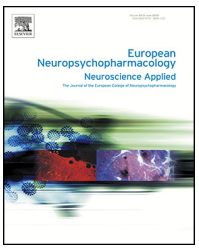
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Title	Gut microbiota modulates expression of genes involved in the astrocyte-neuron lactate shuttle in the hippocampus
Authors	Margineanu, Michael B.;Sherwin, Eoin;Golubeva, Anna V.;Peterson, Veronica L.;Hoban, Alan E.;Fiumelli, Hubert;Rea, Kieran;Cryan, John F.;Magistretti, Pierre J.
Publication date	2020-12-01
Original Citation	Margineanu, M. B., Sherwin, E., Golubeva, A. V., Peterson, V. L., Hoban, A. E., Fiumelli, H., Rea, K., Cryan, J. F. and Magistretti, P. J. (2020) 'Gut microbiota modulates expression of genes involved in the astrocyte-neuron lactate shuttle in the hippocampus', European Neuropsychopharmacology, 41, pp. 152-159. doi: 10.1016/j.euroneuro.2020.11.006
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.euroneuro.2020.11.006
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European Neuropsychopharmacology (2020) 41, 152–159



www.elsevier.com/locate/euroneuro

SHORT COMMUNICATION

Gut microbiota modulates expression of genes involved in the astrocyte-neuron lactate shuttle in the hippocampus



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Received 17 October 2019; received in revised form 6 October 2020; accepted 2 November 2020

KEYWORDS
Gut microbiota;
Brain energy metabolism;
Hippocampus;
Astrocyte-neuron lactate shuttle

Abstract
The gut microbiota modulates brain physiology, development, and behavior and has been implicated as a key regulator in several central nervous system disorders. Its effect on the metabolic coupling between neurons and astrocytes has not been studied to date, even though this is an important component of brain energy metabolism and physiology and it is perturbed in neurodegenerative and cognitive disorders. In this study, we have investigated the mRNA expression of 6 genes encoding proteins implicated in the astrocyte-neuron lactate shuttle (Atp1a2, Ldha, Ldhb, Mct1, Gys1, Pfkfb3), in relation to different gut microbiota manipulations, in the mouse brain hippocampus, a region with critical functions in cognition and behavior. We have

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https://doi.org/10.1016/j.euroneuro.2020.11.006
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discovered that Atp1a2 and Pfkfb3, encoding the ATPase, Na+/K+ transporting, alpha 2 subunit, respectively and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, two genes predominantly expressed in astrocytes, were upregulated in the hippocampus after microbial colonization of germ-free mice for 24 h, compared with conventionally raised mice. Pfkfb3 was also upregulated in germ-free mice compared with conventionally raised mice, while an increase in Atp1a2 expression in germ-free mice was confirmed only at the protein level by Western blot. In a separate cohort of mice, Atp1a2 and Pfkfb3 mRNA expression was upregulated in the hippocampus following 6-week dietary supplementation with prebiotics (fructo- and galacto-oligosaccharides) in an animal model of chronic psychosocial stress. To our knowledge, these findings are the first to report an influence of the gut microbiota and prebiotics on mRNA expression of genes implicated in the metabolic coupling between neurons and astrocytes.
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1. Introduction

The gut microbiota modulates brain physiology, development and behavior (Cryan and Dinan, 2012), and has been implicated as a key regulator in several CNS disorders (Maqsood and Stone, 2016). Its effect on the metabolic coupling between neurons and astrocytes, an important component of brain energy metabolism and physiology (Belanger et al., 2011a, 2011b) implicated in neurodegenerative and cognitive disorders (Jha and Morrison, 2018; Newington et al., 2013), has not been studied yet.

Astrocytes, a predominant type of glial cells in the brain, and neurons engage in complex metabolic interactions, particularly relevant to antioxidant defense and bioenergetics (Belanger et al., 2011a, 2011b; Bolanos, 2016). A role for astrocytes in supplying neurons with energy substrates (astrocyte-neuron lactate shuttle (ANLS)) emerged in the 1990s (Pellerin and Magistretti, 1994). In response to glutamate release at synapses, aerobic glycolysis is stimulated in astrocytes resulting in the release of lactate and its uptake into neurons to fuel the activity-dependent energetic demands.

