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LETTER TO THE EDITOR

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Cognitive Function is Impaired by Obesity and Alleviated by Lorcaserin Treatment in Mice

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Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most common type of dementia in the elderly population. Much effort has been investigated in the risk factors of early onset of AD. Accumulating evidences have shown that western sedentary lifestyle may lead to cognitive dysfunction [1]. Childhood and adult obesity is increasing dramatically and obese individuals who show early impairment of cognitive performance could have earlier onset of dementia.

As for the treatment of obesity, diet and exercise have been the mainstays of weight management in the obese population, but with limited efficacy [2]. Thus, other treatment modalities and medications might be required for some patients. Orlistat, an inhibitor of pancreatic lipases, has been the only remaining anti-obesity drug till June 2012 when lorcaserin (a selective 5-HT_{2C} receptor agonist) was approved by the FDA. We initiated this study to determine whether cognitive dysfunction was linked to obesity and anti-obesity medications.

Diet-induced obese mouse model was established using 40% high fat diet as previously described [3]. We adopted Morris water maze (MWM) to evaluate spatial learning and memory in C57BL/6 mice. Oxidative stress in the mouse hippocampus was assessed by dihydroethidium (DHE) fluorescent staining. Function to adhesion/migrate of bone marrow endothelial progenitor cells (EPCs) and endothelium-dependent vasodilation of thoracic aortae was evaluated to examine endothelial function in mice [4].

Obese mice exhibited impaired cognitive function in mice, which could be partially restored by lorcaserin or orlistat treatment. Latency of obese mice at the 5th training day was significantly longer than that of control mice; lorcaserin/orlistat significantly shortened the latency in anti-obesity treated obese mice (Figure 1A). When the hidden platform was removed, mice in obese group spent less time and distance in the original target quadrant compared with the control group; Lorcaserin/orlistat treatment significantly increased percentage of time and distance in the target quadrant in obese mice (Figure 2B). Furthermore, DHE staining assay showed that lorcaserin/orlistat treatment alleviated obesity-exacerbated oxidative stress in the hippocampus of C57BL/6 mice.

We also found that dietary obesity significantly impaired EPCs function and the endothelium-dependent vasodilation of thoracic artery, which could be restored by lorcaserin/orlistat. Lorcaserin/orlistat significantly ameliorated obesity-impaired BM-EPCs capacity to adhere (control: 1.00 ± 0.054, HFD: 0.805 ± 0.043, HFD + orlistat: 1.14 ± 0.102, HFD + lorcaserin: 1.23 ± 0.078; $P < 0.01$, Figure 2A) and migrate (control: 1.00 ± 0.072, HFD: 0.538 ± 0.051, HFD + orlistat: 1.13 ± 0.121, HFD + lorcaserin: 1.38 ± 0.102, $P < 0.01$, Figure 2B). Endothelium-dependent vasodilation of mouse artery was significantly impaired by obesity and restored by lorcaserin/orlistat administration ($P < 0.01$; Figure 2C).

Obese individuals could have decreased life expectancy and increased cardiovascular risks including diabetes, hypertension, coronary artery disease, strokes, and even cancers. Recent studies showed that high-fat diet intake interferes with hippocampal functioning [5]. While studies in humans suggest that obesity is associated with disruptions in cognitive ability, results from animal studies were a little confusing, with some reports describing significant effects of obesity on performance in the Morris maze and others failing to detect effects of obesity on spatial learning. In the basis of previous studies, we conducted this study. It is shown that lorcaserin significantly alleviated obesity-impaired spatial learning/memory ability in DIO mice. This finding might be

