Astrocytic GLUT1 inhibition: implications for adenosine-mediated neuromodulation

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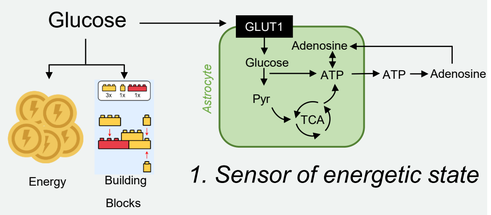
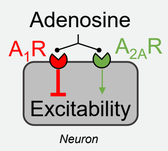
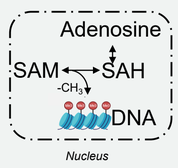
Introduction

State-of-art. GLUT1 deficiency syndrome (DS) is a genetic disease characterized by abnormal neuronal activity. However, the exact impact of reduced brain glucose uptake on neuronal activity remains uncertain. Glucose metabolic products regulate neuronal excitability, with adenosine being a prominent neuromodulator that primarily suppresses neuronal activity. Adenosine serves as:



1. Sensor of energetic state





2. Brake of excitability *3.Epigenetic modulator*

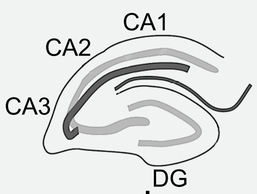
Hypothesis. The levels of adenosine are influenced by astrocytic GLUT1 glucose transport.

Material & Methods

a. *Ex-vivo* brain slices

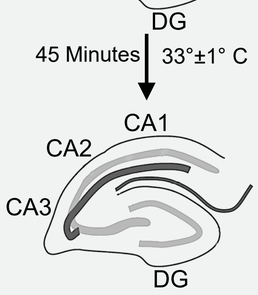
C57BL/6J
Age: 8±0.7 weeks
Male:Female ratio: 1:1

10 Minutes → Brain Isolation Hippocampal Slices

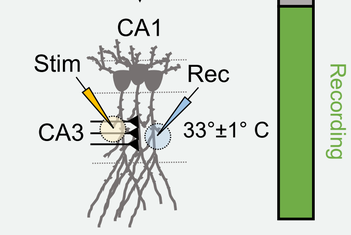


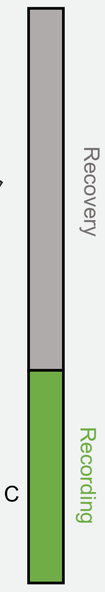
Entorhinal Cortex-Hippocampal horizontal slices

45 Minutes | 33°±1° C

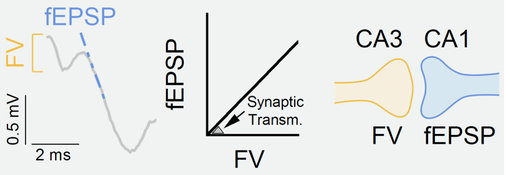


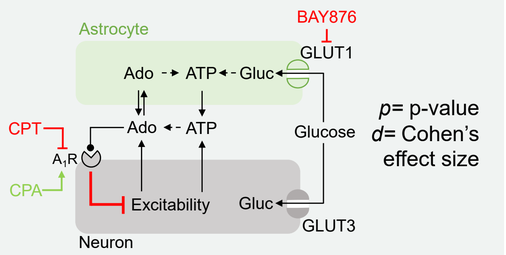
25 Minutes | R.T.

