater responsiveness of the HPA axis generally correlates with abdominal obesity (Rodriguez et al. 2015). In one study, women were subjected to three sessions of stressful activities such as public speaking, math tests, and visuospatial puzzles over the course of 3 days. Unlike lean women, the women with the most central fat secreted high levels of cortisol on the first day. In addition, they failed to show cortisol habituation or a drop in cortisol secretion on subsequent days once the tests were familiar (Epel et al. 2000). Poverty is also associated higher basal cortisol levels and a lack of cortisol habituation (Adler et al. 2000; Gruenewald et al. 2006; Hellhammer et al. 1997; Kirschbaum et al. 1995). These findings likely indicate greater exposure to repeated challenges in these individuals that results in dysregulation of the stress response (Adler and Snibbe 2003).

Chronic cortisol exposure promotes the conversion of preadipocytes to mature adipocytes, expanding the adipose tissue and promoting the secretion of pro-inflammatory cytokines and adipokines (Peckett et al. 2011; Andrews and Walker 1999). These actions contrast with the lipolysis induced by acute glucocorticoid release. It is possible that GRα mediates the lipolytic effects of glucocorticoids, while MR and GRβ mediate adipogenesis during chronic glucocorticoid exposure (John et al. 2016). Excess glucocorticoid secretion may be amplified locally within adipose tissue by the activating enzyme 11β HSD1. 11β HSD1 is elevated in the adipose tissue of people with morbid obesity and metabolic syndrome (Baudrand et al. 2010; Luisella et al. 2007; Valsamakis et al. 2004; Constantinopoulos et al. 2015) and normalized by bariatric surgery (Methlie et al. 2013; Woods et al. 2015). Despite highly promising animal studies (Morton et al. 2004; Tiwari 2010; Morgan et al. 2014), inhibitors of 11β-HSD1 in humans have shown inconsistent results for treating metabolic syndrome in clinical trials (Walker et al. 1995; Andrews et al. 2003; Shah et al. 2011; Feig et al. 2011; Rosenstock et al. 2010). New inhibitors with higher specificity for the enzyme and a preference for adipose tissue may be required before this treatment strategy is viable.

In addition to directly promoting adiposity, stressors can lead to alterations in energy intake. Chronic life stress leads to increased appetite, binge eating, and craving energy-dense foods, snacks, and fast foods (Epel et al. 2001; Steptoe et al. 1998; Oliver and Wardle 1999; Gluck et al. 2004). In female rhesus monkeys, social subordinates under social stress eat more when offered unlimited access to rich foods than social dominants (Arce et al. 2010; Michopoulos et al. 2012). In rodents, anorexia from restraint stress later leads to increased intake of food high in fat and sugar (Foster et al. 2009; la Fleur et al. 2005). Likewise, animals stressed by repeated mild pinch exhibited hyperphagia of sweet food and a large gain in body weight (Pecoraro et al. 2004). These behaviors are under the control of the dopaminergic mesolimbic reward pathways and the HPA axis (Dallman et al. 2006). They are used to calm and sooth emotions to recover from the recurring stressors (Dallman et al. 2006). This strategy is, in fact, effective in reducing HPA activation (Foster et al. 2009; la Fleur et al. 2005; Pecoraro et al. 2004; Ortolani et al. 2011). Eating often improves mood, reduces irritability, and increases calmness (Gibson 2006). The opioid system, which interacts with the mesolimbic dopamine pathway, is a key mediator of this hedonic feeding; mu-opioid receptors mediate the rewarding properties of food and some drugs of abuse (Blasio et al. 2014; Zhang and Kelley 2000; Nathan and Bullmore 2009). So, β-endorphin production by POMC neurons may promote the hyperevaluation of palatable foods, leading to the loss of control during overeating.

Interestingly, a modest amount of sucrose intake can reduce behavioral and physiological

stress responses without leading to obesity. The basolateral amygdala, a key reward- and stress-regulatory brain region, is necessary for sucrose-induced stress relief and undergoes synaptic remodeling following sucrose intake (Ulrich-Lai et al. 2010, 2015). Overall, stress reduction occurs in rats with voluntary intake of limited amounts of sugar or carbohydrates with no increase in body weight (Ulrich-Lai et al. 2015). These results suggest that using small amounts of sweet treats to reduce stress can align with healthy body weight goals (Ulrich-Lai et al. 2010).

