

1 **RESEARCH ARTICLE**

2 **Running Head:** Amino acids, glucagon, and brain glucose in obesity

3

4 **Impact of obesity on aromatic amino acids and brain glucose during acute**  
5 **hyperglycemia**

6

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29 **Abstract**

30 Hyperaminoacidemia is an early hallmark of insulin resistance, with aromatic and branched  
31 chain amino acids particularly associated with insulin resistance and type 2 diabetes. We  
32 previously showed that healthy adults with obesity exposed to acute hyperglycemia have lower  
33 brain glucose levels measured by magnetic resonance spectroscopy (MRS) than lean controls,  
34 suggesting that a blunted brain response to hyperglycemia may be an early marker of insulin  
35 resistance. Here, in a secondary analysis of our prior study, we used targeted mass  
36 spectrometry-based metabolomics to measure plasma amino acids in participants with and  
37 without obesity to determine if changes in peripheral metabolites associated with early insulin  
38 resistance such as amino acids were associated with changes in brain glucose levels during  
39 hyperglycemia. There were few differences in baseline amino acids between groups, but acute  
40 hyperglycemia unveiled higher plasma concentrations of amino acids including cysteine,  
41 cystine, glutamic acid, glutamine, methionine, and aromatic amino acids in obesity. Plasma  
42 glucagon levels were also higher in obesity during acute hyperglycemia. Higher plasma  
43 concentrations of aromatic amino acids and glucagon were significantly correlated with lower  
44 brain glucose levels, illustrating parallel development of central and peripheral metabolic  
45 changes in obesity.

46

47 **Keywords:** obesity, amino acids, glucagon, brain glucose, magnetic resonance spectroscopy

48

49 **New & Noteworthy (75 Word Limit)**

50 We related early insulin resistance-associated peripheral factors with brain glucose measured  
51 by <sup>13</sup>C magnetic resonance spectroscopy during acute hyperglycemia in young, healthy adults  
52 with and without obesity. Plasma amino acids including aromatic amino acids and glucagon  
53 were higher in obesity during acute hyperglycemia. There were negative correlations between

54 aromatic amino acids and glucagon with the change in brain glucose. These findings may be  
55 related to brain oxidative stress and neurotransmitter synthesis in obesity.

## 56 **Introduction**

57           The incidence and prevalence of obesity and type 2 diabetes continue to increase at  
58 alarming rates, with some estimates projecting that nearly half of Americans will have obesity by  
59 2030 (1), and that more than 1 billion people worldwide will have diabetes by 2050 (2).  
60 Furthermore, the sequence of events by which metabolic dysfunction emerges in obesity and  
61 translates into risk for type 2 diabetes remains unclear and, if better understood, could advance  
62 our understanding of its pathophysiology and treatment.

63           Changes in the central nervous system (CNS) may be among the earliest  
64 pathophysiological changes in obesity, which can include altered brain structure, function, and  
65 metabolism (3). Recently published data from our group showed that, compared to lean  
66 controls, adults with obesity exhibited nearly 20% lower brain glucose uptake during  
67 hyperglycemia, as measured by magnetic resonance spectroscopy (MRS) (4). Notably, these  
68 changes occurred in young, otherwise healthy individuals and were observed despite the  
69 absence of any overt clinical signs of metabolic dysfunction, including traditional measures of  
70 insulin resistance calculated from oral glucose tolerance testing. As obesity is the most  
71 significant risk factor for insulin resistance (5), here we have investigated other factors that may  
72 be associated with central changes in these participants by looking for additional subtle signs of  
73 peripheral insulin resistance that may be revealed during a metabolic stressor such as acute  
74 hyperglycemia.

75           Alterations in plasma amino acid signatures and glucagon have been associated with  
76 insulin resistance. Changes in aromatic amino acids and branched chain amino acids (BCAA)  
77 were associated with obesity and insulin resistance as early as the 1960s (6-8), but whether  
78 these profiles are early manifestations of or contributors to insulin resistance remains under  
79 investigation (9). Amino acids stimulate pancreatic  $\alpha$ -cell secretion of glucagon, which promotes  
80 amino acid uptake and catabolism in the liver. Amino acids are also transported from the  
81 periphery across the blood-brain barrier (BBB) for utilization in glucose-fueled neurotransmitter

82 synthesis. The deleterious effects of excess concentrations of aromatic amino acids or BCAA  
83 are most dramatically illustrated by phenylketonuria and maple syrup urine disease, inborn  
84 errors of metabolism caused by mutations in phenylalanine hydroxylase and branched chain  
85 ketoacid dehydrogenase complex enzymes, leading to elevations of phenylalanine and BCAA,  
86 respectively. Accumulation of these amino acids can lead to devastating neurotoxicity (10). In  
87 other studies, supplementation of obesity-inducing diets with extra BCAA results in increases in  
88 anxiety-like behaviors in pre-clinical models (11). As the interplay between CNS and peripheral  
89 metabolism is increasingly appreciated, it becomes important to examine both the CNS and the  
90 periphery in parallel at singular time points along the path to metabolic dysfunction.  
91 Accordingly, here we have investigated the dynamic changes in plasma amino acids and  
92 glucagon during hyperglycemia and their association with brain glucose in a cohort of young  
93 adults with metabolically healthy obesity.

94

## 95 **Materials and Methods**

### 96 *Human subjects*

97 The study was approved by the Yale University Human Investigation Committee, and all  
98 participants provided written informed consent. Detailed inclusion and exclusion criteria and  
99 screening procedures were described previously (4). Briefly, lean adults with BMI 18-25 kg/m<sup>2</sup>  
100 (n=11) and adults with obesity with BMI greater than 30 kg/m<sup>2</sup> up to the weight limit of the MRI  
101 scanner (n=10) were included in the parent study. All participants were without chronic medical  
102 conditions and prescription medication use apart from hormonal contraception. All participants  
103 underwent a standard 75-gram oral glucose tolerance test (OGTT) (on a separate day) prior to  
104 hyperglycemic clamp and <sup>13</sup>C MRS scanning. OGTT data were used to calculate: homeostatic  
105 model assessment for insulin resistance (HOMA-IR) [(fasting insulin (μU/L) x fasting glucose  
106 (nmol/L))/22.5]; Matsuda Index (12); insulinogenic index [ $\Delta$  plasma insulin (μU/L) /  $\Delta$  plasma  
107 glucose (mmol/L) during the first 30 minutes of the OGTT]; and disposition index (insulinogenic

108 index x Matsuda Index). Participants from each group in the parent study (4) who had available  
109 plasma samples (n=8/group) were included in the present study (Figure 1).

110

### 111 *Hyperglycemic clamp and <sup>13</sup>C MRS scanning*

112 After an overnight fast, participants arrived in the morning at the Yale Magnetic  
113 Resonance Research Center. Participants were prepared for concurrent glucose infusion and  
114 MRS scanning by inserting an intravenous (IV) catheter into the distal aspect of each arm – one  
115 for blood sampling and one for 20% [1-<sup>13</sup>C] glucose infusion – and then placed in a 4.0 Tesla  
116 whole-body magnet. Details of <sup>13</sup>C MRS protocols and analyses were described in the parent  
117 study (4). Briefly, after tuning, voxel selection, shimming, and acquisition of baseline MRS data,  
118 the hyperglycemic clamp was initiated using a variable rate IV infusion of 20% [1-<sup>13</sup>C] glucose to  
119 achieve and maintain a target blood glucose of 180 mg/dL for 120 minutes (13). Steady state  
120 plasma percent enrichment was similar between groups (BMI<25: 78.3 ± 18.9%; BMI>30: 82.5  
121 ± 8.6%; p=0.63). Plasma glucose was measured every 5 minutes during the hyperglycemic  
122 clamp. Plasma was also collected at 0, 2, 4, 6, 8, 10, 30, 60, 90, and 120 minutes and stored at  
123 -80°C to -20° for targeted metabolomics and other hormonal analyses. MRS data were acquired  
124 continuously for the duration of the hyperglycemic clamp to quantify the change in brain glucose  
125 and calculate the maximum rate of glucose transport ( $T_{max}$ ) relative to the cerebral metabolic  
126 rate of glucose ( $CMR_{gl}$ ) using the following equation:

$$\frac{T_{max}}{CMR_{gl}} = \frac{G_o V_d + G_i + K_T V_d}{G_o V_d - G_i}$$

127 where  $V_d$  is the volume of distribution of the brain water space [0.77 mL/g (14)],  $\Delta_i$  is the change  
128 in brain glucose ( $\mu\text{M/g}$ ),  $G_o$  and  $G_i$  are the steady-state plasma and brain glucose  
129 concentrations, respectively (mM), and  $K_T$  is the Michaelis-Menten constant for the glucose  
130 transporter (mM). The period of hyperglycemia was terminated prior to 120 minutes for two  
131 participants (one in each group), therefore these participants were excluded from analyses

132 incorporating data from plasma samples collected at 120 minutes (Figure 1). MRS data from  
133 one participant with class 2 obesity had signal-to-noise ratios that did not meet quality control  
134 criteria, therefore this participant's spectroscopy data were excluded (Figure 1).