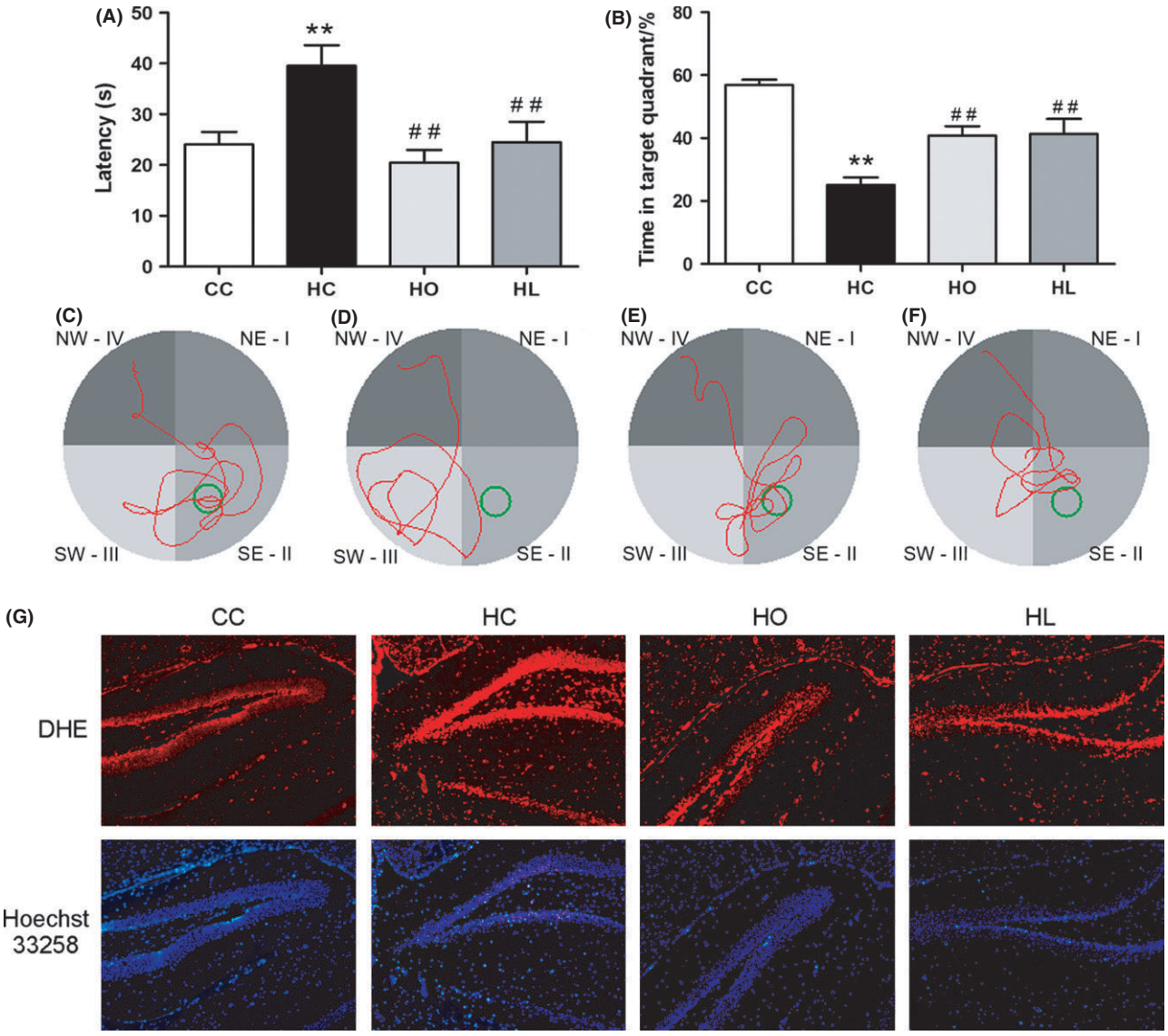

Figure 1 Obesity impaired spatial learning/memory ability in C57BL/6 mice and induced oxidative stress in the hippocampus (**A**–**F**). Obese mice showed shorter latency to original platform site (**A**) and lower percentage of time in target quadrant (**B**) compared to control (**C**–**F**). Representative swimming tracks of control group (**C**), HFD group (**D**), orlistat group (**E**) and lorcaserin group (**F**). (**G**) Representative staining of dentate gyri of the hippocampus with DHE and Hoechst 3325. Magnification: 50×. HFD mice exhibited a higher level of the hippocampal ROS compared to control. (CC: control diet; HC: high-fat diet; HO: high-fat diet + Orlistat; HL: high-fat diet + Lorcaserin). Values are means ± SEM. (*$P < 0.05$, **$P < 0.01$ vs. control diet, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. High-fat diet, n = 6, 12 for each group).

clinically significant to lift the life quality of obese Alzheimer's patients.