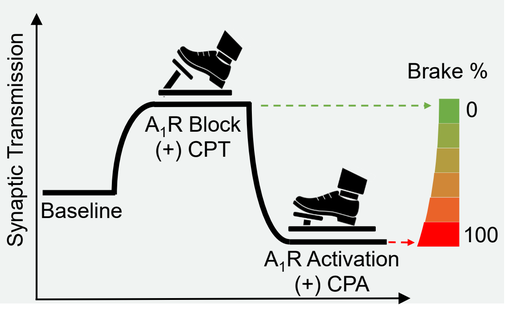




b. Functional Analysis



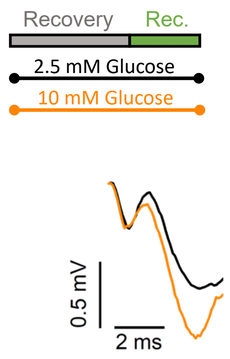


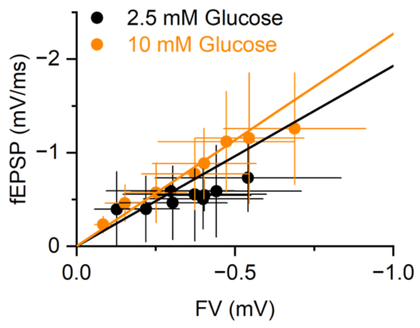


Awarded to M.B.

R01 AG061838-01A1 awarded to P.H.

Figure 1. Synaptic transmission is directly correlated to glucose levels





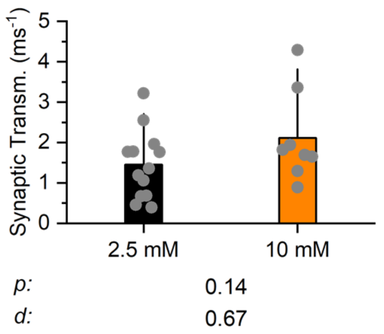


Fig.1. Do glucose levels affect synaptic transmission? We measured the pre-synaptic recruitment (FV) and post-synaptic response (fEPSP) by stimulating CA3 projections and recording CA1 responses using either 2.5 mM or 10 mM glucose (black and orange, respectively. Net synaptic transmission increases with higher glucose levels.

Summary:

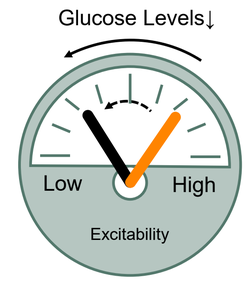
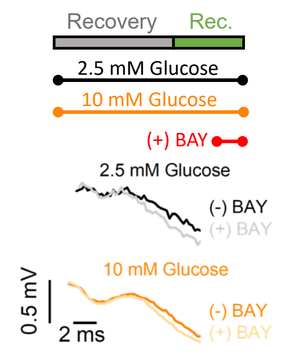
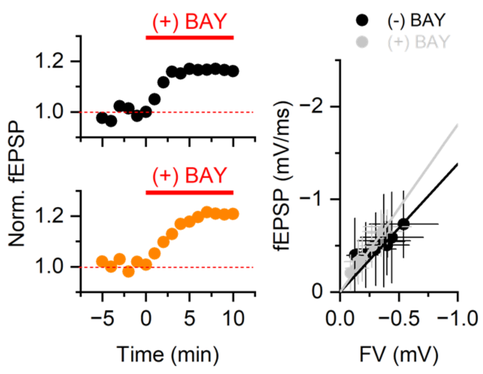
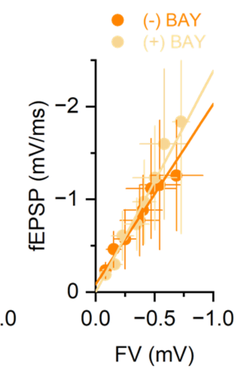


Figure 2. Acute inhibition of astrocytic GLUT1 increases synaptic transmission







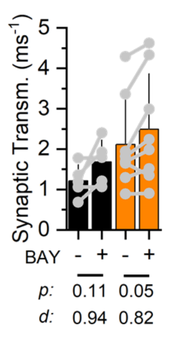
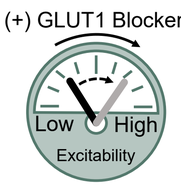


Fig.2. Does the acute inhibition of astrocytic GLUT1 affect synaptic transmission in a glucose-dependent manner? GLUT1 blocker (BAY876) was acutely added during brain slice recording. Acute inhibition of astrocytic GLUT1 increases net synaptic transmission in a glucose-independent manner.

