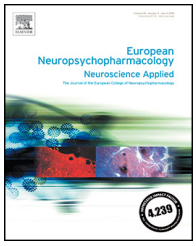
European Neuropsychopharmacology (2019) 29, 137–146

www.elsevier.com/locate/euroneuro



The effect of body mass index on glucagon-like peptide receptor gene expression in the post mortem brain from individuals with mood and psychotic disorders

Rodrigo B. Mansur[a,b,*], Gabriel R. Fries[c], Alisson P. Trevizol[d], Mehala Subramaniapillai[a], Julie Lovshin[e], Kangguang Lin[f], Maj Vinberg[g], Roger C. Ho[h], Elisa Brietzke[a,i,j], Roger S. McIntyre[a,b]

[a] *Mood Disorders Psychopharmacology Unit (MDPU), University Health Network, University of Toronto, Toronto, Canada*
[b] *University of Toronto, Toronto, Canada*
[c] *Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, USA*
[d] *Reference Center for Alcohol, Tobacco and Other Drugs (CRATOD), São Paulo State Secretariat of Health, São Paulo, SP, Brazil*
[e] *Endocrinology & Metabolism Division, Sunnybrook Health Sciences Centre, University of Toronto, Canada*
[f] *Department of Affective Disorders, the Affiliated Hospital of Guangzhou Medical University and GMU-HKU Mood and Brain Sciences Center, Guangzhou, China*
[g] *Psychiatric Center Copenhagen, University of Copenhagen, Copenhagen, Denmark*
[h] *Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*
[i] *Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil*
[j] *Research Group in Molecular and Behavioral Neuroscience of Bipolar Disorder, Departament of Psychiatry, Universidade Federal de São Paulo, SP, Brazil*

Received 15 December 2017; received in revised form 2 October 2018; accepted 23 October 2018

* Corresponding author at: Mood Disorders Psychopharmacology Unit (MDPU), University Health Network, University of Toronto, Toronto, Canada.
E-mail address: rodrigomansur71@uol.com.br (R.B. Mansur).

https://doi.org/10.1016/j.euroneuro.2018.10.007

KEYWORDS
GLP-1R;
GLP-2R;
Mood disorders;
Schizophrenia;
Gene expression;
Obesity

Abstract
There is an increasing interest in the putative role of glucagon-like peptide 1 receptor (GLP-1R) agonists as novel therapeutic agents for mental disorders. Herein, we investigated the expressions of GLP-1R and GLP-2R genes, and its relationship with body mass index (BMI), in the post-mortem brain tissue of patients with mood (MD) and psychotic disorders. Brain samples were localized to the dorsolateral prefrontal cortex (dlPFC) ($n = 459$) and hippocampus ($n = 378$). After adjustment for age, sex, ethnicity, post-mortem interval (PMI) and BMI, we observed significant differences, between healthy controls and MD subjects, in GLP-1R and GLP-2R gene expression in the dlPFC ($\beta = 1.504$, $p = 0.004$; and $\beta = 1.305$, $p = 0.011$, respectively); whereas in the hippocampus, only GLP-1R expression was significantly associated with MD ($\beta = -1.28$, $p = 0.029$). No significant differences were found in relation to schizophrenia. In addition, we observed a moderating effect of MD diagnosis on the associations between BMI, GLP-1R and GLP-2R expression values in the dlPFC ($\beta = -0.05$, $p = 0.003$; and $\beta = -0.04$, $p = 0.004$, respectively). There was a similar moderating effect for GLP-1R in the hippocampus ($\beta = 0.043$, 95% CI 0.003; 0.08 $p = 0.03$), but in an opposite direction than observed in the dlPFC. This is the first evidence of abnormal gene expression of GLP-1R and GLP-2R in post-mortem brain of individuals with MD, providing a rationale for further inquiry and proof of principle interventional studies.

1. Introduction

Mood disorders (MD) and schizophrenia (SCZ) are among the most common chronic and severe mental illnesses. Parsing the underlying molecular substrates within and across MD and SCZ is *sine qua non* before genuinely novel treatment discovery and development may occurs (McIntyre, 2014). Replicated evidence indicates that mood and psychotic disorders share many phenomenological features, as well as genetic and molecular substrates (Ramaker et al., 2017). In addition, SCZ and MD are similarly associated with an increased rate of metabolic comorbidities (Mansur et al., 2015). For example, obesity, Type 2 diabetes and metabolic syndrome are approximately 2 times more frequent in individuals with MD and SCZ, compared to the general population (Vancampfort et al., 2015a, b). A separate line of convergent evidence indicates that metabolic pathways, including, but not limited to, glucose homeostasis, are relevant to the pathophysiology of MD and SCZ (Amare et al., 2017; Brietzke et al., 2011; Carter and Swardfager, 2016; Henderson et al., 2015; Pillinger et al., 2017).