Accumulating studies are showing that oxidative stress is closely connected to impaired cognitive function [6]. It is reported that after prolonged cerebral hypoperfusion, oxidative stress interferes with white matter repair by disrupting renewal mechanisms, thus deteriorating cognitive function [7]. Increase of brain oxidative stress in mild cognitive impairment could serve as a predictor of Alzheimer's disease. Moreover, oxidative stress is one of the risk factors of endothelial dysfunction. Obesity is characteristic of aggravated oxidative stress, thus we postulated that obesity might lead to cognitive dysfunction at least partially owing to aggravated oxidative stress.

Cognitive dysfunction is frequently seen in subjects with endothelial impairment [8]. It is reported that both type I and type II diabetes mellitus have been associated with reduced performance on numerous domains of cognitive function [9]. In research of Alzheimer's disease, a prevailing theory is that vascular disorder is an important pathogenesis. The emerging view is that cerebrovascular dysfunction is a feature not only of cerebrovascular diseases, such as stroke, but also of neurodegenerative conditions, such as AD [8,10]. This article manifested that obese mice with

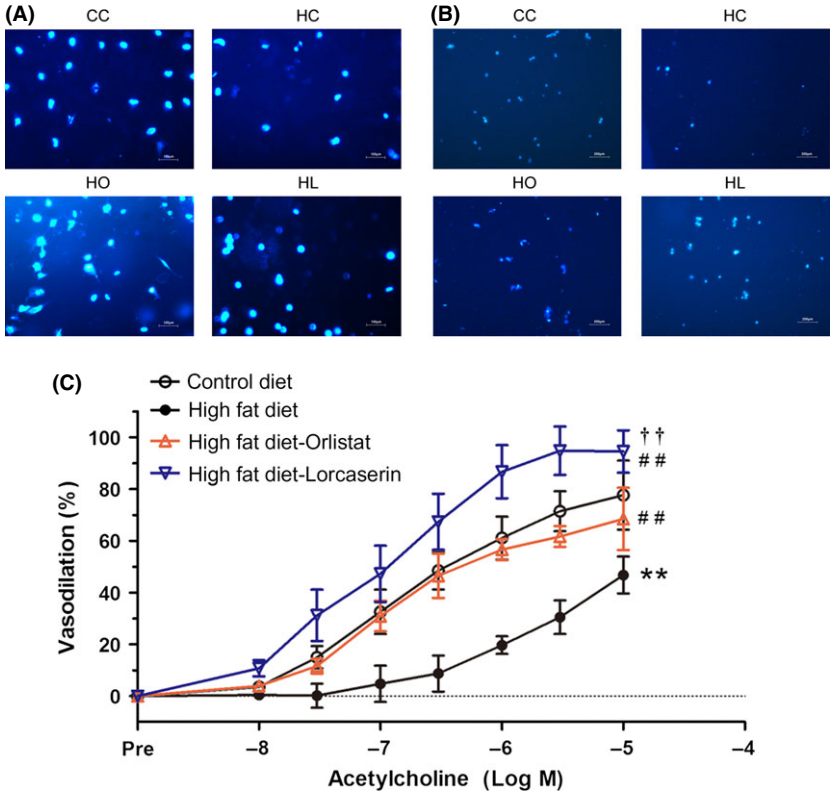

Figure 2 Obesity impaired BM-EPCs function and endothelial-dependent vasodilation in C57BL/6 mice. (**A**). Obesity significantly impaired adhesion ability of BM-EPCs in mice. Magnification: 100× (**B**). Obesity significantly impaired migration ability of BM-EPCs in mice. Magnification: 50× (**C**). Obesity significantly impaired thoracic aortae endothelium-dependent vasodilation in mice. (CC: control diet; HC: high-fat diet; HO: high-fat diet + Orlistat; HL: high-fat diet + Lorcaserin.) Values are means ± SEM. (*$P < 0.05$, **$P < 0.01$ vs. control diet, $^{\#\#}P < 0.01$ vs. high-fat diet, $^{\dagger\dagger}P < 0.01$ vs. High-fat diet + Orlistat, n = 6 for each group).

endothelial dysfunction showed impaired cognitive function, providing another evidence of direct link between endothelial dysfunction and cognitive impairment.

In summary, we report that consumption of HFD induced cognitive dysfunction in mice that were susceptible to DIO, which could be restored by lorcaserin/orlistat administration. This work also identifies a potential link between endothelial dysfunction and cognitive dysfunction in obese subjects.

Acknowledgments

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Conflict of Interests

The authors declare no conflict of interests.

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