CHRONIC DOSING OF THE GLP-1 AGONIST SEMAGLUTIDE RESCUES LTP DEFICITS IN THE APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

Joel Shillinglaw, Brian Haner, Kimberly Kerker, Jodi Gresack, Jose Beltran, Herman B Fernandes, Afshin Ghavami, Taleen Hanania

PsychoGenics Inc, Paramus, NJ, USA

ABSTRACT

OBJECTIVE: The dramatic impact of the class of drugs known as GLP-1 agonists on the treatment and outcomes of patients with diabetes and other metabolic disorders has spawned interest in other chronic conditions that may be amenable to these types of interventions. Among these are chronic neurodegenerative disorders, such as Alzheimer's disease. Recent literature reports have suggested that GLP-1 receptor agonists can rescue deficits in neurotransmission observed in the APP/PS1 mouse model of Alzheimer's disease. This double transgenic mouse model overexpresses human forms of the genes coding for amyloid precursor protein (APP) and Presenilin 1 (PS1), allowing for study of progressive pathology related to amyloid deposition. Using this mouse model, we assessed the impact of chronic administration of the GLP-1 agonists liraglutide and semaglutide on performance in behavioral memory tasks, synaptic neurotransmission and plasticity (assessed electrophysiologically in acute brain slices), A-beta isoform levels and chemokine markers of inflammation.

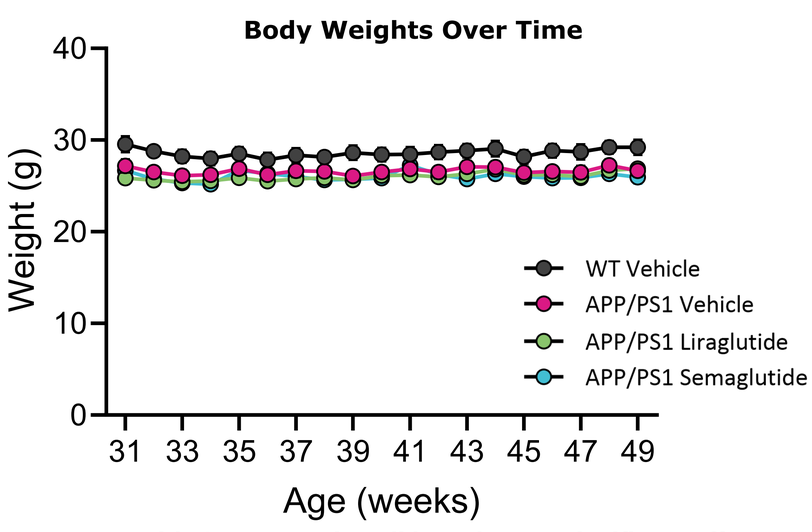
RESULTS: In the Y-maze, spontaneous alternation was lowered in the vehicle-treated APP/PS1 animals compared to the Vehicle-treated WT group, suggesting an impairment in working memory among the APP/PS1 animals. Neither liraglutide nor semaglutide (0.050 mg/kg, SC) rescued spontaneous alternation performance in the APP/PS1 groups. Vehicle-treated APP/PS1 animals made more total arm entries in the Y maze compared to the WT group, consistent with a hyperactivity phenotype among APP/PS1 animals. Treatment with semaglutide, but not liraglutide, normalized the number of arm entries in the APP/PS1 group. Using brain slice electrophysiology to assess hippocampal field responses, we demonstrated that APP/PS1 mice showed deficits in basal synaptic transmission compared to WT animals. Treatment with GLP-1 agonists did not ameliorate this deficit. No changes in basal paired pulse ratio (50 ms interstimulus interval) were noted, nor was it affected by GLP-1 agonists. Brain slices from APP/PS1 animals showed a significant reduction in hippocampal (Schaffer collateral-CA1) LTP compared to WT. Notably, chronic treatment with semaglutide completely ameliorated this deficit, whereas liraglutide did not produce a significant improvement over what was observed in slices from vehicle-treated APP/PS1 mice.

CONCLUSIONS: Here we show that administration of GLP-1 agonists have the potential to alter the disease trajectory in Alzheimer's disease, although positive results were not observed on all outcome measures. Additional studies in tauopathy-focused and other relevant disease models are warranted, as are further investigations into potential mechanisms of action.