Altered CRH levels could mediate some of these effects. Stress induces CRH release by cells in the PVN as well as the medial amygdala. CRH-1 receptor activation increases palatable food consumption and binge eating (Koob 2010; Parylak et al. 2011). Indeed, antagonism of CRH-1 receptors in socially subordinate female rhesus macaques blocks increased palatable food consumption (Moore et al. 2015). Therefore, increased CRH-1 signaling induced by stress could promote excess food intake. In addition, ghrelin, a peptide produced by gastrointestinal endocrine cells that induces feeding and anxious behavior (Currie et al. 2005; Seoane et al. 2004; Kojima et al. 1999), rises in response to stress. In animal models, circulating ghrelin levels increase in response to social defeat (Lutter et al. 2008), restraint stress (Zheng et al. 2009), and chronic stress (Ochi et al. 2008). Mice subjected to social defeat had increased ghrelin levels and consumed more of a high-fat diet (Chuang et al. 2011). Ghrelin appears to increase preference for sweet food independent of calorie content since ghrelin administration increased consumption of a saccharin solution (Disse et al. 2010). Blocking or ablating the ghrelin receptor decreases intake of palatable food compared to standard chow (Egecioglu et al. 2010). Ghrelin directly activates AgRP/NPY neurons to stimulate feeding and increase inhibitory GABAergic input on POMC cells to suppress release of melanocortins (Briggs et al. 2010; Andrews et al. 2008; Andrews 2011). Peripheral and central ghrelin administration also activates CRH neurons (Cabral et al. 2012; Asakawa et al. 2001), which may promote binge eating. Thus, increased ghrelin levels may partly mediate stress-induced feeding.

Glucocorticoids may also have direct actions on food intake. The glucocorticoid receptor is widely expressed in the CNS. It is found in reward areas as well as in key appetite regulatory regions like the arcuate nucleus, lateral hypothalamus, and paraventricular nucleus of the hypothalamus (Morimoto et al. 1996; Reul and de Kloet 1986; Aronsson et al. 1988; Cintra et al. 1987; McEwen et al. 1986). In contrast, the mineralocorticoid receptor in the CNS is mainly restricted to the septum, hippocampus, and amygdala (Sanchez et al. 2000). Glucocorticoids therefore have direct access to brain sites that regulate energy metabolism and reward. In humans, individuals with a strong cortisol response consumed the most food during an experimental stress session (Epel et al. 2001). In addition, glucocorticoid administration caused higher food intake in subjects allowed ad libitum food selection (Tataranni et al. 1996).

Several mechanisms have been suggested for how glucocorticoids induce feeding. Glucocorticoids could stimulate feeding responses by inhibiting CRH release in the hypothalamus (Cavagnini et al. 2000). CRH and related stress peptides like urocortin can act through the CRH-2 receptor to suppress feeding (Stengel and Tache 2014). However, as noted above, a reduction in CRH would also suppress CRH-1 signaling that promotes food intake. Alternatively, glucocorticoids may directly stimulate feeding responses by increasing the release of NPY and/or AgRP in the hypothalamus. Glucocorticoids increase AgRP and NPY expression (Goto et al. 2006; Sato et al. 2005). Likewise, adrenalectomy decreases NPY levels and corticosterone replacement restores them (White et al. 1990). An important recent study found that deletion of GR on AgRP neurons resulted in leanness on chow diet in females and resistance to diet induced obesity in both sexes (Shibata et al. 2016). Interestingly, food intake was unchanged, but metabolic rate was increased due to brown adipose

tissue activity. These results suggest that glucocorticoids can promote obesity by acting in on AgRP neurons to suppress energy expenditure (Shibata et al. 2016). Additional research will be needed to fully understand how glucocorticoids interact with homeostatic feeding circuits.

