**Reviewer 's Confidential Comments to the authors**

This review discusses a possible mechanism for the alternative insulin transporter at the blood-brain barrier, based on the authors' previous research, providing good understanding about the alternative transport system at the BBB. But there are still some questions need to be considered.

**Question1** The background about BBB is too much.

This review focus on insulin transport across the BBB. Of course, the components or roles of BBB should be introduced, but the background of this section is too basic. What's more, the writing is not as clear as the latter part of the review. Especially the paragraph starts from line 102. Different transport systems are not clearly distinguished, like ion channels, active or passive transport. Sentences like “Channels, pores, and carriers typically transport substances……” (line 117) are confusing (Aren't pores a structure of the channel?).

In addition, the authors repeatedly mention in the abstract and introduction part that Identifying the transport system for insulin at the BBB will help control CNS insulin levels in multiple diseases and conditions including Alzheimer’s disease (AD) and obesity. But this part is less mentioned in the main text, perhaps a more direct discussion of the mechanisms or applications related to these disease?

**Question2** Some statements are poorly worded, affecting logic or causing unnecessary misunderstanding. The author needs to check.

Examples are as follows:

**(Line 59)** “The NVU includes microglia, astrocytes, neurons, and mast cells, but it is the astrocytes and pericytes which have received the most attention in regard to their interactions with the BBB.”

Is pericyte also included in NVU? Or it’s one subtype of these cells (microglia, astrocytes, neurons, and mast cells)?

**(Line 102)** “Transport systems can be categorized in various ways and the strict definitions from cellular biology [10, 11] are not always applied in the BBB literature.”

You use reference which published in 1986s and 1987s to give “the strict definitions from cellular biology”? I think cell biology is also evolving.

**(Line 160)** “By investigating insulin BBB transport, independent researchers have identified this transport system is impacted somewhat not surprisingly by metabolic changes, during development and pregnancy, and by exercise and perhaps surprisingly by Alzheimer’s disease and inflammation.”

In AD and inflammatory responses, the permeability of the BBB increases, why “surprisingly”? The following “loss of the BEC insulin receptor had no effect on insulin transport” is more surprisingly.

**(Line 190)** “The involvement of another protein besides the insulin receptor for transporting insulin across the BBB makes evolutionary sense. As the receptor is involved……”

What kind of “evolutionary sense”? No explanation.

**(Line 193)** “The impact of BEC insulin receptor signaling should not be overlooked when investigating insulin interactions at the BBB.”

Insulin interactions with XX? Do you mean “insulin receptor-insulin interactions” or maybe it should be “insulin signaling”?

**Question3** Some sentences lacking references, especially in the second part (Ⅱ.Blood-brain barrier).

Examples are as follows:

(Line 33) “evidence of insulin crossing the brain barriers was identified decades later”

(Line 36) “Once present within the brain……”

(Line 85) “For example, the anti-helminthic ivermectin……”

(Line 96) “The transporters of the BBB also play a homeostatic role for the CNS by regulating electrolyte balance……”

(Line 105) “Many BBB transporters, such as the……”

……

**Reviewer's Confidential Comments to the Editor**

This review discusses a possible mechanism for the alternative insulin transporter at the blood-brain barrier, based on the authors' previous research, providing good understanding about the alternative transport system at the BBB.

However, the author should pay more attention to accuracy of the wording, and the writing of the background part needs to be improved. It is recommended to revise before accepting.