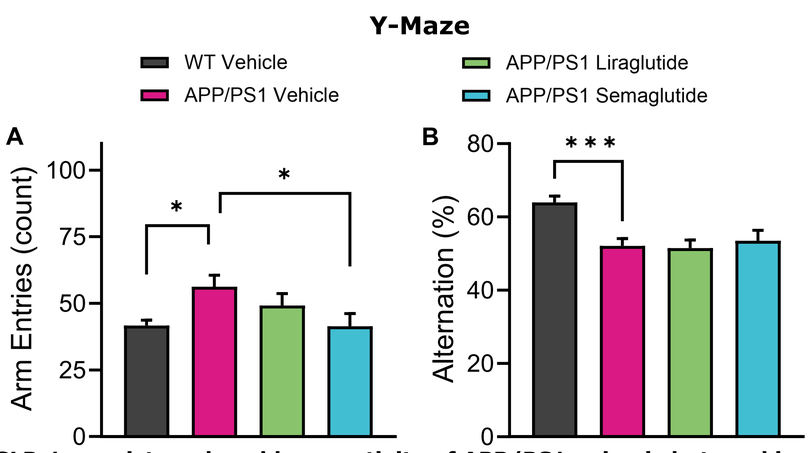
METHODS

Female WT and APP/PS1 littermate mice (bred and subsequently housed at Psychogenics) were dosed daily starting at 7 months of age through 11 months of age with either vehicle, liraglutide (0.93 mg/kg, IP; McClean et al, 2011), or semaglutide (0.05 mg/kg, SC; Zhang et al, 2024). Blood samples were collected via submandibular bleeds at several time points to obtain samples for biomarker assays in plasma. Plasma levels of A-beta 38, 40 and 42 were assessed using meso-scale discovery (MSD) plasma analysis. The same plasma samples were also used for analysis of chemokines associated with neuroinflammatory processes using MSD. One set of animals were assessed on performance in the Y-maze task following 8 weeks of dosing (at ~9 months of age). In another set of animals, electrophysiological assessments were carried out after 16 weeks of dosing (~11 months of age), 24h following the last dose. Acute hippocampal brain slices were prepared, with baseline short-term plasticity and input-output relationships measured. Following a stable baseline period LTP was then induced using 3 trains of 100 stimuli (at 100 Hz), with one train delivered every 5 minutes. LTP was quantified using the average fEPSP slope of the last 5 minutes of a 60-minute window following delivery of the first stimulus train. Body weights over time and survival analysis were assessed including animals from all endpoints.