Proof of concept studies indicate that agents that target metabolic systems, such as antidiabetic drugs, are promising therapeutic agents for mood and psychotic disorders (Calkin et al., 2013; Mansur et al., 2015). A metabolic target of recent interest is the glucagon-like peptide-1 (GLP-1) receptor. GLP-1 and Glucagon like peptide-2 (GLP-2) are gastrointestinal hormones released from enteroendocrine L-type and the nucleus tractus solitarius (NTS). GLP-1 and GLP-2 acts through its specific receptors, GLP-1R and GLP-2R, which are mainly located in the gut and in the brain (Baldassano et al., 2016; Farr et al., 2016). Preclinical data has implicated GLP pathways in neuroprotection and cellular proliferation and differentiation (Gault and Holscher, 2008; Gengler et al., 2012; Wang et al., 2010). GLP-1 and GLP-2, as well as their receptor agonists, have been associated with antidepressant and pro-cognitive effects in murine models (Iwai et al., 2009; McClean and Holscher, 2014; Porter et al., 2010). In humans, GLP-1 receptor agonists, such as liraglutide and exenatide, were developed to treat Type 2 diabetes mellitus (Trujillo et al., 2015). Preliminary clinical studies have documented a potential pro-cognitive effect of adjunctive liraglutide in individuals with MD (Mansur et al., 2017a, b), whereas one recently published trial with exenatide in individuals with SCZ did not find a significant effect (Ishoy et al., 2017). There is, however, a lack of direct or indirect evidence of abnormalities in the GLP system in humans with mood or psychotic disorders, which limits the interpretation of these findings.

Herein, we aimed to assess GLP-1R and GLP-2R gene expression in postmortem brain of individuals with SCZ and MD. Obesity has been previously shown to modulate gene expression in the brain and, animal studies have reported that obesity and conditions analogous to metabolic syndrome are related to reduction in GLP-1 positive cells in cerebral cortex (Kappe et al., 2012). Therefore, we also aimed to assess the relationship between gene expression and body mass index (BMI).

2. Experimental procedures

2.1. Sample selection

The "Gene Expression in Postmortem dlPFC and Hippocampus from Schizophrenia and Mood Disorders" (dbGaP accession number phs000979.v1.p1) database contains microarray data from the dlPFC and hippocampus across nine major mental disorders, with emphasis on SCZ, bipolar disorder (BD) and major depressive disorder (MDD). Post-mortem brains were collected at the Human Brain Collection Core, NIMH with informed consent from the legal next of kin (NIMH protocol 90-M-0142), at the Brain and Tissue Bank for Developmental Disorders of the NICHD (contracts NO1-HD-4-3368 and NO1-HD-4-3383) and through the Stanley Medical Research Institute. The clinical characterization, neuropathological screening, toxicological analyses, and dissection of the dlPFC and hippocampus have been pre-

viously described (Lipska et al., 2006). Lifetime mental disorder diagnosis was based on DSM-IV criteria; healthy controls had no history of psychological or psychiatric problems and negative toxicology results.

The database includes 914 subjects from whom 849 specimens from the dlPFC and 579 from the hippocampus were available. We excluded individuals with diagnoses other than SCZ and MD, individuals younger than 18 or older than 65 years of age, subjects with BMI above 50 or below 15, as well as samples with post-mortem interval (PMI) $>$ 72 h. The dataset used herein comprised 459 specimens from the dlPFC, of which 113 were from individuals with SCZ and 155 from MD; and 378 hippocampal samples, of which 96 were from patients with SCZ and 113 from MD. All samples analyzed had RNA integrity numbers (RINs) above 5. All the data were anonymized in accordance with the rules and regulations of the National Institute of Health.

2.2. mRNA analyses

We analysed mRNA data obtained using HumanHT-12 v4 BeadChip arrays (Illumina). The GLP1R gene (probe ILMN_1787257) and the GLP2R gene (probe ILMN_1770675) were selected *a priori* for analysis, Gene expression mean values were z-transformed (Cheadle et al., 2003). Outliers values, defined as more than 5 standard deviations (SD) above the mean, were excluded.

2.3. Analytic plan

Raw data obtained from the Illumina Human V4-HT12 arrays were analyzed with the Bioconductor limma package, as previously described (Ritchie et al., 2015). Generalized linear models (GLM) were used to assess the association between diagnosis and GLP-1R and GLP-2R gene expression, with relevant covariates included in the models. To assess the differential effects of BMI within groups, BMI, as a continuous variable, and the interaction term (diagnosis * BMI) was included in all models. Many subjects lacked information about laboratorial measures, to avoid underpowering the analysis, we chose to include them in separate models. All model included diagnosis, age, sex, ethnicity, BMI and the interaction term; Model 2 included ethanol and nicotine/cotinine, Model 3 psychotropic medications (i.e., antipsychotics, antidepressants, mood stabilizers and BZDs) and Model 4 drugs (i.e., cocaine and opiates). All statistical analyses were performed using the IBM SPSS Statistics software (Armonk, NY: IBM Corp.).

3. Results

There were significant differences among the three groups in terms of age at death, sex, ethnicity, body mass index (BMI), and post-mortem interval (PMI) (Table 1). When adjusted for age, sex, ethnicity, PMI and BMI, there was a significant difference for both the GLP-1R and GLP-2R gene expression in the dlPFC between HC and MD subjects ($\beta = 1.504$, 95% CI 0.48; 2.52, $p = 0.004$; and $\beta = 1.305$, 95% CI 0.30; 2.30, $p = 0.011$, respectively). There was a moderating effect of diagnosis on the association between BMI, GLP-1R and GLP-2R expression values ($\beta = -0.05$, 95% CI -0.08; -0.01 $p = 0.003$; and $\beta = -0.04$, 95% CI -0.078; -0.01, $p = 0.004$, respectively), indicating that there was a positive association between GLP-1R, GLP-2R and BMI in HCs, but a negative association in individuals with MD (Fig. 1). For GLP-1R, we observed similar results in all the models that included potential confounders (Table 2). For GLP-2R, however, the difference was no longer significant in Model 2, which included age, sex, ethnicity, PMI, ethanol and nicotine/cotinine (Table 2).

