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Review

Effects of deficiency of the G protein $G_s\alpha$ on energy and glucose homeostasis

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ABSTRACT

$G_s\alpha$ is a ubiquitously expressed G protein α-subunit that couples receptors to the generation of intracellular cyclic AMP. The $G_s\alpha$ gene *GNAS* is a complex gene that undergoes genomic imprinting, an epigenetic phenomenon that leads to differential expression from the two parental alleles. $G_s\alpha$ is imprinted in a tissue-specific manner, being expressed primarily from the maternal allele in a small number of tissues. Albright hereditary osteodystrophy is a monogenic obesity disorder caused by heterozygous $G_s\alpha$ mutations but only when the mutations are maternally inherited. Studies in mice indicate a similar parent-of-origin effect on energy and glucose metabolism, with maternal but not paternal mutations leading to obesity, reduced sympathetic nerve activity and energy expenditure, glucose intolerance and insulin resistance, with no primary effect on food intake. These effects result from $G_s\alpha$ imprinting leading to severe $G_s\alpha$ deficiency in one or more regions of the central nervous system, and are associated with a specific defect in melanocortins to stimulate sympathetic nerve activity and energy expenditure.

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Contents

1. Introduction

The heterotrimeric G proteins are a large family of membrane-associated proteins that couple with seven transmembrane receptors to transmit signals to the intracellular compartment. Each G protein is defined by its specific α subunit and is composed of α, β and γ subunits that are the product of separate genes. The G protein G_s contains the $G_s\alpha$ stimulatory α-subunit that couples cell surface receptors to adenylyl cyclase and mediates receptor-stimulated intracellular cAMP generation. $G_s\alpha$ is encoded by *GNAS*, a gene that is affected by genomic imprinting, and therefore heterozygous $G_s\alpha$ mutations in both humans and mice lead to effects on energy and glucose metabolism that are dependent on the parent-of-origin of the mutation (Weinstein et al., 2007). Recent studies show that this is due to $G_s\alpha$ imprinting in the central nervous system which leads to specific impairment on the actions of central melanocortins. In this paper we will review the evidence for $G_s\alpha$ imprinting effects on metabolic regulation and melanocortin action.

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2. $G_s\alpha$ signaling and function

$G_s\alpha$, a product of the imprinted *GNAS* gene, is a ubiquitously expressed G protein α-subunit which couples many seven-transmembrane receptors for hormones, neurotransmitters, and other extracellular stimuli to the stimulation of adenylyl cyclase and the generation of intracellular cyclic AMP (Weinstein et al., 2007). cAMP mediates its effects primarily by activation of protein kinase A, a serine/threonine protein kinase which was classically known to phosphorylate enzymes and other factors to stimulate release of glucose and free fatty acids into the circulation through increased gluconeogenesis, glycogenolysis, and lipolysis, as well as many other cellular substrates. Protein kinase A also chronically stimulates gene expression via phosphorylation of transcription factors such as cAMP response element binding protein (CREB) (Montminy, 1997). In addition, $G_s\alpha$/cAMP mediates the effects of sympathetic nerve activity on peripheral tissues such as brown and white adipose tissue, liver, and muscle as this signaling pathway is stimulated by β adrenergic receptors (Bachman et al., 2002). cAMP also mediates some of its actions, particularly in neuroendocrine cells, by stimulating cAMP-regulated guanine nucleotide exchange factors leading to activation of ras-like proteins such as Rap1 (de Rooij et al., 1998). $G_s\alpha$ may also mediate its effects by stimulating other downstream effectors, such as Ca^{2+} channels (Mattera et al., 1989), and may interact with receptors outside of the seven transmembrane receptor family (Sun et al., 1997).

3. Organization and imprinting of the $G_s\alpha$ gene *GNAS*

The $G_s\alpha$ gene *GNAS* and its mouse ortholog *Gnas* have similar overall organizations and reside within syntenic regions at 20q13.2–13.3 and distal chromosome 2, respectively (Weinstein et al., 2007). *GNAS* and *Gnas* also undergo genomic imprinting and have similar overall imprinting patterns. Genomic imprinting is an epigenetic process in which a specific biochemical imprint 'mark' (e.g. DNA methylation) is erased in primordial germ cells and then reestablished during oogenesis or spermatogenesis (depending on the specific imprinted gene), resulting in suppression of gene expression from one parental allele (Reik and Walter, 2001). All imprinted genes have one or more regions in which the maternal and paternal alleles are differentially methylated. DNA methylation of a gene promoter region leads to silencing, but in other cases DNA methylation may occur on the transcriptionally active allele when it is outside the promoter region.

