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# Innate Obesity, Revealed by Selection Markers, Confers Significant Imprint of Hypothalamic Genes Controlling Energy Expenditure

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**Abstract**
The incidence of obesity is rapidly escalating and has reached epidemic proportions. In all species, including rodents, humans, and sheep, there is large variation in the degree of weight gain across individuals in response to an obesogenic environment. This individual variation is, at least in part, determined by innate differences in energy expenditure, of which adaptive thermogenesis is a key component. The hypothalamus is essential to the control of body weight and adiposity. Appetite-regulating peptides within the hypothalamus exert reciprocal effects on food intake and energy expenditure, such that neuropeptides that stimulate food intake inhibit thermogenesis and vice versa. This review discusses the role of the hypothalamic neuropeptides in determining innate predisposition to obesity in 3 animal models being obesity-prone and obesity-resistant rodents, genetically lean and obese sheep, and animals selected for high/low cortisol responsiveness. In rodents, leptin resistance is a primary feature of the propensity to become obese. This contrasts that of larger mammals, such as sheep, where altered susceptibility to obesity manifests within the melanocortin and/or orexin pathways. This review highlights fundamental species differences within the hypothalamus that lead to altered susceptibility to weight gain and increased propensity to become obese.


## Introduction

Over the past 3 decades, the incidence of obesity and associated metabolic disturbances has rapidly escalated. Body weight and adiposity are determined by the balance between food intake and energy expenditure, where the latter is comprised of basal metabolic rate, physical activity, and adaptive thermogenesis. The hypothalamus is integral to the control of food intake and energy expenditure. Specifically, appetite-regulating peptides in the hypothalamus exert dual and reciprocal effects to control feeding and adaptive thermogenesis [1]. Quintessential observations show that factors that stimulate food intake inhibit thermogenesis and vice versa [1]. Within the hypothalamus, the arcuate nucleus (ARC) is essential to the control of body weight, indicated by chemical lesioning with monosodium glutamate, which results in obesity [2].



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Within the ARC, appetite is stimulated by a single set of neurons that produce both neuropeptide Y (NPY) and agouti-related protein (AgRP) [3]. Within the same nucleus, a different set of neurons produce the pro-opiomelanocortin (POMC)-derived melanocortin peptides, which act as satiety factors. The most widely studied melanocortin is α-melanocyte-stimulating hormone (αMSH) [4, 5]. A number of other hypothalamic nuclei also produce appetite regulating peptides, including the paraventricular nucleus (PVN), the ventromedial hypothalamus, the dorsomedial hypothalamus (DMH), and the lateral hypothalamic/perifornical area (LHA/PeF) [6, 7]. NPY- and αMSH-containing neurons project to the PVN to act at the Y1 receptors or the melanocortin 3 and 4 receptors (MC3/4R), respectively. AgRP is the endogenous antagonist of αMSH and increases food intake by dampening the satiety effect of αMSH primarily through MC4R [4, 5]. In addition to the ARC-to-PVN projections, there is a complex neural circuitry involving other hypothalamic centres that control food intake and body weight [for review see 6]. In particular, neurons in the LHA produce the appetite stimulators orexin A and B (orexins) as well as melanin-concentrating hormone (MCH), which are also important for the control of body weight [8, 9].

As indicated above, the hypothalamic appetite-regulating peptides also regulate energy expenditure, especially adaptive thermogenesis. This is defined as the dissipation of energy through specialised heat production and occurs predominantly in brown adipose tissue (BAT) and skeletal muscle [10, 11]. In BAT, thermogenesis occurs in mitochondria through activation of uncoupling protein 1 (UCP1). UCP1 is located in the inner mitochondrial membrane, where it disassociates protons from the electron transport chain and the production of ATP. Activation of UCP1 occurs in response to either cold or dietary stimuli and is effected via the sympathetic nervous system. Noradrenergic stimulation of brown adipocytes activates UCP1, leading to a proton leak and thus "steals" protons from the ATP synthase pathway. Proton leakage across the inner mitochondrial membrane results in dissipation of energy via heat production.

On the other hand, thermogenesis in skeletal muscle occurs through 2 processes, mitochondrial uncoupling and futile calcium cycling [12–15]. The former is via the UCP1 homologue UCP3 [14–17]. Futile calcium cycling occurs across the sarcoendoplasmic reticulum (SR), whereby activation of the ryanodine receptor 1 pumps calcium out of the SR increasing cytosolic calcium levels. In order to maintain cellular calcium homeostasis, the SR ATPases (SERCA) are activated, specifically the SERCA 1 and 2a isoforms [18]. To propel calcium back into the SR, SERCAs hydrolyse ATP to ADP, with resultant heat production [19, 20]. The cellular processes of adaptive thermogenesis in BAT and skeletal muscle are shown in Figure 1.

