## **Supplementary Material**

## **Zibotentan, an Endothelin Alzheimer’s Disease Receptor Antagonist, Prevents Amyloid-β-Induced Hypertension and Maintains Cerebral Perfusion**

## **Supplementary Figure 1. Change in blood pressure, heart rate, and respiratory rate in Wistars after Aβ40 or saline infusion.** Change in systolic, diastolic, and mean blood pressure (SBP, DBP, MBP), heart rate (HR), and respiratory rate (RR) after Aβ40 (*n*=20) and saline (*n*=11) infusion. Each data point represents the group mean value on a given day during infusion. Best-fit linear regression (solid) and 95% confidence interval (CI) (dotted) lines are shown. A sum-of-squares *F*-test of best-fit regression lines tested the null hypothesis (H0) that a single linear regression line could fit the combined data sets for the change in HR, RR, MBP, SBP and DBP, relative to baseline, after infusion of Aβ or saline. H0 was rejected for each comparison. There was a significant effect of Aβ infusion on (a) MBP (*F*2,615 = 11.7, *p* < 0.0001), (b) SBP (*F*2,615 = 16.2, *p* < 0.0001), (c) DBP (*F*2,615 = 5.23; *p* = 0.0056), (d) HR (*F*2,615 = 5.58; *p* = 0.0040) and (e) RR (*F*2,615 = 65.7; *p* < 0.0001). These findings reflect increases in BP, HR, and RR in the Aβ40 infusion group compared to little change or a slight decline with time in the saline group.



**Supplementary Figure 2. Change in blood pressure, heart rate, and respiratory rate after Aβ40 or saline infusion in Wistars administered Zibotentan.** Change in systolic, diastolic, and mean blood pressure (SBP, DBP, MBP), heart rate (HR), and respiratory rate (RR) after Aβ (*n* = 6) and saline (*n* = 9) infusion in Wistars on Zibotentan. A sum-of-squares *F*-test of best-fit regression lines tested the null hypothesis (H0) that a single linear regression line could fit the combined data sets. With Zibotentan administration, there was no significant effect of Aβ infusion compared to saline in (a) MBP (*F*2,305 = 0.0140, *p* = 0.986), (b) SBP (*F*2,305 = 0.400, *p* = 0.671), (c) DBP (*F*2,305 = 0.0248, *p* = 0.976), (d) HR (*F*2,305 = 0.546, *p* = 0.580), and (e) RR (*F*2,305 = 1.61, *p* = 0.201). A shared best-fit line is shown for all measurements. The fluctuations in telemetry data around day 20 coincided with recovery from carotid flow probe surgery.



## **Supplementary Figure 3. Change in heart rate and systolic blood pressure variability following Aβ40 or saline infusion.** Change in heart rate variability (HRV) and systolic blood pressure variability (SBPV) following Aβ (*n* = 12) or saline (*n* = 9) infusion. A combined best-fit line is shown for both infusion groups when the H0 was accepted (*p* ≥ 0.05: a, b, c, e, f, h). Separate lines for Aβ- and saline infusion groups are shown when the H0 was rejected (*p* < 0.05: d, g). There were no significant effects of Aβ infusion on the (a) very low frequency (VLF) (*F*2,321 = 0.024, *p* = 0.976), (b) low frequency (LF) (*F*2,320 = 1.39, *p* = 0.252), or (c) high frequency (HF) (*F*2,320 = 0.157, *p* = 0.855) components of HRV. There was a significant effect of Aβ infusion on (d) VLF (*F*2,331 = 4.62, *p* = 0.0105), but no change in the (e) LF (*F*2,331 = 0.546, *p* = 0.580), or (f) HF (*F*2,321 = 2.96, *p* = 0.0533), components of SPBV. There was a significant difference in the change in mean baroreceptor gain (Mn.BRG) (g) positive ramps (*F*2,264 = 6.12, *p* = 0.0025), but not in the (h) negative ramps (*F*2,264 = 1.75, *p* = 0.176) during Aβ compared with saline infusion. Data are presented as daily group means, with lines of best-fit (solid) and 95% CI (dotted).

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