GNAS and *Gnas* generate multiple gene products in addition to $G_s\alpha$ through the use of alternative promoters and first exons that splice on to a set of common downstream exons (Fig. 1). The two most upstream promoters generate transcripts for NESP55 (neuroendocrine-specific protein of 55 kDa) (Hayward et al., 1998b; Kelsey et al., 1999; Peters et al., 1999) and the $G_s\alpha$ isoform XLαs (Hayward et al., 1998a; Kehlenbach et al., 1994; Kelsey et al., 1999; Peters et al., 1999), respectively. NESP55 and XLαs are oppositely imprinted, being expressed only from the maternal and paternal allele, respectively, due to methylation of the respective promoter regions on the opposite parental allele (Hayward et al., 1998b; Peters et al., 1999). NESP55 is a chromogranin-like protein expressed primarily in neuroendocrine cells that is unrelated to the G protein family (Ischia et al., 1997), and studies in both humans and mice suggest that it plays no significant role in metabolic regulation (Liu et al., 2000a; Plagge et al., 2005). XLαs is a $G_s\alpha$ isoform with a long amino-terminal extension encoded by its specific first exon that is expressed in the central nervous system and a few other organs, and is capable of also mediating receptor-stimulated cAMP generation (Bastepe et al., 2002). XLαs knockout mice have elevated sympathetic nerve activity and are hypermetabolic with improved glucose metabolism, indicating that XLαs normally plays a role in downregulating sympathetic nerve activity in mice (Plagge et al., 2004; Xie et al., 2006). Alternatively, a truncated form of XLαs (XLN1) highly expressed in neurons (Pasolli et al., 2000) may be a dominant negative regulator of $G_s\alpha$ function. It is unclear whether XLαs plays an important role in metabolic control in humans, as *GNAS* mutations on the paternal allele that disrupt XLαs do not produce a similar phenotype.

The $G_s\alpha$ promoter is not methylated on either allele (Hayward et al., 1998a; Kozasa et al., 1988; Liu et al., 2000b; Peters et al., 1999). In spite of this, $G_s\alpha$ is imprinted in a tissue-specific manner being expressed primarily from the maternal allele in a number of tissues including pituitary somatotrophs, thyroid, renal proximal tubules, ovaries, and the paraventricular nucleus of the hypothalamus while being biallelically expressed in most other tissues (Campbell et al., 1994; Chen et al., 2009b; Davies and Hughes, 1993; Germain-Lee et al., 2002; Hayward et al., 2001; Liu et al., 2003; Mantovani et al., 2002; Weinstein et al., 2001; Yu et al., 1998).

Just upstream of the $G_s\alpha$ promoter region is an imprint control region (the exon 1A or exon A/B promoter region) (Fig. 1) that is methylated on the maternal allele (Ishikawa et al., 1990; Liu et al., 2000a, 2000b). In pseudohypoparathyroidism type 1B, a condition with renal parathyroid hormone resistance, the exon 1A methylation on the maternal allele is absent (Bastepe et al., 2001; Jan de Beur et al., 2003; Liu et al., 2000a, 2005b). Based upon this observation it has been suggested that this region has a negative regulatory cis-acting element that suppresses the paternal $G_s\alpha$ allele in a tissue-specific manner (Liu et al., 2005a; Williamson et al., 2004). For example, there may be a silencer that binds a tissue-specific repressor protein on the paternal allele, but this repressor fails to bind to the maternal allele due to methylation, allowing $G_s\alpha$ to always be expressed from the maternal allele. Consistent with this, mice with paternal deletion of the exon 1A region had reversal of $G_s\alpha$ imprinting with biallelic expression of $G_s\alpha$ in all tissues (Liu et al., 2005a; Williamson et al., 2004).