A study has reported an effect of the microbiota on brain glycolytic metabolism. In their metabolome analysis, Matsumoto et al. (2013) observed a differential increase in the levels of several glycolytic intermediates in the brain of germ-free (GF) mice when compared with GF mice that had been inoculated with a suspension of feces obtained from specific pathogen-free mice 3 weeks earlier (Matsumoto et al., 2013).

In a separate study involving RNA-Seq in the brain, the absence of a microbiota during early life increased activity-related transcriptional pathways in the amygdala of mice, including immediate-early genes such as Fos, Fosb, Egr2 and Nr4a1, and CREB signaling (Stilling et al., 2015). These genes and CREB are known to be modulated by lactate (Margineanu et al., 2018).

These observations suggest a potential link between the gut microbiota, aerobic glycolysis in the brain and implicitly the ANLS. Here, we suggest that the gut microbiota could play an important role in metabolic adaptations at glutamatergic excitatory synapses in the brain.

To test this hypothesis, the expression of 6 genes associated with the ANLS were evaluated in the hippocampus of mice that underwent positive or negative microbiota manipulations. The hippocampus is a brain region where lactate shuttling was shown to be of particular importance to memory consolidation and learning (Suzuki et al., 2011).

We determined that the Pfkfb3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3) gene expression was up-regulated in the hippocampus of germ-free mice. Interestingly, this upregulation was still apparent after colonization of germ-free mice with gut microbiota. The expression of Atp1a2 (ATPase, Na+/K+ transporting, alpha 2 subunit) gene was increased in colonized germ-free mice but not in germ-free mice, compared to conventionally raised mice. However, on further examination at the protein level, it was determined that the expression of Atp1a2 was upregulated in germ-free mice. These data are in line with a separate preclinical study where we show that the manipulation of the microbiota with dietary supplementation with prebiotics (fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS)) can upregulate Atp1a2 and Pfkfb3 gene expression in an animal model of chronic psychosocial stress.

2. Experimental procedures

2.1. Animal samples

Tissue samples from two independent studies with different microbiota manipulations were used in this investigation.

The first study included naïve conventionally raised (CON), germ-free (GF) and colonized germ-free (ex-GF) C57BL/6J male mice, which were housed and euthanatized as previously described (Hoban et al., 2018). The ex-GF mice were all initially raised within the GF isolators until postnatal day 21 when they were removed and housed in a standard animal unit next to CON mice in order to allow for efficient colonization by environmental microbes. The ex-GF mice were put in clean cages with dirty bedding from CON, as mice are coprophagic and this will allow for efficient colonization. All mice, CON, GF and ex-GF received the same autoclaved, pelleted diet and were processed for tissue harvesting at ˜ 10 weeks of life (Hoban et al., 2018).

The second study investigated the potential protective effect of prebiotics (fructo- and galacto-oligosaccharide) against stress-induced changes in physiology and behavior. There were three groups – control non-stressed (CTR), control stressed (STR) and prebiotic stressed groups (PREB). Briefly, all C57BL/6J male mice were stressed according to a temporally unpredictable mixed schedule of social defeat and overcrowding sessions throughout the behavioral

testing period (Burokas et al., 2017). In social defeat sessions mice were exposed to an aggressive CD1 male and interaction was permitted until the first attack by the CD1 mouse occurred followed by a defeat posture from the stressed animal. Mice were then separated by a perforated plexiglass wall that allowed visual, auditory and olfactory but not physical contacts for two hours. Subsequently, the separator was removed and, after another defeat, stressed mice were transferred back to their homecage. The mixed schedule of social defeat and overcrowding sessions continued throughout behavior and on the final day animals were culled within 12 h of the final stressor (Burokas et al., 2017).

Brains were excised, dissected, and brain regions including hippocampus were snap-frozen on dry ice, and stored at −80 °C.

2.2. Ethics statement

All experiments were conducted in accordance with the European Directive 2010/63/EU, and approved by the Animal Experimentation Ethics Committee of University College Cork and Health Products Regulatory Authority (HPRA).

2.3. RNA extraction and quantitative RT-PCR

RNA was extracted from hippocampus using the total RNA isolation procedure with *mir*Vana™ miRNA Isolation Kit with phenol (AM1560, Ambion).

RNA was reverse transcribed to cDNA using the Applied Biosystems High Capacity cDNA reverse transcription kit (Applied Biosystems, Warrington, UK) according to manufacturer's instructions.