11.9.4 Obesity-Induced "Stress"

Obesity is increasingly being described as a state of "energetic stress." Overconsumption of a high-fat, high-sugar diet can in essence serve as a physiological challenge (Gibson 2006; Anderson et al. 1987; Barr et al. 1999; Decastro 1987; Deuster et al. 1992; Dube et al. 2005; Fernandez et al. 2003; Lieberman et al. 1986; Utter et al. 1999). Multiple mechanisms allow energetic stress to interact with neuroendocrine stress response systems, including by impacting the sympathetic nervous system and altering the gut microbiota (Harrell et al. 2016). Although melanocortins normally suppress energy use for inflammation and food seeking to permit a fast response to danger, a chronic rise in inflammation can undermine the ability of POMC neurons to modulate energy use and intake. The result is failure of allostasis or homeostatic adaptation.

High-fat diet feeding rapidly activates multiple inflammatory and stress response pathways in the hypothalamus (De Souza et al. 2005). High-fat diet exposure induces hypothalamic inflammation before body weight gain (Thaler et al. 2012) and before peripheral tissues like the liver develop inflammation (Tolle and Low 2008). For example, saturated fats, but not monounsaturated fats, induce the TLR4 and MyD88 inflammatory signaling cascades within days, compromising hypothalamic function (Lee et al. 2001; Kleinridders et al. 2009; Valdearcos et al. 2014). A high-calorie diet rapidly stimulates microglial reactivity in the mediobasal hypothalamus (Thaler et al. 2012; Gao et al. 2014), leading the microglia to increase TNF-α production.

These findings suggest that the loss of sensitivity of POMC neurons to signals of adiposity caused by inflammation can perpetuate overeating. These pathways cause neuronal insulin and leptin resistance, which leads to the failure of anorexigenic melanocortin circuits to suppress more feeding. In parallel to the early occurrence of inflammation, 3 days of HFD feeding is enough to reduce hypothalamic insulin sensitivity in rodents substantially (Corander et al. 2011). Specifically, brain-specific activation of IKKβ interrupts central insulin and leptin signaling and results in increased food intake and body weight gain (Bouyer and Simerly 2013). Activation of NF-kB induces expression of suppressor of cytokine signaling 3 (S0CS3), which then inhibits neuronal insulin signaling (Bouyer and Simerly 2013). Pharmacologic inhibition of neuronal TLR4 signaling inhibits fatty acid-induced insulin (Schwartz 2000) and leptin resistance (Magoul et al. 1993). In the same way, mice with CNS-specific ablation of MyD88 resist HFD-induced weight gain and deterioration of glucose metabolism (Rinaman 2010).

The ER system further amplifies these HFD-induced perturbations by activating unfolded protein response (UPR) signaling pathways (Jacobowitz and Odonohue 1978; Young 1935; Eddy and Strahan 1968). ER stress and IKK/NF-kB promote each other during HFD feeding and worsen the energy imbalance underlying obesity (Bouyer and Simerly 2013). Central induction of ER stress inhibits the ability of leptin and insulin to reduce food intake and body weight (Vallarino et al. 1988). Conversely, mice with neuron-specific deletion of ER stress activator Xbpl show increased leptin resistance and adiposity (Young 1935). Constitutive expression of Xbpls selectively in POMC neurons represses Socs3 and protein tyrosine phosphatase IB (PtplB) expression and protects against HFD-induced obesity (Vallarino et al. 1989). Therefore, ER stress and the UPR are potent regulators of POMC neurons.

Central inflammatory processes and weight gain lead to low-grade activation of the immune system throughout the body. Obesity tightly correlates with elevations in inflammatory factors, such as tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) (Hotamisligil et al. 1993;

Xu et al. 2003). Prolonged low-grade systemic inflammation results in tissue damage and exacerbates disease processes, such as insulin resistance. TNF-α and IL-6 inhibit serine phosphorylation in the insulin receptor substrate-1 (IRS-1), disrupting insulin signaling transduction and causing insulin resistance (Wellen and Hotamisligil 2005). Low-grade inflammation is an independent risk factor for heart disease (Hansson 2005) stroke (Corrado et al. 2006), diabetes (Pradhan et al. 2001; Spranger et al. 2003), and all-cause mortality (Ford 2005). For example, chronic inflammation that develops within atherosclerotic plaques can cause stroke or myocardial infarction by leading to plaque rupture (Libby 2002). Age-related macular degeneration (Telander 2011) and Alzheimer's disease (Wyss-Coray 2006) and osteoarthritis (Sokolove and Lepus 2013) associate with innate immune activation and low-grade inflammation.