2.5 mM Glucose



10 mM Glucose

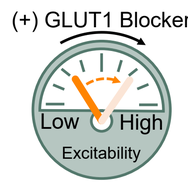
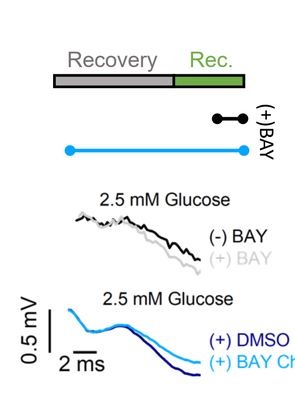
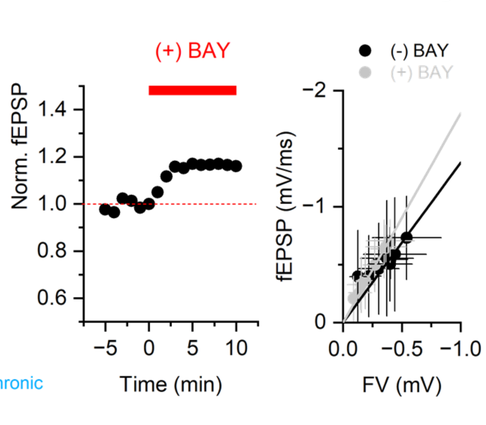
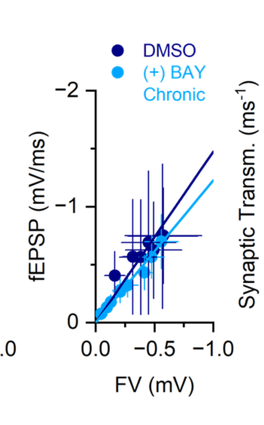


Figure 3. Chronic inhibition of astrocytic GLUT1 does not change synaptic transmission







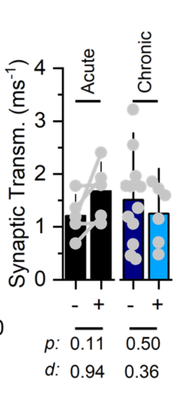
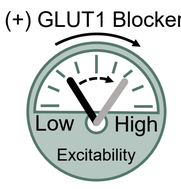


Fig.3. How does acute *vs* chronic inhibition of astrocytic GLUT1 influence synaptic transmission at 2.5 mM glucose? GLUT1 blocker (BAY876) was either acutely added during brain slices recording or kept since brain slice recovery (chronic). Acute inhibition of astrocytic GLUT1 increases net synaptic transmission, while chronic inhibition tends to reduce it.

2.5 mM Glucose Acute



2.5 mM Glucose Chronic

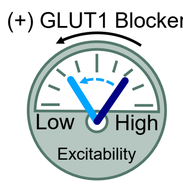
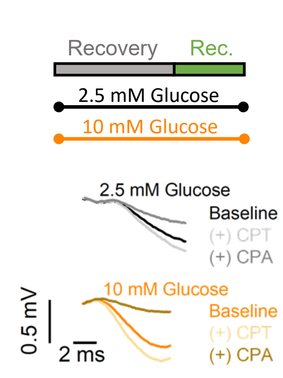
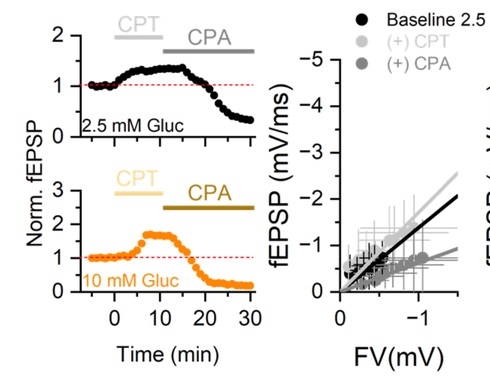
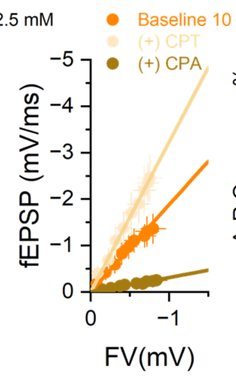


Figure 4. Adenosine 1 receptor (A_1R) occupancy is not affected by glucose levels







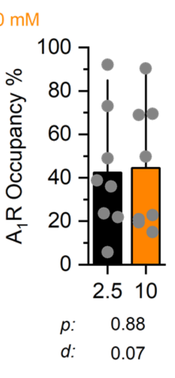


Fig.4. Do glucose levels impact A_1R occupancy? We measured adenosine 1 receptor (A_1R) occupancy with either 2.5 mM or 10 mM glucose. A_1R occupancy indicates how efficiently adenosine suppresses neuronal activity. A_1R occupancy is not affected by glucose levels.