It is apparent that there is significant individual variation in the susceptibility to weight gain and obesity, and various studies in humans have revealed diet-resistant (DR) individuals who gain less weight in response to an obesogenic environment than obesity-prone individuals [21, 22]. Similarly, successful weight loss is highly variable and is influenced by innate changes in energy expenditure [23, 24]. Calorie restriction results in a compensatory reduction in energy expenditure (in order to protect against weight loss), which is at least partly determined by the inhibition of thermogenesis [25]. To date, however, the mechanisms that underpin the inherent differences in the control of thermogenesis in humans remain elusive. This review will discuss the role of the hypothalamus and the relevant neuropeptides in determining susceptibility to obesity in polygenic rodent and sheep models, with a particular emphasis on innate variation in energy expenditure.

## Diet-Resistant and Obese Rodent Models

The divergence in weight and fat gain in response to a high-fat diet (HFD) was first reported by Schemmel and colleagues in 1970 [26], who demonstrated great variability in weight gain in response to high-fat feeding within and across 7 strains of rats. Subsequently, bimodal subpopulations of rodents referred to as either obesity prone/diet-induced obese (DIO) or DR were identified based on differential weight gain in response to high-fat feeding [27, 28].

DIO animals gain vastly more adipose tissue than their DR counterparts and become obese when fed either a low-fat diet or HFD. DIO animals eat more on an HFD than DR animals [29, 30], but there is also evidence to invoke a role for energy expenditure in determining the 2 phenotypes [31]. Without feeding a high-fat diet, the rate of thermogenesis was found to be the same in DIO and DR male rats, whereby both basal and noradrenaline-induced oxygen consumption was similar in each [30]. It is important to note that this work was conducted at 24°C, which is below ambient thermoneutrality, so there could have been confounding effects on thermogenesis (cold-induced thermogenesis). On the other hand, after 16 weeks of feeding a cafeteria diet, DIO rats have elevated body weights and increased adiposity compared to DR,