135

#### 136 *Targeted metabolomics*

137 Amino acids were measured by liquid chromatography-tandem mass spectrometry by the Duke  
138 Molecular Physiology Institute's Metabolomics Core Laboratory, using a method adapted from  
139 the literature (15). Ten  $\mu$ l of plasma was spiked with a mixture of stable isotope-labeled internal  
140 standards and deproteinized with methanol. The supernatants were derivatized with AccQTag  
141 reagent (Biosynth-Carbosynth) at 55 °C for 10 minutes. Chromatographic separation was  
142 performed using a Waters Acquity UPLC system (Milford, MA) equipped with a Waters Acquity  
143 UPLC HSS T3 column (1.8  $\mu$ m, 2.1  $\times$  100 mm). Mobile phase A consisted of 0.1% formic acid in  
144 water, and mobile phase B was acetonitrile. The flow rate was set to 0.6 ml/min, and the column  
145 temperature was maintained at 40°C. The gradient program was as follows: 0–1.0 min, 0% B;  
146 1.0–6.0 min, linear increase to 95% B; followed by a 1-min wash and a 1-min re-equilibration.  
147 Analytes were detected in the positive ion mode using multiple reaction monitoring (MRM) on a  
148 Waters Xevo TQ-XS mass spectrometer.

149

#### 150 *Laboratory analysis*

151 Plasma glucose was measured every 5 minutes during the hyperglycemic clamp by  
152 glucose oxidase method (YSI Inc.). Plasma insulin levels were measured by double-antibody  
153 radioimmunoassay (Millipore). Plasma glucagon was measured by ELISA (Merckodia) by UNC's  
154 Respiratory TRACTS Core.

155

#### 156 *Statistics*

157 Analyses were performed using SPSS Version 29 or GraphPad Prism 10. Continuous  
158 dependent variables were compared by independent samples t-tests or, if Levene's test for  
159 equality of variances was violated, by Welch's t-test. Given the small sample size, we accepted  
160 non-normally distributed data by Shapiro-Wilk's test. Plasma glucose, GIR, and plasma insulin  
161 time courses during the hyperglycemic clamp were compared by mixed effects analysis.  
162 Individual and summed amino acid concentrations were compared by one-way ANCOVA with  
163 baseline concentration as a covariate. Correlations were performed by Pearson's product-  
164 moment correlations or Spearman's rank correlations. A p value <0.05 was considered  
165 statistically significant.

166

## 167 **Results**

### 168 *Peripheral metabolic characterization of study participants*

169 Demographics, baseline clinical data obtained from participants' screening visit and labs,  
170 and measures of insulin resistance and beta cell function derived from 75-gram oral glucose  
171 tolerance test data are displayed in Table 1. By study design, body mass index (BMI) was  
172 higher in the participants with obesity (p<0.001). As expected from our prior work in a larger  
173 cohort inclusive of these participants (4), the insulinogenic index, a measure of pancreatic beta  
174 cell function, and systolic blood pressure were higher in the obesity group (p=0.02 and p=0.04,  
175 respectively). Other standard clinical metabolic parameters including A1c, total cholesterol and  
176 cholesterol subspecies, and liver enzymes were not different between groups.

177 All participants were exposed to acute hyperglycemia via a hyperglycemic clamp of 120  
178 minutes' duration with target glucose 180 mg/dL, permitting clamp-derived approximations of  
179 glucose tolerance, beta cell function, and tissue sensitivity to insulin. Prior to initiation of IV [1-  
180 <sup>13</sup>C] glucose infusion, fasting plasma glucose, insulin, and glucagon were not significantly  
181 different between participants with and without obesity (p=0.07, p=0.17, and p=0.16,  
182 respectively) (Figure 2A-C). Over the course of the hyperglycemic clamp, plasma glucose levels

183 were similar between groups (Figure 2D). The glucose infusion rate (GIR), an approximation of  
184 glucose tolerance, and steady state GIR, or the GIR averaged between 90 and 120 minutes of  
185 the hyperglycemic clamp, were not different between groups ( $p=0.24$ ) (Figure 2E-F). The  
186 interaction between time and obesity status on insulin during the hyperglycemic clamp was non-  
187 significant ( $p=0.19$ ), and the area under the curve of the summary data was not different  
188 between groups ( $p=0.18$ ) (Figure 2G-H), suggesting similar beta cell responses to IV glucose.  
189 The ratio of steady state GIR to insulin approximates peripheral tissue sensitivity to insulin (13,  
190 16); this measure trended lower in obesity ( $p=0.06$ ). In summary, most clamp-derived measures  
191 of whole-body glucose metabolism and insulin secretion and sensitivity were not significantly  
192 different between participants with and without obesity.

### 193 *Plasma amino acids and relationship with brain glucose during hyperglycemia*

194 Alterations in amino acid signatures have been associated with obesity and type 2  
195 diabetes. We utilized liquid chromatography-tandem mass spectrometry to measure plasma  
196 amino acids at baseline and at multiple time points during acute hyperglycemia (Figure 3). At  
197 baseline, there were few differences in amino acids. Glutamic acid was higher in obesity ( $154 \pm$   
198  $34$  vs.  $109 \pm 37$   $\mu\text{M}$ ,  $p=0.03$ ), and glycine was lower in obesity ( $201 \pm 37$  vs.  $261 \pm 56$   $\mu\text{M}$ ,  
199  $p=0.02$ ) (Table 2). There was a statistically significant positive correlation between glutamic acid  
200 and BMI ( $r=0.54$ ,  $p=0.03$ ) and statistically significant negative correlations between glycine and  
201 BMI ( $r=-0.55$ ,  $p=0.03$ ), and glycine and insulin ( $r=-0.55$ ,  $p=0.03$ ). There were no correlations  
202 between either glutamic acid or glycine and fasting glucose or glucagon.

203 We then examined plasma amino acids during acute hyperglycemia mid-way through  
204 the hyperglycemic clamp at 60 minutes and at the conclusion of the hyperglycemic clamp at 120  
205 minutes. Statistically significant differences between groups at each of these individual time  
206 points and averaged between the two time points after adjustment for baseline concentrations  
207 are summarized in Table 2. The baseline elevation in glutamic acid in obesity persisted  
208 throughout hyperglycemia. Cysteine, cystine, glutamine, methionine, tryptophan, and tyrosine

209 emerged as additional amino acids with differential responses to hyperglycemia in obesity. Of  
210 particular note, we observed changes in summed aromatic amino acids during acute  
211 hyperglycemia. In contrast, we did not observe changes between groups in BCAA either  
212 individually or summed.

213 We then examined relationships between individual and summed aromatic amino acids  
214 and the ratio of brain glucose transport to metabolism ( $T_{\max}/CMR_{gl}$ ) measured by  $^{13}C$  MRS  
215 during acute hyperglycemia. In our prior study, the brain glucose metabolic or utilization rate  
216 ( $CMR_{gl}$ ) was not different between obesity and lean controls, therefore differences in brain  
217 glucose were attributed to differences in the maximum rate of brain glucose transport ( $T_{\max}$ ) (4).  
218 We observed significant negative correlations between concentrations of each individual  
219 aromatic amino acid as well as the summed concentration of aromatic amino acids with  
220  $T_{\max}/CMR_{gl}$ , such that higher aromatic amino acid concentrations were associated with lower  
221  $T_{\max}/CMR_{gl}$  (Figure 4). Similarly, higher cystine and methionine concentrations were associated  
222 with lower  $T_{\max}/CMR_{gl}$  (cystine at  $t=120''$ :  $\rho=-0.64$ ,  $p=0.02$ ; methionine averaged between  $t=60''$   
223 and  $t=120''$ :  $\rho=-0.71$ ,  $p<0.01$ ). Other correlations between cysteine, cystine, glutamic acid, and  
224 glutamine with  $T_{\max}/CMR_{gl}$  during hyperglycemia were not significant. In addition, for amino  
225 acids that were not different between groups, we also observed some significant correlations  
226 with  $T_{\max}/CMR_{gl}$  at multiple timepoints: (1)  $t=60''$ : alanine ( $\rho=-0.68$ ,  $p<0.01$ ), arginine ( $\rho=-0.63$ ,  
227  $p=0.01$ ), histidine ( $\rho=-0.68$ ,  $p<0.01$ ), isoleucine ( $\rho=-0.65$ ,  $p<0.01$ ), methionine ( $\rho=-0.69$ ,  $p<0.01$ ),  
228 proline ( $\rho=-0.76$ ,  $p<0.001$ ), and threonine ( $t=60''$ :  $\rho=-0.55$ ,  $p=0.03$ ); (2)  $t=120''$ : proline ( $\rho=-0.63$ ,  
229  $p=0.02$ ); and (3)  $t=60-120''$  averaged: arginine ( $\rho=-0.60$ ,  $p=0.03$ ), histidine ( $\rho=-0.62$ ,  $p=0.02$ );  
230 isoleucine ( $\rho=-0.61$ ,  $p=0.03$ ), leucine ( $\rho=-0.57$ ,  $p=0.04$ ), methionine ( $\rho=-0.71$ ,  $p<0.01$ ), and  
231 proline ( $\rho=-0.69$ ,  $p<0.01$ ).