In the hippocampus, GLP-1R expression was significantly associated with MD, in comparison to HC ($\beta = -1.28$, 95% CI -2.42; -0.13 $p = 0.029$) (Table 2). We similarly observed a moderating effect of diagnosis on the association between BMI and GLP-expression ($\beta = 0.043$, 95% CI 0.003; 0.08 $p = 0.03$), but in an opposite direction of what was observed in the dlPFC, insofar that there a negative association between GLP-1R and BMI in HCs and a positive association in individuals with MD (Fig. 2). Significant differences in the expression of GLP-2R were observed only in Model 3, after adjusting for the use of psychotropic medications (Table 3).

4. Discussion

To our knowledge, this is the first study to investigate mRNA expression of GLP-1R and GLP-2R in postmortem brain of individuals with mood and psychotic disorders. After adjustment for relevant covariates, we found significant differences in the expression of GLP-1R and GLP-2R genes in the dlPFC and hippocampus of individuals with MD, but not SCZ, compared to HCs. Although this finding is preliminary and requires further investigation, it enhances knowledge regarding GLP-1 role in mental disorders. Animal studies have suggested that development of diabetes is associated with a reduction in the expression of GLP-1R in the hippocampus (Gumuslu et al., 2018). In addition, decreased hypothalamic expression of GLP-1R in individuals with Type 2 diabetes has been previously documented (Ten Kulve et al., 2016). It is, therefore, possible to hypothesize that the differences in GLP-1R expression reported herein are a result of mechanistic pathways shared by MD and Type 2 diabetes, such as dysregulation of glucose homeostasis and feeding behavior (Mansur et al., 2015). However, as this is a cross-sectional study, it is not possible to determine causality. It is also unknown how many subjects in this study had a clinical diagnosis of diabetes and/or were treated with anti-diabetic agents, which could also have affected the results (Ten Kulve et al., 2016).

Our results are in accordance with extant literature indicating that GLP-1 acts as a neurotransmitter or neuromodulator in anatomically and functionally distinct areas of the central nervous system (CNS) (Farr et al., 2016; Heni et al., 2015; Richard et al., 2014; van Bloemendaal et al., 2014). Other neuroprotective functions of GLP-1 include modulation of autonomic and stress response through the hypothalamic-pituitary-adrenal (HPA) axis activation, in humans and rodents (Rinaman, 1999; Weina et al., 2018). It is further demonstrated that GLP-1 is neuroprotective and

Table 1 Sample characteristics.

	dlPFC sample				Hippocampus sample			
	Healthy controls ($n = 191$)	SCZ ($n = 113$)	MD ($n = 155$)	p-value	Healthy controls ($n = 169$)	SCZ ($n = 96$)	MD ($n = 113$)	p-value
Age at death (years), mean (SD)	42.58 (13.55)	46.04 (11.55)	40.81 (12.10)	0.003[a]	41.41 (13.54)	45.88 (11.69)	41.83 (11.66)	0.017[a]
Sex (Female), *n* (%)	52 (27.2)	36 (31.9)	69 (44.5)	0.003[b]	47 (27.8)	28 (29.2)	49 (43.4)	0.017[b]
Race (Caucasian), *n* (%)	88 (46.1)	52 (46.0)	135 (87.1)	< 0.001[b]	70 (41.4)	40 (41.7)	98 (86.7)	< 0.001[b]
BMI (kg/m^2), mean (SD)	29.98 (6.75)	28.49 (5.78)	27.74 (5.87)	0.005[a]	29.88 (6.76)	28.54 (6.52)	27.49 (5.88)	0.015[a]
Obesity (BMI $\geq 30\,kg/m^2$), *n* (%)	89 (46.6)	47 (41.6)	44 (28.4)	0.002[b]	74 (43.8)	41 (42.7)	32 (28.3)	0.022[b]
PMI (hours), mean (SD)	30.78 (15.01)	36.35 (18.48)	32.41 (19.97)	0.017[a]	30.06 (14.43)	35.89 (17.44)	33.34 (21.11)	0.020[a]
Ethanol (yes), *n* (%)	9 (4.7)	12 (10.6)	47 (30.3)	< 0.001[b]	8 (4.7)	10 (10.4)	31 (27.4)	< 0.001[b]
Nicotine/cotinine (yes), *n* (%)	51 (26.7)	66 (60.6)	56 (44.4)	< 0.001[b]	47 (27.8)	60 (62.5)	52 (54.7)	< 0.001[b]
Antipsychotics (yes), *n* (%)	0 (0)	84 (74.3)	31 (21.1)	< 0.001[b]	0 (0)	71 (74.0)	18 (16.8)	< 0.001[b]
Antidepressants (yes), *n* (%)	1 (0.8)	35 (31.0)	77 (52.0)	< 0.001[b]	0 (0)	32 (33.3)	58 (53.7)	< 0.001[b]
Mood Stabilizers (yes), *n* (%)	1 (0.9)	21 (18.6)	41 (27.7)	< 0.001[b]	0 (0)	18 (18.8)	26 (24.1)	< 0.001[b]
Benzodiazepines (yes), *n* (%)	0 (0)	10 (8.8)	46 (31.3)	< 0.001[b]	0 (0)	7 (7.3)	29 (26.9)	< 0.001[b]
Cocaine (yes), *n* (%)	0 (0)	3 (2.7)	14 (9.3)	< 0.001[b]	0 (0)	2 (2.1)	11 (10.2)	< 0.001[b]
Opiates (yes), *n* (%)	8 (4.2)	8 (7.1)	44 (29.1)	< 0.001[b]	5 (3.0)	6 (6.3)	26 (23.6)	< 0.001[b]

SCZ: schizophrenia; MD: mood disorders; SD: standard deviation; BMI: body mass index; PMI: post-mortem interval.

