Inhibition of MCT2 expression in hypothalamic neurons alters feeding behavior

Coca A, Órdenes P, Elizondo-Vega R, García-Robles MA.
Departamento de Biología Celular, Facultad de Ciencias Biológicas, Universidad de Concepción, Chile.
(acoca2017@udec.cl) Supported by FONDECYT 1180871

INTRODUCTION

In the arcuate nucleus (ARC) of the hypothalamus, glia-neuron interactions regulate glucose homeostasis and feeding behavior. Previously, we demonstrated that inhibition of monocarboxylate transporters (MCT) 1 and 4 localized in glia affects feeding behavior. MCT2 is localized in the ARC orexigenic (NPY/AgRP) and anorexigenic (POMC/CART) neurons.

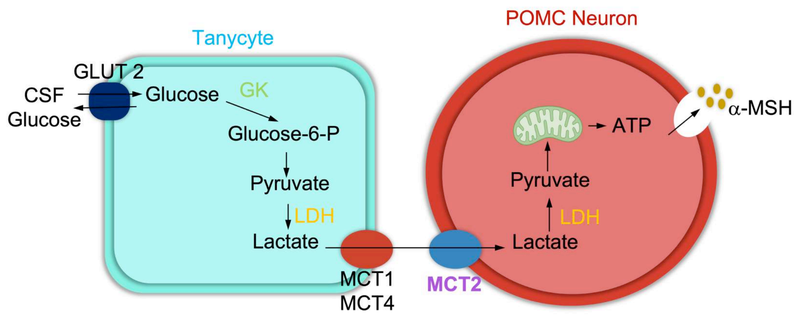

Figure 1: Schematic model representing the role of MCT2 in the tanycyte-neuron POMC glucosensing model.
Mechanism of neuronal activation in response to an increase in CSF glucose concentration. In tanycytes, glucose enters via GLUT1-2 and is metabolized, producing lactate. Lactate released by tanycytes is incorporated by POMC neurons through MCT2 and triggers an anorexigenic response.

METHODS

Female Sprague-Dawley rats were bilaterally injected in the ARC using a fine pulled-glass pipette with an adeno-associated virus (AAV-sh-MCT2-syn-tdTomato) for generating MCT2-neuron knockdown rats.
The reduction of MCT2 mRNA level was confirmed using real-time PCR.
The rats were subjected to a fasting-feeding cycle that consisted of 24 h of fasting followed by 24 h of feeding. After each period, glycemia, food intake, and body weight were measured in MCT2-inhibited rats and compared with rats injected with a control AAV.

We analyzed the effect of MCT2 inhibition on meal pattern parameters macrostructure and microstructure of food intake, such as meal frequency, intermeal intervals, meal size and meal duration.

RESULTS

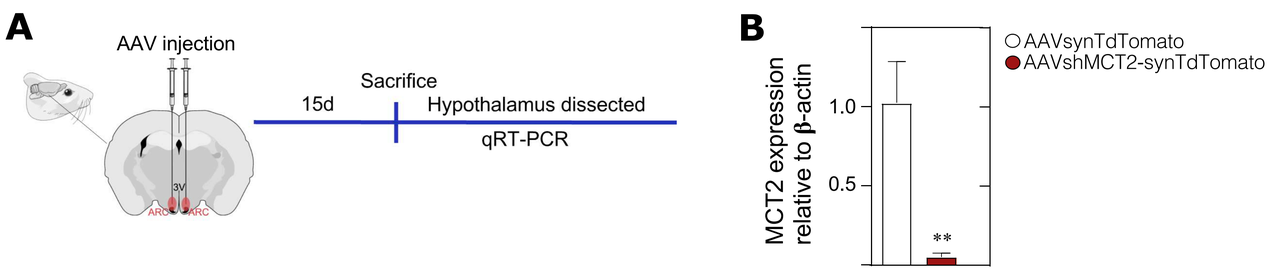

Figure 2: AAVshMCT2 injected in the ARC generates an effective MCT2 inhibition.
A: Scheme of the experimental protocol.
B: qRT-PCR analysis of MCT2 mRNA expression after injection of AAV-syn-tdTomato (control) (closed bar) or AAV-sh-MCT2-syn-tdTomato (red bar); n=4 AAV-syn-tdTomato and n=3 AAV-sh-MCT2-syn-tdTomato rats. Data are expressed as mean +-SD. (** p<0.01 unpaired t-test).