232

233 *Plasma glucagon and relationship with brain glucose during acute hyperglycemia*

234 Amino acid metabolism is regulated in part by glucagon, which promotes proteolysis and  
235 amino acid uptake in the liver in times of low energy availability. We therefore measured  
236 glucagon in lean participants and those with obesity and observed a similar pattern of response  
237 as described for aromatic amino acids: Plasma glucagon was higher in obesity compared to  
238 lean participants during acute hyperglycemia ( $4.43 \pm 2.38$  pg/mL in obesity vs.  $2.15 \pm 1.30$   
239 pg/mL in lean participants,  $p=0.047$ ) (Figure 5A). Higher glucagon levels were associated with  
240 lower  $T_{\max}/CMR_{gl}$  (Figure 5B). Of the aromatic amino acids, only tryptophan showed a significant  
241 correlation with glucagon ( $\rho=0.543$ ,  $p=0.045$ ).

242

## 243 Discussion

244 Capturing cohorts of individuals with obesity who are early on the pathway to metabolic  
245 dysfunction can shed light on the stepwise deterioration of metabolic health. Here, we have  
246 performed peripheral metabolic phenotyping in a subset of participants from our prior study that  
247 used  $^{13}C$  MRS to measure brain glucose transport and metabolism during acute hyperglycemia  
248 in young, healthy adults with and without obesity (4). We have also related these peripheral  
249 changes to changes in brain glucose. Young adults with obesity had higher BMI, systolic blood  
250 pressure, and insulinogenic index calculated from OGTT data but still met existing criteria for  
251 metabolically healthy obesity (17). Fasting glucose, insulin, and glucagon were not significantly  
252 different between groups. We found minimal baseline amino acid differences in obesity, which is  
253 in contrast to studies describing increased aromatic amino acids and BCAA and decreased  
254 glycine in adults with obesity (6-8) (18), presumably reflective of greater age and/or more  
255 advanced obesity pathophysiology in these cohorts. We also investigated hyperglycemic clamp-  
256 derived assessments of metabolic health and did not find differences in steady state GIR,  
257 suggestive of similar glucose tolerance between groups – a conclusion further supported by  
258 equivalent two-hour OGTT plasma glucose concentrations. Together, data acquired at baseline  
259 and across hyperglycemic clamp-derived metabolic variables suggest that we have captured a

260 cohort of individuals with obesity who may be at an early step in progression to metabolic  
261 dysfunction.

262 Our findings are consistent with other works suggesting that hyperaminoacidemia and  
263 hyperglucagonemia are early, subtle signs of insulin resistance (19, 20). Despite few significant  
264 baseline differences, the group with obesity showed higher plasma concentrations of cysteine,  
265 cystine, glutamic acid, glutamine, methionine, and aromatic amino acids during exposure to  
266 acute hyperglycemia, which may be early manifestations of insulin resistance. Of note, we did  
267 not observe any parallel differences in BCAA during hyperglycemia. While both sexes were  
268 represented in both groups, higher levels of BCAA and their derived metabolites have been  
269 found in men with obesity compared to women with obesity (21). Our cohorts were small and  
270 predominantly female, which could underestimate population-level differences in BCAA in  
271 obesity. Aromatic amino acids have received less attention in the literature than BCAA, but  
272 several potential mechanisms of insulin resistance have been identified, including insulin  
273 receptor modifications by phenylalanine (22) and tryptophan (23). While we cannot draw  
274 conclusions about whether diminished suppression of amino acids during acute hyperglycemia  
275 is a sign of developing insulin resistance or a contributor to worsening insulin resistance, this  
276 change is likely one occurring early in the development of metabolic dysfunction.

277 Fasting and post-prandial hyperglucagonemia are well-described features of obesity and  
278 type 2 diabetes and parallel insulin resistance due to the role of insulin in regulation of glucagon  
279 secretion (24). We observed a trending but nonsignificant increase in fasting plasma glucagon  
280 and significantly higher levels of plasma glucagon during acute hyperglycemia generated by  
281 hyperglycemic clamp, which is potentially explained by stronger suppression of glucagon by IV  
282 than oral glucose (25). Alternatively, CNS control of glucagon secretion by glucose-sensing  
283 neurons in the hypothalamus may be impaired in obesity due to obesity-associated  
284 hypothalamic inflammation.

285 In the periphery, glucagon secreted by pancreatic  $\alpha$ -cells promotes amino acid transport  
286 into the liver, decreasing circulating amino acids and therefore decreasing glucagon – a  
287 feedback circuit termed the liver- $\alpha$  cell axis (26-28). The effect of visceral adiposity of metabolic  
288 dysfunction-associated steatotic liver disease (MASLD) on the liver- $\alpha$  cell axis and glucagon  
289 resistance remains uncertain. Several studies concluded that MASLD is associated with  
290 glucagon resistance and hyperaminoacidemia (29, 30). In another study, a short-term  
291 hypercaloric diet induced glucagon resistance and hyperaminoacidemia in young, lean men  
292 (31). In contrast, other studies have demonstrated equivalent amino acid responses to glucagon  
293 infusion irrespective of MASLD, obesity, and type 2 diabetes (32, 33). We did not quantify  
294 hepatic fat content in our study, but concurrent elevations in amino acids and glucagon during  
295 hyperglycemia could be consistent with glucagon resistance.

296 Available animal data involving genetic manipulation of the glucagon receptor suggest that  
297 glucagon-mediated effects may be specific to individual amino acids. In one study comparing  
298 changes in serum amino acids between wild type and glucagon receptor (*Gcgr*) knockout (*Gcgr*<sup>-/-</sup>)  
299 mice, phenylalanine and tryptophan showed the smallest, statistically significant difference  
300 between groups compared to many other amino acids (34). In another study, serum amino  
301 acids were compared between wild type and *Gcgr*<sup>-/-</sup> mice with the addition of two wild type  
302 groups treated with glucagon receptor antagonists; phenylalanine and tryptophan were  
303 unchanged in each of these cases (35). These animal data suggest that glucagon receptor  
304 signaling has less effect on aromatic amino acids compared to other amino acids. Therefore,  
305 the changes we see in aromatic amino acids during acute hyperglycemia in obesity may not be  
306 secondary to higher glucagon levels and glucagon resistance.

307 In the present study, we also observed negative correlations of cystine, methionine,  
308 aromatic amino acids, and glucagon with  $T_{\max}/\text{CMR}_{\text{gl}}$  during acute hyperglycemia, such that  
309 higher circulating amino acid and glucagon concentrations were associated with lower brain  
310 glucose. This observation suggests that central and peripheral changes exist

311 contemporaneously in early obesity pathophysiology. Cystine and glutamic acid share a  
312 transport system, system  $x_c^-$ , which is expressed in the brain and transports cystine  
313 intracellularly to support glutathione production and redox balance (36). The altered relationship  
314 between cystine and brain glucose during acute hyperglycemia could have implications for both  
315 neuroprotection and neurotoxicity. Aromatic amino acids are also highly important for brain  
316 function; tryptophan serves as a precursor for serotonin, kynurenine, and kynurenic acid, and  
317 tyrosine serves as a precursor for dopamine and catecholamines. Both aromatic amino acids  
318 and BCAA belong to a family of amino acids termed large neutral amino acids (LNAA) that  
319 share a common transporter across the BBB. Therefore, alterations in circulating amino acid  
320 levels may result in altered availability of neurotransmitter precursors in the CNS (11).

321 Amino acid catabolism can supply tricarboxylic acid (TCA) cycle intermediates to re-  
322 supply those consumed via anabolic processes, a concept termed anaplerosis (37). Regarding  
323 aromatic amino acids in particular, phenylalanine and tyrosine are catabolized to intermediates  
324 that enter the TCA cycle directly via fumarate and indirectly via acetoacetate, which can be  
325 converted to acetyl-CoA. Tryptophan metabolism can generate acetyl-CoA as well as pyruvate  
326 via conversion to alanine. It is not known whether aromatic amino acid elevation in early obesity  
327 pathophysiology reflects ongoing proteolysis or impairment in amino acid catabolism. While  
328 speculative, ongoing proteolysis and flux through amino acid catabolic pathways could robustly  
329 replenish TCA cycle intermediates, lessening the demand for glucose entry into the brain.  
330 However, effects of hyperglycemia and developing insulin resistance on cellular metabolism in  
331 the brain are likely cell type-specific and represent an area ripe for investigation.

