

Addressing the comments from the reviewers to the paper:

Brain Changes in Diabetes Mellitus Patients with Gastrointestinal Symptoms

Dear Editor Fang-Fang Ji,

We appreciate the constructive comments from the reviewer and these have been addressed accordingly in the point-by-point response below and in the original edition attached. Revisions in the manuscript are highlighted. We hope that you consider the revised manuscript acceptable for publication in "World Journal of Diabetes" (resubmission of manuscript ID: 21452)

On behalf of all authors

Anne Mohr Drewes

Reviewers' Comments to Author:

Reviewer # 1

The study entitled: "Brain Changes in Diabetes Mellitus Patients with Gastrointestinal Symptoms" is an interesting review about this limited matter not very studied in the medical literature. The authors analyse the relationship between brain changes in patients with gastrointestinal symptoms with diabetes mellitus especially with EEG and show changes in the insula and in relationship with other cerebral changes. They thought that in the future patients with gastrointestinal symptoms would be treated based on modulation of the central nervous system reorganisation, either pharmacologically or with afferent nerve stimulation.

Our reply: We thank the reviewer for the positive comments

Reviewer # 2

The paper is scientifically accurate and requires small changes. PLEASE see comments.

Our reply: We thank the reviewer for the thorough edits and suggestions for grammatical improvements. These have all been corrected in the revised manuscript

Reviewer # 3

This is a well-written and comprehensive review on a new and understudied topic, i.e. the interplay between central nervous system and gastrointestinal symptoms in patients with diabetes mellitus. It would be interesting if the authors added a small section regarding the potential role of currently used antidiabetic agents in the management of gastrointestinal symptoms in diabetic patients and the mechanisms implicated in these effects.

Our reply: We appreciate the comments and have now added the suggested section 6 about antidiabetics in the management of gastrointestinal symptoms. It reads: “Many antidiabetics can potentially protect against harmful changes in the CNS. Hence, according to the pathophysiology section above improved blood sugar control and sparing of exogenous insulin will likely result in less neuronal damage. Furthermore, new antidiabetics such as the incretin hormone GLP-1 may be beneficial. Despite its insulinotrophic actions it has many unexplored extra-pancreatic effects. Hence, GLP-1 receptors are, in addition to the pancreas, found in the heart, lungs, kidneys and elsewhere in the gastrointestinal tract, and its function in many of these locations is not yet fully understood (Bak et al. 2011). In the central nervous system it primarily affects stimulation of glucose-dependent insulin secretion (Holst and Gromada 2004) and inhibition of glucagon secretion (Orskov et al. 1988). Interestingly, GLP-1 also acts as a neuropeptide with direct effect on regulation of vagal activity, consequently modulating the homeostatic regulation of the gut. (Orskov, Holst, & Nielsen 1988). Recently, potential neuroprotective function through activation of the GLP-1 axis has received more attention (Holst et al. 2011), and GLP-1 expression has been identified in neurons of the nodose ganglion including sensory afferents critical to many autonomic reflexes. Furthermore, diabetes patients with autonomous neuropathy were shown to have altered incretin effect as compared to patients without neuropathy (Kazakos et al. 2008). Therefore - although it is not recommended to use GLP-1 agonists in patients with diabetic gastroparesis – such drugs may be neuroprotective and human studies are highly warranted.”