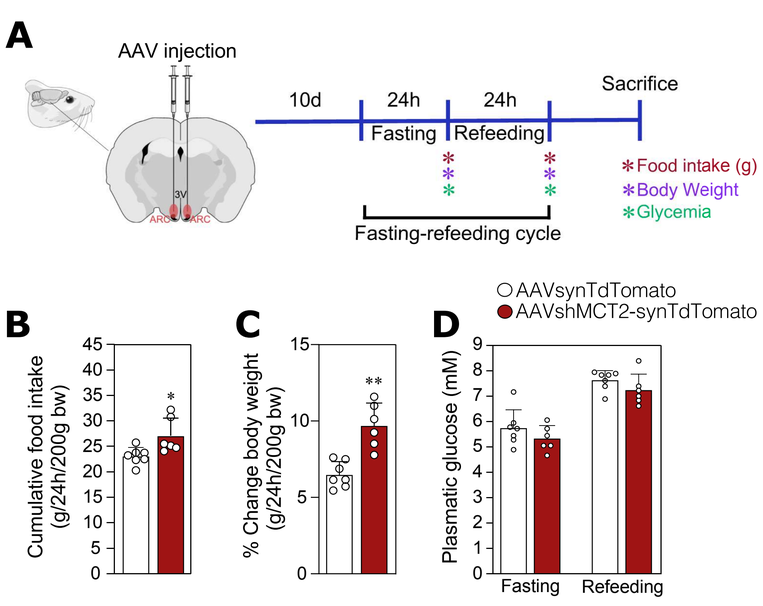

Figure 3: MCT2 knockdown rats increases food intake and body weight.
A: Experimental protocol. Adult female rats were injected with AAV-syn-tdTomato (control) (closed bar) or AAV-sh-MCT2-syn-tdTomato. At 10 days post-AAV injection, the rats were subjected to 24h of fasting followed by 24h of feeding. Food intake, body weight and glycemia were measured. **B:** Quantification of food intake over 24h after feeding was expressed as g/200g body weight. **C:** Percentage of change in body weight. **D:** Quantification of glycemia after fasting and refeeding; n=7 AAV-syn-tdTomato and n=6 AAV-sh-MCT2-syn-tdTomato rats (* p<0.05, ** p<0.01 unpaired t-test).

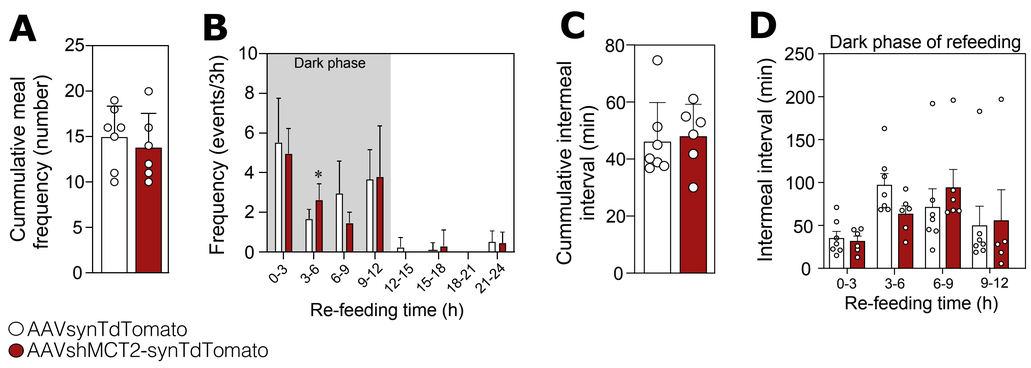

Figure 4: MCT2 inhibition increases feeding frequency during the first 6h of the dark phase.
A: Cumulative meal frequency over 24h. **B:** Analysis of meal frequency every 3h. **C:** Cumulative intermeal intervals over 24h were determined. **D:** Quantification of intermeal intervals every 3h in the dark phase.
(* p<0.05 two-way ANOVA, uncorrected Fisher's LSD test).

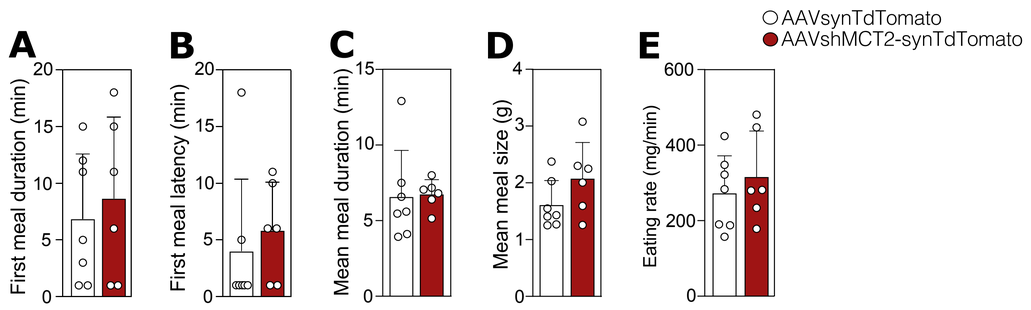

Figure 5: Absence of significant differences in the microstructure of food intake in MCT2 knockdown rats was detected.
A: Duration of the first meal after refeeding. **B:** Latency of the first meal after refeeding. **C:** Mean duration of meal events 24 h after feeding. **D:** Mean meal size (g/number of events) 24 h after feeding. **E:** Eating rate, estimated as the total amount of food consumed in total meal duration .

CONCLUSIONS

The macrostructure of food intake showed a significant increase in cumulative intake and body weight gain without changes in glycemia. Changes in the microstructure of food intake have origin in the dark phase of feeding. In the second period of this phase, the feeding frequency is significantly higher than control, and the intermeal intervals show a tendency to decrease (p0.058), indicating a decrease in satiety.
Feeding behavior in the MCT2 knockdown rats agrees with the model of cell communication between glia and POMC neurons through monocarboxylates.