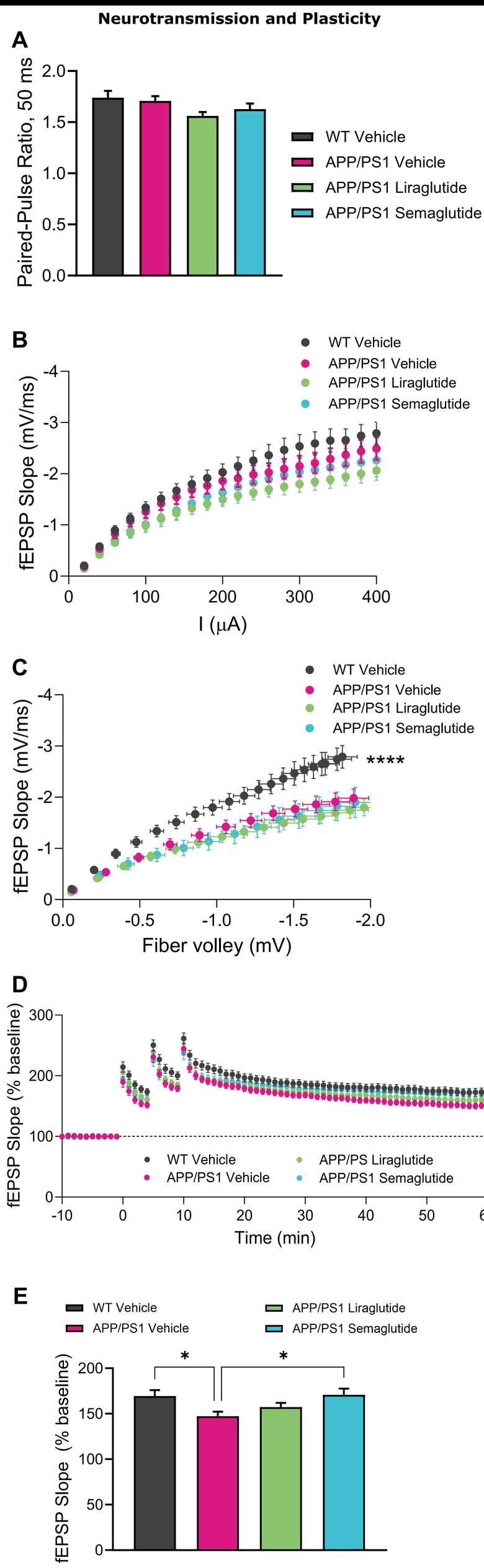
RESULTS



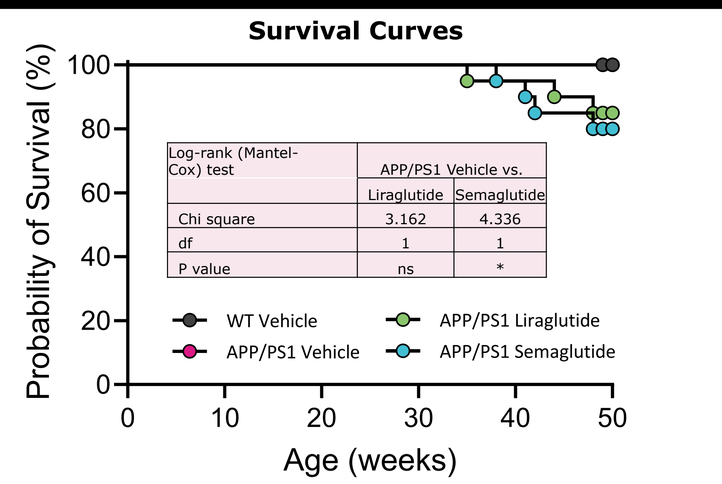
Treatment with GLP-1 agonists did not have a significant effect on body weights over the course of the study. Mixed-effects analysis, Dunnett's post-hoc test (vs. APP/PS1 Vehicle).



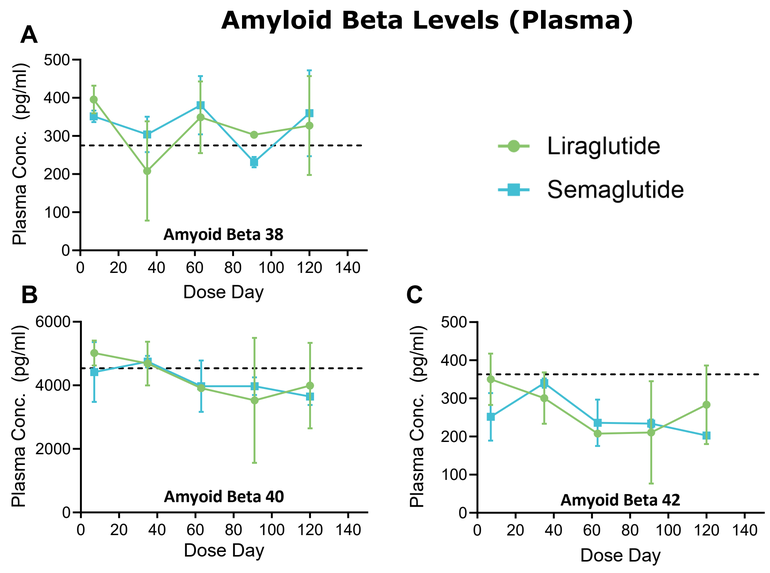
GLP-1 agonists reduced hyperactivity of APP/PS1 animals but working memory was not improved. The total number of arm entries reflects global activity, while alternations between different arms of the maze represent a useful measure of working memory. **(A)** Total arm entries were reduced by semaglutide treatment, reducing activity to WT levels. (**B**) Percent alternations were reduced in APP/PS1 mice, and GLP-1 agonist treatment did not significantly alter this, consistent with a deficit in working memory. *p<0.05, ***p<0.001, 1-way ANOVA, Dunnett's post-hoc test vs. APP/PS1 Vehicle.