332 Our study is a small secondary analysis, and our observed relationships between amino  
333 acids, brain glucose, and obesity are correlative. However, these data underscore the need for  
334 ongoing inquiry into metabolic interplay between the brain and the periphery, especially in the  
335 context of epidemic metabolic diseases like obesity and type 2 diabetes; more work is needed  
336 to define these relationships and associated mechanisms.

337 In summary, we demonstrate that in a cohort of young, healthy individuals with obesity  
338 exposed to acute hyperglycemia, there are higher plasma levels of select amino acids, including  
339 aromatic amino acids, and glucagon as well as altered dynamics of metabolites such as  
340 glutamate and cystine associated with the system  $x_c^-$  carrier and reductive stress. These  
341 changes correlate with diminished uptake of brain glucose and suggest possible mechanisms  
342 for parallel development of central and peripheral changes in early obesity pathophysiology.

343

#### 344 **Data Availability**

345 Data presented in the current study are available from the corresponding author upon  
346 reasonable request.

347

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354

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364 part as abstracts at ENDO in June 2024 in Boston, Massachusetts, and the American Diabetes  
365 Association's 85<sup>th</sup> Scientific Sessions in June 2025 in Chicago, Illinois (Ref).

366

### 367 **Disclosures**

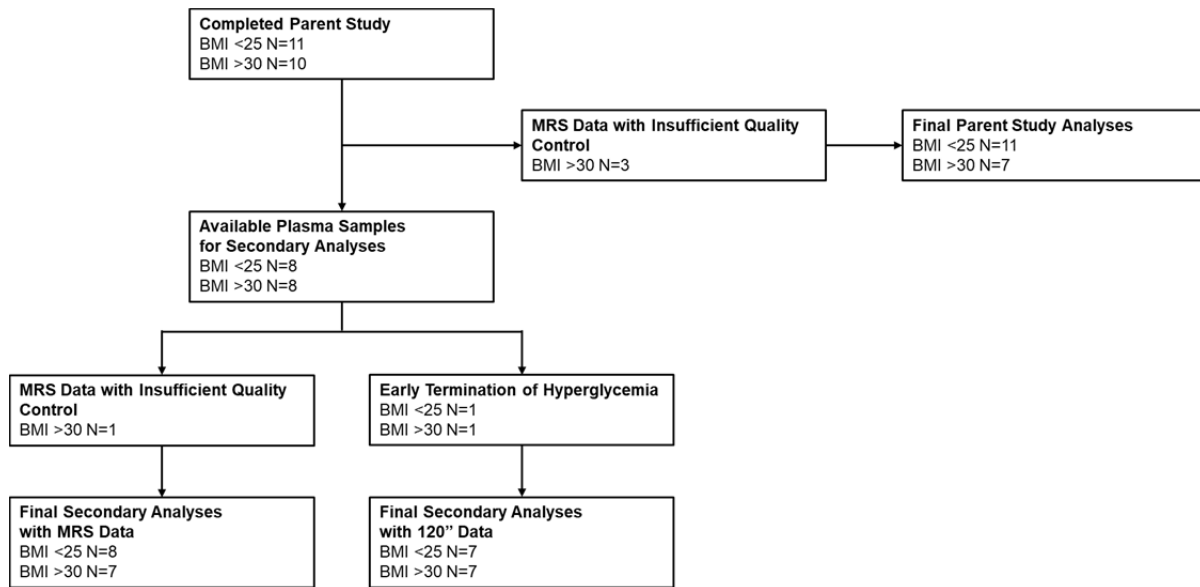
368 The authors do not have perceived or potential conflicts of interest to disclose relevant to the  
369 present study.

370

### 371 **Author Contributions**

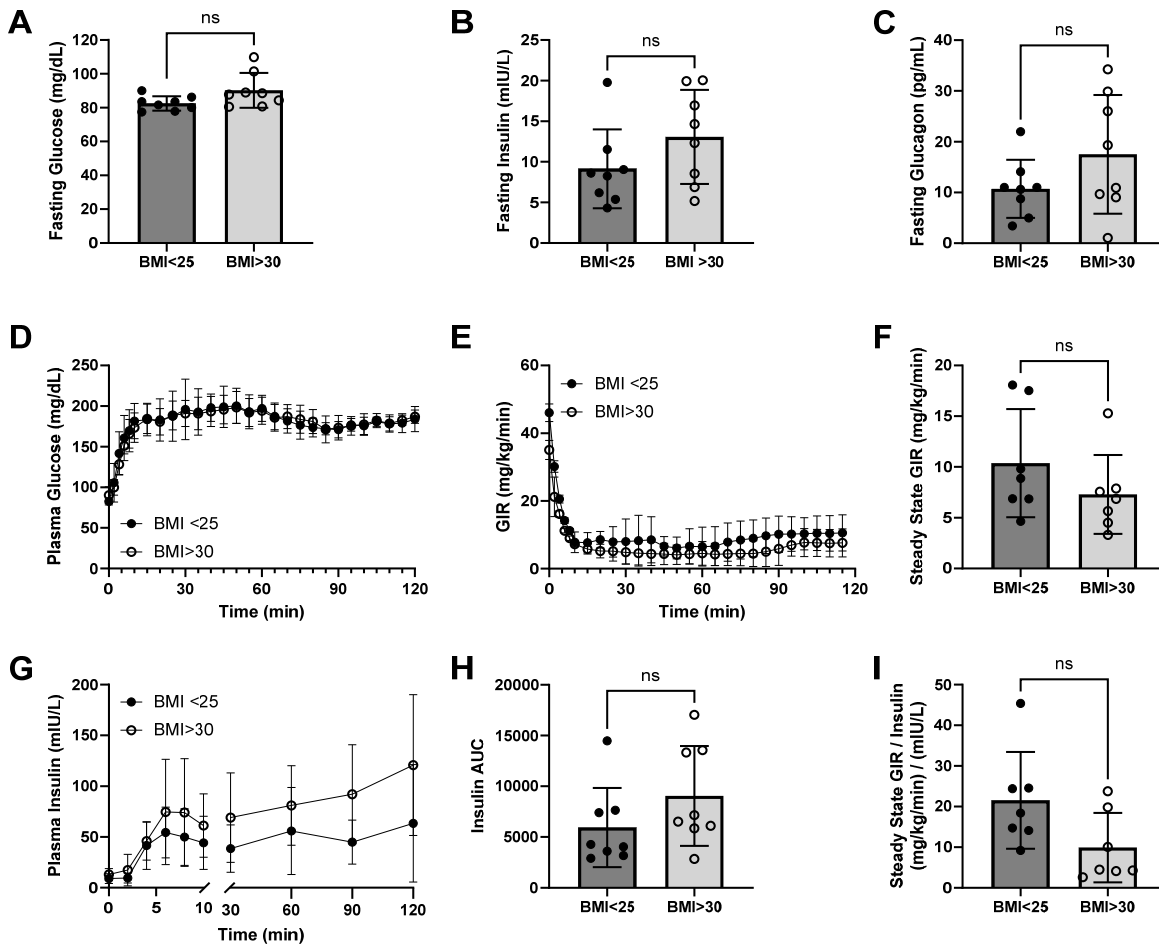
372 DLR, GFM, CBN, and JJH conceived of and designed the research; FG, OI, and JJH performed  
373 experiments; BCM and GFM analyzed data; BCM, FG, GFM, CBN, and JJH interpreted results  
374 of experiments; BCM prepared figures; BCM and JJH drafted the manuscript; BCM, FG, GFM,  
375 OI, CBN, and JJH edited and revised the manuscript; and all authors approved the final version  
376 of the manuscript.

