

**Figure** **S1.** The effects of PS128 supplementation on anxiety behavior in 3×Tg-AD mice treated with icv-STZ. (A) The timeline of PS128 and icv-STZ treatment in mice. (B) Peripheral blood glucose levels in mice. The peripheral blood glucose levels were not different among all groups on day 47 (n = 15–20 animals /group). (C) The total distance traveled was not different among the groups, indicating the lack of a significant difference in the exploratory activity of all the groups (n = 15–20 mice/group). (D) The time spent in the central zone was not different among the mice in all groups (n = 15–20/group). (E) The time spent in the open arms was also not different among the mice in all groups (n = 15–20/group). These results indicated no difference in the anxiety behaviors of all the groups. The data presented as the means ± SEM. OFT, open field test; EPM, elevated plus maze; MWM, Morris water maze; BG, blood glucose; SCFA, short-chain fatty acid.



**Figure** **S2.** The effects of PS128 supplementation on the levels of the tau (pS202), IDE, and NEP protein expression in 3×Tg-AD mice treated with icv-STZ. (A) Representative image of western blots. (B-D) Quantitative densitometry results for the ratios of tau (pS202)/Ht7 (total tau), IDE/GAPDH, and NEP/GAPDH. GAPDH served as the internal control. The quantitative data are presented as the means ± SEM (n = 5–8 mice/group). IDE: insulin-degrading enzyme, NEP: neprilysin.

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**Figure S3.** Original Uncropped Western blots for GSK3β related protein. (A) GSK3β (pS9), (B) GSK3β, and (C) GAPDH. (*a, b, c)* for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*d, e, f)* for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.

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**Figure S4.** Original Uncropped Western blots for phosphorylated Tau protein. (A) pT231, (B) HT7 (total tau), and (C) GAPDH. (*a, b, c*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*d, e, f*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.



**Figure S5.** Original Uncropped Western blots for 6E10 protein. (A) 6E10, and (B) GAPDH. (*a, b*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*c , d*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.



**Figure S6.** Original Uncropped Western blots for BACE1 protein. (A) BACE1, and (B) GAPDH. (*a, b*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*c , d*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.



**Figure S7.** Original Uncropped Western blots for AβPP protein. (A) AβPP, and (B) GAPDH. (*a, b*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*c, d*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.



**Figure S8.** Original Uncropped Western blots for PSD95 protein. (A) PSD95, and (B) GAPDH. (*a, b*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (*c, d*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.



**Figure S9.** Original Uncropped Western blots for synaptophysin protein. (A) Synaptophysin, and (B) GAPDH. (*a, b*) for B6 mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline. (c, *d*) for 3×Tg-AD mice 1st-2nd lane: Saline/icv-Saline; 3rd-4th lane: PS128/icv-Saline; 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. 5th-6th lane: Saline/icv-STZ, 7th-8th lane: PS128/icv-STZ. Arrow indicated band site.