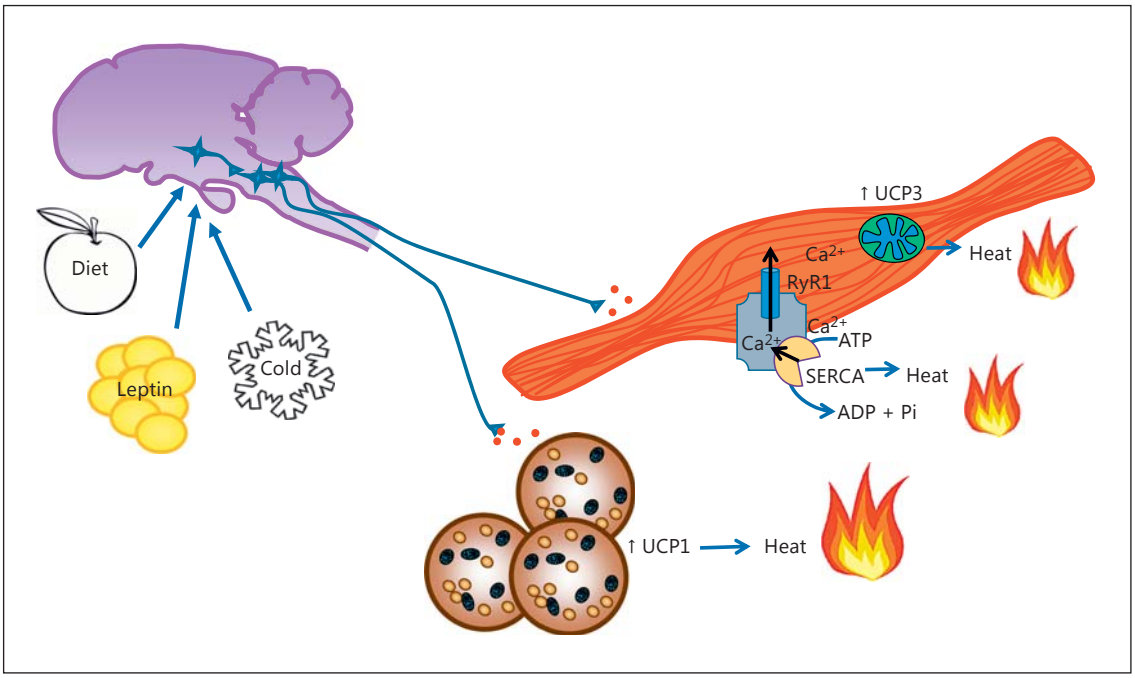


**Fig. 1.** Cellular pathways that underpin adaptive thermogenesis in BAT and skeletal muscle. In BAT, uncoupling protein (UCP) 1 is the primary driver of thermogenesis and heat production. In skeletal muscle, thermogenesis occurs via 2 mechanisms including mitochondrial uncoupling and futile calcium cycling. In muscle, mitochondrial uncoupling occurs via the UCP1 homologue, UCP3. Futile calcium ($Ca^{2+}$) cycling: activation of the ryanodine receptor 1 (RyR1) propels $Ca^{2+}$ out of the SR leading to increased cytosolic $Ca^{2+}$ levels. To maintain cellular $Ca^{2+}$ homeostasis, the SR ATPases (SERCA 1 and 2a) are activated. When activated, SERCAs lead to the hydrolysis of ATP and heat production. Thermogenesis in skeletal muscle and BAT is known to be increased by cold exposure, food intake, and the adipose-derived hormone leptin. In each case, stimuli act at the brain to increase activity of the sympathetic nervous system, leading to an induction of thermogenesis. Pi, orthophosphate.

which is associated with a reduction in BAT temperature [31]. Similar results have been shown in humans, whereby the incidence of active BAT as measured by PET-CT scanning is inversely related to adiposity [32–34]. As to whether this reduction in thermogenesis precedes the onset of obesity or is caused by the obese state remains unknown. Despite this, UCP3 mRNA expression is increased in response to a high-energy diet in DR but not DIO [35], suggesting that skeletal muscle thermogenesis may be mitigated in DIO animals. Thus, impaired thermogenesis may be important in facilitating weight gain in the DIO model.

On the other hand, in response to food restriction, DIO rats show a greater reduction in 24-h urine noradrenaline levels indicative of greater metabolic compensation within the sympathetic nervous system [36]. This is consistent with a larger than expected decrease in resting energy expenditure in response to weight loss in DIO animals; resting energy expenditure was reduced by 15% in response to a 10% reduction in body weight [37]. Thus, it is likely that metabolic flexibility, determined by innate differences in thermogenesis, contributes to differences in weight gain and weight maintenance in DIO and DR rodents.

The hypothalamus is known to drive the inherent differences in energy balance in DIO and DR rodents. A key feature of the DIO rodent is leptin resistance, which has been shown to manifest independent of obesity [38–40]. At baseline (normal body weight, chow diet), leptin crosses the blood-brain barrier in both DIO and DR rats, but central administration of leptin does not induce STAT3 phosphorylation in the DIO group [39]. After high-fat feeding, chronic central leptin administration using AAV technology neither reduces food intake nor causes weight loss in DIO animals; this is associated with attenuated leptin-induced STAT-3 phosphorylation in multiple hypothalamic nuclei [41]. Furthermore, in control chow-fed and high-fat-fed DR rats, rAAV-leptin treatment increases both the expression of POMC mRNA in the ARC and UCP1 mRNA in BAT, effects that are abolished in DIO rats [41]. Similarly, leptin resistance develops in DIO mice

fed an HFD, as demonstrated by upregulated SOCS3 expression in cells of the ARC [42]. In rodents, acute high-fat feeding initially reduces NPY and AgRP expression, yet this effect is abrogated within 1 week [43]. Thus, in mice, cellular leptin resistance results in impaired leptin-induced inhibition of NPY and AgRP production as well as a reduction in the leptin-induced stimulation of αMSH secretion [42]. In addition, there are structural changes within the ARC in DIO rats and mice in response to high-fat feeding, such as glial ensheathment of both NPY and POMC neuronal perikarya and dendrites [44], reducing close associations between neurons and blood vessels.