TaqMan quantitative PCR assays using primers synthetized by Integrated DNA Technologies and TaqMan probes designed by Applied Biosystems were carried for Atp1a2 (ATPase, Na+/K+ transporting, alpha 2 sub-unit), Ldha (lactate dehydrogenase A), Ldhb (lactate dehydrogenase B), Mct1 (monocarboxylic acid transporter 1), Gys1 (glycogen synthase), Pfkfb3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3). Primer sequences are provided in Supplementary Table S1. β-actin was used as an endogenous control.

All reactions were performed in triplicate using the LightCycler®480 System as recommended by the manufacturer (Roche). Cycle threshold (Ct) values were normalized to that of β-actin and transformed using the $2^{-\Delta\Delta CT}$ method.

2.4. Western blot

Hippocampus was sonicated in RIPA buffer (ThermoFisher Scientific) with protease (cOmplete™ ULTRA Tablets, Roche) and phosphatase (PhosSTOP™, Roche) inhibitors' cocktails. The lysate was cleared with centrifugation at 14,000 g, 15 min, +4 °C. The protein yield in supernatant was quantified by BCA assay (Pierce), diluted to 1.4 mg/mL with 5X Sample Buffer (GenScript), heated at 95 °C for 5 min, stored at −20 °C.

60 μg of protein were loaded onto 4–20% Bis-Tris Gels in Tris-MOPS running buffer (all from GenScript) and wet-transferred to Immun-Blot® PVDF membrane (BioRad, 100 V for 60 min). The membranes were blocked for 1 h at RT in 0.09% Tween 20 in Tris-buffered saline (TBST) and 5% fat-free milk, and then incubated overnight at 4 °C with Atpla2 (Millipore, # AB9094-I, rabbit, 1:4000) or Pfkfb3 (Abcam, # ab181861, rabbit, 1:5000) antibody diluted in the blocking solution containing 0.02% sodium azide.

After washings with TBST, the blots were incubated for 2 h at RT with the anti-rabbit HRP-conjugated secondary antibody (Sigma), 1:10.000 and 1:100.000 in 0.09% TBST and 5% fat-free milk for Atp1a2 and Pfkfb3, respectively. After washings with 0.09% TBST, the peroxidase activity was detected by chemiluminescence using Amersham enhanced chemiluminescence (ECL) Prime Detection Reagent (GE Healthcare) for the Atp1a2 blots and FEMTO SuperSignal™ substrate (Thermo Scientific) for the Pfkfb3 blots.

After washings with TBST, chemiluminescence for Atpla2 and Pfkb3 blots were detected using the ECL Prime Detection Reagent (GE Healthcare) or the FEMTO SuperSignal™ substrate (Thermo Scientific), respectively.

The membranes were re-stained against alpha-tubulin (Sigma).

2.5. Data analysis and statistics

For qRT-PCR, normality of distribution was checked with the Shapiro–Wilk test and differences between groups were compared with one-way ANOVA tests followed by Bonferroni and Dunnett's post hoc tests or Kruskal–Wallis tests followed by Dunn's post hoc test, based on the results of the normality test, in SPSS.

For western blots, the signal intensity of protein bands was analyzed in ImageJ software. To merge the results obtained on different blots, both the target gene and the loading control data on each gel were first normalized to the reference sample. The target genes were then normalized to the loading control. The differences between groups were compared with independent Student's *t*-test; datasets were checked for the normality of distribution with the Shapiro–Wilk test and for the homogeneity of variances with the Levene's test.

3. Results

3.1. Microbiota deficient mice have increased Atp1a2 and Pfkfb3 expression

In order to first test a direct contribution of the microbiota presence in the regulation of ANLS genes' expression, RNA was extracted from hippocampus of naïve conventional (CON), germ-free (GF) and colonized germ-free (ex-GF) mice (GF mice exposed to standard housing conditions and colonized with microbes). mRNA expression of ANLS genes were evaluated by RT-qPCR, and results showed significant up-regulation for Pfkfb3 in GF ($p = 0.000$) and ex-GF mice ($p = 0.048$) compared to the conventional mice, and for Atp1a2 in ex-GF mice ($p = 0.022$) (Fig. 1). An upregulation tendency was observed for the other genes tested in ex-GF mice vs. conventional mice, with a high standard deviation.