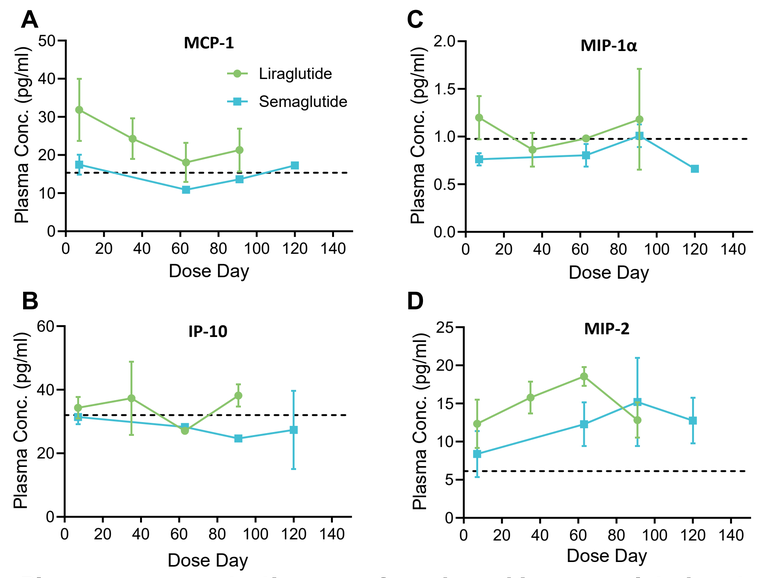
Chronic Semaglutide treatment rescues deficits in hippocampal long-term potentiation (LTP) but not basal synaptic transmission. (A) Chronic treatment with GLP-1 agonists did not affect basal paired-pulse facilitation (short-term plasticity) in APP/PS1 animals. No significant differences were observed across groups. ns, 1-way ANOVA. **(B)** Despite an overall significant Treatment X Stimulation interaction, synaptic input-output relationships were not different at any given stimulus intensity across groups. 2-way RM-ANOVA, Bonferroni post-hoc. **(C)** However, for a given fiber volley amplitude, the postsynaptic fEPSP slope observed in APP/PS1 animals, regardless of treatment, was significantly reduced (*p<0.0001, fitted linear regression). **(D)** Timecourse of LTP (induced as described), demonstrating both a deficit in APP/PS1 (compared to WT Vehicle) and rescue by chronic semaglutide – as quantified in **(E)**, the last 5 minutes of the experiment. *p<0.05, one-way ANOVA, Dunnett's post-hoc test (vs. APP/PS1 Vehicle).



Survival analysis showed no difference between WT and APP/PS1 survival through 50 weeks, although chronic semaglutide treatment had a small but significant impact on survival. Mantel-Cox analysis of survival data (as illustrated by Kaplan-Meier survival curves) found no difference in survival of WT and APP/PS1 animals through 50 weeks, and while a small number of deaths were observed in the group chronically dosed with liraglutide, the number of deaths was not significant.



Plasma levels of amyloid beta isoforms of interest were not altered by chronic GLP-1 agonist administration. Plasma levels of amyloid beta 38 **(A)**, 40 **(B)** and 42 **(C)** did not vary significantly from those observed in vehicle-treated APP/PS1 mice (dashed line) through 120 days of dosing with either liraglutide or semaglutide.



Plasma concentrations of chemokines related to neuroinflammation are not significantly altered by chronic GLP-1 agonist treatment. Levels of **(A)** MCP-1 (recruits monocytes, microglia), **(B)** IP-10 (recruits CXCR3+ T cells), **(C)** MIP-1α (recruits monocytes, macrophages, T cells) and **(D)** MIP-2 (recruits neutrophils) are not significantly altered from those in vehicle-treated APP/PS1 mice (dashed lines).

SUMMARY

- We characterized behavioral, electrophysiological, and biomarker profiles of the APP/PS1 mouse model of Alzheimer's disease chronically dosed with the GLP-1 receptor agonists liraglutide (0.93 mg/kg IP) or semaglutide (0.05 mg/kg SC). Dosing was initiated at 7 months of age, with behavior assessed following 8 weeks of dosing and electrophysiology assessed after 16 weeks of dosing.
- No effect of chronic treatment was observed on body weight, while semaglutide treatment resulted in a small but statistically significant decrease in long-term survival due to mortalities late in the study.
- APP/PS1 mice made more frequent arm entries in the Y-maze; semaglutide (but not liraglutide) significantly reduced entry number. No effect of treatment was observed on spontaneous alternations.
- Hippocampal LTP was impaired in APP/PS1 animals, as were some aspects of basal synaptic transmission. While chronic administration of GLP-1 agonists had no observed effect on basal neurotransmission, semaglutide treatment was found to restore LTP to levels observed in vehicle-treated WT animals.
- Chronic treatment with GLP-1 agonists did not significantly impact plasma levels of A-beta isoforms or chemokines.
- Our results show that GLP-1 agonists may ameliorate aspects of disease trajectory in Alzheimer's disease. Additional studies focused on potential mechanisms of action are warranted.