In conclusion, early-onset development of leptin resistance is an important physiological determinant of differential weight gain in DR and DIO rodents. This state is further exacerbated in DIO animals after high-fat feeding, which facilitates weight gain in this model. To date, however, there is little evidence to suggest that leptin resistance determines susceptibility to weight gain in large animal models such as the sheep (discussed below) or humans. It has been well documented in humans that leptin resistance manifests in the obese state and leptin treatment is ineffective in causing weight loss in obese individuals [45]. For example, the ratio of leptin in the CSF:plasma is reduced in obese subjects due to impaired transport of leptin across the blood-brain barrier [46, 47]. Furthermore, measurement of αMSH and NPY within CSF obtained from lumbar puncture shows similar levels in lean and obese humans [47]. It is important to note that lumbar puncture does not provide a direct measurement of NPY and αMSH within the ARC and in this case CSF levels are derived from multiple sources. As to whether innate differences in leptin sensitivity precede the onset of obesity in humans requires further consideration. Nonetheless, in humans, low plasma leptin levels forecast weight gain in pre-pubertal children [48]. Furthermore, low fasting leptin levels were shown to predict weight gain in Pima Indians [49], which suggests that low leptin levels predict propensity to gain weight. Accordingly, this review will focus on 2 large animal models that display innate differences in the susceptibility to weight gain and the possible hypothalamic mechanisms that underpin this.

## Genetic Selection for Obese and Lean Phenotypes in Sheep

Quantitative genetics stipulate that continuous traits such as height, milk production, or birthweight are polygenic, and this has been used to facilitate selective breeding programs in domestic animals. Quantitative genetic principles have been applied to select for fatness in outbred populations in numerous species including chickens [50], pigs [51, 52], and sheep [53, 54]. We have characterised the neuroendocrine and physiological mechanisms that underpin disparate adiposity in genetically lean and obese sheep. This model was originally developed with selection based on back-fat thickness in a population of approximately 3,000 animals. Lean and fat animals were chosen and then selectively bred for 10–15 generations, creating the genetically lean and obese lines [53, 55, 56]. A series of studies consistently show that the lean and fat lines have similar body weights, despite large differences in adiposity; genetically fat sheep accumulate significant amounts of adipose tissue within the abdominal/visceral compartment [55, 57]. The inherent differences in adiposity are not due to differences in food intake, as genetically lean and fat sheep eat similar amounts [55, 58], but the key physiological determinant of the 2 differing phenotypes is adaptive thermogenesis [58].

Adult sheep are unlike rodents in that they do not have a demarcated brown fat depot, but have brown adipocytes interspersed within white adipose depots [59, 60]. In adult sheep, UCP1 expression is higher in the retroperitoneal adipose tissue than in subcutaneous adipose tissue, indicative of more brown adipocytes in the former [60]. Consistent with this, the thermogenic response to feeding, leptin, and oestrogen treatment is greater in retroperitoneal fat than subcutaneous gluteal fat [61, 62]. Longitudinal temperature profiling reveals elevated post-prandial thermogenesis in retroperitoneal adipose tissue of lean sheep, and this coincides with greater post-prandial expression of UCP1 in the lean genotype than that in the obese genotype [58]. It would be of great interest to determine whether increased thermogenesis in genetically obese sheep can reverse the increased levels of adiposity.

Unlike the DIO rodents, genetically obese sheep are not leptin resistant, since central leptin treatment reduces food intake to an equivalent degree in both lean and obese lines [58]. This is not surprising given that the plasma leptin concentration is not increased in the obese genotype compared to normal body weight controls [55]. Furthermore, expression of ObRb in the ARC is similar in obese and lean animals [55]. Consistent with this, expression of POMC and NPY mRNA in the ARC is similar in lean and fat sheep [55], suggesting a similar "set-point" at this level. Differences in the production of appetite-regulating peptides do, however, manifest within the LHA, DMH, and the PeF. At these levels, expression of both

