

A novel neuronal circuit: Tanycytes mediate defensive metabolic responses following acute high-temperature exposure

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The core body temperature, plays a vital role in influencing metabolic rate, enzyme activity, and various other physiological processes.^[1] Significant progress has been achieved in unraveling the neural mechanisms responsible for lowering body temperature during illness, commonly observed in conditions like fever.^[2] It has been established that populations of neurons in the ventral medial preoptic area of the hypothalamus are activated after systemic inflammation. They respond to locally secreted immune molecules such as prostaglandin E₂, interleukin-1 β (IL-1 β), and C-C motif ligand 2 (CCL2), and form connections with other brain areas, some of which known to control pain sensation, thirst or social interactions, contributing to survival during infection.^[2] However, little is known about how the brain orchestrates responses to dissipate excess heat in response to acute thermal challenges encompassing unavoidable environmental exposure (e.g. air-conditioned environments) and elective exposure (e.g. sauna).

A recent study titled “A brainstem–hypothalamus neuronal circuit reduces feeding upon heat exposure” reveals the neural circuitry mechanism by which tanycytes mediate defensive metabolic responses following acute exposure to high temperatures.^[3] Tanycytes, brain cells contacting CSF, have synaptic connections with neurons and are divided into α and β types, though their full significance remains unclear. Viral tracer technology was used to demonstrate tanycytes in the arcuate nucleus of the hypothalamus (ARC) receiving excitatory synaptic input. Despite lacking depolarizing activity, tanycytes show excitatory postsynaptic currents, responding to neuronal activity, as evidenced by calcium increases blocked by AMPA antagonists. Acute exposure of mice to 40°C significantly reduced feeding within 24 h and activated pontine parabrachial nucleus (PBN) brain area and α -tanycytes within an hour. Glutamatergic neurons in the PBN directly innervate tanycytes. Interestingly, to further clarify whether vascular

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endothelial growth factor A (VEGFA) produced by tanycytes functions independently from its diffusion in CSF, the authors exposed adult rats to either 40°C or 25°C for 1 h, and immediately after thermal manipulation, aspirated CSF from their cerebellomedullar cistern.^[3] Conspicuously, acute heat had not increase the amount of VEGFA in the CSF significantly. Tanycytes appear to translate extrahypothalamic sensory information into chemical signals that impact hypothalamic neurocircuits through direct communication with neurons. Virus tracing experiments proved that there were synaptic connections between PBN neurons and α -tanycytes in the ARC brain area. Chronic activation of excitatory neurons in the PBN through chemogenetics can activate α -tanycytes in the ARC. Acute exposure to a high temperature environment of 40°C increased the expression of VEGFA in α -tanycytes, which also occurred after activation of excitatory neurons in the PBN. Acute exposure to a high temperature environment of 40°C promoted the production of VEGFA by tanycytes and function independent from its diffusion in CSF.

The activation of tanycytes could lead to the reduction in food intake via modulating orexigenic neurons involving the neuropeptide Y (NPY)/agouti-related protein (AGRP)-containing neurons which increase food intake.^[4] All these results suggest the existence of a PBN-tanycytes-ARC loop that is involved in regulating feeding behavior (Figure 1).

In summary, acute high temperature exposure activates excitatory neurons in the PBN, promotes the release of VEGFA from tanycytes, and acts on AGRP neurons in the ARC brain area through the receptor Flt1 to inhibit feeding behavior. This study sheds light on the neural mechanisms that regulate food intake during high-temperature exposure and paves the way for a myriad of potential applications and advancements in various fields.

While the study presents significant advancements in understanding how tanycytes mediate defensive metabolic responses following acute high-temperature exposure, there are still several limitations. The findings may not be universally applicable to all populations. Further research is needed to assess whether the neural circuits identified operate similarly across diverse demographic groups and geographic regions. Understanding how individual behaviors and societal norms influence feeding responses to heat would enrich the findings' relevance and practical implications. Besides, the study primarily focuses on short-term appetite suppression in response to heat. However, it is essential to investigate the long-term implications of manipulating these neural pathways, particularly regarding metabolic health and sustainability of interventions over time.^[5] Also, how behavioral factors intersect with these physiological processes should be further explored. The brain is intricate, and this circuit likely interacts with other neural pathways. Investigating cross-talk with stress, reward, and satiety circuits would provide a more comprehensive picture. Further studies are needed to address the above questions and challenges, which would amplify the impact of

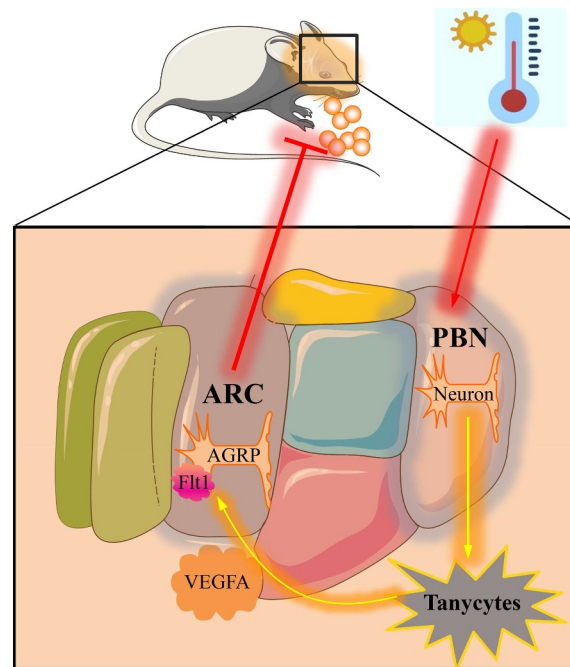


FIGURE 1 A schematic diagram of a proposed neural circuit for high temperature-induced feeding inhibition. Acute high temperature exposure activates excitatory neurons in the parabrachial nucleus brain area, promotes the release of vascular endothelial growth factor A from tanycytes, and acts on agouti-related protein neurons in the ARC brain area to inhibit feeding behavior.

this research area and pave the way for practical translation and applications.

AUTHOR CONTRIBUTIONS

Qi Chen: Funding acquisition; methodology; project administration; resources; supervision; validation; writing - original draft. **Anke Brüning-Richardson:** Methodology; writing—review & editing. **Ruoli Chen:** Methodology; writing—review & editing. **Shuang Zou:** Funding acquisition; software; visualization; writing—original draft. **Yu-Long Lan:** Conceptualization; funding acquisition; visualization; writing - review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Ethics approval was not needed in this study.

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