Title

Neurogenic Hypothesis of Anti-obesity Action: is it on the horizon?

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Significance Statement

This commentary explores the emerging connection between hypothalamic adult neurogenesis (hAN), obesity, and anti-obesity medications (AOMs). It highlights recent findings suggesting that AOMs influence hAN and may act, at least in part, through neurogenic mechanisms. This commentary debates a neurogenic hypothesis of obesity and its treatment, offering a conceptual framework that could open new therapeutic avenues and enhance our understanding of energy homeostasis regulation.

Since 2018, prescriptions of anti-obesity medications (AOMs), sometimes referred to as obesity management drugs (OMDs), have doubled, making them among the most prescribed new drugs globally[1]. This increase in usage is mainly driven by the second and third generation of stable peptidic agonists of glucagon-like peptide 1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide (GIP) receptor -Semaglutide (Ozempic/Wegowy) and Tirzepatide (Zepbound), respectively. The primary indication of AOMs is obesity, as they reduce food intake by increasing satiety, leading to decreased body weight. However, beyond this primary anorexigenic function, several non-canonical benefits of AOMs have recently emerged, including increased neuroprotection[2], suggesting a broader spectrum of cellular targets and more complex mechanisms of action.

Neuroactive AOMs (such as GLP-1 receptor agonists) discussed in this commentary directly target neurons in the medial basal hypothalamus (MBH), which regulates energy homeostasis. Liraglutide and Semaglutide activate anorexigenic proopiomelanocortin-expressing (POMC+) neurons and indirectly inhibit orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons[3]. Notably, Semaglutide is taken up and shuttled

across the blood-brain barrier into the MBH parenchyma by tanycytes[4], which line the walls of the third brain ventricle and serve dual roles as hypothalamic gatekeepers and as hypothalamic adult neural stem cells (htNSCs)[5, 6]. During the process of hypothalamic adult neurogenesis (hAN), htNSCs produce new POMC+ and NPY+/AgRP+ adult-born neurons in the MBH to help regulate energy homeostasis[5, 6]. Taken together, these findings suggest that AOMs may influence hAN.

We recently tested this hypothesis by exposing mice to a High-Fat Diet (HFD) of varying durations, along with concurrent administration of two AOMs: Liraglutide and a lipidized analogue of the Prolactin-releasing Peptide (PrRP), referred to as LiPR[7]. Our results show that AOMs affects multiple aspects of hAN under both HFD and control diet conditions. LiPR and Liraglutide preserved htNSCs by reducing their activation and proliferation during HFD exposure. Interestingly, we also observed an antiproliferative effect of AOMs in the MBH parenchyma, suggesting they act similarly on cell proliferation despite binding to different receptors. Additionally, our findings indicate that AOMs reduce cell proliferation even under physiological conditions. Taken together, these results suggest that AOMs reduce cell proliferation and increase the quiescence of htNSCs and hypothalamic neural progenitors, potentially preserving adult neurogenesis in the context of diet-induced obesity.

As mentioned above, previous studies have demonstrated the neuroprotective potential of AOMs in adverse conditions such as stroke and neurodegeneration. However, the neuroprotective effects of these compounds are not limited to neurodegenerative diseases or embryonically generated neurons. AOMs have also been shown to increase adult neurogenesis in the hippocampus (reviewed by Au *et al.*[8]), which is associated with specific forms of learning and memory, and with mood control. Our findings complement this work by showing that AOMs increase the number of newly generated MBH neurons under HFD conditions, indicating they promote neuronal survival in the hypothalamus as well[7]. Preserving or increasing hAN through AOMs may partly contribute to their anorexigenic effects, as ablation of hAN results in greater weight gain in HFD-fed animals, while increased hAN offers protection against the adverse effects of an HFD[9]. In other words, functional hAN may rewire hypothalamic circuits that control energy homeostasis by incorporating more adult-born neurons with distinct electrophysiological and connectivity profiles. If this is the case, AOMs could offer extended benefits that persist beyond the treatment period.