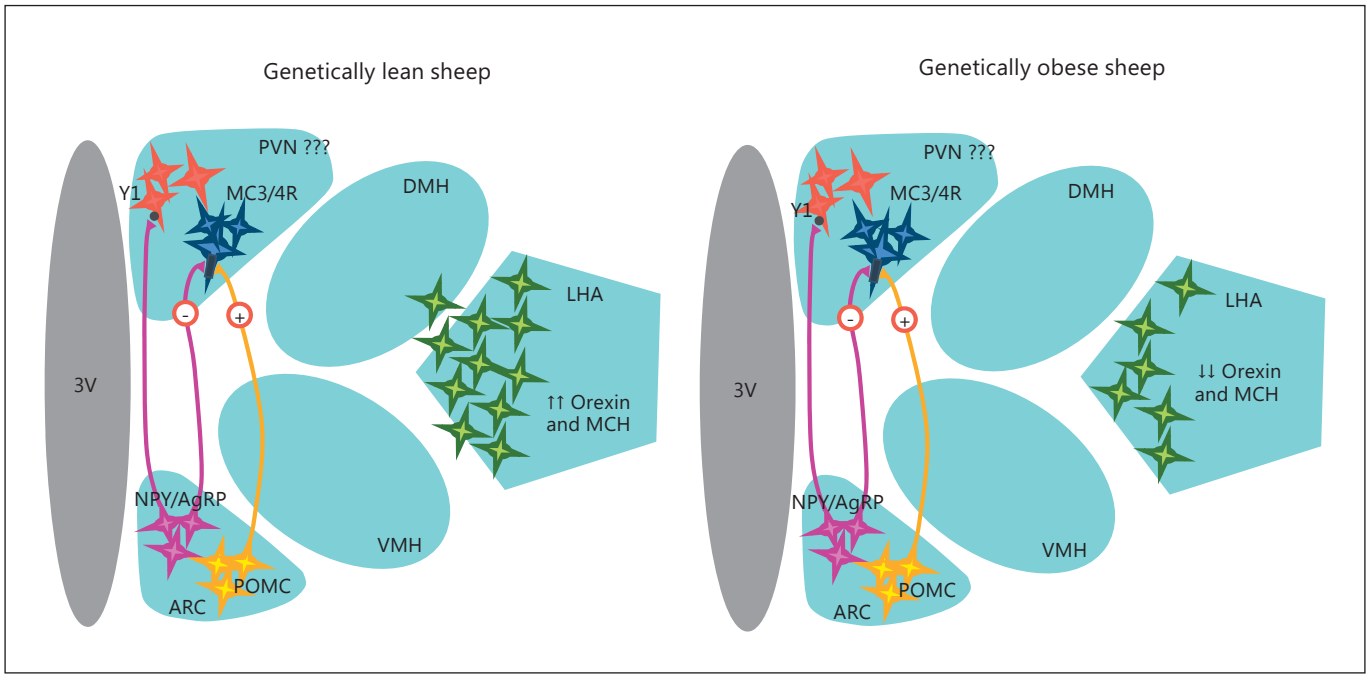


**Fig. 2.** Schematic representation of the differences in hypothalamic gene expression in genetically lean and obese sheep. Gene expression is similar in the arcuate nucleus (ARC) of genetically lean and obese sheep. The predominant changes in gene expression occur in the lateral hypothalamic area (LHA), where expression of both melanin-concentrating hormone (MCH) and orexin is increased in lean compared to obese animals. There are reports detailing differences in gene expression in the paraventricular nucleus (PVN). NPY, neuropeptide Y; AgRP, agouti-related protein; POMC, pro-opiomelanocortin; VMH, ventromedial hypothalamus; DMH, dorsomedial hypothalamus; Y1, NPY Y1 receptors; MC3/4R, melanocortin 3/4 receptors; 3V, third ventricle.

MCH and prepro-orexin mRNA are inversely proportional to levels of adiposity with greatest expression observed in the genetically lean animals [55] (Fig. 2). Both MCH and orexin are known to increase food intake, but the 2 neuropeptides exert differential effects on energy expenditure. Central infusion of MCH reduces rectal temperature, and this is accompanied by lowered UCP 1 expression in BAT [63]. Furthermore, blockade of endogenous MCH activity via central infusion of SNAP-7941 increases BAT temperature in rats [1], consistent with the notion that MCH reduces thermogenesis. On the other hand, orexin increases energy expenditure in rodents by influencing both physical activity and adaptive thermogenesis [64, 65]. A subpopulation of orexin neurons in the LHA/PeF project to the raphe pallidus, and microinjection of orexin into the latter increased BAT thermogenesis [66]. Furthermore, a recent study demonstrated that obesity in orexin-knockout mice is associated with reduced adaptive thermogenesis in BAT, which is manifest during development via an inability of brown pre-adipocytes to differentiate into mature brown adipocytes [67]. In conclusion, increased expression of MCH is unlikely to drive a higher level of post-prandial thermogenesis in genetically lean sheep. On the other hand, selection for an obese or lean phenotype leads to differences in the "set-point" of orexin expression and the action of this peptide to regulate thermogenesis in this model requires further investigation (Fig. 2).