377 **Figures**



378

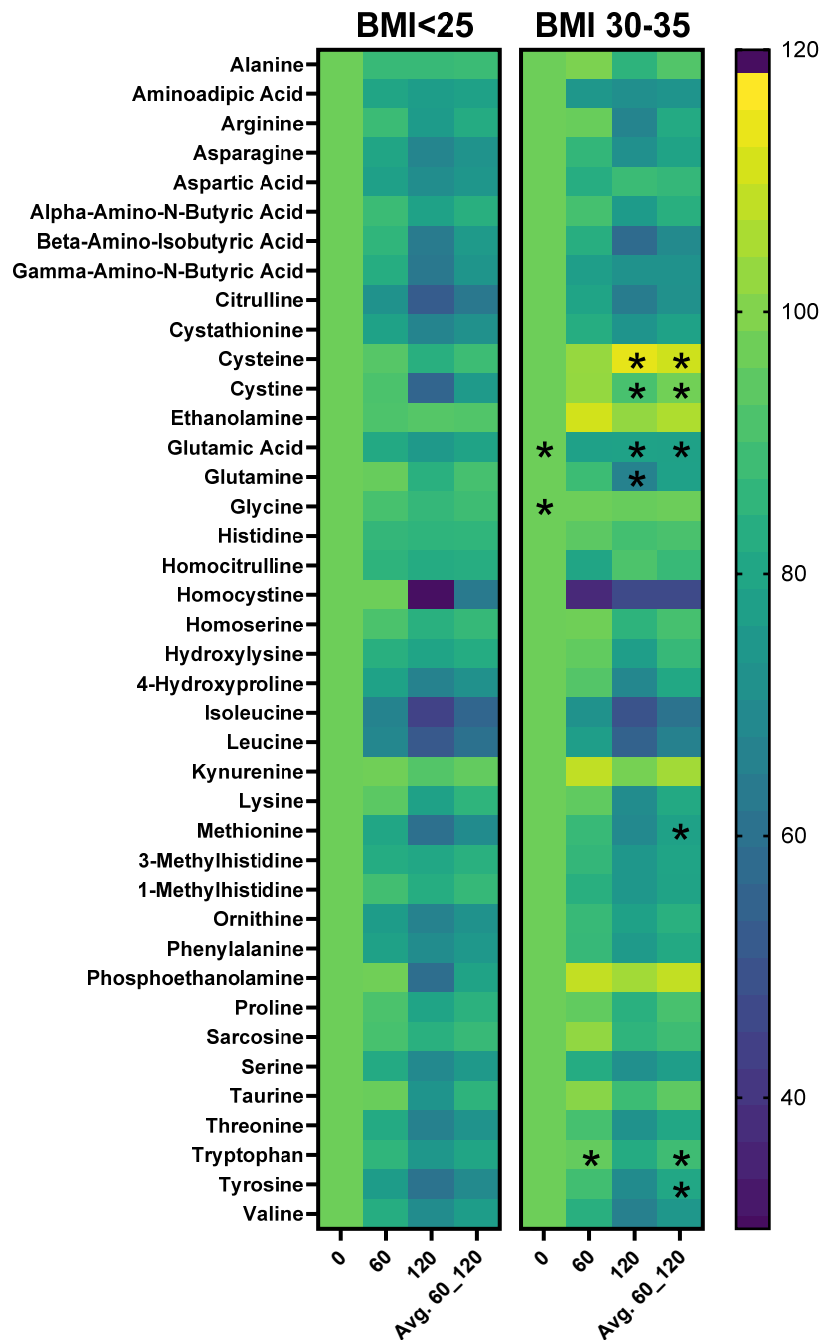
379 **Figure 1. CONSORT diagram illustrating participants who completed the parent study (4)**  
380 **and had available samples for secondary analyses presented in the current study. BMI,**  
381 **body mass index; MRS, magnetic resonance spectroscopy.**



383

384 **Figure 2. Metabolic characterization of lean participants and those with obesity at**  
 385 **baseline (fasting) and during acute hyperglycemia. (A-C)** Fasting plasma glucose ( $p=0.07$ )  
 386 (A), insulin ( $p=0.17$ ) (B), and glucagon ( $p=0.16$ ) (C) compared by independent samples t-tests.  
 387 (D) Plasma glucose during the hyperglycemic clamp, target 180 mg/dL ( $p=0.80$  for obesity  
 388 status,  $p>0.83$  for two-way interaction between time and obesity status, mixed effects analysis).  
 389 (E) Glucose infusion rate (GIR) during the hyperglycemic clamp ( $p=0.10$  for two-way interaction  
 390 between time and obesity status, mixed effects analysis). (F) Steady state GIR expressed as  
 391 the average GIR between 90 and 120 minutes of the hyperglycemic clamp ( $p=0.24$ ,  
 392 independent samples t-test). (G) Plasma insulin during the hyperglycemic clamp ( $p=0.19$  for  
 393 two-way interaction between time and obesity status, mixed effects analysis). (H) Area under  
 394 the curve (AUC) of the insulin time course in (G) ( $p=0.18$  by Welch's t-test). (I) Ratio of steady  
 395 state GIR to steady state insulin averaged between 90 and 120 minutes of the hyperglycemic

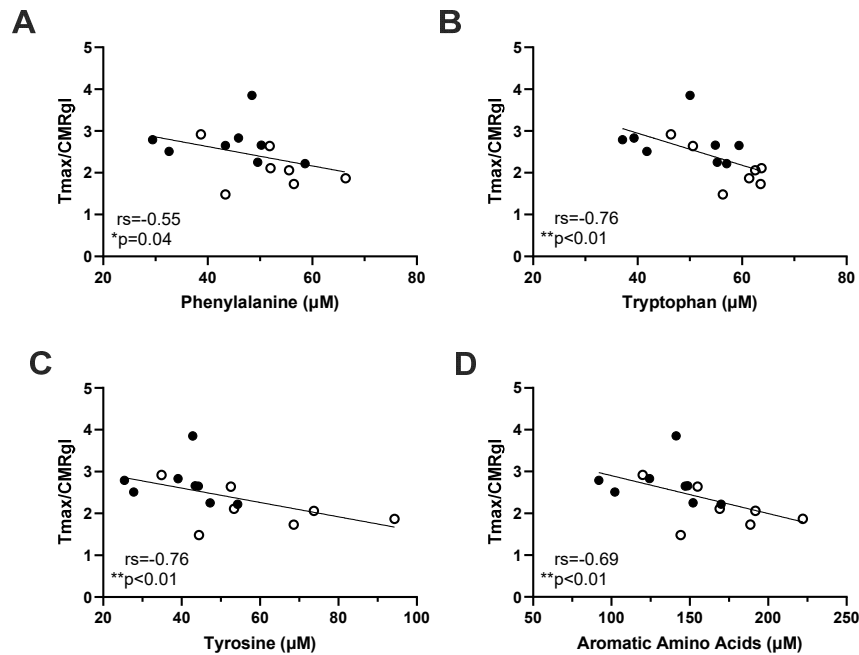
396 clamp ( $p=0.06$ , independent samples t-test). All data are expressed as mean  $\pm$  standard  
397 deviation.



398

399 **Figure 3. Amino acids measured by liquid chromatography-tandem mass spectrometry at**  
 400 **baseline and during acute hyperglycemia in participants with and without obesity.**

401 Individual amino acid concentrations at 60 minutes, 120 minutes, and averaged between 60 and  
 402 120 minutes are displayed as a percentage of baseline concentration. Asterisks denote  
 403 statistically significant comparisons of individual amino acids between the two BMI groups at the  
 404 indicated time points by one-way ANCOVA with baseline concentration as a covariate.



405

406 **Figure 4. Relationships between individual and summed aromatic amino acids with the**

407 **ratio of brain glucose transport to metabolism ( $T_{max}/CMR_{gl}$ ) during acute hyperglycemia.**

408 Plasma concentrations of phenylalanine (A), tryptophan (B), tyrosine (C), and summed aromatic

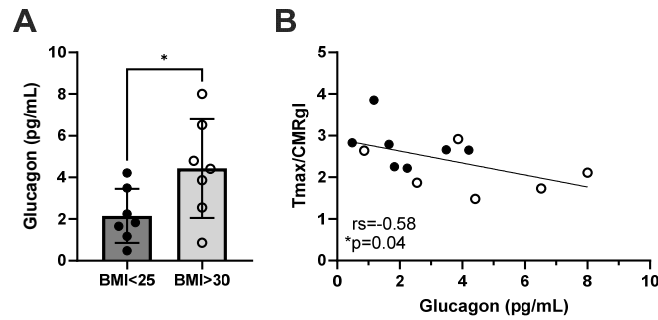
409 amino acids (D) at 60 minutes during the hyperglycemic clamp correlated with  $T_{max}/CMR_{gl}$ . Brain

410 glucose data from one participant with obesity with BMI>35 did not meet quality control

411 standards, therefore n=7 in the obesity group. All correlations were statistically significant by

412 Spearman's correlation. Closed dots represent lean controls, and open dots represent

413 participants with obesity.