Extended overnutrition perpetuates hypothalamic inflammatory interactions between neurons and non-neuronal cell populations. These effects ultimately lead to overeating and further weight gain (Jais and Bruning 2017). Persistent microglial reactivity and TNF-α production have a specific harmful effect on POMC neurons (Thaler et al. 2012). Recently it was reported that TNF-α released by microglia induces mitochondrial stress in POMC neurons; TNF-α acts on POMC neurons to promote mitochondrial ATP production, cause mitochondrial fusion in neurites, and elevate neuronal excitability and firing rates (Yi et al. 2017). In the long run, these actions may disrupt the ability of POMC neurons to suppress feeding and increase energy use, leading to obesity.

11.10 Conclusions

The current obesity crisis is being driven by increased consumption of widely available, palatable, high-calorie food coupled with decreased activity in daily life. The neural pathways underlying the motivation for and enjoyment of foods high in fat and sugar have been well studied (Castro et al. 2015). These include dopaminergic pathways projecting from the nucleus accumbens to the ventral tegmental area and areas of the NA and ventral pallidum sensitive to endogenous opioids. Arcuate POMC neurons can influence this system at several levels. POMC neurons innervate key neural nodes of the mesocorticolimbic system, including the VTA and NAc (Lim et al. 2012; King and Hentges 2011). While β-endorphin has only a minor impact on the enjoyment of foods (Mendez et al. 2015), melanocortins like α-MSH can influence the motivation to obtain food. Intra-VTA α-MSH acts through the MC4R to increase NAc dopamine levels (Lindblom et al. 2001).

As we have seen, chronic stress increases the consumption of certain palatable foods ("comfort foods") in both animals and humans (Pecoraro et al. 2004; Dallman et al. 2003; Fairburn 1997). It can also precipitate eating disorders like binge eating (Cifani et al. 2009; Hagan et al. 2003). In fact, binge eating can be induced in rodents with a combination of stress and caloric restriction (Hagan et al. 2002; Boggiano and Chandler 2006). No pharmaceuticals have been approved for reducing common forms of emotional eating in response to chronic life stress. However, binge eating disorder shows improvement when treated with amphetamines, which regulate dopamine release, as well as off-label antidepressants and anti-seizure medications. Developing technologies may permit pharmaceuticals that specifically target emotional eating to be designed in the future (Caruso et al. 2014; Hill and Faulkner 2017). Until such drugs are available, obesity treatment should be individualized using tailored strategies to address the type of hedonic eating in each patient. For instance, some patients may benefit from becoming more selective in the food they eat, demanding higher quality and eating slowly to enable them to maintain the same satisfaction while eating less food (Scarinci 2004). Learning alternative methods for coping with stress (such as exercise, focused breathing, progressive muscle relaxation, mediation) may assist patients in avoiding stressed-induced overeating.

A wise health professional will also address the underlying causes of stress to promote the overall well-being of the patient. As previously mentioned, this approach is more effective in reducing obesity than efforts to improve diets directly in at-risk populations. For example, low socioeconomic status populations may not use exercise facilities made available to them (Giles-Corti and Donovan 2002). Likewise, giving money or food to a low socioeconomic population in rural Mexico causes weight gain rather than loss (Leroy et al. 2013). Another study found that increasing government food vouchers to $2000 per year had no effect on BMI disparities between social strata (Jones and Frongillo 2006). Hoarding calories appears to be a psychological mechanism to buffer against the stress of low socioeconomic status (Dhurandhar 2016). Instead, interventions focused on improving socioeconomic opportunity, with no focus on nutrition or physical activity, may improve rates of obesity and diabetes. For example, randomizing families to move to a more well-off neighborhood reduced average BMI without additional assistance (Ludwig et al. 2011). These data demonstrate that, unlike nutrition programs, social interventions can reduce obesity. Therefore, obese patients with the most stress-filled lives, including those in poverty or recovering from trauma, require referral to assistance programs that focus on the underlying causes of insecurity.