3.2. Mice undergoing chronic stress and supplemented with prebiotics show increased expression of Atp1a2 and Pfkfb3 genes

We further tested the contribution of a dietary supplementation with prebiotics, shown to produce gut microbial community changes and to exert anti-depressant and anxiolytic effects (Burokas et al., 2017) on the regulation of ANLS genes expression.

Atp1a2 ($p = 0.014$) and Pfkfb3 ($p = 0.000$) were upregulated more than two fold upon prebiotics supplementation in chronically stressed mice versus mice that were chronically stressed and received a normal diet (Fig. 2). No other significant changes were observed.

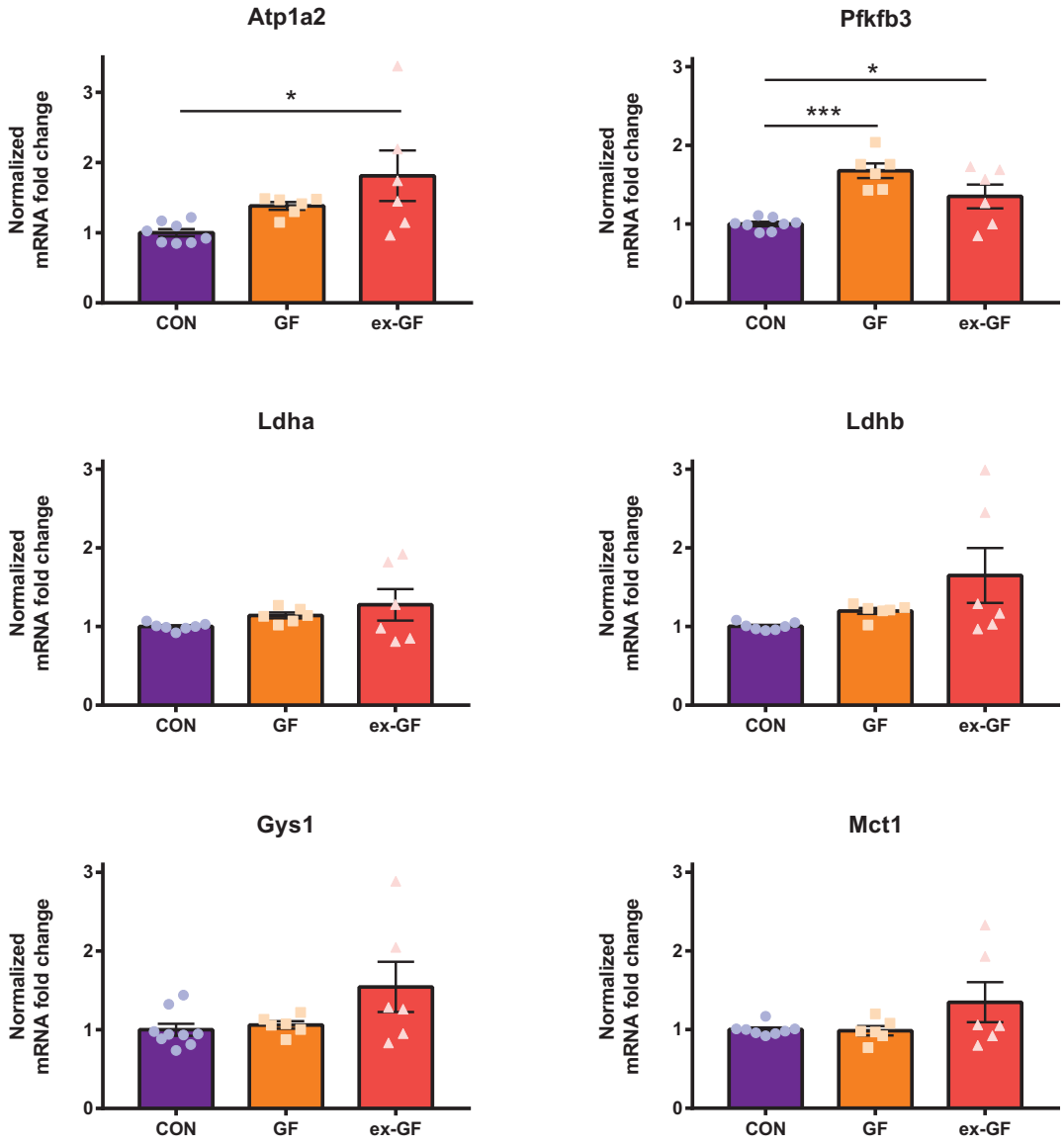


Fig. 1 mRNA expression of ANLS genes evaluated by RT-qPCR in hippocampus tissue from a GF study. Error bars correspond to SEM values. Multiple comparisons test' significance: $p<0.05$ *, $p<0.001$ ***. Number of biological replicates: naïve conventional (CON): $N = 8$, germ-free (GF): $N = 6$, colonized germ-free (ex-GF): $N = 6$.