[a] Kruskal Wallis Test.

[b] Chi-square test.

Table 2 Gene expression in the dorsolateral prefrontal cortex.

	HC vs. SCZ			SCZ × BMI			HC vs. MD			MD × BMI		
	β	95%CI	*p*-value	β	95%CI	*p*-value	β	95%CI	*p*-value	β	95%CI	*p*-value
Model 1 – Adjusted for age, sex, ethnicity and PMI ($n = 459$)												
GLP-1R	0.723	−0.414; 1.821	0.217	−0.030	−0.068; 0.008	0.118	1.504	0.484; 2.524	0.004	−0.053	−0.088; −0.019	0.003
GLP-2R	0.741	−0.352; 1.834	0.184	−0.026	−0.063; 0.011	0.164	1.305	0.308; 2.302	0.010	−0.044	−0.078; −0.010	0.011
Model 2 – Adjusted for age, sex, ethnicity, PMI, ethanol and nicotine/cotinine ($n = 426$)												
GLP-1R	0.723	−0.371; 1.816	0.195	−0.033	−0.070; 0.004	0.079	1.369	0.278; 2.461	0.014	−0.047	−0.085; −0.010	0.013
GLP-2R	0.746	−0.325; 1.817	0.172	−0.029	−0.065; 0.007	0.116	1.051	−0.019; 2.120	0.054	−0.034	−0.071; 0.003	0.068
Model 3 – Adjusted for age, sex, ethnicity, PMI, antipsychotics, antidepressants, mood stabilizers and BZDs ($n = 365$)												
GLP-1R	0.581	−0.676; 1.838	0.365	−0.029	−0.070; 0.013	0.178	1.426	0.255; 2.596	0.017	−0.053	−0.093; −0.014	0.008
GLP-2R	0.816	−0.423; 2.056	0.197	−0.031	−0.072; 0.010	0.139	1.437	0.283; 2.591	0.015	−0.050	−0.089; −0.012	0.011
Model 3 – Adjusted for age, sex, ethnicity, PMI, cocaine and opiates ($n = 454$)												
GLP-1R	0.739	−0.378; 1.857	0.195	−0.031	−0.069; 0.007	0.109	1.587	0.554; 2.619	0.003	−0.054	−0.089; −0.018	0.003
GLP-2R	0.783	−0.309; 1.876	0.160	−0.027	−0.064; 0.010	0.149	1.382	0.372; 2.391	0.007	−0.044	−0.079; −0.010	0.012

HC: healthy controls; SCZ: schizophrenia; MD: mood disorders; BMI: body mass index; CI: confidence interval.

Table 3 Gene expression in the hippocampus.

	HC vs. SCZ			SCZ × BMI			HC vs. MD			MD × BMI		
	β	95%CI	*p*-value	β	95%CI	*p*-value	β	95%CI	*p*-value	β	95%CI	*p*-value
Model 1 – Adjusted for age, sex, ethnicity and PMI ($n = 378$)												
GLP-1R	−0.588	−1.714; 0.539	0.307	0.019	−0.018; 0.057	0.316	−1.280	−2.426; −0.134	0.029	0.043	0.003; 0.082	0.035
GLP-2R	−0.435	−1.563; 0.694	0.450	0.010	−0.028; 0.048	0.597	−0.985	−2.133; 0.163	0.093	0.030	−0.010; 0.070	0.138
Model 2 – Adjusted for age, sex, ethnicity, PMI, ethanol and nicotine/cotinine ($n = 360$)												
GLP-1R	−0.588	−1.729; 0.553	0.313	0.020	−0.018; 0.058	0.304	−1.399	−2.605; −0.193	0.023	0.044	0.002; 0.086	0.038
GLP-2R	−0.452	−1.602; 0.698	0.441	0.010	−0.028; 0.049	0.596	−0.877	−2.091; 0.338	0.157	0.026	−0.017; 0.068	0.235
Model 3 – Adjusted for age, sex, ethnicity, PMI, antipsychotics, antidepressants, mood stabilizers and BZDs ($n = 365$)												
GLP-1R	−0.260	−1.532; 1.012	0.689	0.020	−0.022; 0.061	0.351	−1.018	−2.295; 0.259	0.118	0.042	−0.001; 0.086	0.056
GLP-2R	−0.401	−1.660; 0.858	0.532	0.020	−0.021; 0.062	0.328	−1.327	−2.591; −0.063	0.040	0.045	0.002; 0.088	0.042
Model 4 – Adjusted for age, sex, ethnicity, PMI, cocaine and opiates ($n = 373$)												
GLP-1R	−0.603	−1.736; 0.529	0.297	0.020	−0.018; 0.058	0.310	−1.410	−2.585; −0.234	0.019	0.048	0.007; 0.089	0.021
GLP-2R	−0.445	−1.578; 0.688	0.442	0.010	−0.028; 0.048	0.599	−1.151	−2.328; 0.025	0.055	0.035	−0.006; 0.076	0.093

HC: healthy controls; SCZ: schizophrenia; MD: mood disorders; BMI: body mass index; CI: confidence interval.