415

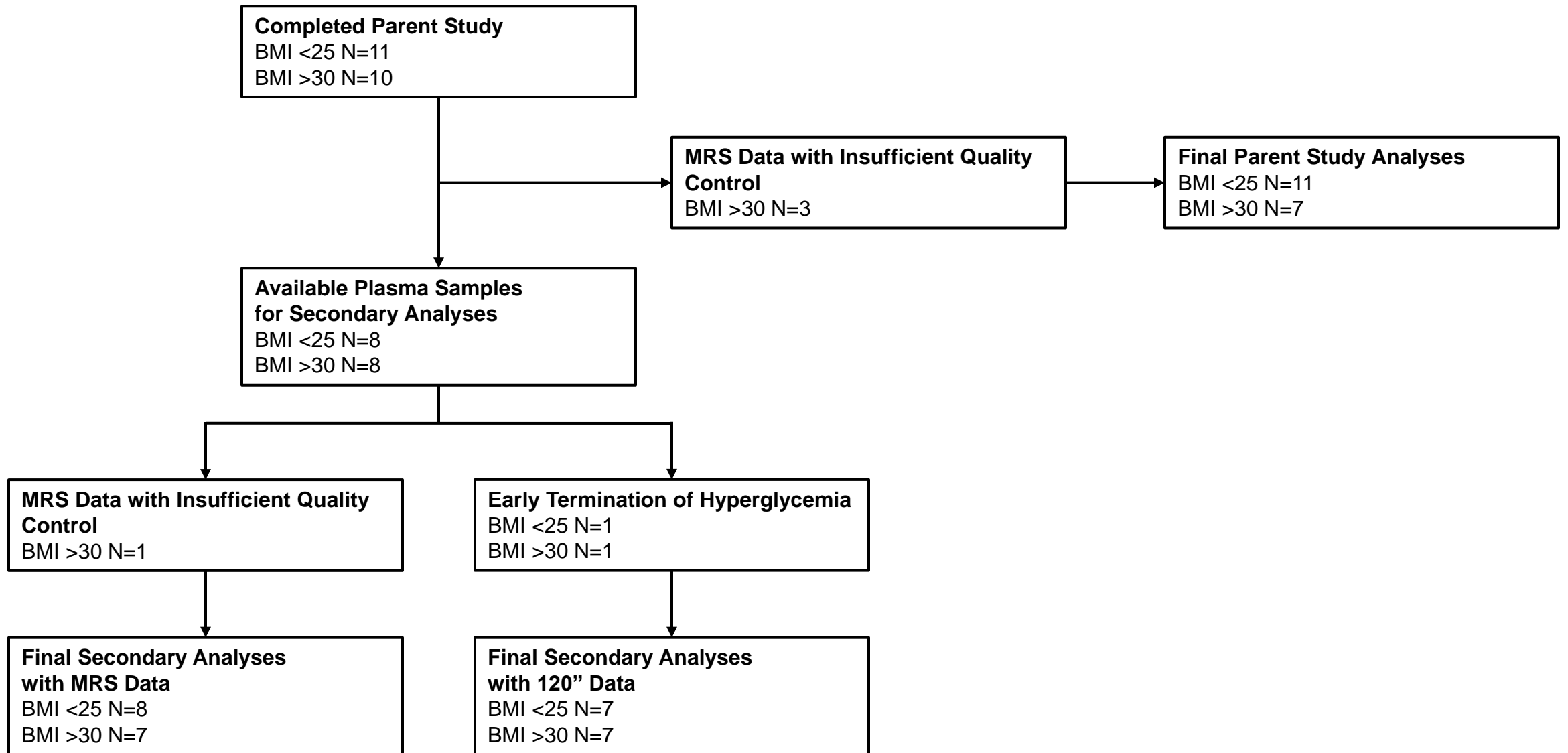
416 **Figure 5. Plasma glucagon and relationship between plasma glucagon and ratio of brain**  
 417 **glucose transport to metabolism ( $T_{max}/CMR_{gl}$ ) during acute hyperglycemia. (A)** Plasma  
 418 glucagon averaged between 60 and 120 minutes of hyperglycemic clamp ( $p=0.046$ ,  
 419 independent samples t-test). Data are expressed as mean  $\pm$  standard deviation. **(B)** Plasma  
 420 glucagon averaged between 60 and 120 minutes of the hyperglycemic clamp correlated with  
 421  $T_{max}/CMR_{gl}$  by Spearman's correlation. Closed dots represent lean controls, and open dots  
 422 represent participants with obesity.