### Cortisol Responsiveness Identifies Obesity-Prone Individuals in Sheep

It has long been recognised that a bidirectional relationship exists between the hypothalamo-pituitary-adrenal (HPA) axis and obesity, whereby body weight and adiposity influence stress responsiveness, and vice versa [68]. In humans, abdominal obesity is associated with a heightened cortisol response to stress, corticotropin-releasing factor, or adrenocorticotropin (ACTH) [69–71]. The amplified glucocorticoid response is thought to be caused by impaired negative feedback [72], as suggested

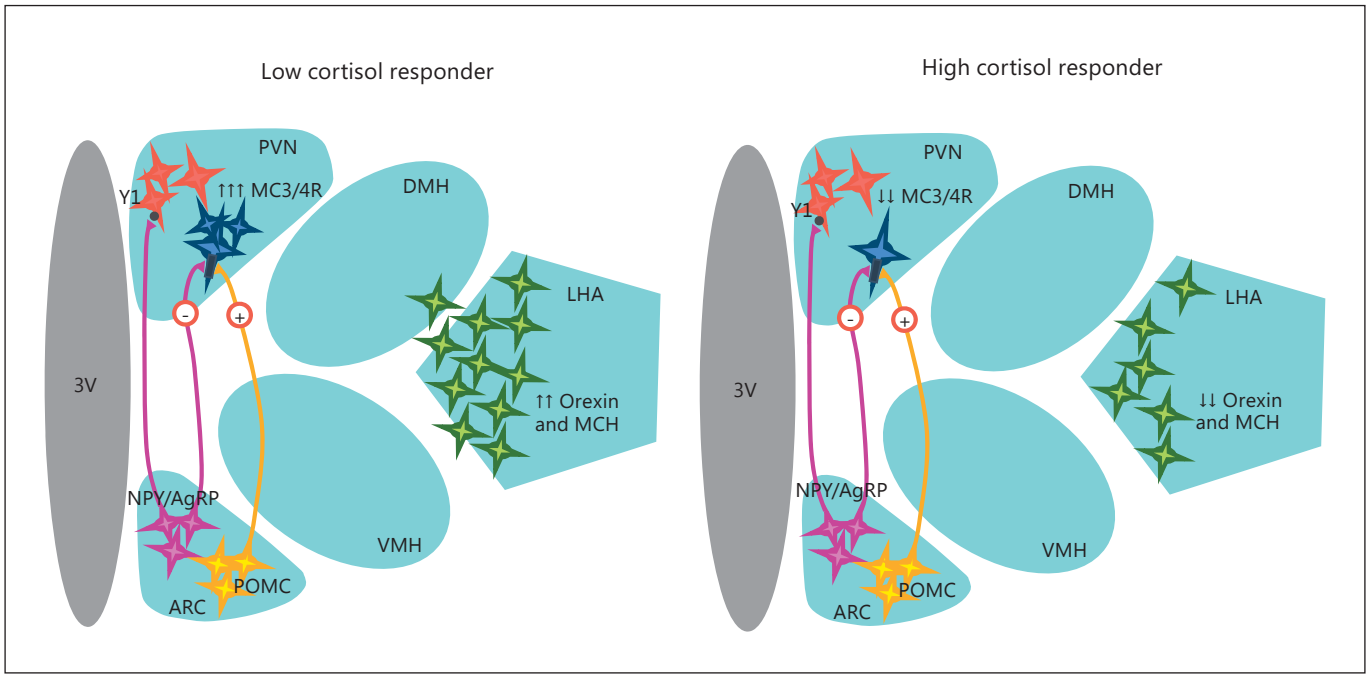


**Fig. 3.** Schematic representation of the differences in hypothalamic gene expression in sheep selected for high (HR) and low (LR) cortisol responsiveness. Gene expression is similar in the arcuate nucleus (ARC) of LR and HR sheep. The predominant changes in gene expression occur at the level of the paraventricular nucleus (PVN) and in the lateral hypothalamic area (LHA). Expression of the melanocortin 3 and 4 receptors (MC3/4R) was reduced in the PVN of HR animals. Furthermore, expression of both melanin-concentrating hormone (MCH) and orexin is lower in HR compared to LR animals. NPY, neuropeptide Y; AgRP, agouti-related protein; POMC, pro-opiomelanocortin; VMH, ventromedial hypothalamus; DMH, dorsomedial hypothalamus; Y1, NPY Y1 receptors; 3V, third ventricle.

by the dexamethasone suppression test. These initial observations lead to the hypothesis that obesity causes hyper-activation of the HPA axis. Recent work, however, suggests that increased cortisol secretion in response to ACTH may in fact be a marker for propensity to gain weight. This will be discussed in detail below.