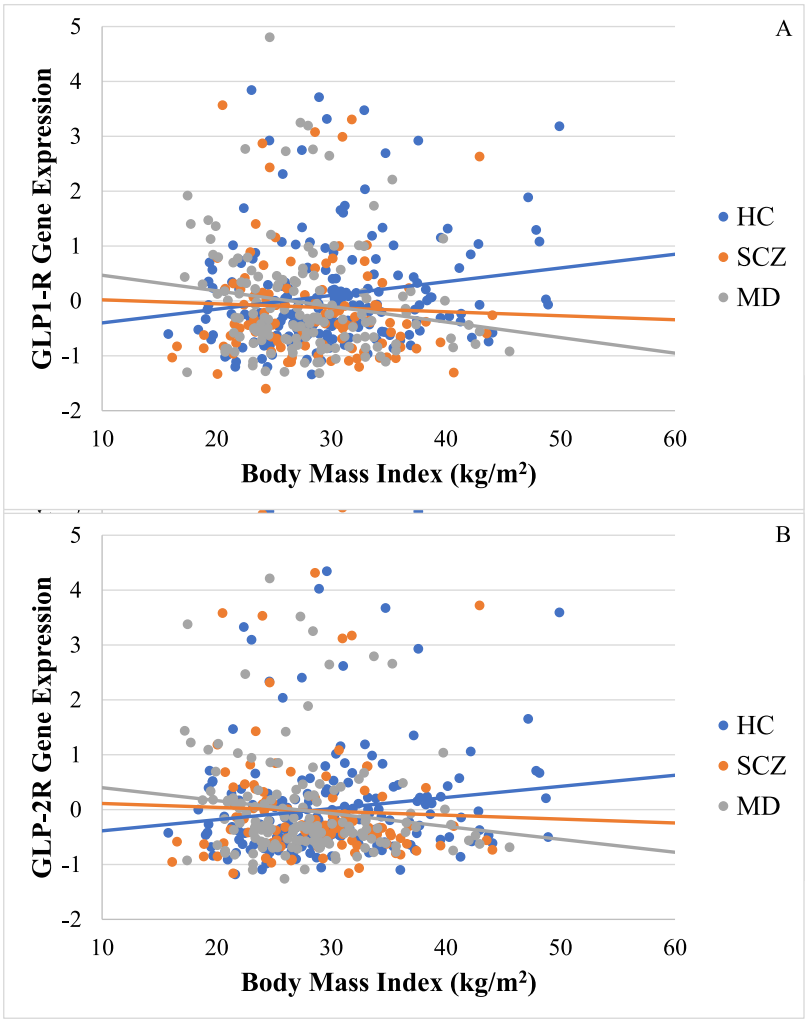


Fig. 1 Associations between body mass index and (A) GLP-1R and (B) GLP-2R gene expression, according to diagnosis, in the dorsolateral prefrontal cortex. HC: healthy controls; SCZ: schizophrenia; MD: mood disorders.

anti-apoptotic (Gault et al., 2010; McClean et al., 2011; Porter et al., 2010). Possible mechanisms of the neuroprotective action of GLP-1 agonism are via attenuation of microglial activation, consequently reducing release of M1 activation (e.g., tumor necrosis factor alpha [TNF-alpha] and interleukin-1 beta [IL-1])(Lee et al., 2012). In rats, GLP-1 modulates the synaptic transmission and plasticity in the hippocampus of rats, at least partly mediated by glutamate uptake (Kobayashi et al., 2013). In addition, GLP-1R was demonstrated to be expressed in astrocytes and to be associated with the inhibition of neural inflammation (Iwai et al., 2006). Activation of the GLP-1R was linked with neurite outgrowth in cultured cells (Perry et al., 2002) and with neurotrophic effects including hippocampal neurogenesis (Bertilsson et al., 2008; Li et al., 2010). Further studies demonstrated that GLP-1R knockout animals are deficient in spatial learning, while the overexpression of the receptor in the hippocampus was related to improvements in learning and memory (During et al., 2003).

We also observed differential associations between GLP1-R and GLP-2R gene expressions and BMI in individuals with MD, relative to HCs. A similar, but non-significant, pattern was observed in patients with SCZ. Genetic studies have documented an association between GLP-1R mRNA expression and BMI in intestinal and pancreatic cells (Ritze et al., 2015; Segerstolpe et al., 2016); this is the first study to observe this association in the brain. Evidence from neuroimaging studies indicates that BMI effects on brain structure and function are heterogeneous and topographically influenced (Opel et al., 2017; Weise et al., 2017). The differential effects of BMI on GLP-1R and GLP-2R expression in individuals with MD are consistent with literature indicating that individuals with MD and comorbid obesity have a partially distinct clinical and biological signature, including, but not limited to, differences in neuroimaging parameters and peripheral biomarkers (Mansur et al., 2015).

The expression levels of GLP-1R and GLP-2R were derived from individual probes in a microarray, which are limited to the specific transcript being hybridized to the BeadChip. Further analyses can benefit from looking at their mRNA levels by targeted methods (such as quantitative real-time PCR) and by investigating the expression of different transcript variants of these genes. In addition, whether