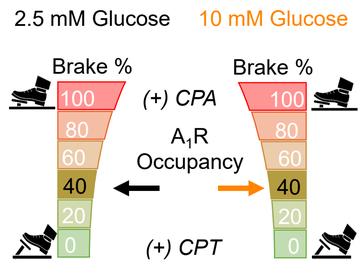
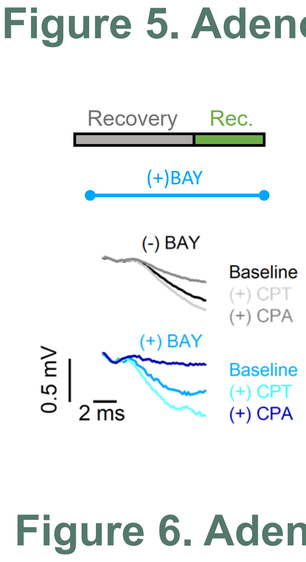
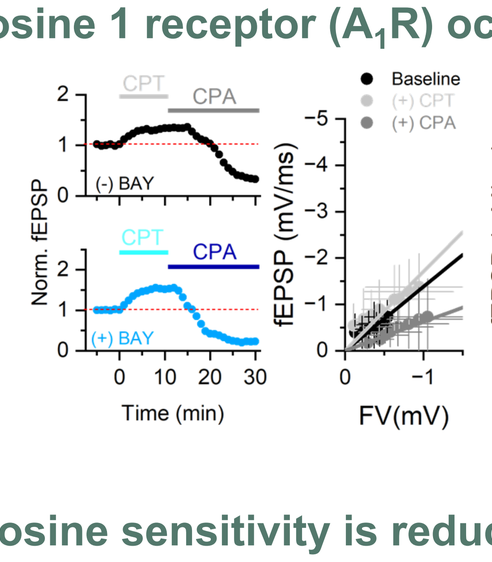
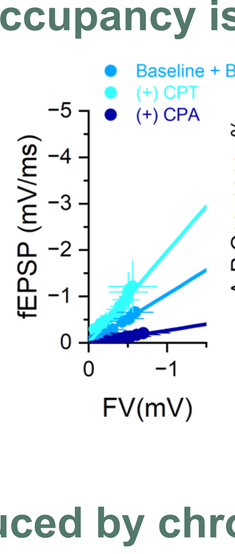


Figure 5. Adenosine 1 receptor (A_1R) occupancy is not affected by astrocytic GLUT1 activity







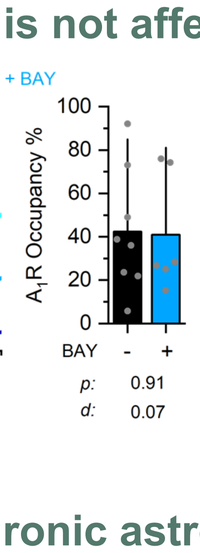


Fig.5. Does astrocytic GLUT1 function impact A_1R occupancy? We measured adenosine 1 receptor (A_1R) occupancy with or without astrocytic GLUT1 blocker BAY876 at 2.5 mM glucose. A_1R occupancy is not affected by astrocytic GLUT1 activity.

Figure 6. Adenosine sensitivity is reduced by chronic astrocytic GLUT1 inhibition

Fig.6. Does astrocytic GLUT1 activity influence adenosine sensitivity? We graphed basal synaptic transmission against A_1R occupancy. The slope indicates adenosine sensitivity, with steeper slopes suggesting higher sensitivity. Blocking astrocytic GLUT1 reduces sensitivity to A_1R-mediated inhibition.

2.5 mM Glucose (-) BAY

2.5 mM Glucose (+) BAY