upregulation of α-MSH was thought to mediate anorexigenic effects of insulin, as application of a melanocortin antagonist prevents the insulin-induced reduction in food intake (25). The exact interplay of these regulatory networks and their regulation by insulin has been the subject of numerous reviews (27–31). The analogous nature of insulin signaling to the well-characterized hypothalamic effects of leptin, which also suppresses NPY/AgRP expression and stimulates POMC expression, has led to the notion that insulin and leptin exert similar effects on regulatory entities in the hypothalamus.

Insulin and leptin activate signaling via different classes of receptor molecules: leptin signals through a cytokine receptor, and insulin signals through a membrane-bound tyrosine kinase receptor. Leptin robustly activates POMC gene expression via activation of STAT3, while insulin fails to significantly activate STAT3 phosphorylation (32). However, recently a novel mechanism of PI3K/FOXO1-dependent regulation of both AgRP and POMC transcription has been described. STAT3 and FOXO1 bind to partially overlapping motifs in the promoter region of both the Agrp and the Pome genes (33). While STAT3 increases and FOXO1 decreases POMC promoter activity, STAT3 activation decreases and FOXO1 increases Agrp promoter activity. Taking into account that leptin activates STAT3 and insulin inactivates FOXO1, transcriptional regulation of POMC and AgRP expression by these transcription factors may represent a mechanism to reconcile leptin and insulin signaling in the hypothalamus (Figure 1).

Although many studies have focused on the regulation of NPY/AgRP transcription, the obvious lack of a phenotype in energy homeostasis of mice with targeted disruption of the Agrp and/or Npy gene(s) has put the importance of this pathway into question (34). This finding challenged the critical role of AgRP neurons in energy homeostasis. Only recently has a study demonstrated that AgRP-deficient mice exhibit an age-dependent lean phenotype arising from increased energy expenditure (35). Furthermore,