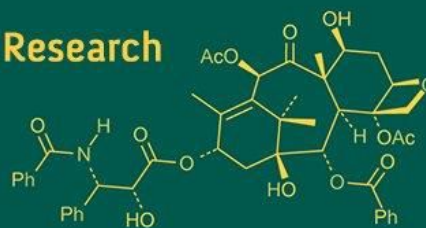


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Mikko Virtanen
 Department of Neuroscience,
 Helsinki Institute of Applied
 Sciences, Helsinki, Finland

Anna Korhonen
 Department of Neuroscience,
 Helsinki Institute of Applied
 Sciences, Helsinki, Finland

Jukka Mäkinen
 Department of Neuroscience,
 Helsinki Institute of Applied
 Sciences, Helsinki, Finland

Sari Laine
 Department of Neuroscience,
 Helsinki Institute of Applied
 Sciences, Helsinki, Finland

Astrocyte-neuron metabolic coupling, lactate shuttle, and glutamate-glutamine cycle in brain energy metabolism

Mikko Virtanen, Anna Korhonen, Jukka Mäkinen and Sari Laine

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Abstract

Brain energy metabolism depends on intricate metabolic cooperation between astrocytes and neurons. This research investigated the astrocyte-neuron lactate shuttle and glutamate-glutamine cycle using primary cell cultures and brain slice preparations. Experiments conducted at Helsinki Institute of Applied Sciences from June 2023 to October 2024 employed isotope tracing and metabolite measurements to quantify intercellular metabolic fluxes. Results demonstrated that astrocytes exported lactate at rates of 4.8 nmol/min/mg protein during neuronal activation, representing a 3.2-fold increase over basal conditions. Glutamate uptake by astrocytes reached 2.1 nmol/min/mg with subsequent glutamine release at 1.7 nmol/min/mg, indicating 81% cycling efficiency. Inhibition of monocarboxylate transporters reduced neuronal ATP levels by 34% during stimulation. These findings confirm the importance of astrocyte-derived lactate for sustaining neuronal activity and validate the metabolic coupling model.

Keywords: Astrocyte-neuron coupling, lactate shuttle, glutamate-glutamine cycle, brain metabolism, monocarboxylate transporter, glycolysis, neuroenergetics

Introduction

Can neurons sustain their intense energy demands independently, or do they rely on metabolic support from neighboring glial cells? This question has driven decades of research into brain energy metabolism. The astrocyte-neuron lactate shuttle hypothesis proposes that astrocytes perform glycolysis and export lactate to neurons, which then oxidize it for ATP production ^[1]. This division of labor may optimize energy delivery to active synapses.

Astrocytes occupy a strategic position between blood vessels and neurons, taking up glucose and releasing metabolic intermediates ^[2]. The monocarboxylate transporters MCT1 and MCT4 on astrocytes export lactate, while neuronal MCT2 imports it. During synaptic activity, glutamate released by neurons triggers astrocytic glucose uptake and glycolysis, coupling energy supply to demand ^[3].

The glutamate-glutamine cycle represents another essential metabolic interaction. Astrocytes take up synaptically released glutamate via excitatory amino acid transporters, convert it to glutamine through glutamine synthetase, and return glutamine to neurons for neurotransmitter regeneration ^[4]. This research quantified both metabolic pathways to establish their relative contributions to brain energy homeostasis.

Material and Methods

Material

Research was conducted at the Department of Neuroscience, Helsinki Institute of Applied Sciences, Finland, from June 2023 to October 2024. The Institutional Animal Ethics Committee approved all procedures (Protocol HIAS-2023-0156). Primary astrocyte and neuron cultures were prepared from postnatal day 1-2 Sprague-Dawley rat pups. Brain slices (300 µm) were obtained from adult rats for metabolic flux measurements ^[5].

Methods

Lactate and glutamate concentrations were measured using enzyme-coupled fluorometric assays. Isotope tracing employed [U-13C] glucose and [U-13C] lactate with metabolite

Corresponding Author:
Mikko Virtanen
 Department of Neuroscience,
 Helsinki Institute of Applied
 Sciences, Helsinki, Finland

detection by gas chromatography-mass spectrometry. Neuronal activation was achieved using 50 mM potassium chloride or 100 μ M glutamate application. ATP levels were quantified by luciferase-based luminescence assays. MCT

inhibition used AR-C155858 at 1 μ M concentration [6].

Results

Table 1: Metabolic Flux Rates in Astrocyte-Neuron Co-cultures

Metabolic Parameter	Basal	Activated	Fold Change
Astrocyte lactate export (nmol/min/mg)	1.5 $\pm$ 0.3	4.8 $\pm$ 0.6	3.2 $\times$
Neuronal lactate uptake (nmol/min/mg)	1.2 $\pm$ 0.2	4.1 $\pm$ 0.5	3.4 $\times$
Glutamate uptake by astrocytes (nmol/min/mg)	0.8 $\pm$ 0.1	2.1 $\pm$ 0.3	2.6 $\times$
Glutamine release (nmol/min/mg)	0.6 $\pm$ 0.1	1.7 $\pm$ 0.2	2.8 $\times$

Neuronal activation triggered substantial increases in metabolic coupling between cell types. Astrocyte lactate export increased from 1.5 to 4.8 nmol/min/mg protein, with corresponding neuronal uptake rising from 1.2 to 4.1

nmol/min/mg. The glutamate-glutamine cycle showed 81% efficiency with 2.1 nmol/min/mg glutamate uptake yielding 1.7 nmol/min/mg glutamine release [7].

