Molecular hydrogen modulates brain glutamate/GABA-glutamine cycle in overweight humans

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Abstract

Introduction: We evaluated whether 12-week intake of molecular hydrogen (H_2) in 5 overweight adults (3 women; age: 50.2 ±11.9 years, body mass index: 29.4 ±2.1 kg/m^2) affects brain levels of the glutamate-glutamine-GABA cycle, critical amino acid neurotransmitters in the mechanism of neuronal activation during appetite regulation.
Methods: A 1.5-T single-voxel proton magnetic resonance spectroscopy was used to assess the tissue concentrations of relevant metabolites.
Results: The mean glutamate and glutamate-plus-glutamine levels at the posterior cingulate gyrus decreased significantly during the study; this was accompanied by a significant drop in GABA levels at left prefrontal white matter, and glutathione levels at anterior cingulate gyrus. No changes in the brain metabolites were found in the comparable group of overweight individuals (n = 4, 2 women; age: 41.0 ±13.9, BMI 26.8 ±1.3 kg/m^2) followed-up in the past without this treatment.
Conclusions: We showed a possible hydrogen-driven upregulation of neurotransmitters involved in appetite stimulation leading to hunger suppression and weight loss. Further studies analyzing appetite-controlling metabolic pathways affected by H_2 would require monitoring of additional biomarkers of satiation and satiety during different feeding regimens.

Key words: hydrogen-rich water, overweight, proton MRS, white matter, grey matter.

Molecular hydrogen (H_2) is an experimental biomedical gas that positively impacts overweight, obesity, and other metabolic disorders [1]. This could be partly due to its ability to tackle anorexigenic and orexigenic signalling in the brain [2]. We evaluated whether the medium-term intake of molecular hydrogen in overweight adults affects brain levels of the glutamate-glutamine-GABA cycle, critical amino acid neurotransmitters in the mechanism of neuronal activation during appetite regulation [3].

Methods. The present study was an interventional pilot study with historical controls; the study was conducted at the Applied Bioenergetics Lab at the University of Novi Sad from June to December 2022. The participants comprised 5 apparently healthy adults (3 women; age: 50.2 ±11.9 years) with body mass index (BMI) ≥ 25.0 kg/m^2 (mean: 29.4 ±2.1 kg/m^2; 95% CI, from 26.7 to 32.0) and no recent history of using anti-obesity medications; free from acute injuries and major chronic diseases. All par-