One hypothesis arising from this reasoning is that AOMs may promote a higher proportion of anorexigenic neurons being generated and integrated into the adult hypothalamus. To test this, we exposed human hypothalamic neurons derived from induced pluripotent stem cells (iPSCs) to PrRP or Semaglutide and quantified the proportion of POMC+ neurons[10]. Contrary to our expectations, we did not observe any difference in the proportion of POMC+ neurons between AOM-treated and control cells. Similarly, treating mice with

LiPR did not alter the proportion of POMC+ neurons in the MBH. These findings suggest that AOMs do not affect the proportion of anorexigenic neurons. However, they do not rule out the possibility that AOMs exert other neurogenic effects, due to methodological limitations of our study. Our experiments were conducted under physiological rather than obesity conditions and focused on neuronal maturation rather than differentiation. However, previous studies examining the phenotype of adult-generated hypothalamic neurons also concluded that HFDs do not alter the ratio of anorexigenic to orexigenic neurons[11]. This suggests that hAN may influence MBH circuitry not by altering neuron subtype ratios, but through changes in connectivity and function - and that external interventions (e.g., obesity or AOMs) should not be expected to alter these ratios either.

Although our data suggest for the first time that AOMs influence hAN, we have not demonstrated that hAN is required for the anorexigenic effects of AOMs. Addressing this would require ablating hAN in the context of HFD and determining whether such ablation reduces the anorexigenic efficacy of AOMs. This approach could pave the way for a neurogenic hypothesis of obesity and its treatment. Notably, the current understanding of the relationship between AOMs and hAN resembles the trajectory of antidepressant research approximately 25 years ago, when a seminal paper by Malberg *et al.* first showed that antidepressants increase hippocampal neurogenesis[12]. But it was a follow-up study by Santarelli *et al.* using specific neurogenesis ablation, that demonstrated intact hippocampal neurogenesis is necessary for antidepressant efficacy[13], thereby solidifying the neurogenic hypothesis of depression.

Establishing a neurogenic hypothesis of obesity and anti-obesity treatment will undoubtedly face multiple challenges. Adult neurogenesis in the hypothalamus is often considered to have a lower cellular turnover and less functional impact than in the hippocampus, though this assumption may be incorrect. In mice, more than half of embryonically generated neurons in the primary nutrient-sensing arcuate nucleus of the MBH are replaced by adult-generated neurons during early adulthood[11], and blocking cell proliferation in the MBH exacerbates diet-induced obesity[9]. Importantly, pioneering studies have suggested a connection between hypothalamic adult neurogenesis (hAN) and the etiology of obesity. For example, Kokoeva *et al.* proposed that the weight-loss effects of ciliary neurotrophic factor (CNTF) depend on hAN[14], while Lee *et al.* demonstrated that ablating hAN increases weight gain in mice exposed to a high-fat diet[15]. However, these seminal studies employed ablation strategies that were not specific to neurogenic cells, such as anti-mitotic agents (i.e., Ara-C) or hypothalamic irradiation. Consequently, the observed effects on body weight cannot be attributed exclusively to hAN. To avoid off-target effects, more selective genetic ablation approaches should be employed. For instance, crossing Rax-CreERT2 and NSE-DTA mice would allow inducible expression of a suicide gene (diphtheria toxin fragment A, DTA) in Rax+ tanycytes and adult-generated neurons[16, 17]. While this method is more specific, it still

presents a conceptual limitation: the ablation of tanycytes not only removes them as neural stem cells but also disrupts their essential functions in glucose sensing or hormone transcytosis[5], complicating efforts to isolate the contribution of hAN to AOM effects from broader endocrine roles of tanycytes.

Despite these technical challenges, exploring the link between hypothalamic adult neurogenesis, obesity, and anti-obesity pharmacology is crucial. It has the potential to reveal new therapeutic strategies and deepen our understanding of energy homeostasis regulation. Rather than asking whether the neurogenic hypothesis of obesity is plausible, the question should be: how far is it on the research horizon?

Acknowledgement

The author thanks all researchers in hypothalamic adult neurogenesis for advancing the field.