In all species studied to date, there is marked variation in the cortisol response to stress or ACTH challenge [73–79]. Studies in our laboratory and those of others have consistently shown in outbred populations of sheep individuals can be identified as high or low cortisol responders [73, 74, 80, 81]. Recent evidence suggests that the degree of cortisol response may determine the metabolic sequelae to stress. Indeed, women with high cortisol responsiveness display increased food intake in response to psychosocial stress [78, 82]. Recent work in sheep suggests that ewes with high cortisol responses (HR) to ACTH gain more adipose tissue in response to a high-energy diet than ewes with low cortisol responses (LR) [73]. This contrasts that of HR mice, which have reduced body weight compared to LR mice [83]. In sheep, however, this innate difference in the susceptibility to gain weight is underpinned by a compilation of neuroendocrine, metabolic, and behavioural traits [73–75].

Similar to the genetically lean and obese sheep, when at normal body weight, LR and HR animals are equally sensitive to the satiety effect of leptin [73]. This strongly suggests that a state of leptin resistance does not contribute to increased susceptibility to weight gain in HR animals. Nonetheless, differences in leptin sensitivity may manifest if the animals were studied in the obese state. In keeping with this, at normal body weight, expression of NPY and POMC mRNA is similar in the LR and HR animals, which again indicates that any difference in hypothalamic "set-point" does not manifest within the ARC. On the other hand, distinct differences in gene expression exist at the level of the PVN and in the orexin cells of the LHA. The expression of both the MC3R and MC4R is lower in the PVN of HR compared to LR animals [75] (Fig. 3). This confers a difference in the sensitivity to the melanocortins, such that intracerebroventricular infusion of αMSH reduces food intake in LR animals only

[75]. Furthermore, expression of orexin is greater in LR than HR [75] (Fig. 3), and this may relate to inherent variation in the control of food intake, energy expenditure, or physical activity as detailed below.

*Divergent Metabolic and Behavioural Responses to Stress in LR and HR Animals*

At metabolic equilibrium, LR and HR animals have similar food intake, but HR animals become relatively more obese on a high-energy diet [73]. Also at equilibrium, post-prandial thermogenesis in skeletal muscle is lower in HR than in LR [73, 75]. Thus, in the resting state, the primary driver of increased propensity to obesity is most likely due to an inherently lower level of thermogenesis in the skeletal muscle of HR animals.

The majority of humans over-eat in response to stress, with only a small subpopulation reducing food intake [82]. Recent studies have linked over-eating, especially the consumption of high-fat/high-sugar comfort foods, to the individual's cortisol response to stress. In women characterised as HR, appetite is greater and there is an increased preference for comfort foods after psychosocial stress than in those characterised as LR [78]. We have shown similar results in LR and HR sheep, whereby psychosocial stress (introduction of a barking dog) reduces food intake in LR sheep only [74]. Likewise, immune challenge (lipopolysaccharide: LPS treatment) reduced food intake in both LR and HR sheep, albeit the effect was greater in the former [74]. This indicates clear divergence in the catabolic effects of stress, which associate with inherent differences in cortisol responsiveness. This may not be so surprising given the role of the melanocortin system in modulating food intake in response to stressful episodes. In sheep, for example, the melanocortin system is essential to the inhibition in food intake caused by LPS [84]. Thus, reduced expression of MC3R and MC4R in the PVN of HR animals may be a fundamental cause of the attenuated catabolic effect of stress on food intake.

In addition to altered food intake following stress, HR animals display greater heat production in skeletal muscle than LR animals with LPS challenge [74]. It is unlikely that this is driven by a greater immune response to LPS, since plasma levels of interleukins 4, 6, 10, and 12, and tumour necrosis factor-α levels were similar in LR and HR before and after injection of LPS [74]. In rodents, the hypothalamus is integral to the response to cold-, immune-, and stress-induced BAT thermogenesis [85]. The DMH is thought to be the command centre driving these thermogenic responses during stress [86]. There is some evidence from mice that the effects of leptin and the melanocortins to regulate thermogenesis manifest within the DMH [87]. It would be interesting to ascertain whether LR and HR animals exhibit differential expression of MC4R in this nucleus, as seen in the PVN; this could be important for differential control of thermogenesis during stress.

As stated above, the orexin neurons in the PeF/LHA are a prominent component of the hypothalamic circuitry controlling thermogenesis [65–67]. Ablation of the orexin neurons in the LHA eliminates cold-, stress-, and immune-induced BAT thermogenesis [88, 89]; an effect that may, however, be due to glutamate signalling [88]. Nonetheless, the increased expression of orexin in the LHA of LR animals may be important in mediating the enhanced skeletal muscle thermogenic response to immune challenge.