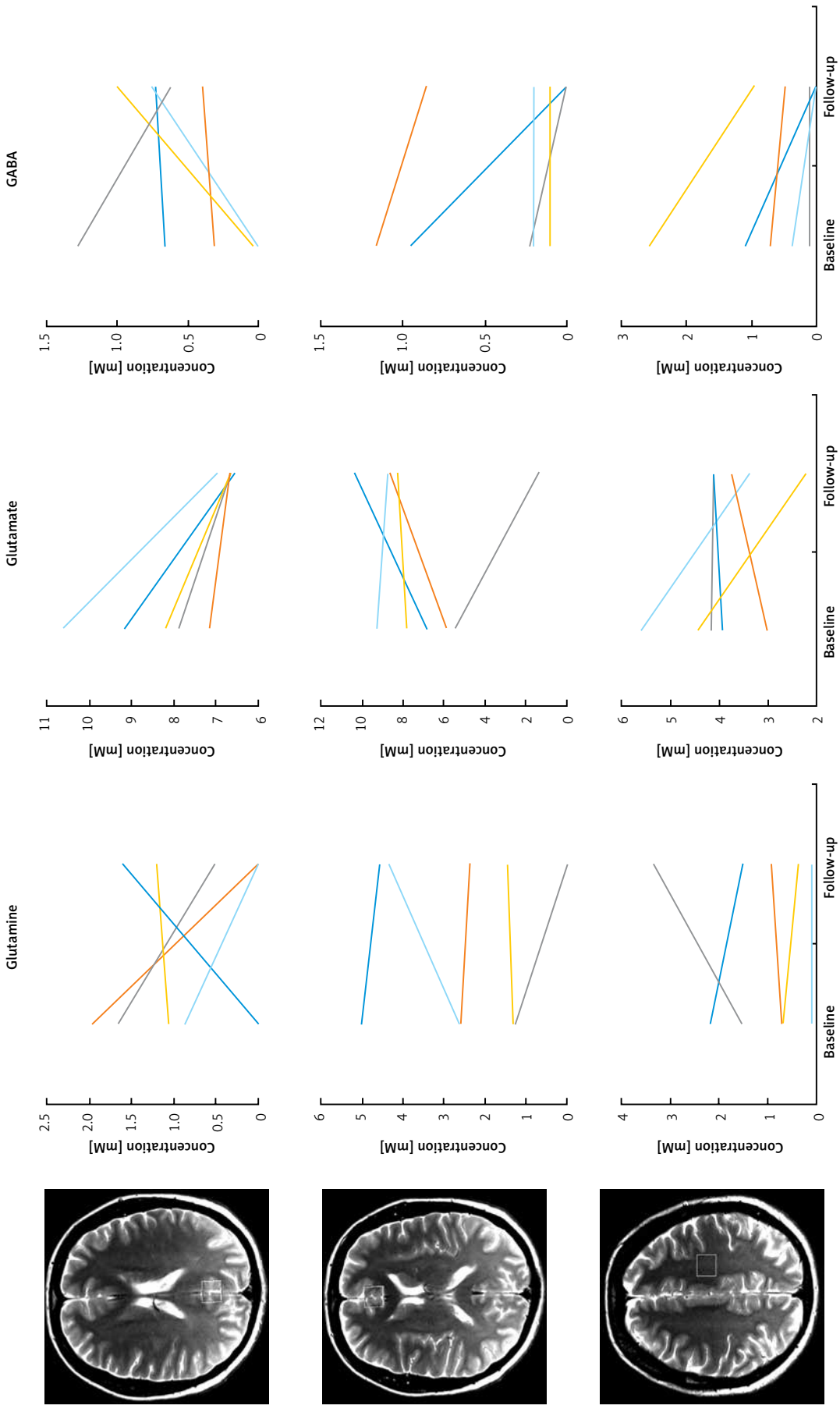

Figure 1. The individual changes in glutamine, glutamate, and GABA concentrations (mM) after a 12-week intervention with hydrogen-rich water across 3 different brain regions (regions of interest (ROI) recorded with 1.5-T proton magnetic resonance spectroscopy are marked by white squares) in overweight adults; coloured lines indicate changes for individual participants (1-5)

ticipants consumed 7.5 mg of H_2 per day for 12 weeks, administered as hydrogen-rich water (Natural Health Products Inc., New Westminster, Canada). The main outcome measures were the absolute concentrations of glutamate, glutamine, gamma-aminobutyric acid (GABA), glutathione, glucose, alanine, glycerophosphocholine, and taurine assessed by a single-voxel proton magnetic resonance spectroscopy (MRS) at 1.5 T in the anterior and posterior cingulate gyrus, and left prefrontal white matter (Figure 1), with point-resolved spectroscopy repetition time/echo time 1500/30 ms. The absolute concentrations of the above metabolites were calculated via Tarquin software to prevent inter-subject variability of the denominator values in metabolite ratios [4]. All participants voluntarily signed an informed constent form, and the study protocol was approved by the local IRB (#46-06-01/2022-HRW2).

Results. The mean glutamate and glutamate-plus-glutamine levels at the posterior cingulate gyrus decreased significantly during the study from 8.60 ±1.34 mM to 6.70 ±0.16 mM (p = 0.01), and from 9.71 ±1.10 mM to 7.37 ±0.62 mM (p = 0.01), respectively. This was accompanied by a significant drop in GABA levels in left prefrontal white matter (from 0.95 ±0.99 mM to 0.29 ±0.43; p = 0.05), and glutathione levels in the anterior cingulate gyrus (from 0.65 ±0.23 mM to 0.32 ±0.23; p < 0.01). Other metabolites were not affected by hydrogen intervention (p > 0.05), except for a significant rise in brain taurine levels in the posterior cingulate gyrus (from 0.58 ±0.50 mM to 1.00 ±0.23 mM, p = 0.04). Individual changes in glutamate-glutamine-GABA levels are depicted in Figure 1. No changes in the brain glutamate-glutamine-GABA cycle were found in the comparable group of overweight individuals (historical controls, n = 4, 2 women; age: 41.0 ±13.9 years, BMI: 26.8 ±1.3 kg/m^2) followed up in the past without this treatment (p > 0.05).

Discussion. Hydrogen intake induced a notable reduction in glutamate-glutamine-GABA concentrations across the brain of overweight individuals, modulating both excitatory (glutamate) and inhibitory (GABA) neurotransmitters in this population. This implies a possible hydrogen-driven upregulation of glutamate-glutamine cycling that might attenuate glutamate- and GABA-dependent hypothalamic appetite stimulation, leading to hunger suppression and weight loss. Increased brain taurine induced by hydrogen might also contribute to appetite regulation via its anorexigenic effects [5]. Our study enrolled a small number of overweight participants due to the high cost of proton MRS per patient and time-consuming procedures, which partially limits the interpretation of our findings. In addition, we provided no analyses of whether the decrease in metabolites correlated to weight or weight change. Finally, no information has been provided regarding the long-term effects of molecular hydrogen on brain glutamate/GABA-glutamine cycle in the overweight population. Nevertheless, our findings corroborate previous *in vitro* research reporting neuroprotective effects of hydrogen via glutamate-GABA modulation, in which hydrogen-rich water reduced the glutamate toxicity-induced death of neurons in a dose-dependent fashion [6]. Further well-sampled longitudinal studies analysing appetite-controlling metabolic pathways affected by molecular hydrogen would require monitoring of additional biomarkers of satiation and satiety (including food intake and body weight change) during different feeding regimens.

Conflict of interest

SMO co-owns patent "Agent for Inhibiting Deterioration of Recognition Function Comprising Hydrogen Gas" at the Japan Patent Office (2016-163322), and has received research support related to molecular hydrogen during the past 36 months from the Serbian Ministry of Education, Science, and Technological Development, the Provincial Secretariat for Higher Education and Scientific Research, Natural Health Products Inc, Evo-Drop, and SeaCret Direct. SMO is the founder of Centram, a biotechnology startup developing and commercializing innovative nutraceuticals that can support and rejuvenate energy metabolism, the gut-brain-muscle axis, and immunity across various health domains. SMO does not own stocks and shares in any organization. DK, JO, and NT declare no conflict of interest.

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