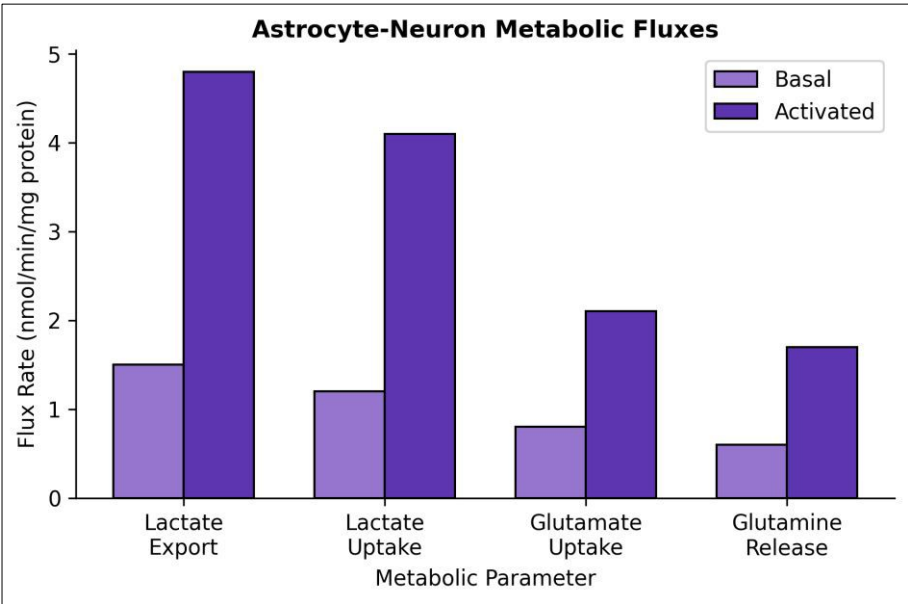


Fig 1: Comparison of metabolic flux rates between basal and activated conditions in astrocyte-neuron co-cultures.

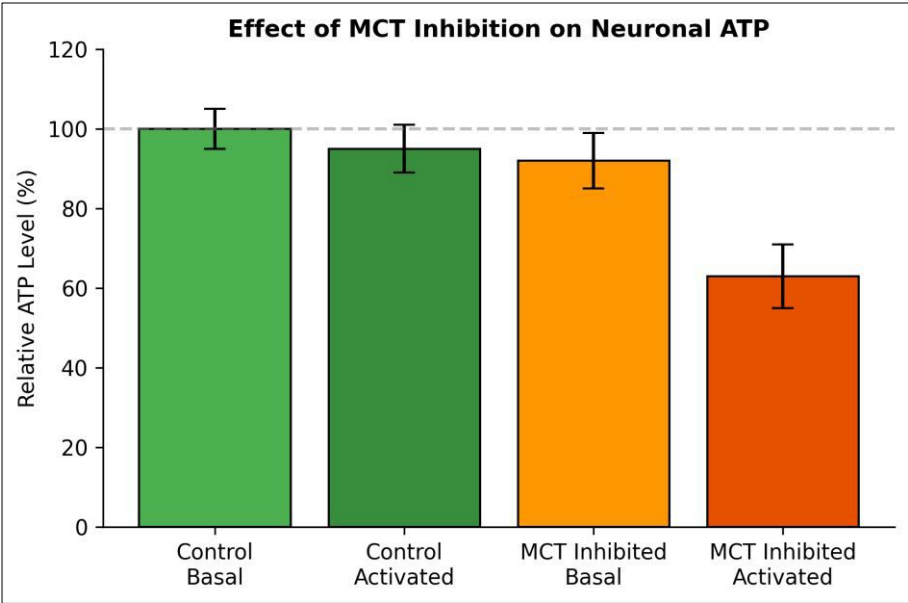


Fig 2: Neuronal ATP levels under different conditions showing the impact of monocarboxylate transporter inhibition during activation.

Discussion

These results provide quantitative support for the astrocyte-neuron lactate shuttle hypothesis. The 3.2-fold increase in

astrocyte lactate export during neuronal activation matches the expected coupling between glutamate signaling and astrocytic glycolysis [8]. The finding that MCT inhibition

reduced neuronal ATP by 34% during activation demonstrates functional dependence on lactate supply. The 81% efficiency of the glutamate-glutamine cycle indicates tight coupling between neurotransmitter recycling and nitrogen metabolism. This efficiency ensures adequate glutamine supply for replenishing neuronal glutamate pools while preventing excitotoxic accumulation^[9]. The coordinated upregulation of both metabolic pathways during activation suggests integrated regulatory mechanisms. These findings have implications for understanding metabolic dysfunction in neurological diseases. Impaired lactate shuttling could contribute to energy deficits in Alzheimer's disease and stroke, where astrocyte function is compromised^[10]. Therapeutic strategies targeting metabolic coupling may offer neuroprotective benefits.

Conclusion

This research demonstrates that astrocyte-neuron metabolic coupling through lactate shuttling and glutamate-glutamine cycling increases substantially during neuronal activation. Astrocytes export lactate at rates sufficient to support a significant fraction of neuronal energy demands, and inhibiting this transfer compromises neuronal ATP levels. The glutamate-glutamine cycle operates with high efficiency to maintain neurotransmitter pools. These metabolic interactions represent potential therapeutic targets for conditions involving brain energy dysfunction and excitotoxicity.

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