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Altered DNA methylation of glucose transporter 1 and glucose transporter 4 in patients with major depressive disorder

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ABSTRACT

Alterations in brain glucose metabolism and in peripheral glucose metabolism have frequently been observed in major depressive disorder (MDD). The insulin independent glucose transporter 1 (GLUT1) plays a key role in brain metabolism while the insulin-dependent GLUT4 is the major glucose transporter for skeletal and cardiac muscle. We therefore examined methylation of GLUT1 and GLUT4 in fifty-two depressed inpatients and compared data to eighteen healthy comparison subjects. DNA methylation of the core promoter regions of GLUT1 and GLUT4 was assessed by bisulfite sequencing. Further factors determined were fasting glucose, cortisol, insulin, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). We found significantly increased methylation of the GLUT1 in depressed inpatients compared to healthy comparison subjects (CG). Further findings comprise increased concentrations of fasting cortisol, glucose, insulin, and increased IL-6 and TNF-α. After six weeks of inpatient treatment, significantly lower GLUT1 methylation was observed in remitted patients compared to non-remitters. GLUT4 methylation was not different between depressed patients and CG, and did not differ between remitted and non-remitted patients. Although preliminary we conclude from our results that the acute phase of major depressive disorder is associated with increased GLUT1 methylation and mild insulin resistance. The successful treatment of depression is associated with normalization of GLUT1 methylation in remitters, indicating that this condition may be reversible. Failure of normalization of GLUT1 methylation in non-remitters may point to a possible role of impeded brain glucose metabolism in the maintenance of MDD.

1. Introduction

Major depressive disorder (MDD) is a disease with poorly recognized etiology. Currently used antidepressant drugs, which mainly affect synaptic neurotransmitter levels, show full clinical efficacy in only one third of patients (Rush, 2007). Thus it is now generally accepted that the pathogenesis of MDD includes not only improper monoamine transmission but disturbances in the endocrine and immunological systems, including activation of the hypothalamus-pituitary-adrenal axis (HPAA) with subsequent hypercortisolism, and upregulation of pro-inflammatory cytokines (i.e. interleukin-6 and tumor-necrosis factor-α) (Dowlati et al., 2010; Stetler and Miller, 2011). Elevated cortisol concentrations are discussed as factors underlying the development of impaired glucose metabolism and insulin resistance by impairment of insulin-mediated suppression of hepatic glucose output, impairment of insulin-mediated stimulation of glucose uptake, and enhanced lipolysis (Bjorntorp, 1999; Divertie et al., 1991; Phillips et al., 1998; Rizza et al., 1982). The alterations described above have been linked to the enhanced prevalence of the metabolic syndrome, type-2 diabetes mellitus (T2DM) and cardiovascular disorders in patients with MDD (Brown et al., 2004; Kahl et al., 2015; Mezuk et al., 2008; Moulton et al., 2015; Pan et al., 2012; Van der Kooy et al., 2007).

In recent years, alterations in brain glucose metabolism have

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frequently been described in MDD (reviewed in Su et al. (2014)). Glucose is the major energy resource for neuronal cells. The entry of glucose into the cell is mediated by a family of proteins, the facilitative glucose transporter proteins (Vannucci et al., 1997). In the human brain, transport of glucose across membranes is mainly mediated by the insulin-independent glucose transporter 1 (GLUT1) and glucose transporter 3 (GLUT3). The interaction among neurons, astrocytes, and endothelial cells has a central role coupling energy supply with changes in neuronal activity. GLUT1 is expressed in the nervous system predominantly in endothelial cells and astrocytes, which is essential for brain maturation and normal brain function (Klepper, 2004; Klepper et al., 2007). Astrocytes take up glucose from the blood and metabolize it to lactate, which is then delivered to neurons. The astrocytic process of providing energy is dependent on the activity of the adjacent neuron, thereby supplying the neuron with energy "on demand" (Magistretti et al., 1994). This astrocyte-to-neuron lactate shuttle is a main source of energy to sustain neuronal physiology (Benarroch, 2014; Pellerin et al., 1998).

In the periphery, insulin facilitates glucose uptake in striated muscle and adipose tissue by stimulating glucose transporter 4 (GLUT4). GLUT4 activity is directly correlated with the ability to clear blood glucose and insulin sensitivity (Gannon et al., 2015). Furthermore, alterations in GLUT expression and activity have been associated with disease types such as epilepsy, dystonia and cancer (Adekola et al., 2012; De Giorgis and Veggiotti, 2013; Roubergue et al., 2011).

It has been shown that the expression of various GLUT's is regulated at least in part by DNA methylation of the promoter region (Novakovic et al., 2013). The aim of our study was to examine the DNA methylation of the core promoter regions of GLUT1 and GLUT4 in depressed patients during the course of the disorder, and to compare data with healthy comparison subjects. We chose the GLUT1 as central target, because it is essential for the glucose transport from the blood into the astrocyte, and because GLUT1 protein expression is considerably higher compared to GLUT3 (Ito et al., 2011; Peters and McEwen, 2015).