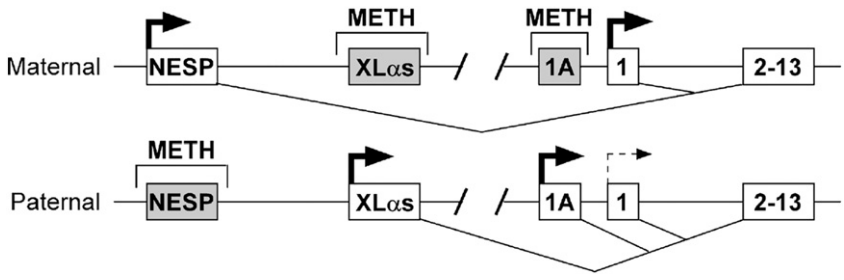

Fig. 1. Organization and imprinting of the *GNAS* gene. The maternal and paternal alleles of the *GNAS* gene are depicted showing four alternative first exons for NESP55 (NESP), XLαs, 1A mRNA transcripts, and $G_s\alpha$ (exon 1) splicing onto common exons 2 through 13 (shown as a single box). Regions of differential methylation (METH) are shown above and splicing patterns are shown below each allele. Active promoters are shown in white with horizontal arrows while inactive promoters are shown in gray. The thin and dashed arrow for the paternal $G_s\alpha$ promoter indicates that this promoter is suppressed in a tissue-specific manner due to genomic imprinting.

4. Parent-of-origin metabolic effects of $G_s\alpha$ mutation in humans and mice

4.1. Role of $G_s\alpha$ in energy balance in humans

Heterozygous $G_s\alpha$ loss-of-function mutations lead to Albright hereditary osteodystrophy, a congenital disorder characterized by the presence of short stature, brachydactyly (shortening of various long bones in the hands and feet), subcutaneous ossifications, and neurobehavioral abnormalities (Weinstein et al., 2006). When the mutation is on the maternal allele patients also develop multi-hormone resistance to parathyroid hormone, thyrotropin, growth hormone-releasing hormone, and gonadotropins, a condition known as pseudohypoparathyroidism type 1A. In contrast patients with mutations on the paternal allele only develop the features of Albright hereditary osteodystrophy without multihormone resistence, a condition known as pseudopseudohypoparathyroidism (Davies and Hughes, 1993; Weinstein et al., 2006). This is the direct result of tissue-specific $G_s\alpha$ imprinting, as mutation of the active maternal $G_s\alpha$ allele leads to severe $G_s\alpha$ deficiency and hormone resistance wheras mutation of the inactive paternal allele has little effect on $G_s\alpha$ expression or hormone sensitivity (Germain-Lee et al., 2002; Hayward et al., 2001; Liu et al., 2003; Mantovani et al., 2002; Yu et al., 1998).

Albright hereditary osteodystrophy is also a monogenic obesity disorder, with early onset obesity (within the first year) but only in patients with $G_s\alpha$ mutations on the maternal allele (pseudohypoparathyroidism type 1A but not pseudopseudohypoparathyroidism) (Long et al., 2007). Although adipocytes from pseudohypoparathyoidism type 1A patients have reduced lipolytic responses to epinephrine due to reduced $G_s\alpha$ levels (Carel et al., 1999), this is unlikely to be the cause of obesity as there is no evidence for $G_s\alpha$ imprinting in adipose tissue (Chen et al., 2005a; Germain-Lee et al., 2005; Mantovani et al., 2004). A more likely explanation for obesity in pseudohypoparathyroidism type 1A is a defect in the central nervous system leading to low sympathetic nerve activity and metabolic rate, as children with pseudohypoparathyroidism type 1A were shown to have extremely low serum norepinephrine levels when compared to controls or even similarly obese children without pseudohypoparathyroidism type 1A (Carel et al., 1999). In one recent case report, severe obesity developed in a pseudohypoparathyroidism type 1A patient in the first year of life even in the absence of hyperphagia, also consistent with obesity in this disorder being primarily the result of low energy expenditure (Dekelbab et al., 2009). The incidence of insulin resistance and diabetes in pseudohypoparathyroidism type 1A has not been systematically examined, although severe insulin resistance in a young pseudohypoparathyroidism type 1A patient has been recently reported (Nwosu and Lee, 2009).

Other studies have shown an association of $G_s\alpha$ single nucleotide polymorphisms with obesity or weight loss. For example the silent T393C polymorphism was associated with increased obesity and insulin resistance in German women with polycystic ovarian syndrome, but not in a larger unselected population (Hahn et al., 2006). Another polymorphism within the $G_s\alpha$ promoter was shown to affect binding of the transcriptional factor upstream stimulatory factor 1, $G_s\alpha$ expression, lipolytic rates in adipocytes, and short-term weight loss, but was not associated with differences in baseline obesity (Frey et al., 2008a, 2008b).

