ENERGY HOMEOSTASIS

Seeing the forest for the trees in obesity

GABA-expressing neurons in the arcuate nucleus of the hypothalamus regulate obesity in mice. A recent study indicates the importance of unexamined cell types.

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For two decades, models of appetite control and energy homeostasis have emphasized a yin–yang relationship between two intermingled molecularly defined neuron subpopulations in the hypothalamic arcuate nucleus (ARC)[1]. Proopiomelanocortin (POMC) neurons decrease food intake and increase body weight, whereas Agouti-related neuropeptide (AGRP) neurons have the opposite effect. Moreover, AGRP neurons inhibit POMC neurons, and the neuropeptides released by these two neurons also have antagonistic effects at downstream targets. Recent efforts have aimed at identifying additional subpopulations of molecularly defined ARC neurons that regulate appetite. In this issue, Zhu et al.[2] pursued a subtractive approach to determine whether AGRP neurons are the major appetite-controlling cell type in the ARC and found that chronic control of appetite is likely to be regulated by additional subpopulations of ARC neurons.

AGRP neurons have been investigated primarily for their functions in acutely eliciting avid food seeking and consumption[3,4]. AGRP neurons contribute to elevated appetite during food deprivation with moderate-palatability food but not high-palatability food[5]; therefore, AGRP neurons can modulate hunger, but they are not a necessary component of appetitive behaviour. AGRP neurons also express leptin receptors and are inhibited by leptin. Mixed evidence has suggested that leptin's effects on appetite and body weight rely primarily on AGRP neurons[6]. However, a recent study has strongly indicated an essential role of AGRP neurons in long-term leptin control of energy homeostasis[7].

Zhu et al. expand this picture and conclude that AGRP neurons are not the primary mediators through which leptin regulates appetite and body weight. They report that neurons within the ARC that express *Vgat* (official symbol *Slc32a1*) increase appetite and decrease energy expenditure, thus producing massive obesity. They observed that the effects of ARC^{VGAT}-neuron activation on appetite, energy expenditure and body weight was maintained even after elimination or suppression of AGRP neurons. Moreover, leptin sensitivity was maintained when AGRP neurons were ablated, and chronic inhibition of AGRP neurons did not affect food intake or body weight in obese, leptin-deficient *ob/ob* mice. In contrast, chronic inhibition of ARC^{VGAT} neurons decreased food intake, increased energy expenditure, normalized the body weight of *ob/ob* mice and also decreased body weight in lean, leptin-positive mice.

These findings underscore the case for further evaluation of ARC neuronal subtypes for their roles in appetite control (Fig. 1). Prior work has shown that *Th*-expressing neurons in the ARC, which coexpress VGAT, can also increase appetite, although the acute effect of ARCTH-neuron activation is smaller than that of AGRP neurons[8]. The role of these neurons in leptin sensitivity is unclear, although chronic inhibition has been reported to decrease body weight[8]. Recently, 26 molecularly defined neuronal subtypes have been predicted for the ARC, on the basis of single-cell RNA-sequencing transcriptional similarity analysis, and *Vgat* coexpression is present in 19 of these predicted cell types[9]. *Sst*-expressing ARC populations also partially overlap with AGRP neurons but may additionally contribute to energy homeostasis[9]. Moreover, three of the glutamatergic cell types are subdivisions of appetite-suppressing POMC neurons; another appetite-suppressing glutamatergic population expresses *Oxtr*[10], whereas glutamatergic ARC neurons coexpressing *Tac2* and *Kiss1* do not affect appetite[9]. The results from Zhu et al. emphasize the importance of further investigation of the functional role of the ARC^{VGAT} neurons to uncover more extensive parcellation of appetite-controlling functional responses in the ARC.

One issue with the study by Zhu et al. is the potential contribution of modulation of *Vgat*-expressing neurons outside the ARC, which was not entirely excluded, on the basis of the data presented. Nevertheless, there are good indications that other

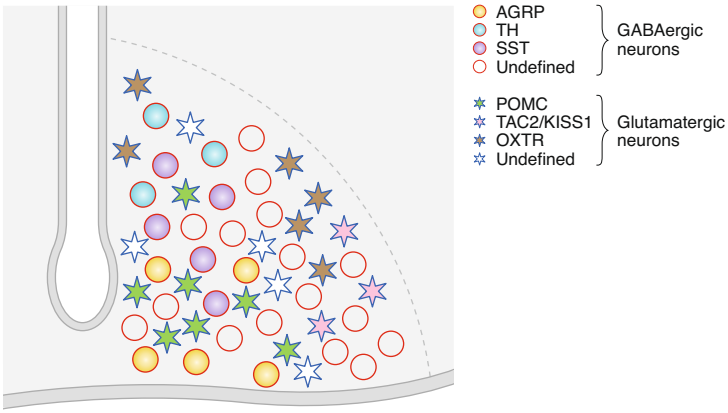

Fig. 1 | Cell-type hierarchies in the ARC. Cells in the ARC are GABAergic (circles) or glutamatergic (stars). These categories of ARC neurons are further subdivided into cell types. Only subsets of these molecularly defined cell types have been examined for roles in appetite regulation. Many cell types remain to be examined for roles in body-weight control. Zhu et al. examine the contributions of ARC^{VGAT} neurons to appetite, body weight and leptin sensitivity by using a subtractive approach based on AGRP-neuron ablation. TH, tyrosine hydroxylase; SST, somatostatin; TAC2, tachykinin 2; KISS1, kisspeptin 1; OXTR, oxytocin receptor.

inhibitory non-AGRP-neuron ARC cell types have appetite-regulatory roles[8,9]. Another consideration is that strong compensatory processes are associated with a loss of AGRP neurons in neonates[11] and cannot be excluded in assessing the relative circuit contributions of ARC^{VGAT} neurons in AGRP-neuron-ablated mice.

Despite these caveats, this study highlights the importance of sifting through the diversity of ARC cell types to establish the core set of appetite-regulating neurons. Determining the importance of one molecularly defined grouping of neurons relative to that of another is currently a slow and labour-intensive process, because it relies on distinct molecular markers and the consideration of compensatory processes when one population is selectively suppressed. Thus, discerning the forest from the trees can be difficult when this highly reductionist approach is used at the outset. By taking a step back, Zhu et al. remind us of how much we have left to learn about the functional organization of the diverse range of molecularly defined cell types in the ARC.

Now that a series of studies in the ARC have been conducted, a hierarchical approach appears to potentially be best for understanding this brain structure. The main functional response types (for example, glutamatergic or GABAergic) have been examined, and this picture can be iteratively refined through further splitting by using molecular markers associated with each branch point along the hierarchy of transcriptional similarity to ultimately identify the most narrowly defined cell-type subpopulations. Using either perturbations or neuronal dynamics measurements would provide a multiscale perspective on cell-type-specific functional specialization in the ARC.

In addition, the profound suppression of weight gain reported here is interesting from an obesity-treatment perspective, and it suggests at least two possibilities. Either an additional highly selective, leptin-sensitive ARC cell type will be found that complements the AGRP neurons or consideration of a broader grouping of several VGAT-expressing cell types will be necessary for the effects reported by Zhu et al. The findings here broaden the search space for understanding the subset of cell types corresponding to leptin responsiveness, appetite and energy expenditure in the ARC as a necessary step toward defining more effective drug targets for improved regulation of body weight. ❐

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Published online: 27 July 2020
https://doi.org/10.1038/s42255-020-0259-9

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Competing interests

The author declares no competing interests.