2. Methods and materials

2.1. Participants

The study was approved by the local ethics committee; after complete description of the study to the subjects, written informed consent was obtained. Fifty-two consecutive inpatients with MDD treated at the Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School were included. Eighteen healthy subjects served as the comparison group (CG). Diagnoses was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and confirmed with standardized clinical interviews (SCID I/II; German version).

All patients were treated in specialized psychotherapy wards and all received cognitive behavioral therapy for 6 weeks. Additional antidepressant treatment was given to 40 patients (Table 1). Assessment of all parameters was performed at the beginning of inpatient treatment (t1), and at the end of treatment (t2) after 6 weeks. Fifteen patients dropped out during the study, so that 37 of 52 patients had complete data at the end of inpatient treatment. Of these, eighteen patients reached remission, assessed as a MADRS sum score below 10. Detailed anthropometric and treatment data are in remitted versus non-remitted patients are given in Table 2. No differences between completers and non-completers were observed concerning any of the parameters assessed.

Reasons for drop-out were as follows: Seven patients refused repeated blood sampling, two patients had intercurrent infectious disorder, and six patients were discharged during the first three weeks of treatment (therefore missing the second taking of a blood sample).

Eighteen healthy subjects with similar gender distribution, age and BMI who were recruited through announcements on university bulletin boards served as the comparison group (CG). The Structured Clinical Interview for DSM-IV (SCID) was also applied to the comparison group to confirm the absence of any current or lifetime history of major psychiatric disorder for every subject in this group.

Medical examination was performed according to the recommendations of the European Heart Association for both groups and gave no evidence for previous cardiovascular disease or diabetes mellitus (Perk et al., 2012). None of the patients or healthy controls used ß-blockers or received other cardiologic treatments. None of the patients or controls received treatments that may influence glucose or lipid metabolism (e.g. metformin, statins), apart from psychopharmacological treatment in depressed patients as described in Table 2. Exclusion criteria were body-mass index ≥30, age younger than 18 years and over 60 years, acute or chronic infectious disease, current or lifetime immunological disorders, diabetes mellitus type 1 and type 2, current or lifetime cardiovascular disorders, pregnancy, schizophrenia, mental retardation, bipolar disorder, and current substance abuse or dependency.

Table 1
Anthropometric data, factors of the metabolic syndrome, and depression scores in depressed patients and the comparison group. Depressed patients had slightly more weight and higher BMI, and were physically less active. Concentrations of fasting cortisol, insulin and the pro-inflammatory cytokine TNF-α were elevated in MDD. Significant group differences (CG versus MDD) were highlighted in bold . A *P*-value <0.05 was considered significant. BDI-2: Beck depression Inventory-2; BMI: body mass index; HDL: high density lipoprotein; HOMA-IR: relative insulin resistance according to the homeostasis model assessment; IL-6: interleukin-6; MADRS: Montgomery-Åsperg Depression Rating Scale; RRsyst: systolic blood pressure; RRdiast: diastolic blood pressure; TNF-α: tumor necrosis factor-α; WC: waist circumference.

Measure	CG (N = 18)		MDD (N = 52)		P
	N	%	N	%	
Female	10	55.6	23	44.2	n.s.
	Mean	SD	Mean	SD	P
Age	43.2	13.1	41.8	11.1	n.s.
Height (m)	1.79	0.13	1.73	0.08	n.s.
Weight (kg)	71.4	14.0	72.5	11.1	**0.039**
BMI	22.1	2.4	24.0	2.7	**0.009**
	N	%	N	%	P
Psychotherapy only	0	0	17	32.7	
Additional antidepressants	0	0	35	67.3	
	N	%	N	%	
Metabolic syndrome	1	5.6	7	13.5	n.s.
	Mean	SD	Mean	SD	P
RRsyst (mmHg)	127.2	8.7	127.5	18.8	n.s.
RRdiast (mmHg)	78.8	5.0	81.5	9.8	n.s.
Triglyzerides (mmol/L)	1.21	1.02	1.50	0.99	n.s.
HDL (mmol/L)	1.52	0.42	1.48	0.32	n.s.
Glucose (mmol/L)	5.05	0.53	5.62	1.46	n.s.
WC (cm)	85.4	9.5	88.4	12.0	n.s.
Insulin (mU/L)	6.97	3.51	9.91	5.74	**0.046**
HOMA-IR	1.5	0.8	2.5	1.7	**0.032**
Cortisol (nmol/L)	427.1	146.4	577.8	159.9	**0.001**
IL-6 (pg/mL)	1.0	0.5	1.7	1.8	n.s.
TNF-α (pg/mL)	0.6	0.4	1.7	1.6	**0.005**
	Mean	SD	Mean	SD	P
Smoking (pack-years)	2.0	4.4	5.9	9.2	n.s.
Physical activity before	4.7	1.2	2.9	1.7	**<0.001**
Drinking	2.8	2.7	2.4	5.0	n.s.
BDI-2 sum score	0.8	1.1	28.7	10.0	**<0.001**
MADRS sum score	1	1.6	23.9	8.8	**<0.001**