4.2. Parent-of-origin metabolic effects of $G_s\alpha$ mutations in mice

Similar to what is observed in pseudohypoparathyroidism type 1A and pseudopseudohypoparathyroidism patients (Long et al., 2007), mutation of the maternal but not the paternal $G_s\alpha$ allele (deletion of $G_s\alpha$ exon 1) leads to severe obesity which is associated with reduced sympathetic nerve activity and energy expenditure, with no primary abnormality in food intake (Chen et al., 2005a; Germain-Lee et al., 2005; Xie et al., 2008). In addition these mice also develop glucose intolerance, insulin resistance and hyperlipidemia, a phenotype reminiscent of the metabolic syndrome (Chen et al., 2005a). Other models with mutation of the maternal $G_s\alpha$ allele also develop obesity with reduced energy expenditure as well (Kelly et al., 2009; Yu et al., 2000).

The similar parent-of-origin effects of $G_s\alpha$ mutations on energy balance in humans and mice strongly suggests that obesity associated with maternal $G_s\alpha$ mutations results from severe $G_s\alpha$ deficiency in one or more tissues due to mutation of the active maternal $G_s\alpha$ allele and suppressed $G_s\alpha$ expression from the inactive paternal allele due to tissue-specific imprinting. Consistent with this hypothesis, reversal of imprinting resulting from the presence of the 1A imprint control region deletion on the paternal allele led to complete reversal of the maternal $G_s\alpha$ metabolic phenotype (Xie et al., 2008).

5. $G_s\alpha$ imprinting in the central nervous system underlies the parent-of-origin metabolic effects of $G_s\alpha$ mutations

Although $G_s\alpha$ is expressed in liver, adipose tissue, pancreatic islets and muscle, these tissues are not involved in the parent-of-origin effects of $G_s\alpha$ mutations as $G_s\alpha$ expression is not affected by imprinting in these tissues (Germain-Lee et al., 2005; Mantovani et al., 2004; Weinstein et al., 2007; Yu et al., 1998, 2000) and $G_s\alpha$ knockouts in these tissues do not produce a phenotype similar to the germline maternal $G_s\alpha$ knockout (Chen et al., 2009a, 2009b, 2010; Xie et al., 2007, 2010). However studies of mice with disruption of either the maternal or paternal $G_s\alpha$ allele in the central nervous system (mBrGsKO and pBrGsKO mice, respectively) that were generated by reciprocal matings of Nestin-cre and $G_s\alpha$-floxed mice indicate that $G_s\alpha$ imprinting in the central nervous system underlies the parent-of-origin effects of $G_s\alpha$ mutations on energy and glucose metabolism (Chen et al., 2009b). mBrGsKO mice develop severe obesity associated with lower sympathetic nerve activity and energy expenditure and greater metabolic efficiency (weight gain/calorie intake), but without hyperphagia. In addition, mBrGsKO mice became glucose intolerant and insulin resistant even before the development of obesity, indicating that $G_s\alpha$ deficiency in the central nervous system has a primary effect on peripheral glucose metabolism. In contrast, pBrGsKO maintain a normal metabolic phenotype.

Studies examining $G_s\alpha$ expression within the central nervous system in mice with maternal and paternal $G_s\alpha$ mutations show that $G_s\alpha$ undergoes imprinting in the paraventricular nucleus of the hypothalamus, but not in the nucleus of the solitary tract or hippocampus (Chen et al., 2009b). As the paraventricular nucleus is a major site of metabolic regulation it may at least account for some of the parent-of-origin effects of $G_s\alpha$ mutations on metabolism. In fact, mice with maternal $G_s\alpha$ mutation restricted to the paraventricular nucleus and a few other sites made using Single minded 1 (Sim1) promoter-cre recombinase mice also develop mild obesity, glucose intolerance, insulin resistance, and reduced energy expenditure, although the effects were more prominent in males than females and overall much milder than in mBrGsKO mice (M.C., L.S.W., unpublished results). These findings indicate that the paraventricular nucleus plays a role in the metabolic effects observed in mice with maternal $G_s\alpha$ mutations, but that other brain regions are likely to be involved as well. In contrast, mice with hetero- or homozygous $G_s\alpha$ mutation in the ventral medial nucleus of the hypothalamus (made using steroidogenic factor 1 (Sf1) promoter-cre mice) showed no abnormalities in energy or glucose metabolism (M.C., L.S.W., unpublished results). Overall, our findings in mBrGsKO and pBrGsKO mice show that the metabolic phenotype generated by germline maternal $G_s\alpha$ mutation is due to an effect of $G_s\alpha$ imprinting in the central nervous system.

