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BRAIN NETWORKS ENCODING RECTAL SENSATION IN TYPE 1 DIABETES

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Abstract—*Introduction:* It has been shown that patients with type 1 diabetes mellitus and gastrointestinal (GI) symptoms have abnormal processing of sensory information following stimulation in the oesophagus. In order to find less invasive stimuli to study visceral afferent processing and to further elaborate the gut–brain network in diabetes, we studied brain networks following rectal electrical stimulations.

***Methods:* Twelve type 1 diabetes patients with GI symptoms and twelve healthy controls were included. A standard ambulatory 24-h electrocardiography was performed. 122-channel-evoked brain potentials to electrical stimulation in the rectum were recorded. Brain source-connectivity analysis was done. GI symptoms were assessed with the gastroparesis cardinal symptom index and quality of life (QOL) with SF-36. Any changes in brain source connectivity were correlated to duration of the disease, heart beat-to-beat intervals (RRs), clinical symptoms, and QOL of the patients.**

***Results:* Diabetic patients with GI symptoms showed changes relative to controls in the operculum–cingulate network with the operculum source localized deeper and more anterior ($P \leqslant 0.001$) and the cingulate source localized more anterior ($P = 0.03$). The shift of operculum source was correlated with the duration of the disease, severity of GI symptoms, and decreased RR ($P < 0.05$). The shift of the cingulate source was correlated with the mental QOL ($P = 0.04$). In healthy controls, the contribution of the cingulate source to the network was higher than the contribution of the operculum source ($P \leqslant 0.001$), whereas in patients the contribution of the two sources was comparable.**

***Conclusion:* This study gives further evidence for CNS involvement in diabetes. Since network reorganizations were correlated to GI symptoms, irregularities of rectal-evoked potentials can be viewed as a proxy for abnormal bottom-up visceral afferent processing. The network changes might serve as a biomarker for disturbed sensory visceral processing of GI symptoms in diabetes patients.**

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Key words: diabetes, operculum, cingulate, rectal-evoked potentials, brain source analysis.

INTRODUCTION

Diabetic autonomic neuropathy (DAN) is one of the most common complications of long-standing diabetes mellitus (DM) and it seems to play a central role in the development and progression of gastrointestinal (GI) dysfunction and discomfort (Vinik et al., 2003; Horowitz and Samsom, 2004). The GI symptoms, which are often severe, include nausea, vomiting, bloating, early satiety, abdominal pain, and diarrhoea (Bytzer et al., 2000). These symptoms lead to reduced quality of life (QOL) and management of patients is difficult (Talley et al., 2001). Therefore, a better understanding of sensory processing from the GI tract is necessary in order to explore the underlying mechanisms and improve treatment.

Previous studies of patients suffering from type 1 DM and GI symptoms have primarily focused on the upper GI tract. An overall decrease in sensitivity accompanied by an increase in somatic-referred pain areas in the oesophagus and the duodenum to experimental stimulations was observed (Frokjaer et al., 2007). Since the referred pain area to visceral pain reflects convergence between somatic and visceral afferents in the central nervous system (CNS), this study indicated the involvement of the CNS in symptom generation. A few studies have investigated the CNS involvement in DM, utilizing evoked potentials (EPs) to gut stimulation. The early studies which used only a few electroencephalogram (EEG) electrodes have shown that the EPs tended to have reduced quality and were

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Abbreviations: ANOVA, analysis of variance; CNS, central nervous system; DAN, dabetic autonomic neuropathy; DM, diabetes mellitus; EEG, electroencephalogram; EPs, evoked potentials; GI, gastrointestinal; LORETA, low-resolution tomography; MMP, multichannel matching pursuit; PAGI-SYM, patient assessment of upper GI disorder severity symptom index; QOL, quality of life; RR, heart beat-to-beat interval; SF-36, short form questionnaires; VAS, visual analogue scale.

