OPEN PEER REVIEW REPORT 1

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Title: OBESITY: Implications for neural diseases
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COMMENTS TO AUTHORS

In the current review manuscript, the authors focused on a novel and important topic and systematically reviewed recent discoveries on obesity, its potential pathogenetic mechanisms and its relationships with some neurological diseases. Although the chosen topic is innovative and timely and will be of great interests to extensive readers, the manuscript overall is ambitious, seems more focused on obesity and adipose tissue instead of neural diseases, and misses considerable key components or research in the field. My major comments and suggestions are listed below:

1. First, the title of the review seems not accurate and does not match its contents well, in several aspects:
A) Although the topic is on obesity, but the authors need to keep in mind that obesity is a very complicated condition, with diet, environment and genetic factors involved, and are caused by both the central (likely the major part) and the peripheral dysfunctions. Obesity has also many complications including endocrine dysregulation and cardiovascular diseases, which can also contribute to neural problems. For example, in a rare genetic disease condition called "Prader-Willi Syndrome", both obesity and neural cognitive dysfunctions are observed. The current manuscript actually only focused on one slim part of obesity, i.e. the diet-induced obesity, adipose dysfunction and its related systematic inflammation. Therefore, a title like "Adipose tissue, systematic inflammation and neural diseases" seems more appropriate.
B) Similarly, "neural diseases" is also a big term. The currently manuscript spent a lot of pages describing adipose tissue and its relationship with inflammation but barely touched the neural system, the pathogenesis of the mentioned neural diseases, and where the two conditions may crosstalk, except for the central inflammation. The authors indeed mentioned the relationship of obesity and some diseases including depression, AD, and Parkinson's Disease and some conditions in model animals. However, these diseases are just a tip of an iceberg above the surface for all neural diseases. Maybe "neurodegenerative diseases" is a more accurate description.

2. At this moment, although accumulating epidemiological evidence has suggested that in obesity population, higher incidences of many neurological disorders are observed, the causal evidence, however, is still missing. Whether inflammation in the brain, although being studied as an important contributor, causes these neurological diseases has not been established, yet. In this context, the axis that authors proposed in the manuscript, i.e. obesity - adipose tissue - inflammation - neural diseases, can only be one possibility. Given this, many other possibilities, particularly the major ones, shall at least be discussed and brought to readers' attention as a balanced review, such as, shared vulnerable genes, signal pathways (insulin signaling in the hippocampus, for example), or shared microbiome dysbiosis.

3. The authors discussed some interesting findings made recently that obesity causes inflammation in the brain, particularly in the hypothalamus. Although this is an intriguing mechanism, whether it links obesity with neurological diseases is still unknown. Particularly, Depression, AD and PD are caused by

dysfunctions of different brain regions and in different neuronal types outside of the hypothalamus. Whether obesity causes similar inflammation in these brain regions as that in the hypothalamus has not been well studied.

4. In #6, the authors interestingly discussed anti-obesity drugs and their effects on the brain. This is an innovative aspect and could be a great indirect support to link the two conditions. However, some key anti-obesity drugs are left undiscussed unfortunately. For example, GLP-1 related drugs, which treats both obesity and diabetes and are believed to work on the brain to achieve the effects. Topiramate is another one. At the same time, it is also known that many neurological drugs have effects on body weight, which unfortunately were left out in the manuscript.

5. Finally, some citations were not accurate or missing. For example, the authors kept citing one review article (Ikeda 2018) for related description of adipose tissue classification and functions. It will be much better if the authors can cite the original research articles or point out that Ikeda 2018 is a great review paper and summarize all the related resource if readers need to learn more.