6. $G_s\alpha$ deficiency in the central nervous system impairs the stimulation of energy expenditure by central melanocortins

The status of energy balance is communicated to the brain through various signals, including hormones (e.g. leptin, ghrelin, insulin), nutrients (e.g. glucose, fatty acids) and afferent neural inputs from the gut (Saper et al., 2002). The hypothalamus integrates these signals to regulate food intake and energy expenditure, and the brainstem also receives signals to primarily control hunger and satiety (Cone, 2005). Several hypothalamic nuclei are involved in control of energy balance, including the arcuate, paraventricular, and ventromedial nuclei and the lateral hypothalamic area. The arcuate nucleus, one of main targets of leptin and insulin, contains neurons expressing orexigenic polypeptides (neuropeptide Y and agouti-related protein), and others expressing anorexigenic polypeptides (proopiomelanocortin and cocaine- and amphetamine- regulated transcript).

Proopiomelanocortin neurons located in the arcuate nucleus are activated by leptin to inhibit food intake and stimulate sympathetic nerve activity and energy expenditure, leading to negative energy balance (Brito et al., 2007; Butler and Cone, 2002; Nogueiras et al., 2007). These neurons project to the paraventricular and ventral medial nuclei of the hypothalamus and other sites where they release α-melanocyte stimulating hormone, which activates melanocortin MC_3 and MC_4 receptors in downstream neurons (Bagnol et al., 1999; Cowley et al., 1999; Xu et al., 2003). Melanocortin MC_4 and MC_3 receptors are seven transmembrane receptors known to couple to $G_s\alpha$. Most of the effects of central melanocortins on energy balance are mediated via melanocortin MC_4 receptors (Chen et al., 2000b; Marsh et al., 1999). In addition to their locations in the hypothalamus, melanocortin MC_4 receptors are also expressed in other locations of the central nervous system involved in energy balance, including the hindbrain and the sympathetic preganglionic neurons in the intermediolateral nucleus of the spinal cord, the latter of which also receive neural projections from the paraventricular nucleus of the hypothalamus (Elias et al., 1998; Kishi et al., 2003; Saper et al., 1976; Swanson and Kuypers, 1980).

Melanocortin MC_4 receptor mutations are the most common cause of monogenic obesity in humans (Farooqi et al., 2003; Krude et al., 1998; Vaisse et al., 1998; Yeo et al., 1998) and also lead to severe obesity in mice (Huszar et al., 1997; Marsh et al., 1999), in both cases being associated with both hyperphagia and reduced sympathetic nerve activity and energy expenditure. In contrast, melanocortin MC_3 receptor mutation in mice results in more subtle changes in adiposity (Chen et al., 2000a). In addition to their effects on energy balance, melanocortin MC_4 receptor mutations also lead to increased linear growth and primary effects on peripheral glucose metabolism (Fan et al., 2000; Nogueiras et al., 2007; Obici et al., 2001).

Mice with central nervous system-specific (mBrGsKO) or germline disruption of the maternal $G_s\alpha$ allele partially mimic melanocortin MC_4 receptor null mice in that they develop severe obesity with reduced sympathetic nerve activity and energy expenditure as well as glucose intolerance and insulin resistance (Chen et al., 2005a, 2005b). These effects on sympathetic nerve activity and energy expenditure are likely due to impaired responsiveness of mBrGsKO mice to the effect of central melanocortins on energy expenditure, as mBrGsKO mice have a reduced increase in energy expenditure in response to a melanocortin agonist (Chen et al., 2009b). Consistent with this finding, mBrGsKO have evidence of reduced sympathetic nerve activity (reduced norepinephrine content in brown adipose tissue, heart rate, and diastolic blood pressure) and impaired diet-induced thermogenesis, a process known to be dependent on melanocortin MC_4 receptor signaling (Butler et al., 2001; Voss-Andreae et al., 2007). This mechanism also likely underlies the obesity in pseudohypoparathyroidism type 1A patients, as these patients have low circulating norepinephrine levels (Carel et al., 1999).

