Yale SCHOOL OF MEDICINE

Department of Comparative Medicine

TAMAS L. HORVATH, DVM, PHD

Jean and David W. Wallace Professor of Comparative Medicine

Professor of Neuroscience and Obstetrics, Gynecology and Reproductive Sciences

Chair, Department of Comparative Medicine

PO Box 208016
New Haven CT 06520-8016
T 203 785-2525
F 203 785-7499
tamas.horvath@yale.edu
medicine.yale.edu/compmed

courier
Brady Memorial Laboratory (BML)
Room 330D
310 Cedar Street
New Haven CT 06510

May 13, 2025

Comments on the doctoral thesis of the Hu8ngarian Academy of Sciences by Dr. Zsuzsanna Tóth

The applicant generated significant new scientific data.
In Aim 1, they further developed a novel immunocytochemical technique:
The introduced a new easily reproducible, simple and sensitive immunohistochemical staining procedure to prevent cross-reactions.
They demonstrated that post-transplant monitoring of donor-derived GFP-expressing bone marrow stem cells can be performed by immunohistochemical staining combined with tyramide signal amplification.

In Aim 2, they pursued studies on energy metabolism
The unmasked that icv. administration of nesfatin-1 increased body temperature, and that tis effects on food and water intake are long-term and related to the circadian oscillations, including sleep-wake cycles speficially regarding REM sleep.
In a rat model, they revealed that prediabetic state that develops primarily in adulthood, despite normal body weight, as a result of intrauterine malnutrition and that it is due to nesfatin-1 resistance in the hypothalamus, especially in the arcuate nucleus. In non-resistant animals, chronic icv nesfatin-1 treatment improved glucose tolerance and insulin sensitivity.
They identified a cell group in the medial shell of the nucleus accumbens that reflects the reward value of food and that it is mediated, at least in part, by D1 dopamine receptors.

In Aim 3, they studied of the fine-tuning of the stress response
Here again, they pursued nesfatins in the regulation of the HPA axis.
In addition, they found that in the noradrenergic neurons of the medulla, which play a primary role in the activation of the HPA axis, the co-expression ratio of PrRP and noradrenaline
shifts towards PrRP under the influence of chronic restraint stress.

Finally, and surprisingly, they described a novel brain pathway through which PrRP inhibits hypothalamic MCH-containing neurons and enhances the inhibitory effect of noradrenaline on MCH neurons. Using rat models, they revealed that impaired PrRP

signaling in the dorsolateral hypothalamus is associated with “depression-like” behavior, and confirmed the relevance of this in brain samples from suicide victims.

Overall, it is a well-written and highly complex thesis with great quality publications.

Sincerely,

Tamas L. Horvath, DVM, PhD.
Jean and David W. Wallace Professor of Comparative Medicine and Professor of Neuroscience and of Obstetrics, Gynecology, and Reproductive Sciences
Chair, Department of Comparative Medicine