We further examined the protein expression of Atp1a2 and Pfkfb3 in hippocampi of mice from the germ-free study. Remarkably, we found an increase in Atp1a2 protein expression levels in the hippocampus of GF mice as compared with conventional counterparts (Fig. 3A, $p = 0.042$) albeit at the transcriptional level expression of Atp1a2 was not significantly increased in GF mice ($p = 0.510$). No significant change in Pfkfb3 protein level was found but a trend for increased expression was observed (Fig. 3B, $p = 0.107$).

4. Discussion

In this study we have shown for the first time that the genes involved in the ANLS encoding for Pfkfb3 and Atp1a2 proteins are subjected to regulation by gut microbes. The colonization of germ-free animals after weaning (3 weeks of age) did not reverse the increases in gene expression, suggesting a key role of gut microbiota in cellular metabolism, or at least on Atp1a2 and Pfkfb3 expression, in the critical early life window. However, further work interrogating the role of microbiota in cellular metabolism in early life is warranted.

Atp1a2 encodes the alpha 2 subunit of the Na^+/K^+ ATPase, and is primarily expressed in astrocytes in the central nervous system (Cholet et al., 2002; Moseley et al., 2003), playing an important role in maintaining resting membrane potential and controlling extracellular K^+ concentration during neuronal activity. The Na^+/K^+ ATPase mediates excitatory amino acid-dependent stimulation of aerobic glycolysis in astrocytes (Pellerin and Magistretti, 1996).

Pfkfb3, the other up-regulated gene in GF and ex-GF mice, is a master regulator of glycolysis. It produces fructose-2,6-bisphosphate, a potent activator of the rate-

