

Anatomical and functional heterogeneity of ‘hypothalamic’ peptidergic neuron populations

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Omar Al-Massadi and colleagues published an excellent Review on the role of melanin-concentrating hormone (MCH) in the control of energy homeostasis (Al-Massadi, O. et al. Multifaceted actions of melanin-concentrating hormone on mammalian energy homeostasis. *Nat. Rev. Endocrinol.* **17**, 745–755; 2021)¹. However, it has come to my attention that the authors referred to all the MCH-containing neurons as a single population restricted to the lateral hypothalamic area (LHA) and zona incerta¹. Furthermore, the LHA is represented as being the sole hub for the connections with other feeding-related areas of the brain in figure 2 of the Review¹. This view represents an oversimplification of the anatomical complexity of MCH distribution in the mammalian brain.

In the brain of rats, 12 groups of MCH-synthesizing neurons exist throughout the forebrain, diencephalon and brainstem² Supplementary Figure 1. The economic description of MCH distribution included in the Review by Al-Massadi et al¹, also disregards the dimorphic characteristics and differential temporal expression of MCH neurons related to lactation and maternal behaviour^{3–6}, and differences between the projection targets of LHA and zona incerta neurons. The issue of proper MCH anatomical localization reported in the Review by Al-Massadi et al¹, and in the wider literature is further compounded by the uncertainty that surrounds the zona incerta. This region remains poorly defined in terms of borders, connections and neurochemical organization.

Our group has previously demonstrated that the A13 group of dopaminergic cells in the rostromedial zona incerta (rmZI) is partially intermingled with local MCH-immunoreactive

cells, which form a distinct neurochemical subdivision of the diencephalon⁷. The lateral zona incerta preferentially innervates lateral brain areas, whereas the rmZI targets predominantly medial structures. This finding led us to propose a reclassification of the rmZI as being the incerto-hypothalamic area, to better reflect the fundamental differences between the two subdivisions⁸.

Among the 12 nuclei that express MCH in mammals Supplementary Figure 1, the LHA is the most conspicuous area and by far the most studied with respect to feeding behaviour. Moreover, we still do not know whether one or more types of cells that inhabit the LHA are solely responsible for those effects on feeding behaviour. The LHA receives many inputs and sends several outputs. In addition, just one cell type of the LHA targets two or more regions, neuropeptides, neurotransmitters and transporters⁹. Therefore, more specific data concerning the groups of cells that are implicated in feeding behaviour are needed. In a similar example, substantial expression of substance P (a neuropeptide) in the primary layers of the dorsal horn of rodents enabled the discovery of an association between substance P and pain modulation. However, this association has remained ingrained in the literature of substance P and obscures the fact that substance P is expressed in other areas of the central nervous system that have roles unrelated to pain¹⁰.

To summarize, the main point of this Correspondence is that by presenting an incomplete morphological distribution of MCH neurons, the general literature neglects a complex network of associations between function and regions where neuropeptides or neuroactive molecules were discovered.

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Competing interests

The author declares no competing interests.

Supplementary information

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