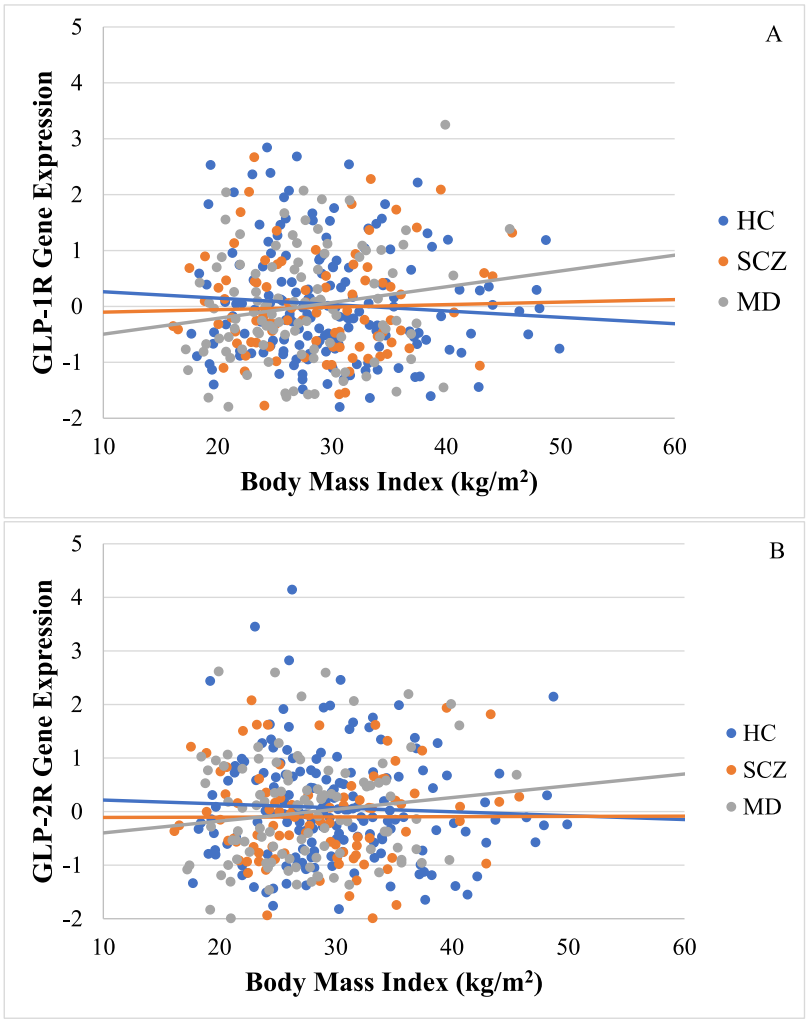


Fig. 2 Associations between body mass index and (A) GLP-1R and (B) GLP-2R gene expression, according to diagnosis, in the hippocampus. HC: healthy controls; SCZ: schizophrenia; MD: mood disorders.

the changes in mRNA expression detected in our analyses reflect alterations in protein levels remains unknown. In addition, gene expression profiles can significantly vary between different cell types, even within the same tissue of origin. In this sense, it is possible the GLP-1R and GLP-2R may have different functions in neurons, astrocytes, and microglial cells, and our gene expression analysis performed in bulk tissue might have masked important findings. Lastly, we cannot rule out the possibility that GLP-1R and GLP-2R act in complex networks with several other genes to mediate the effects of BMI and ultimately determine the risk for metabolic disturbances in patients with severe mental illnesses. Future analysis of co-expression networks and of the additive effects of multiple genes involved in this system will likely provide a more comprehensive and coherent understanding of the molecular mechanisms underlying the metabolic disturbances in MDs.

Taken together, the results of this study suggest that GLP-1R and GLP-2R expression could be different between individuals with MD and healthy controls, with a greater vulnerability associated with greater BMI. Our findings corroborate to the initial data on the role of GLP-1 and GLP-2 in the brain, underscoring a possible target for intervention in psychiatric disorders.

Author disclosure

Role of funding source

This research was supported by the Intramural Research Program of the NIMH (NCT00001260, 900142). The funder had no role in the analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Contributors

RBM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RBM and RSM designed the study and requested and obtained the data. GF, AT, MS and EB contributed to the analysis and interpretation of data. RBM, AT

and EB drafted the manuscript. GF, MS, JL, KL, MV, RH and RSM revised critically the manuscript for important intellectual content.

Conflict of interest

The authors declare no conflict of interest related to this work.

Acknowledgments

We thank the families who donated tissue to this research. We also thank Mr. Carl Virtanen and Mr. Zhibin Lu for their excellent technical assistance.

References

Amare, A.T., Schubert, K.O., Klingler-Hoffmann, M., Cohen-Woods, S., Baune, B.T., 2017. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. Trans. Psychiatry 7, e1007.

Baldassano, S., Amato, A., Mule, F., 2016. Influence of glucagon-like peptide 2 on energy homeostasis. Peptides 86, 1–5.

Bertilsson, G., Patrone, C., Zachrisson, O., Andersson, A., Dannaeus, K., Heidrich, J., Kortesmaa, J., Mercer, A., Nielsen, E., Ronnholm, H., Wikstrom, L., 2008. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson's disease. J. Neurosci. Res. 86, 326–338.

Brietzke, E., Kapczinski, F., Grassi-Oliveira, R., Grande, I., Vieta, E., McIntyre, R.S., 2011. Insulin dysfunction and allostatic load in bipolar disorder. Expert Rev. Neurother. 11, 1017–1028.

Calkin, C.V., Gardner, D.M., Ransom, T., Alda, M., 2013. The relationship between bipolar disorder and Type 2 diabetes: more than just co-morbid disorders. Ann. Med. 45, 171–181.

Carter, J., Swardfager, W., 2016. Mood and metabolism: anhedonia as a clinical target in type 2 diabetes. Psychoneuroendocrinology 69, 123–132.

Cheadle, C., Vawter, M.P., Freed, W.J., Becker, K.G., 2003. Analysis of microarray data using Z score transformation. J. Mol. Diagn. 5, 73–81.