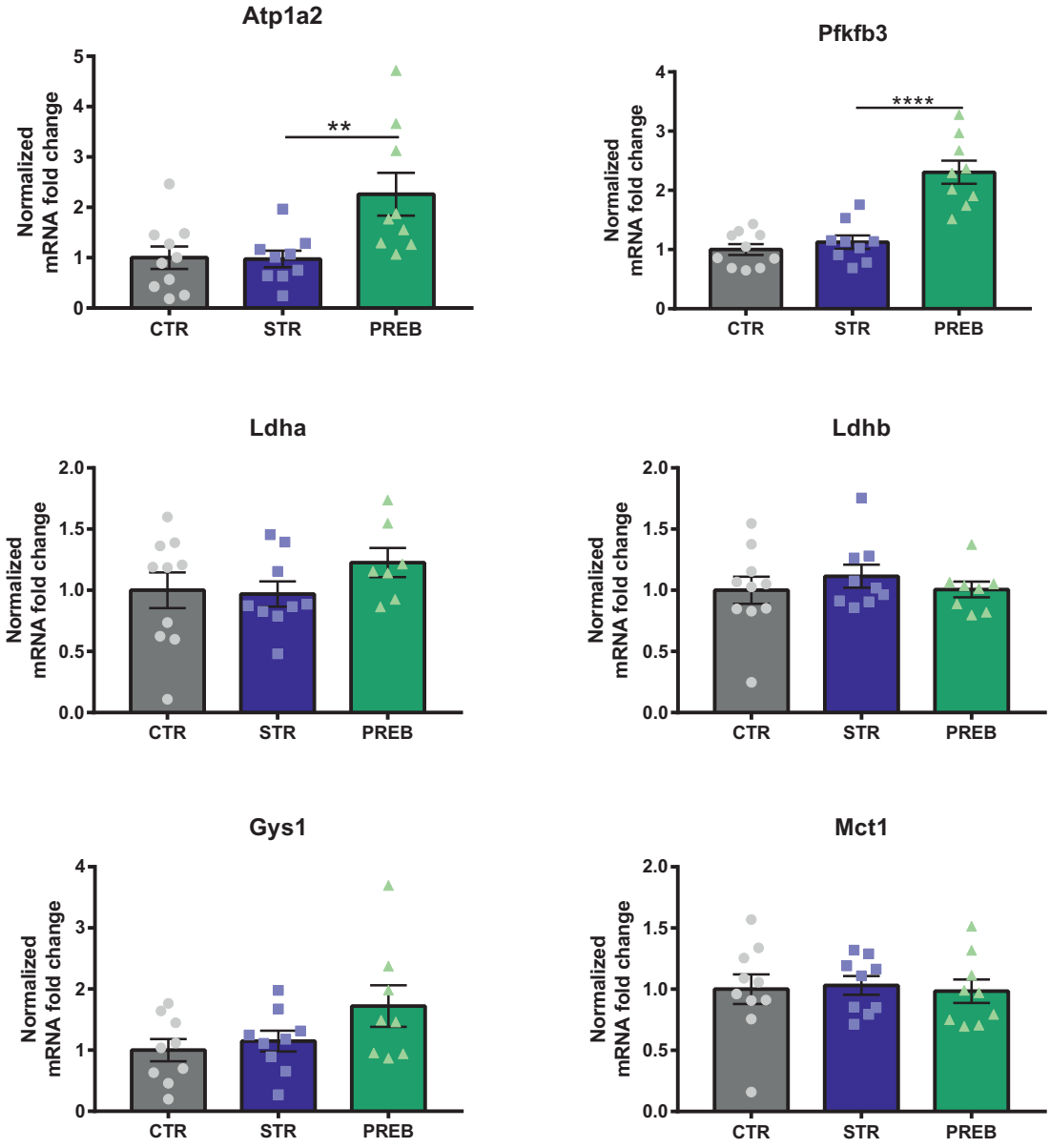


Fig. 2 mRNA expression of ANLS genes evaluated by RT-qPCR in hippocampus tissue from a prebiotics study. Error bars correspond to SEM values. Multiple comparisons test' significance: $p<0.05$ *, $p<0.0001$ ****. Number of biological replicates: CTR: $N = 10$, STR: $N = 9$, PREB: $N = 9$.

limiting enzyme in glycolysis 6-phosphofructo-1-kinase, and is predominantly expressed in astrocytes (Bolanos, 2016). Pfkfb3 is absent from neurons in the brain cortex as it is constantly subject to proteasomal degradation by the action of the E3 ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C)-Cdh1. By contrast, astrocytes have low APC/C-Cdh1 activity, and Pfkfb3 persists in these cells (Herrero-Mendez et al., 2009).

The increased expression of Atp1a2 and Pfkfb3 in GF and ex-GF mice, compared to conventionally raised mice, could indicate a neuroenergetic adaptation to a hyperactivity phenotype characterized by higher locomotor activity (Luo et al., 2018), increased activity-dependent transcriptional pathways in the amygdala region (Hoban et al., 2018), and altered levels of several excitatory amino acids in the hippocampus (Kawase et al., 2017), as previously reported in germ-free mice.

Upregulation of Pfkfb3 mRNA was also observed in the amygdala of GF mice compared to conventionally raised mice (Hoban et al., 2018). Furthermore, our observations are in line with the findings of Matsumoto et al. (2013), who reported increased levels of glycolytic intermediates in GF compared to ex-GF mice (Matsumoto et al., 2013).

In mice that were chronically stressed, we observed that mRNA levels of Atp1a2 and Pfkfb3 were increased upon dietary intervention with prebiotics by more than two fold. We have not assessed in this study the effect of prebiotics administered to mice that were not chronically stressed. However, we consider that the changes we observed are not conditional to the stressor – there were no changes in

