

December 3rd, 2014

Dear Editor

Please find enclosed the edited manuscript in Word forma (file name: [14951_revisel_review](#))

- Title: Effects of exercise on brain functions in diabetic animal models
- Author : Sun Shin YI
- Name of Journal: *World Journal of Diabetes*
- ESPS manuscript No: 14951

The manuscript has been improved according to the suggestions of reviewers:

Reviewer #1

- **Comment 1:** The author should focus the effects of exercise on the brain in diabetic models in greater detail. In addition, it would be better to revise the tables to focus the effects of exercise on the brain in diabetes.
- **Answer:** I appreciate your great suggestion. First of all, I agree that the reviewer's comments that it would be better to re-edit the tables focusing the effects of exercise on the brain in diabetes. The tables in the manuscript have introduced many kinds of pathologic and genetic factors triggering different diabetic pathologic fates in the animal models. Those destinations of the disease are considered extremely important in clinic against human DM patients. Therefore, I'd like to show the many animal models can connect with the measuring of brain function potentially in the future. I expect the all the animal models in the table can be applied in exercise studies, although few evidence yet has performed exercise studies with those DM represented animals. According to the reviewer's comments, I additionally inserted the expecting uses with those animal exercise models in the Table 3 and indicated with [blue color](#) in the table.

Reviewer #2

- **Comment 1:** In the section "DM and Brain", it should be divided into multiple sub-heading such as "DM and peripheral nervous system (PNS)" and "DM and central nervous system (CNS)". The main heading should read "DM and the neural system.

☞ **Answer:** For more specific heading for relationship between DM and nervous system, according to reviewer's comment, the author renamed "DM AND THE NEURAL SYSTEM", and the sub-heading titled with "1) DM and central nervous system (CNS)" and "2) DM and peripheral nervous system (PNS)". The Title and sub-title are indicated with [blue color](#). In addition, I placed the "Hyperphagia and leptin regulation governing by brain and hippocampal neurogenesis" moving into the 1) DM and central nervous system (CNS). [The author indicated the part with blue colors in the manuscript.](#)

- **Comment 2:** The effect of forced exercise on neurobehavior should be mentioned as separate section of paragraph

☞ **Answer:** The effect of forced exercise on neurobavior is very interesting and practical issues in diabetic condition as well as in normal physical condition. Common advantages and differences between voluntary and involuntary exercises were introducing in the manuscript with parallel structure. The author has been thinking

it is not a bad structure of description. However, the author separated a paragraph about forced exercise on page 11 according to the reviewer's comments.

- **Comment 3:** The exercise-induced stress behavior often explains why the beneficial effects of exercise are not observed in certain behavioral test. More information on DM and stress-related behavior as well as aberrant HPA function (Glucocorticoids as stress hormones) should be presented or diagramed (i.e., to answer how DM induces stress behavior).

☞ **Answer:** The points that the reviewer's indicated is very important. The exercise-induced stress behaviors have been observed different at the many studies due to various governing of hormonal homeostasis by HPA axis regulation. It is recognized that the amount of psychological stress that an animal encounters determines the degree of response of the hypothalamic-pituitary-adrenal (HPA) axis. It has been reported that animals performing an exercise at the stress-induced physiological and environmental factors can be affected. Therefore, there would be enough possibilities to show different effects of various kinds of stress in exercise animal models such as metabolic DM and psychological depression/anxiety disorders. Cayado et al.(2006) reported that different training showed different exercise effects at the horse exercise training. Martinez-Mota et al.(2011) indicated that the HPA axis response can be different according to sex and age at the exercise animal model. I added the several sentences have the above information about the rationales of different HPA axis regulation in the manuscript and indicated that with blue color at the page 8.

- **Comment 4:** Regarding myokines, it is better to provide evidence that these myokines can pass the blood-brain barrier into the CNS.

- **Answer:** The evidence that myokines can across the BBB is a very important thing can support that myokines can affect and influence the brain microenvironments. Therefore, I added the follow sentence in the manuscript at page 13~14 according to the reviewer's request; "IL-6 can also alter brain function after peripheral administration, moreover, some myokines might be able to cross the blood-brain barrier (BBB)"

- **Comment 5:** On page 12 of the manuscript; "Both T2DM and neurodegenerative disease are associated with impaired glucose tolerance and cognitive decline in the human and animal studies". The cited references are missing.

☞ **Answer:** The author inserted the missing reference in the manuscript according to the reviewer's comment.

Thank you again for publishing my manuscript in the *World Journal of Diabetes*

Sincerely yours



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