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Reviewer 2: This is a very comprehensive mini-review on the multiple contributors in AD pathology and how to link these factors together. The manuscript can be improved by adding a bit more on the basics of metabolism of iron.

Response: The basics regarding the metabolism of iron have been added.

Reviewer 3: My major criticism is, that the title is overly ambitious and not reflecting the scientific content of the mini-review (to address what the title reads is far beyond the scope of a mini-review anyway). There is not enough scientific evidence to support the central role of thrombin in AD pathogenesis and thrombin inhibitors as major therapeutic drugs. As the authors declare in the cover letter, the presented findings and hypotheses are not new, and their major input is to link the possible pathways (see Figure). The Reviewer thinks this complex and poorly understood problem (i.e. AD pathogenesis) is rather oversimplified in the manuscript and therefore misleading for the non-expert readers.

Response: My co-authors and I are aware of the fact that this mini-review renders the multiple etiopathogenic pathways of Alzheimer's disease oversimplified but , as a matter of fact, this is a major objective that guided us through the redaction of this manuscript and we need to remain simple in our approach of the subject in order for us to be able to prove, more clearly, that all these pathways are inter-related.

Reviewer 4: This manuscript provides interesting insights into the role of iron in the pathogenesis of Alzheimer's disease (AD) and on the use of thrombin inhibitors as a treatment strategy. The manuscript provided a relatively comprehensive, yet concise, review showing the inter-relationships between vascular dysfunction and AD and the well-studied pathways involved in AD. There are a few editorial suggestions, which may help the reader: P1, L3 (from bottom): change "trialing" to "conducting trials of" P2, L10 (from bottom): change "determined" to "classified" P5, L3: insert comma after "lesions" P5, L18: change "clot forming" to "clot-forming" P6, L16: change "stress related" to "stress-related" and put a comma after "injury" P7, L10: change "As a matter of fact," to "Accordingly," P8, L1-2: put commas after "compounds" and "ensue" P8, L10: put comma after "decompartmentalization" P8, L16-17: change "for" to "that" and "to start focusing on trialing" to "focus on testing" and put comma after "treatments" P8, L20: put comma after "mini-review" P8, L4 (from bottom): put comma after "individuals"



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Response: My coauthors and I have made all the necessary editorial modifications suggested by the reviewer.

Reviewer 5: The authors have addressed nicely to the pathogenesis of AD to the link of dysfunction of neurovascular system. The argument is sound. Nonetheless, such link has been known for a while. Although the authors have mentioned alterations in hypoxic stress, iron metabolism and thrombin, I would suggest an in-depth description of a specific novel molecule(s) that is directly involved. Figure 1 is somewhat difficult to read. Please increase the font size and link every path as a specific route so that it would be easier to follow. Also, specify the meaning of each color-coded box. This would be helpful.

Response: We have added further information regarding dabigatran and have adjusted the figure according to the reviewer's recommendations.



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