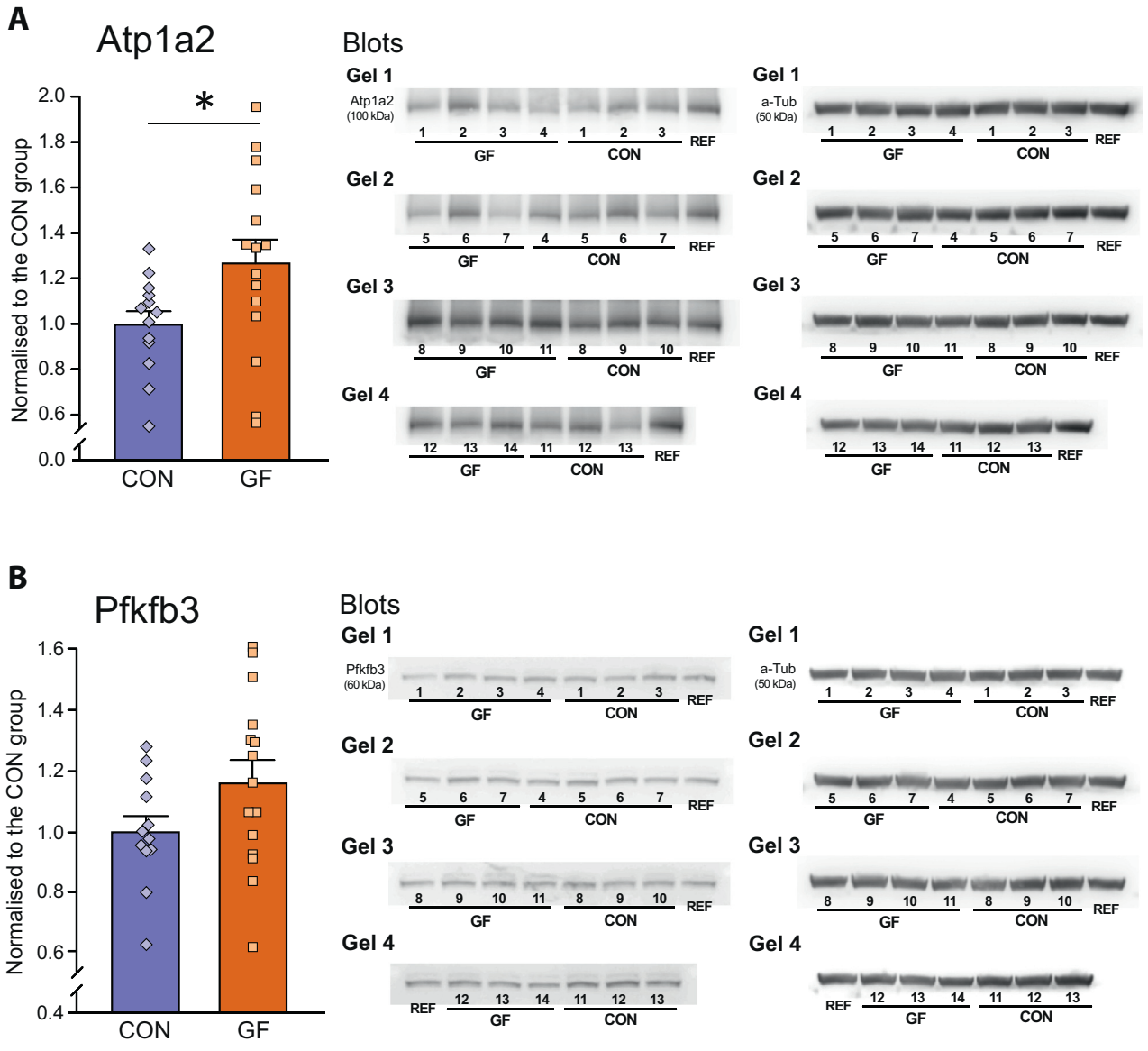


Fig. 3 Western blot results evaluating protein expression levels for Atp1a2 and Pfkfb3 in hippocampus tissue from germ-free (GF) ($N = 14$) and conventional (CON) mice ($N = 13$). A) Atp1a2 and alpha-tubulin blots and expression levels. B) Pfkfb3 and alpha-tubulin blots and expression levels. Alpha-tubulin was used as loading control for normalization of protein expression. *t*-test conducted for significance ($p = 0.042 < 0.05$ *).

expression of these genes in mice that were chronically stressed compared to mice that were not stressed.

In the mice from which hippocampus tissue was collected and used for the evaluation of ANLS genes expression, prebiotics treatment was shown to protect from the negative effects of chronic stress on social interaction and long-term memory. Interestingly, this treatment is known to reduce depression-like behavior induced by chronic stress (Burokas et al., 2017). Moreover, beneficial effects of prebiotics to the host health were previously linked to enhanced short-chain fatty acids (SCFA) production and the selective stimulation of the growth of *Bifidobacteria* and *Lactobacilli*, bacterial species that produce lactic acid as a metabolic end-product (Roberfroid et al., 2010).