During, M.J., Cao, L., Zuzga, D.S., Francis, J.S., Fitzsimons, H.L., Jiao, X., Bland, R.J., Klugmann, M., Banks, W.A., Drucker, D.J., Haile, C.N., 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat. Med. 9, 1173–1179.

Farr, O.M., Sofopoulos, M., Tsoukas, M.A., Dincer, F., Thakkar, B., Sahin-Efe, A., Filippaios, A., Bowers, J., Srnka, A., Gavrieli, A., Ko, B.J., Liakou, C., Kanyuch, N., Tseleni-Balafouta, S., Mantzoros, C.S., 2016. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. Diabetologia 59, 954–965.

Gault, V.A., Hölscher, C., 2008. GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. Eur. J. Pharmacol. 587 (1–3), 112–117. doi:10.1016/j.ejphar.2008.03.025.

Gault, V.A., Porter, W.D., Flatt, P.R., Holscher, C., 2010. Actions of exendin-4 therapy on cognitive function and hippocampal synaptic plasticity in mice fed a high-fat diet. Int. J. Obes. (Lond.) 34, 1341–1344.

Gengler, S., McClean, P.L., McCurtin, R., Gault, V.A., Holscher, C., 2012. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. Neurobiol. Aging 33, 265–276.

Gumuslu, E., Cine, N., Ertan, M., Mutlu, O., Komsuoglu Celikyurt, I., Ulak, G., 2018. Exenatide upregulates gene expression of glucagon-like peptide-1 receptor and nerve growth factor in streptozotocin/nicotinamide-induced diabetic mice. Fundam. Clin. Pharmacol. 32, 174–180.

Henderson, D.C., Vincenzi, B., Andrea, N.V., Ulloa, M., Copeland, P.M., 2015. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry 2, 452–464.

Heni, M., Kullmann, S., Gallwitz, B., Haring, H.U., Preissl, H., Fritsche, A., 2015. Dissociation of GLP-1 and insulin association with food processing in the brain: GLP-1 sensitivity despite insulin resistance in obese humans. Mol. Metab. 4, 971–976.

Ishoy, P.L., Fagerlund, B., Broberg, B.V., Bak, N., Knop, F.K., Glenthoj, B.Y., Ebdrup, B.H., 2017. No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia. Acta Psychiatr. Scand..

Iwai, T., Ito, S., Tanimitsu, K., Udagawa, S., Oka, J., 2006. Glucagon-like peptide-1 inhibits LPS-induced IL-1beta production in cultured rat astrocytes. Neurosci. Res. 55, 352–360.

Iwai, T., Suzuki, M., Kobayashi, K., Mori, K., Mogi, Y., Oka, J., 2009. The influences of juvenile diabetes on memory and hippocampal plasticity in rats: improving effects of glucagon-like peptide-1. Neurosci. Res. 64, 67–74.

Kappe, C., Tracy, L.M., Patrone, C., Iverfeldt, K., Sjoholm, A., 2012. GLP-1 secretion by microglial cells and decreased CNS expression in obesity. J. Neuroinflammation 9, 276.

Kobayashi, K., Iwai, T., Sasaki-Hamada, S., Kamanaka, G., Oka, J., 2013. Exendin (5–39), an antagonist of GLP-1 receptor, modulates synaptic transmission via glutamate uptake in the dentate gyrus. Brain Res. 1505, 1–10. doi:10.1016/j.brainres.2013.01.012.

Lee, Y.S., Park, M.S., Choung, J.S., Kim, S.S., Oh, H.H., Choi, C.S., Ha, S.Y., Kang, Y., Kim, Y., Jun, H.S., 2012. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. Diabetologia 55, 2456–2468.

Li, Y., Duffy, K.B., Ottinger, M.A., Ray, B., Bailey, J.A., Holloway, H.W., Tweedie, D., Perry, T., Mattson, M.P., Kapogiannis, D., Sambamurti, K., Lahiri, D.K., Greig, N.H., 2010. GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. J. Alzheimers Dis. 19, 1205–1219.

Lipska, B.K., Deep-Soboslay, A., Weickert, C.S., Hyde, T.M., Martin, C.E., Herman, M.M., Kleinman, J.E., 2006. Critical factors in gene expression in postmortem human brain: focus on studies in schizophrenia. Biol. Psychiatry 60, 650–658.

Mansur, R.B., Ahmed, J., Cha, D.S., Woldeyohannes, H.O., Subramaniapillai, M., Lovshin, J., Lee, J.G., Lee, J.H., Brietzke, E., Reininghaus, E.Z., Sim, K., Vinberg, M., Rasgon, N., Hajek, T., McIntyre, R.S., 2017a. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: a pilot, open-label study. J. Affect Disord. 207, 114–120.

Mansur, R.B., Brietzke, E., McIntyre, R.S., 2015. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci. Biobehav. Rev. 52, 89–104.

Mansur, R.B., Zugman, A., Ahmed, J., Cha, D.S., Subramaniapillai, M., Lee, Y., Lovshin, J., Lee, J.G., Lee, J.H., Drobinin, V., Newport, J., Brietzke, E., Reininghaus, E.Z., Sim, K., Vinberg, M., Rasgon, N., Hajek, T., McIntyre, R.S., 2017b. Treatment with a GLP-1R agonist over four weeks promotes weight loss-moderated changes in frontal-striatal brain structures in individuals with mood disorders. Eur. Neuropsychopharmacol.

McClean, P.L., Holscher, C., 2014. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 76 (Pt A), 57–67.