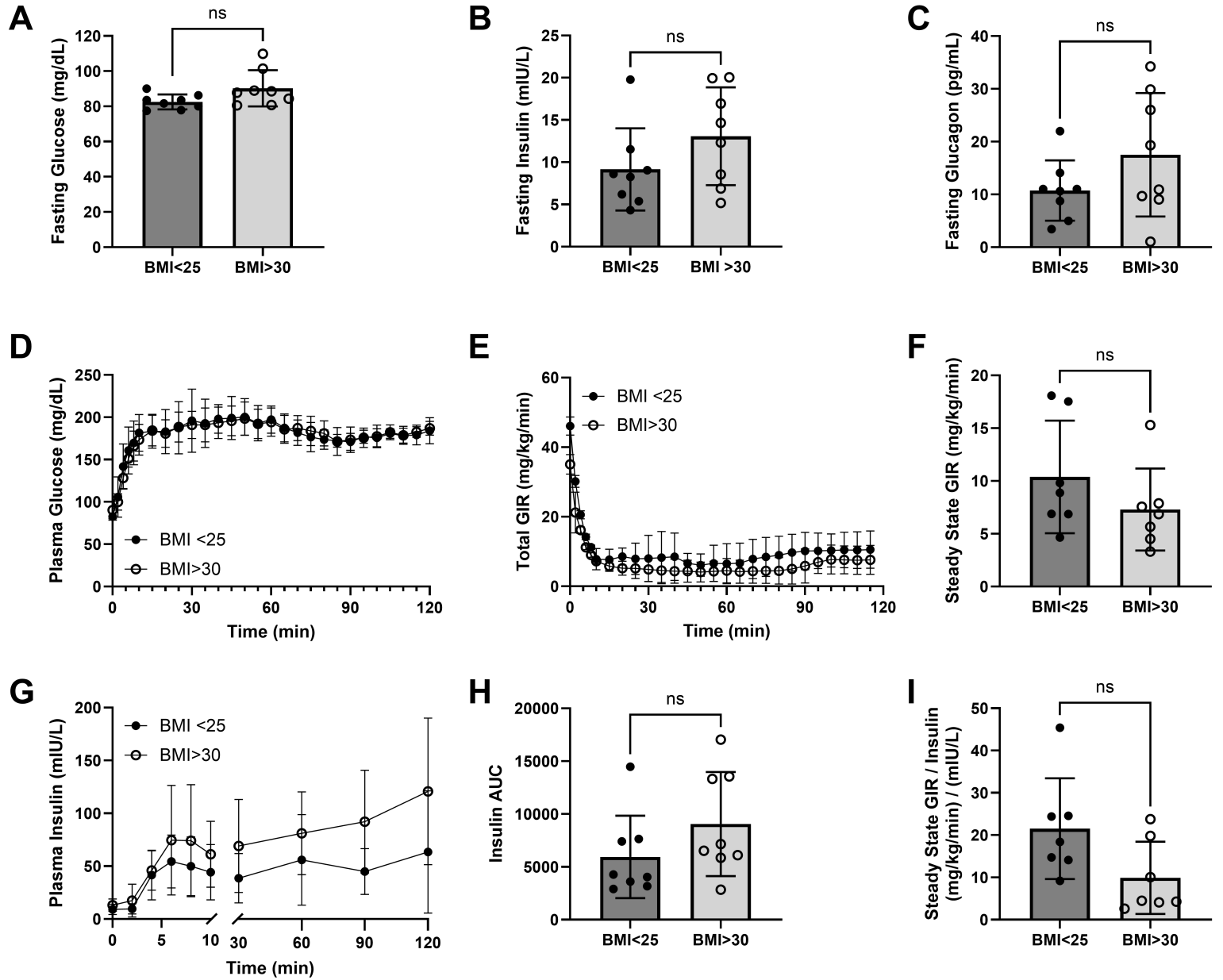
423 **REFERENCES**

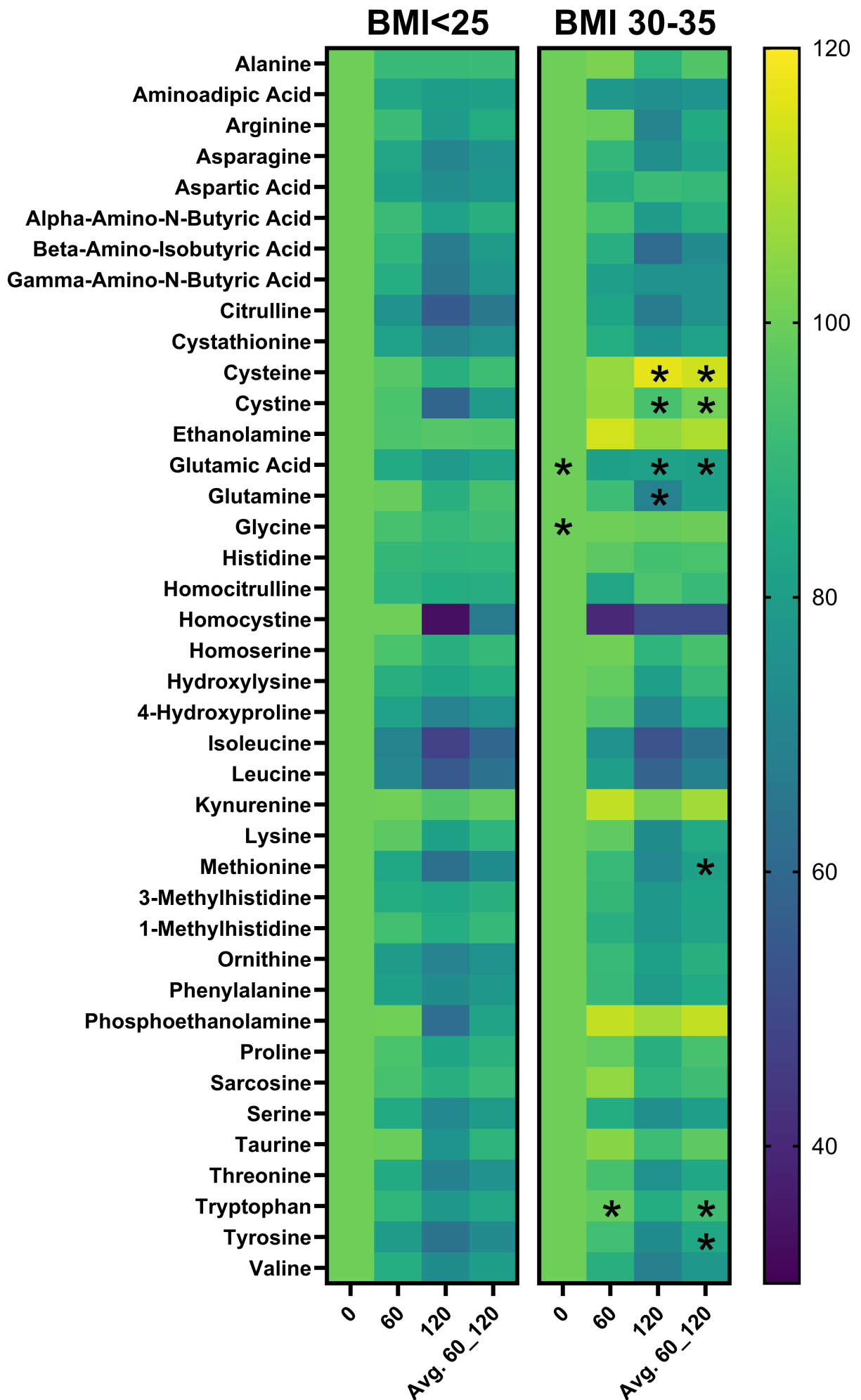
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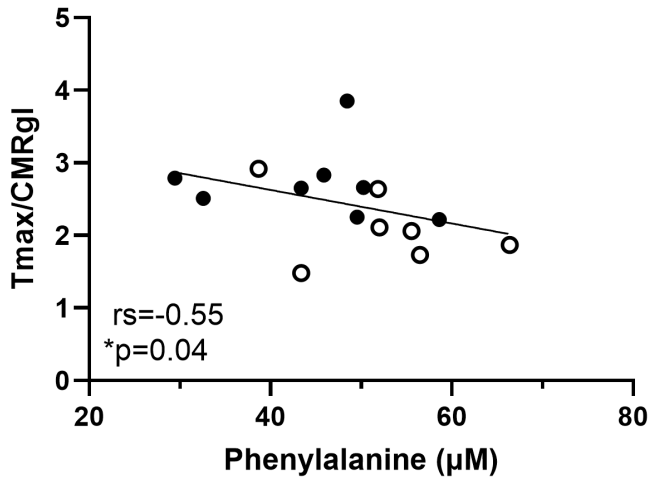
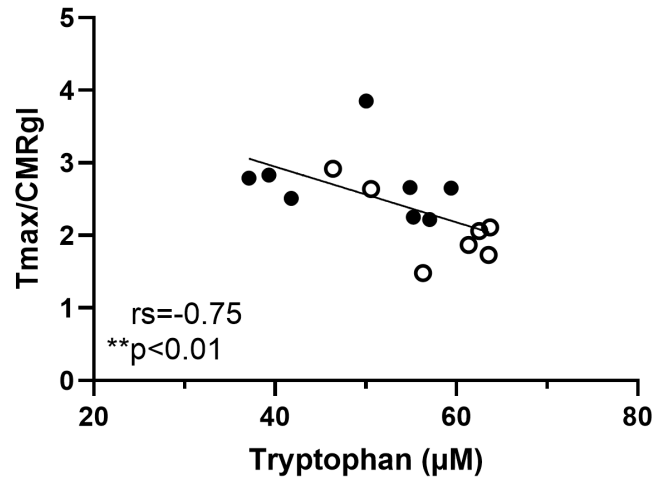
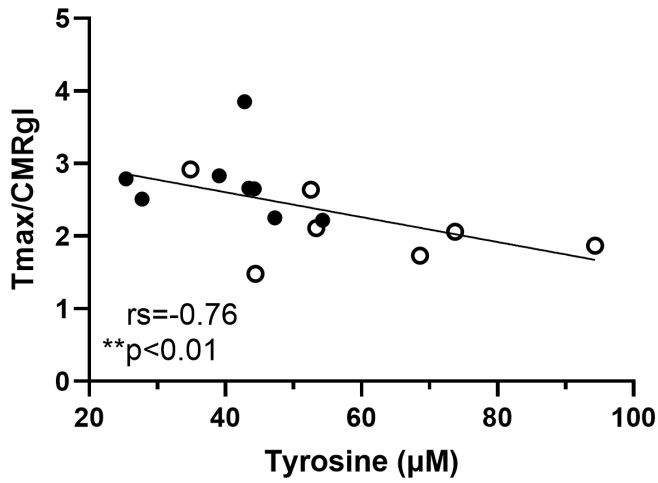
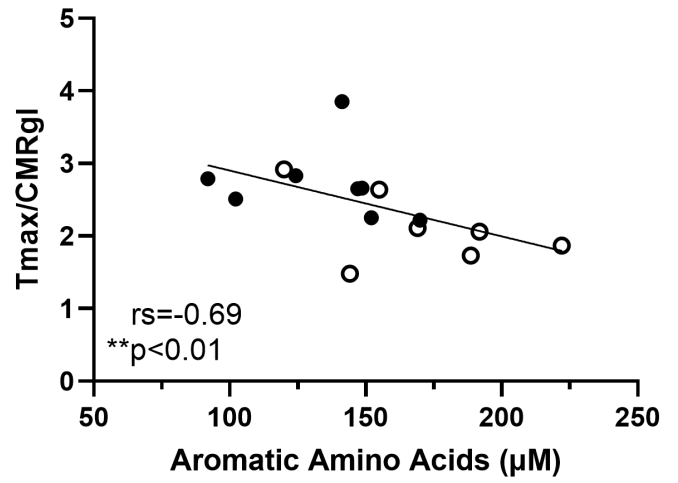
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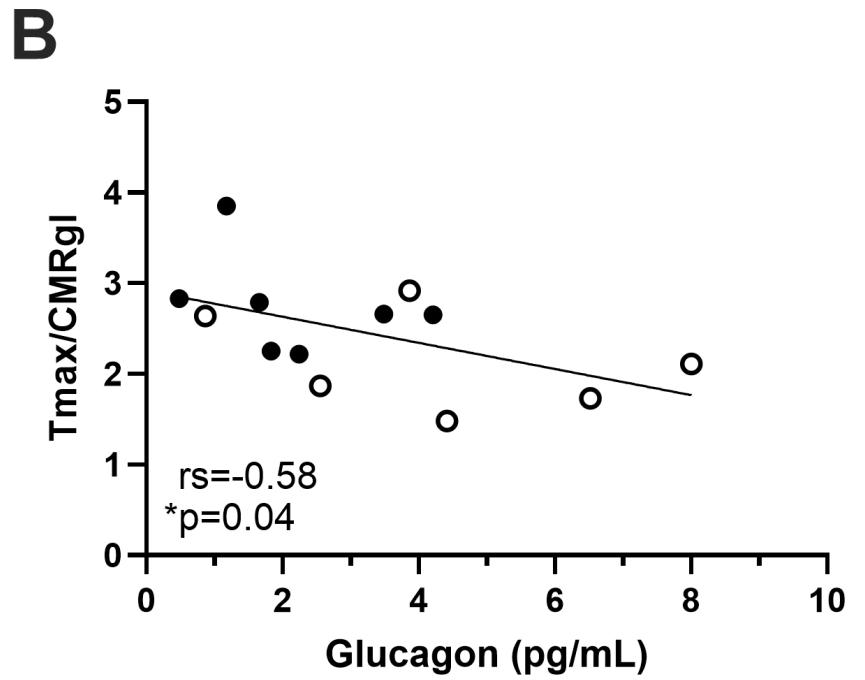
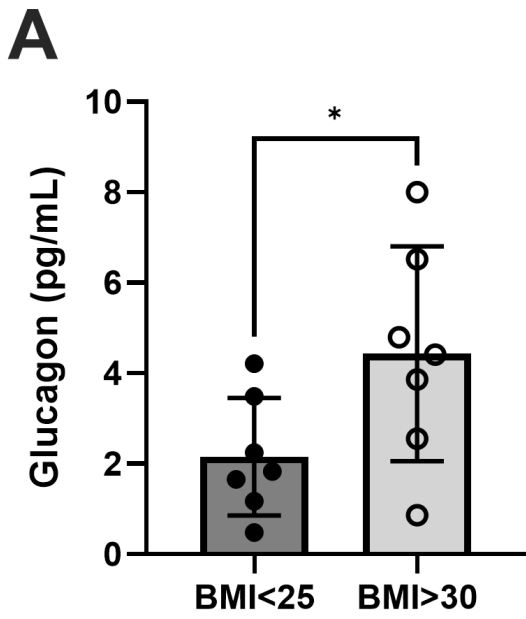