Lactate, the end-product of glycolysis, produced in astrocytes and utilized by neurons as an energy substrate, is required for memory consolidation (Suzuki et al., 2011) and was shown to have an antidepressant-like effect in chronically stressed mice (Carrard et al., 2016).

Psychiatric disorders such as bipolar disorder, schizophrenia and major depressive disorder are all associated with changes in the levels of glycolytic enzymes in the brain pointing to glycolysis as a key pathway implicated in the pathophysiology of these diseases (Zuccoli et al., 2017). Bipolar disorder and schizophrenia were also associated with alterations in the activity or levels of the Na,K-ATPase in the brain, which could directly impact glutamate reuptake at synapses and lactate production by astrocytes (Corti et al., 2011; El-Mallakh and Wyatt, 1995).

As Pfkfb3 and Atp1a2 encode proteins that regulate glycolysis, energy homeostasis and glutamate reuptake by astrocytes, respectively, our findings that gut microbiota manipulations (germ-free, prebiotics) modify their mRNA and protein expression levels in the hippocampus suggest that therapeutic interventions targeting the gut microbiota could improve mental health by modulating brain energy metabolism. Given observations that microbiota can regulate many central nervous system processes, including neurogenesis, microglia maturation and activation state, further work investigating the contribution of the gut microbiota to metabolic changes in the brain is warranted.

In these studies we have shown that germ-free status and prebiotic administration both increase Pfkfb3 gene expression and that microbial colonization of germ-free mice and prebiotic administration increase Atp1a2 gene expression. Germ-free animals display an altered behavioral and physiological phenotype compared to their conventional controls, while some stress-related changes in behavior and physiology were reversed with prebiotic treatment. Prebiotics can lead to the production of short-chain fatty acids, through the breakdown of dietary fibers by colonic commensal bacteria. SCFAs have been shown to positively modulate centrally mediated events including the reversal of microglia deficits in germ-free animals. It is difficult to ascertain whether the changes observed in the cellular metabolic responses are causal to behavior or whether they are in response to a behavioral event – and further work in this field is required.

Altered neuroimmune responses which can be generated by both types of manipulations, as well as the presence of SCFAs such as acetate (inferred from literature but not evaluated in our germ-free animal cohorts) could influence gene expression in the brain. Acetate is known to inhibit histone deacetylase activity and expression in the brain (Soliman and Rosenberger, 2011) and pro- and anti-inflammatory cytokines are known to affect the metabolic profile of astrocytes (Belanger et al., 2011a, 2011b).

Overall, based on the germ-free and prebiotics supplementation in chronically stressed mouse models investigated, Atp1a2 and Pfkfb3 emerge as ANLS markers associated with manipulations of the gut microbiota.

Follow-up studies should be conducted to validate whether gene expression changes are specific to hippocampal astrocytes (not taking place also in other cell types) and whether prebiotics also induce changes in gene expression in the absence of chronic stress.

As novel therapies for neuropsychiatric and neurodegenerative disorders aim to target astrocyte-neuron cooperation and in particular energy metabolism-related pathways, these fascinating results, though preliminary, point to candidate enzymes, predominantly expressed in astrocytes in the brain, that play a key role in energy metabolism, and could be indirectly modulated by targeting the microbiota, an attractive non-invasive approach.

Role of the funding source

MBM is supported by a doctoral fellowship from King Abdullah University of Science and Technology (KAUST). HF and PJM are supported by research grants from King Abdullah University of Science and Technology (KAUST).

APC Microbiome Ireland is a research institute funded by Science Foundation Ireland (SFI) through the Irish Government's National Development Plan. ES, AG, VP, AH, KR, and JFC are supported by SFI (Grant Nos. SFI/12/RC/2273_2).

These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

MBM and ES designed the experiments. PJM and JFC supervised the experiments. MBM, ES, and AG performed the experiments. VP, AH, and KR provided tissue for gene expression evaluation. MBM wrote the initial draft of the manuscript. ES, KR, HF, PJM and JFC wrote subsequent versions of the manuscript.

Conflict of Interest

JFC has research support from Mead Johnson, Cremo, 4D Pharma, Suntory Wellness, and Nutricia, and has spoken at meetings sponsored by food and pharmaceutical companies. All other authors report no potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2020.11.006.

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