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non-reproducible, reflecting damage of neuronal pathways (Rathmann et al., 1991; Tougas et al., 1992; Kamath et al., 1998). Studies with only a few recording electrodes allow investigation of EP amplitudes and latencies, but not of the brain generators underlying the EP signals. Investigation of brain generators of the EPs requires at least 60 recording electrodes for a reliable solution. In order to explore the active brain sources, our group has expended the model to use 62-electrode EEG recording to electrical stimulation in the oesophagus (Frokjaer et al., 2011; Brock et al., 2012a). Evidence of reorganization within anterior cingulate cortex and insular cortex was seen. Recently, we exploited 122-electrode EEG recordings to painful oesophageal stimulation in order to look into brain networks in diabetes patients. A number of irregularities within the sensory brain networks were seen, mainly involving operculo-insular cortex (Lelic et al., 2012a). The operculum source consistently shifted deeper and more anterior. These modifications within the operculo-insular cortex were related to the patient symptom scores and therefore give further evidence that DM is a disease affecting the neurons in the CNS (as well as in the periphery). The previous studies with oesophageal EPs have given a lot of insight into the nature of diabetes-related GI complications and give evidence of the insula's central role in symptom generation. However, since many of these patients suffer from nausea and intense reflux and therefore an oesophageal probe can be very difficult for them to tolerate, the rectum would be an easier organ to stimulate for diagnostic purposes. Thus, if there are differences in rectal EPs between patients and healthy controls, and these differences correlate to upper GI symptoms, then rectal EP irregularities can be seen as a proxy for abnormal bottom-up visceral afferent processing and can then be used instead of oesophageal EPs. In the present study, we investigated brain networks underlying EPs to painful electrical stimulation of the rectum in patients with type 1 DM, in order to observe how these are modified due to the disease.

We hypothesized that the brain networks involved in visceral sensation processing are reorganized in patients suffering from type 1 DM with GI symptoms. Therefore, the aims of this study were to: (1) investigate differences in brain networks underlying the rectal EPs between healthy controls and patients, and (2) correlate the differences within the brain networks to duration of the disease, severity of GI symptoms, QOL, and heart beat-to-beat interval (RR).

EXPERIMENTAL PROCEDURES

Subjects

Twelve type 1 diabetes patients with GI symptoms and twelve healthy controls were included in the study. Patients were recruited at the Department of Endocrinology and Gastroenterology at the Haukeland University Hospital, Bergen, Norway. All patients (3 males and 9 females, mean age 44.5 ± 9.7 years) had a verified diagnosis and disease duration of 26.2 ± 9.7 years. Treatment was managed with multiple insulin injection regimens or insulin pumps. Twelve age and gender-matched healthy controls (four males and eight females, mean age 44.6 ± 6.5 years) were included. Six of the healthy controls were recruited at the Department of Endocrinology and Gastroenterology at the Haukeland University Hospital and six were recruited at the Department of Gastroenterology and Hepatology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark. A standard 24-h ambulatory electrocardiography (Holter monitoring) was performed in all participants, and RR was used for analysis as this has been shown to correlate to mortality and disease (Pop-Busui, 2010). The local Ethics Committees at both hospitals approved the study protocol (Bergen: 2010/2562-6 and Aalborg: N20090008).

Gastroparesis cardinal symptom index (GCSI)

To enable the patients to assess the severity of their symptoms, we have used the patient assessment of upper GI disorder severity symptom index (PAGI-SYM) (Revicki et al., 2004b). In its short form, the GCSI, which consists of the first nine questions of PAGI-SYM, is a reliable and valid tool for measuring symptom severity in patients with gastroparesis (Revicki et al., 2004a). The GCSI is based on three subscales: (1) nausea/vomiting (three items), (2) postprandial fullness/early satiety (four items), and (3) bloating (two items). The patient is asked to rate the severity of the symptoms during the preceding 2 weeks. The GCSI items range from 0 – no symptoms, to 5 – very severe symptoms.

Short-form questionnaires (SF-36)

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores and two summary scores (physical component summary and mental component summary scores) (Ware et al., 1993, 1994). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. The SF-36 questionnaire enables the patients to estimate their physical and mental health and it covers four weeks.

Electrical stimulation

Following 6-h fasting, the blood glucose level was adjusted in all subjects to 6 mmol/l by the use of a hyperinsulinaemic-euglycaemic clamp technique (DeFronzo et al., 1979; Andrews et al., 1984). Healthy volunteers were also clamped in order to avoid any changes to GI sensitivity caused by hyperinulinaemia (Søfteland et al., 2011). A custom-made 40-cm-long probe with stainless steel electrodes mounted on the tip was used (Ditens, Århus, Denmark). Detailed information on the probe has been described previously (Brock et al., 2008). An enema containing docosat and sorbitol (Klyx®; Ferring, Copenhagen, Denmark) was administered 30 min prior to the experiment. Subjects rested on their left side. Stimulation was carried out via an 8.5-cm-long anoscope (Cat. No. E-03. 19. 925; Heine Optotechnik, Herrsching, Germany) in position. The stimulation probe was advanced through the lumen of the anoscope and positioned for stimulation at the rectosigmoid junction (Brock et al., 2010). Electrical stimulation was delivered by a computer-controlled constant current stimulator (DIGITIMER Ltd., Welwyn Garden City, United Kingdom). To ensure sufficient mucosal contact and the right position, the probe was hand held and the impedance across the electrodes was kept below 2 kΩ

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