**A****B****C****D**



	BMI<25 (n=8)	BMI>30 (n=8)	BMI<25 vs. >30
<b><u>Demographic Data</u></b>			
Age (years)	27.3 (5.7)	27.3 (4.7)	p=1.00
<b>Sex (n)</b>			
Female	6	5	
Male	2	3	
<b>Race (n)</b>			
White	6	5	
Black	0	3	
Asian	2	0	
BMI (kg/m <sup>2</sup> )	20.8 (1.8)	32.3 (2.5)	**p<0.001
<b><u>Glycemic Data</u></b>			
A1c (%)	5.4 (0.2)	5.4 (0.2)	p=0.74
2h OGTT (mg/dL)	103.8 (32.8)	101.4 (35.0)	p=0.89
HOMA-IR	2.4 (1.7)	3.4 (1.4)	p=0.25
Matsuda Index	5.6 (2.2)	4.1 (2.6)	p=0.23
Insulinogenic Index	1.1 (0.8)	3.5 (2.1)	*p=0.02
Disposition Index	5.3 (2.4)	14.3 (15.5)	p=0.15
<b><u>Other Metabolic Data</u></b>			
Systolic BP (mmHg)	107.6 (7.5)	115.3 (5.9)	*p=0.04
Diastolic BP (mmHg)	68.0 (6.9)	72.0 (7.5)	p=0.29
Total Cholesterol (mg/dL)	162.1 (22.2)	161.4 (43.4)	p=0.97
LDL Cholesterol (mg/dL)	91.1 (20.9)	91.5 (28.9)	p=0.98
HDL Cholesterol (mg/dL)	56.0 (11.5)	50.8 (17.0)	p=0.48
Triglycerides (mg/dL)	74.9 (38.5)	96.4 (38.7)	p=0.28
AST (U/L)	12.3 (6.0)	11.5 (2.5)	p=0.75
ALT (U/L)	4.1 (8.3)	4.8 (8.0)	p=0.88
TSH (μIU/mL)	2.3 (1.2)	2.0 (0.7)	p=0.55

**Table 1. Demographic, glycemic, and clinical metabolic characteristics of participants.** All laboratory values were obtained under fasting conditions. Glycemic variables, with the exception of A1c, were derived from 75-gram oral glucose tolerance test data. Scale variables are expressed as mean (standard deviation). Categorical variables are expressed as frequency. Comparisons between groups were made by independent samples t-tests or by Welch's t-test if Levene's test for equality of variances was violated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; h, hour; HDL, high-

density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; TSH, thyroid stimulating hormone.

	<b>BMI&lt;25</b>	<b>BMI&gt;30</b>	<b>BMI&lt;25 vs. &gt;30</b>
<b>0" (n=8/group)</b>			
Glutamic Acid	109.4 ± 37.1	154.2 ± 34.4	p=0.03
Glycine	260.9 ± 55.6	201.2 ± 37.0	p=0.02
<b>60" (n=8/group)</b>			
Tryptophan	49.4 ± 8.7	56.3 ± 7.6	p=0.03
AAAs (Summed)	134.7 ± 26.5	166.0 ± 33.5	p=0.02
<b>120" (n=7/group)</b>			
Cysteine	15.8 ± 2.5	23.3 ± 5.5	p=0.01
Cystine	0.05 ± 0.01	0.16 ± 0.09	p<0.01
Glutamic Acid	78.0 ± 14.7	122.4 ± 23.1	p<0.01
Glutamine	477.2 ± 97.1	364.9 ± 82.2	p=0.02
<b>Average 60-120" (n=7/group)</b>			
Cysteine	16.7 ± 2.5	22.5 ± 4.8	p=0.03
Cystine	0.06 ± 0.02	0.18 ± 0.12	p=0.03
Glutamic Acid	83.6 ± 20.0	121.5 ± 20.4	p=0.03
Methionine	16.2 ± 2.5	20.6 ± 6.2	p=0.02
Tryptophan	47.3 ± 6.7	51.4 ± 6.5	p=0.02
Tyrosine	38.0 ± 6.9	49.3 ± 17.0	p=0.03
AAAs (Summed)	129.0 ± 19.0	149.0 ± 29.9	p<0.01

**Table 2. Statistically significant differences in individual plasma amino acids compared between lean participants and those with obesity exposed to acute hyperglycemia.** Variables are expressed as unadjusted mean ( $\mu\text{M}$ )  $\pm$  standard deviation. Significant comparisons at baseline by independent samples t-tests and at all other time points by one-way ANCOVA with baseline concentration as a covariate are shown. The duration of hyperglycemia for one participant in each group was less than 120 minutes, therefore only 7 participants per group are included in calculations incorporating measurements at 120 minutes. AAA, aromatic amino acids (phenylalanine, tryptophan, and tyrosine).

# Impact of obesity on aromatic amino acids and brain glucose during acute hyperglycemia

## METHODS



BMI < 25

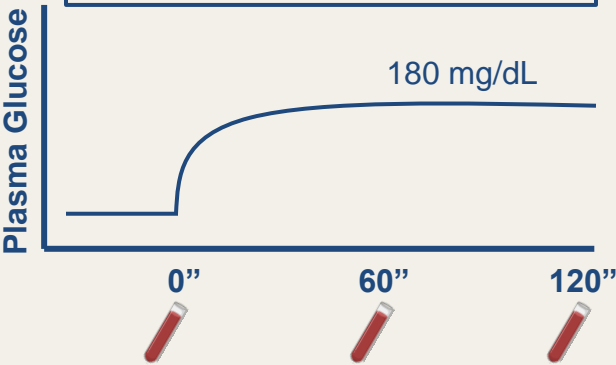
vs.



BMI 30-35

<sup>13</sup>C Magnetic Resonance Spectroscopy

180 mg/dL



- Amino Acids by Targeted Metabolomics
- Glucagon by ELISA

## OUTCOMES

Differentially regulated amino acids in obesity:

Fasting

↑ Glutamic Acid

↓ Glycine

Acute Hyperglycemia

↑ Cysteine

↑ Cystine

↑ Glutamic Acid

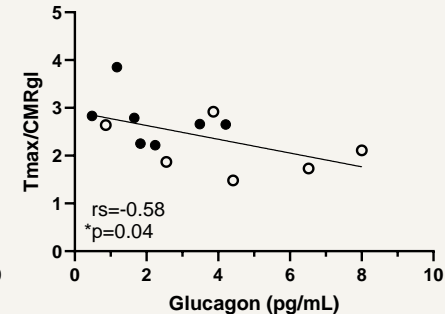
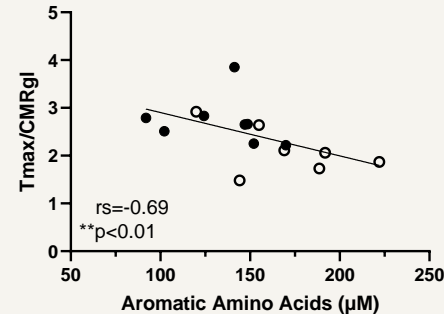
↓ Glutamine

↑ Methionine

↑ Tryptophan

↑ Tyrosine

Higher plasma aromatic amino acids and glucagon associated with lower brain glucose uptake, represented as  $T_{max}/CMR_{gl}$ , during acute hyperglycemia:



**CONCLUSION** In young, healthy adults with obesity exposed to acute hyperglycemia, higher plasma levels of select amino acids and glucagon were associated with diminished brain glucose uptake.