LR and HR sheep also display distinct behavioural traits that align with increased energy expenditure. A series of behavioural tests show that LR animals exhibit proactive coping strategies [74]. This contrasts work in mice, in that HR mice show hyper-activity in response to stress [83]. Nonetheless, LR ewes show greater physical activity in response to isolation stress, reduced fear towards humans, reduced freezing and increased initiative to reach a food reward [74]. It has previously been hypothesised that animals that exhibit a proactive coping style rather than a reactive style may be more likely to expend energy [90, 91]. A proactive coping strategy is typically associated with increased aggression and physical activity, low cortisol secretion and heightened sympathetic output in response to stress [90, 91], all of which are consistent with increased energy expenditure. Indeed, in pigs, genetic studies have linked increased stress responsiveness with heightened aggression [77]. The orexin system has been implicated in arousal and sleep-wake cycles, and mutations in either the prepro-orexin gene or the gene that encodes the orexin 2 receptor cause narcolepsy in dogs, rodents, and humans [92–95]. Thus, increased expression of orexin in LR animals is consistent with the increased physical activity of these animals [75]. This is further indicative of the orexin system being fundamental to determining both behavioural and metabolic responses to stress in animals characterised as LR and HR.

In summary, the LR and HR animals display a cohesive set of neuroendocrine, metabolic, and behavioural traits that influence metabolic function and energy homeostasis. Sheep characterised as HR have reduced muscle thermogenesis, impaired satiety to αMSH, a relative increase in food intake in response to stress, and reduced physical activity. Collectively, a net increase in food intake and re-

**Table 1.** Summary of the species differences in leptin resistance at normal body weight and in the obese state

| Model | At normal body weight | Obesity | Ref. |
|---|---|---|---|
| DIO | Impaired leptin sensitivity precedes weight gain | Leptin resistant | 38–42 |
| Humans | Reduced leptin levels can predict weight gain | Leptin resistant | 45–49 |
| Genetically obese sheep | ? | No change in leptin sensitivity | 55, 58 |
| HR sheep | No change in leptin sensitivity | ? | 73 |

duced energy expenditure culminates in an obesity-prone phenotype. Gene expression analyses within the hypothalamus indicate that reduced expression of MC3R and MC4R in the PVN and/or reduced expression of orexin in the LHA underpin the physiological and metabolic phenotype in HR animals. Furthermore, identifying individuals that exhibit HR may be a means to develop personalised weight loss strategies. A number of the new generation of anti-obesity drugs are known to target the melanocortin pathway, including Contrave, Lorcaserin, and Liraglutide [96–98]. The current data suggest that HR individuals may be less responsive to these pharmacotherapies and thus would greatly benefit from alternative weight loss strategies and therapies. This, however, remains to be formally tested.

## Conclusions

There is great individual variation in the susceptibility to gain weight and develop obesity. On the flip side, weight loss is also vastly variable across populations. A key component that determines individual differences in either weight gain or the ability to successfully lose weight is influenced by inherent variation in energy expenditure. This review describes the role of energy expenditure and, in particular, thermogenesis, in determining differences in the propensity to gain weight in 3 animal models, the DIO and DR rodents, genetically lean and obese sheep, and selection for high/low cortisol responsiveness in sheep. In all 3 models, an innate reduction in thermogenesis is associated with the increased susceptibility to become obese. Changes at the level of the hypothalamus are thought to underpin these differences in energy homeostasis. It is apparent, however, that the hypothalamic pathways involved in weight control differ between species. In rodents, a principal difference between DR and DIO animals is the development of leptin resistance, which occurs at baseline [39] and is exacerbated by high-fat feeding [38, 40]; this is somewhat similar to humans (Table 1). This leads to fundamental differences at the level of the ARC [42, 44]. Neither sheep model shows inherent differences in leptin sensitivity [58, 73], and there are there no functional differences at the level of the ARC [55, 75] (Table 1). Still, in sheep selected for high cortisol responsiveness, increased susceptibility to obesity is associated with resistance to the satiety effect of αMSH and reduced MC3R/MC4R expression in the PVN [75]. Furthermore, inherent differences in thermogenesis in sheep are consistently associated with altered expression of orexin in the LHA, irrespective of the model studied [55, 75].

This review describes species differences within the hypothalamus that are associated with altered energy expenditure, leading to a propensity to develop obesity. This highlights the importance of utilising large animal models in order to gain a better understanding of the neural pathways that govern predisposition to weight gain.



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