McClean, P.L., Parthsarathy, V., Faivre, E., Holscher, C., 2011. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J. Neurosci. 31, 6587–6594.

McIntyre, R.S., 2014. A vision for drug discovery and development: novel targets and multilateral partnerships. Adv. Ther. 31, 245–246.

Opel, N., Redlich, R., Kaehler, C., Grotegerd, D., Dohm, K., Heindel, W., Kugel, H., Thalamuthu, A., Koutsouleris, N., Arolt, V., Teuber, A., Wersching, H., Baune, B.T., Berger, K., Dannlowski, U., 2017. Prefrontal gray matter volume mediates genetic risks for obesity. Mol. Psychiatry 22, 703–710.

Perry, T., Haughey, N.J., Mattson, M.P., Egan, J.M., Greig, N.H., 2002. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J. Pharmacol. Exp. Ther. 302, 881–888.

Pillinger, T., Beck, K., Gobjila, C., Donocik, J.G., Jauhar, S., Howes, O.D., 2017. Impaired glucose homeostasis in first-episode Schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 74, 261–269.

Porter, D.W., Kerr, B.D., Flatt, P.R., Holscher, C., Gault, V.A., 2010. Four weeks administration of liraglutide improves memory and learning as well as glycaemic control in mice with high fat dietary-induced obesity and insulin resistance. Diabetes Obes. Metab. 12, 891–899.

Ramaker, R.C., Bowling, K.M., Lasseigne, B.N., Hagenauer, M.H., Hardigan, A.A., Davis, N.S., Gertz, J., Cartagena, P.M., Walsh, D.M., Vawter, M.P., Jones, E.G., Schatzberg, A.F., Barchas, J.D., Watson, S.J., Bunney, B.G., Akil, H., Bunney, W.E., Li, J.Z., Cooper, S.J., Myers, R.M., 2017. Post-mortem molecular profiling of three psychiatric disorders. Genome Med. 9, 72.

Richard, J.E., Farkas, I., Anesten, F., Anderberg, R.H., Dickson, S.L., Gribble, F.M., Reimann, F., Jansson, J.O., Liposits, Z., Skibicka, K.P., 2014. GLP-1 receptor stimulation of the lateral parabrachial nucleus reduces food intake: neuroanatomical, electrophysiological, and behavioral evidence. Endocrinology 155, 4356–4367.

Rinaman, L., 1999. Interoceptive stress activates glucagon-like peptide-1 neurons that project to the hypothalamus. Am. J. Physiol. 277, R582–R590.

Ritchie, M.E., Phipson, B., Wu, D., Hu, Y., Law, C.W., Shi, W., Smyth, G.K., 2015. Limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 43 (7), e47. doi:10.1093/nar/gkv007.

Ritze, Y., Hengelhaupt, C., Bardos, G., Ernst, B., Thurnheer, M., D'Haese, J.G., Bischoff, S.C., Schultes, B., 2015. Altered intestinal neuroendocrine gene expression in humans with obesity. Obesity (Silver Spring) 23, 2278–2285.

Segerstolpe, A., Palasantza, A., Eliasson, P., Andersson, E.M., Andreasson, A.C., Sun, X., Picelli, S., Sabirsh, A., Clausen, M., Bjursell, M.K., Smith, D.M., Kasper, M., Ammala, C., Sandberg, R., 2016. Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes. Cell Metab. 24, 593–607.

Ten Kulve, J.S., van Bloemendaal, L., Balesar, R., RG, I.J., Swaab, D.F., Diamant, M., la Fleur, S.E., Alkemade, A., 2016. Decreased hypothalamic glucagon-like peptide-1 receptor expression in type 2 diabetes patients. J. Clin. Endocrinol. Metab. 101 (5), 2122–2129. doi:10.1210/jc.2015-3291.

Trujillo, J.M., Nuffer, W., Ellis, S.L., 2015. GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther. Adv. Endocrinol. Metab. 6, 19–28.

van Bloemendaal, L., RG, I.J., Ten Kulve, J.S., Barkhof, F., Konrad, R.J., Drent, M.L., Veltman, D.J., Diamant, M., 2014. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes 63, 4186–4196.

Vancampfort, D., Mitchell, A.J., De Hert, M., Sienaert, P., Probst, M., Buys, R., Stubbs, B., 2015a. Prevalence and predictors of type 2 diabetes mellitus in people with bipolar disorder: a systematic review and meta-analysis. J. Clin. Psychiatry.

Vancampfort, D., Mitchell, A.J., De Hert, M., Sienaert, P., Probst, M., Buys, R., Stubbs, B., 2015b. Type 2 diabetes in patients with major depressive disorder: a meta-analysis of prevalence estimates and predictors. Depress Anxiety 32, 763–773.

Wang, X.H., Li, L., Holscher, C., Pan, Y.F., Chen, X.R., Qi, J.S., 2010. Val8-glucagon-like peptide-1 protects against Abeta1-40-induced impairment of hippocampal late-phase long-term potentiation and spatial learning in rats. Neuroscience 170, 1239–1248.

Weina, H., Yuhu, N., Christian, H., Birong, L., Feiyu, S., Le, W., 2018. Liraglutide attenuates the depressive- and anxiety-like behaviour in the corticosterone induced depression model via improving hippocampal neural plasticity. Brain Res..

Weise, C.M., Piaggi, P., Reinhardt, M., Chen, K., Savage, C.R., Krakoff, J., Pleger, B., 2017. The obese brain as a heritable phenotype: a combined morphometry and twin study. Int. J. Obes (Lond.) 41, 458–466.