Format for ANSWERING REVIEWERS

June 3, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16808-review.doc).

Title: Hypocretin (Orexin) Pathology in Alzheimer's Disease

Author: Thomas C Thannickal

Name of Journal: ***World Journal of Neurology***

ESPS Manuscript NO: 16808
The manuscript has been improved according to the suggestions of reviewers:

Reviewed by 00646534 (Review 1)

1. The author describes the overview of the hypocretin system as well as the relation between hypocretin and neurological disorders with particular attention to Alzheimer's disease (AD). However, it is unclear what the focus of this review article is.
Response: The editorial is focused on role of hypocretin in Alzheimer's disease.
2. It appears that the introductory part describing the overview is too long and detailed, while the part describing the relation between hypocretin and AD is rather superficial and incomplete.
Response: According to reviewer suggestions the length of the overview is reduced and relation between hypocretin and Alzheimer's disease explained in more detail.
3. On the relation between hypocretin and AD, the author should be more careful about the organization of the manuscript. For example, the part "Dysregulation of Hypocretin System Associated with AD" should be revised extensively to describe the previous studies more in detail. More references should be cited in this part.
Response: The part "Dysregulation of Hypocretin System Associated with AD" is revised and more references cited.
4. It may help readers' understanding to present a diagram or a schema.
Response: Figure 1 shows the distribution of hypocretin neurons in human hypothalamus.
A table added to show the important findings of hypocretin in Alzheimer's disease
5. The part "Hypocretin as a CSF biomarker" is also not comprehensive, because the author does not describe the previous work correctly.
Response: This part is revised accordingly.
6. Abstract and Conclusions should also be corrected extensively to convey in a more informative manner the current view about the relation between the hypocretin system and AD.
Response: Abstract and conclusion part is revised.
7. It is not clear how important the part on the general functions of the hypocretin system

is in this paper. It seems better to omit the parts not directly related to the main theme of this paper.
Response: Functions of the hypocretin system is removed.

Reviewed by 00646541 (review 2)

1. The running titled, need to be shorter. Example: Hypocretin and Alzheimer's disease.
Response: changed to Hypocretin and Alzheimer's disease
2. Define the abbreviation Hcrt and PVN.
Response: Hypocretin - Hcrt, paraventricular nucleus - PVN
3. Avoid repetitive abbreviations AD.
Response: Use of repetitive abbreviations avoided.
4. In the sentence: "The pathogenesis of AD may therefore involve dysregulation of the Hcrt system", is needed show that the pathogenesis of AD is multiple and complex, including the large description of the functions of the hypocretin in other systems need to be shorter because the title of the editorial is related to a specific topic.
Response: The functions of the hypocretin system removed and focused on Alzheimer's disease.
5. In this sentence:" Two post-mortem autopsy studies showed a variable (85–100%) loss of hypocretin mRNA and absence of hypocretin peptides in the hypothalami of patients with narcolepsy", what type of narcolepsy?.
Response: It is changed to narcolepsy with cataplexy.
6.In: CSF Hcrt-1 levels are found to be normal in most patients with sleep-wake disorders other than narcolepsy with definite cataplexy, including patients with narcolepsy without cataplexy, idiopathic hypersomnia, fatal familial insomnia, and Kleine–Levin syndrome[18,19,24,30].
Response: This sentence is removed.
7. Low CSF Hcrt-1 levels have been reported on rare occasions in patients with narcolepsy without cataplexy, idiopathic hypersomnia, and symptomatic narcolepsy/hypersomnia in association with diencephalic stroke, hypothalamic neoplasms, and acute disseminated encephalomyelitis Is possible to combine: CSF Hcrt-1 levels are found to be normal or low in ….Also, why there are several paragraphs to list all the neurological diseases with low CSF Hcr-1.
Response: The sentence is modified and this part made into one paragraph.
8. In this study, we assessed whether the neurodegenerative process of AD also affects hypothalamic hypocretin/orexin neurons. This sentence is incorrect because is an editorial.
Response: The sentence is modified and reference cited.
9.In the section: Coexistence of narcolepsy and Alzheimer's disease", what is the prevalence of narcolepsy in AD patients.
Response: The reported study showed 33% prevalence of Alzheimer's disease in narcolepsy with cataplexy.
10. Justify why is needed to search other new biomarker in AD.

Response: CSF hypocretin levels were directly correlated with t- tau protein levels in the AD. With a rising prevalence of Alzheimer's disease around the world, there is an urgent need to identify opportunities for prevention and treatment of the disease.

11. "The preclinical AD is a stage without cognitive abnormalities", I think that is incorrect because the MCI is the key hallmark of this stage.

Response: This sentence is removed.

12. The sleep as biomarker is vague, what is the role of the PSG recordings? Sleep in normal or pathological stages?, in both what stage REM sleep and other?

Response: This part is removed and focused on hypocretin.

Reviewed by 00401043 (review 3)

1. The manuscript is too long and redundant in some parts. The author should shorten the text by omitting somewhat peripheral material.

Response: **Response**: The length of the manuscript is reduced and redundant parts removed.

2. Conclusions should be expanded as well as conflicting results should be better discussed. In particular, conclusions of chapter "Hypocretin as CSF biomarker" is unrelated to the study previously discussed (severe Alzheimer's disease versus preclinical stage).

Response: Conclusions expanded and conflicting results detailed.

3.The Author should add additional impressive Figures and informative Tables for better understanding.

Response: Figure showing the cell groups in the arousal mechanism is removed and a table showing important relationship between hypocretin and Alzheimer's disease is included.

4. Even if the Author is from US, the quality of written English needs some language corrections.

Response: Made a major revision of the manuscript.

Sincerely,

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