However, mice with maternal $G_s\alpha$ mutations do not develop all the features seen with melanocortin MC_4 receptor mutations, such as hyperphagia or increased linear growth (Chen et al., 2005a, 2005b). Consistent with the lack of hyperphagia, the ability of a melanocortin agonist to acutely reduce food intake was unaffected in mBrGsKO mice (Chen et al., 2009b). Early-onset obesity in the absence of hyperphagia has been well documented in at least one child with pseudohypoparathyroidism type 1A (Dekelbab et al., 2009). Sim1 is a transcription factor expressed almost exclusively in the paraventricular nucleus that is upregulated by melanocortin MC_4 receptor signaling and mediates some of the effects of melanocortins (Kublaoui et al., 2006b). Sim1 mutations in humans and mice also lead to obesity, but in contrast to mBrGsKO mice, this effect is associated with hyperphagia and increased linear growth, with no primary effects on energy expenditure or glucose metabolism (Faivre et al., 2002; Holder et al., 2000; Holder et al., 2004; Kublaoui et al., 2008; Kublaoui et al., 2006a). Moreover, Sim1 haploinsufficient mice have the opposite pattern of melanocortin responsiveness to that seen in mBrGsKO (normal increase in energy expenditure and impaired ability to inhibit food intake) (Kublaoui et al., 2006a). Based upon these observations, we propose the possibility that melanocortins mediate their actions through independent signaling pathways downstream of melanocortin MC_4 receptors: a $G_s\alpha$-dependent pathway involved in regulating sympathetic nerve activity, energy expenditure, and glucose metabolism, and a $G_s\alpha$-independent pathway working through Sim1 involved in food intake and linear growth. Further studies are required to determine whether is hypothesis is correct, and if so, whether other G proteins are involved in the melanocortin MC_4 receptor/Sim1 pathway. We are also examining whether there is $G_s\alpha$ imprinting in other regions of the central nervous system.

7. Divergent metabolic effects of $G_s\alpha$ deficiency in different peripheral tissues

In addition to its effects in the central nervous system, $G_s\alpha$ plays important roles in peripheral tissues that also are involved in energy and glucose metabolism. We have generated several tissue-specific $G_s\alpha$ knockouts (in each case homozygous null) to examine these effects in other metabolically active tissues. Liver-specific $G_s\alpha$ knockout mice have increased insulin sensitivity and fasting hypoglycemia, associated with hepatic glucagon resistance and islet cell hyperplasia (Chen et al., 2005b). Skeletal-muscle $G_s\alpha$ specific knockout mice have impaired glucose tolerance in the absence of insulin deficiency and resistance, most likely as the result of reduced skeletal muscle mass. In addition, there appears to be a switch of the muscle fiber type towards aerobic, slow twitch (red) fibers even though the muscles have metabolic characteristics more typical of anaerobic, fast-twitch (white) fibers (Chen et al., 2009a). Adipose tissue-specific $G_s\alpha$ knockout mice have markedly impaired adipogenesis (Chen et al., 2010). While these mice have reduced cold-induced thermogenesis due to resistance of brown adipose tissue to sympathetic stimulation, diet-induced thermogenesis is maintained indicating that these two forms of adaptive thermogenesis may occur in separate tissues. Finally, studies in pancreas-specific $G_s\alpha$ knockout models (Xie et al., 2007, 2010) indicate that $G_s\alpha$ signaling is required for normal β cell proliferation and maintanence of β cell mass and that $G_s\alpha$ may have opposite effects on proliferation of pancreatic α and β cells.

8. Conclusion

One widely accepted hypothesis underlying the imprinting process is the parental conflict hypothesis which predicts that paternally transmitted alleles promote fetal growth as the father wants to maximize survival of his offspring while maternally transmitted alleles inhibit fetal growth so the mother can reserve resources for multiple litters (Haig, 2004). Imprinted genes also appear to be

involved in postnatal energy metabolism as several diseases caused by mutations in imprinted genes lead to obesity (e.g. Prader–Willi syndrome, pseudohypoparathyroidism type 1A) and population studies have identified a number of chromosomal regions associated with parent-of-origin effects on energy balance in humans (Dong et al., 2005; Gorlova et al., 2003; Lindsay et al., 2001; Rance et al., 2005). The effect of *GNAS* imprinting on energy balance is consistent with the parental conflict hypothesis, a loss of the paternally expressed XLαs leads to a lean phenotype with increased sympathetic nerve activity and energy expenditure while the oppositely imprinted *GNAS* gene product $G_s\alpha$ leads to obesity due to opposite effects on sympathetic nerve activity and energy expenditure.

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