Equilibrium in body weight is described as a "set point" of adiposity that the body defends against intentional or unintentional weight loss or gain. By definition, homeostatic processes cannot initiate obesity. However, the homeostatic processes suppressing body weight gain seem weaker than those preventing drops in body weight. Whether this fact is due to beneficial effects of storing additional energy in case of famine or because modern humans face few negative short-term consequences of obesity is unclear (Speakman 2008; Sellayah et al. 2014). In many individuals, the hedonic drive to overconsume in a food environment of easily obtainable, palatable, and energy-dense foods succeeds in increasing body weight, which the homeostatic system then defends against weight loss. Increased body weight leads to cellular leptin resistance in arcuate circuits regulating feeding that diminishes the ability of hyperleptinemia to act on the melanocortin system to suppress food intake and increase energy expenditure (Myers et al. 2010).

Intentional weight loss causes leptin and insulin levels to decrease (Rosenbaum and Leibel 2014). Interestingly, leptin falls more than expected from the magnitude of fat loss (Myers et al. 2010) and remains low if weight loss is maintained (Kissileff et al. 2012; Naslund et al. 2000). In response, arcuate melanocortin and NPY circuitry increase the drive for food and to reduce energy expenditure. In addition, circulating levels of the orexigenic hormone ghrelin increase while the anorexigenic hormones CCK, PYY, and GLP-1 fall (Melby et al. 2017). These changes result in increased hunger (Chaput et al. 2007), food cravings (Gilhooly et al. 2007), and less satiation after eating (Cornier et al. 2004). Weight loss also chronically suppresses energy expenditure, including resting metabolic rate, the thermic effect of food, exercise energy expenditure, and non-exercise activity thermogenesis (Kissileff et al. 2012; Melby et al. 2017; Fothergill et al. 2016; Martin et al. 2007; Byrne et al. 2012; Knuth et al. 2014). Because of these effects, current approaches to substantial weight loss maintenance require constant vigilance and motivation on the part of the patient (Melby et al. 2017). The frequent failure of individuals to maintain weight loss discourages patients from attempting to lose weight. A method of altering the body weight set point would be transformative for patient care.

Recently, an important study has made advances in understanding the biological basis of the set point. Exogenous leptin normally suppresses food intake and induces weight loss. In obese humans (Zelissen et al. 2005) and animals (Enriori et al. 2007; Frederich et al. 1995), leptin administration fails to have this effect, likely as a result of leptin resistance induced by chronic exposure to hyperleptinemia (Knight et al. 2010; Gamber et al. 2012). Weight loss reverses this resistance, allowing leptin to assist in the maintenance of weight loss (Rosenbaum and Leibel 2014; Chhabra et al. 2016).

Similarly, weight-reduced MC4R-null mice respond to leptin treatment (Marsh et al. 1999). Previous work had shown that mice lacking POMC expression develop obesity, hyperleptinemia, and leptin resistance (Bumaschny et al. 2012). Interestingly, reducing the weight of these mice through food restriction did not restore the ability of leptin to inhibit feeding. In other words, simply restoring intracellular leptin signaling was insufficient to restore the effects of leptin; rather, a second defect downstream of the leptin receptor exists in these mice. Given that both MC4RKO (responsive to leptin when lean) and the arc POMCKO mice (not responsive to leptin when lean) have no activation of MC4R pathways, another receptor responsive to POMC products is responsible for conveying leptin responsiveness. Chhabra and coworkers next examined how to restore leanness to arc POMCKO mice. They found that reactivating POMC expression after to the establishment of obesity did not normalize body weight. However, if the mice were first calorie restricted to reduce their body weight, POMC reexpression permitted them to maintain that weight at a new, lower set point (Chhabra et al. 2016). Critically, this normalization could be prevented by inducing hyperleptinemia with exogenous leptin. Therefore, both hypothalamic leptin sensitivity and *Pomc* gene expression regulate the body weight set point. If true, weight loss in the obese patient restores the effects of leptin (Rosenbaum and Leibel 2014; Chhabra et al. 2016; Quarta et al. 2016) both due to improved intracellular signaling by leptin and also increased activation of a receptor for POMC products other than MC4R, such as the MC3R or mu-opioid receptor.