Figure legend

The neurogenic hypothesis of obesity and anti-obesity treatment. (A) In the medial basal hypothalamus (MBH), tanycytes function as hypothalamic neural stem cells (htNSCs), generating new adult-born neurons. (B) Under high-fat diet (HFD) conditions, the survival of adult-generated hypothalamic neurons is reduced. (C) Anti-obesity medications (AOMs) can rescue the survival and help preserve the htNSC pool by reducing their activation and proliferation. This neurogenic effect may contribute to the anorexigenic actions of AOMs, although this relationship remains unconfirmed. (D) The necessity of hypothalamic adult neurogenesis (hAN) for AOM efficacy can be tested by selectively disrupting neurogenesis in the hypothalamus.

Keywords

Adult neurogenesis, hypothalamus, obesity, anti-obesity medications

Author contribution (CReDiT)

Conceptualization: DP; Writing – original draft: DP; Writing – review and editing: DP.

Conflict of Interests

None

Funding

No funding contributed to this manuscript.

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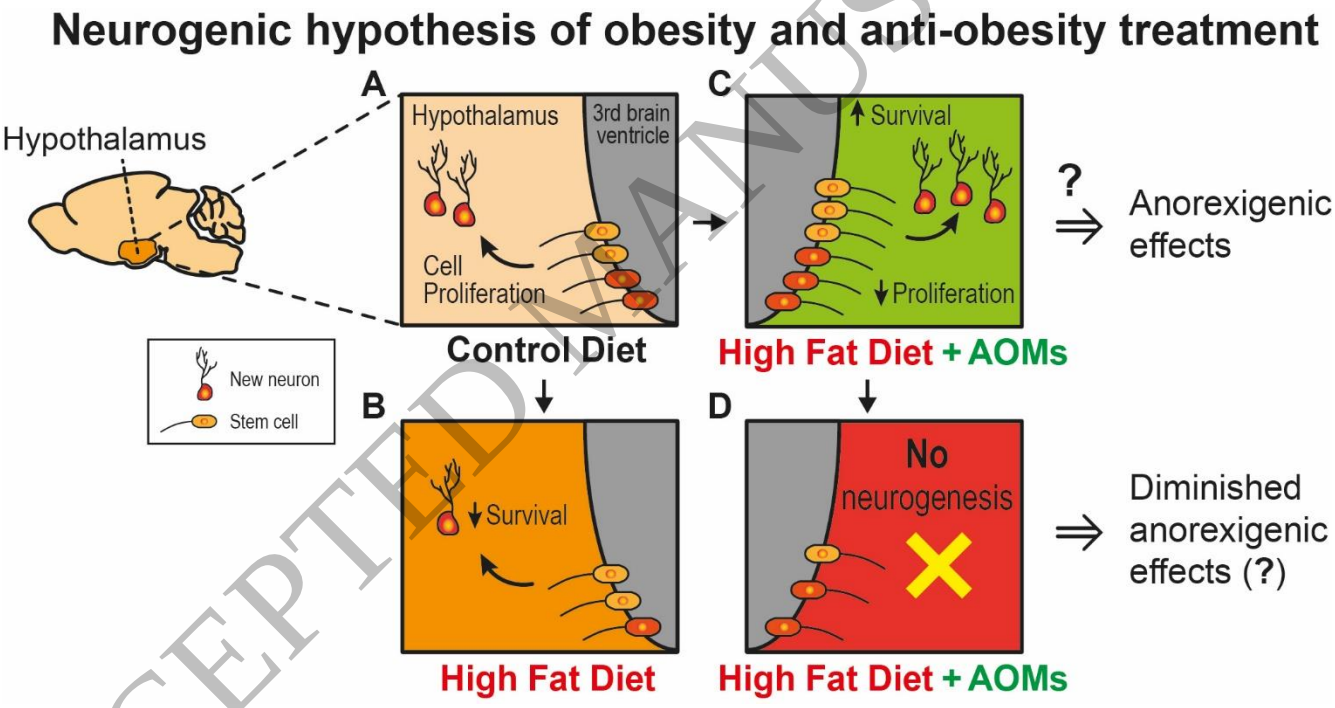

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