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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

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^{5,2}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.

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^{5,3}Conflict of Interest

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

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 postmortem brain of individuals with MD, providing a rationale for further inquiry and proof of principle interventional studies.

Keywords

GLP-1R; GLP-2R; Mood Disorders; Schizophrenia; Gene Expression; Obesity

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; Mansur et al., 2017b), 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 dIPFC and Hippocampus from Schizophrenia and Mood Disorders” (dbGaP accession number phs000979.v1.p1) database contains microarray data from the dIPFC and hippocampus across nine major mental disorders, with emphasis on SCZ, bipolar disorder (BD) and major depressive disorder (MDD). Postmortem 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 dIPFC and hippocampus have been previously 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 dIPFC 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) > 72hs. The dataset used herein comprised 459 specimens from the dIPFC, 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 (Figure 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 (Figure 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 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 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.

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Figure 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.

Figure 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

Table 1–**Sample Characteristics**

	dIPFC 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 ≥ 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 x BMI			HC vs. MD			MD x 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 x BMI			HC vs. MD			MD x 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.