

PEER-REVIEW REPORT

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Title: Alzheimer's disease and type 2 diabetes mellitus: Pathophysiologic and pharmacotherapeutics links

Reviewer's code: 02991432

Position: Peer Reviewer

Academic degree: MD

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Reviewer's Country/Territory: Italy

Author's Country/Territory: Venezuela

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In the Manuscript, titled "Alzheimer's disease and type 2 diabetes mellitus: pathophysiologic and pharmacotherapeutics links", Rojas M et al. summarize the current knowledge on the association between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD), focusing on pathophysiological mechanisms and therapeutic approaches that can overlap and address both diseases. The topic is very interesting for the scientific community, but some aspects of the manuscript need to be extensively improved. I strongly advice the authors all the following major and minor remarks.

Major revisions: Authors state that insulin resistance may contribute to the pathogenesis and development of AD and describe key evidence and ongoing trials on the effects of anti-diabetic drug on cognitive disorders. - A long-term condition of insulin resistance may not result in long-lasting diabetes. What are the evidences on the association of insulin resistance (without hyperglycemia) and Alzheimer's disease? - The authors list the effects of different anti-diabetic drugs on cognitive status. Effect of diet and exercise should also be included, as they are the first choice of treatment in insulin-resistant patients with and without diabetes. - Some authors have suggested that the latest antidiabetic drugs, the SGLT2 inhibitors, may exert neuroprotective effects by acting on synaptic plasticity. I recommend including SGLT2 inhibitors in the overview of potential beneficial drugs. - Regarding antidiabetic drugs, molecules with well-known hypoglycemic effects are mentioned (insulin, sulfonylureas). However, hypoglycemia represents a serious side-effect of these therapies, leading in some cases to major cardiovascular events or death. Moreover, repeated episodes of hypoglycemia are linked to cognitive decline. This aspect should be emphasized, as it represents a limitation to the use of these drugs in the treatment of cognitive problems. Minor revision - Moreover, numerous complications have been associated with Alzheimer's disease, among which



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are renal disease[6], retinopathy[7], dermatopathy[8], peripheral vasculopathy[9], and cognitive alterations[10]. These complications have been associated with T2DM, not with Alzheimer's disease. The manuscript is well written, but it should be revised by a native English speaker, for example: - in 4.1 Other factors, such as the MAPK pathway, GSK-3, insulin-degrading enzyme (IDE), and microvascular dysfunction, also have an important role in tau hyperphosphorylation has to be replaced with: play an important role.