Work described in the previous section has led to the concept of MC3Rs sensitizing AgRP neurons to the metabolic state of the animal and regulating hunger (Girardet et al. 2017). If MC3Rs modulate the metabolic "set point" in conjunction with leptin, effective leptin signaling induced by relatively low levels of leptin needs to be synchronized with a normal level of hunger and energy expenditure through modulation of MC3R action or expression. In theory, this combination can restore a set point in the normal body weight range. Therapies targeting melanocortin signaling may restore normal body weight only when plasma leptin levels are below a critical threshold. Regular exercise may also heighten the brain's sensitivity to leptin (MacLean et al. 2009), suggesting it could also be useful in combination therapy.

Pharmaceuticals targeting the melanocortin system hold promise for numerous disorders that range from opioid addiction to shock to PTSD. In the case of ischemic or neurodegenerative disorders, they are already showing exciting clinical potential (Arnason et al. 2013; Leone et al. 2013; Spaccapelo et al. 2013). As described above, targeting this system to alter the body weight set point could also be enormously useful for combating rising rates of obesity. This potential has led to many preclinical and clinical studies investigating how melanocortins can be harnessed to stimulate weight loss. Targeting melanocortin receptors for the treatment of obesity, however, has proven challenging. Clinical trial has revealed problematic side effects of MCR agonists, including cardiovascular actions like tachycardia and elevated arterial pressure (Royalty et al. 2014; Greenfield et al. 2009; Girardet and Butler 2014; Skibicka and Grill 2009; Kuo et al. 2003). Indeed, melanocortins promote hypertension (Harrell et al. 2016); POMC neuron stimulation by leptin leads to SNS hyperactivity (da Silva et al. 2013), likely via activation of MC4Rs in the VMH (Lim et al. 2016). The extensive role of melanocortins in the stress response makes these findings unsurprising.

A recent MCR agonist that just entered phase 3 clinical trials for patients with POMC deficiency has thus far avoided such side effects. Setmelanotide is an eight-amino acid cyclic peptide that acts as a full agonist of human MC4R. It binds with ~10-fold selectivity over human MC3R (Fani et al. 2014). Preclinical studies in obese rhesus macaques indicated subcutaneous setmelanotide reduced overall food intake, decreased body weight, improved glucose tolerance, and did not induce negative cardiac effects (Kievit et al. 2013). Phase 1 and 2 studies have successfully evaluated the safety, efficacy, toler-

ability, pharmacokinetics, and pharmacodynamics of the octapeptide in obese volunteers (Ericson et al. 2017; Chen et al. 2015; Kuhnen et al. 2016). The reason for a lack of cardiovascular side effects has not been established, but several possible explanations exist (Kievit et al. 2013). These include (1) differing receptor pharmacology or mechanism for activating the MC4R; (2) higher affinity for the MC3R than previous drugs, since MC3R activity may counteract sympathetic stimulation mediated by MC4R signaling (Wikberg and Mutulis 2008); or (3) lack of penetration by setmelanotide to brain regions controlling heart rate and blood pressure. Until the cause of the lack of side effects in this drug is clear, it will be hard to replicate its success. Future techniques that allow targeting of MC3R or MC4R receptors in specific brain regions such as the VTA may also have clinical potential (Vogel et al. 2016).

The evolution of melanocortins from serving solely as stress hormones to also serving as critical anorexigenic neuropeptides demonstrates the opportunistic nature of biology. Yet, this system remains profoundly integrated with the physiological stress response. This knowledge should guide clinical care and pharmaceutical development. Overall, a critical need exists for studies that focus more broadly on how the CNS coordinates behavioral, endocrine, and autonomic responses to stressors. Investigating the melanocortin system in this light may hold the key to future medical advances.

Summative Questions

1. *What peripheral actions of melanocortins can affect adiposity? Which MC receptors are involved?*
2. *How do glucocorticoids affect behavior?*
3. *How does α-MSH treat shock?*
4. *Contrast the effects of melanocortins and beta-endorphin on pain.*
5. *Why are MCs a promising target in the treatment of PTSD?*
6. *How does the consumption of sweet treats interact with stress?*
7. *What are the most effective treatment options for obese patients facing food insecurity?*

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