GLP-1 Receptor Agonists Attenuate Pain-Like Behavior in an Animal Model of Chronic Migraine

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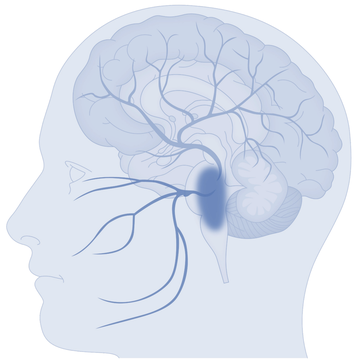
BACKGROUND AND AIMS

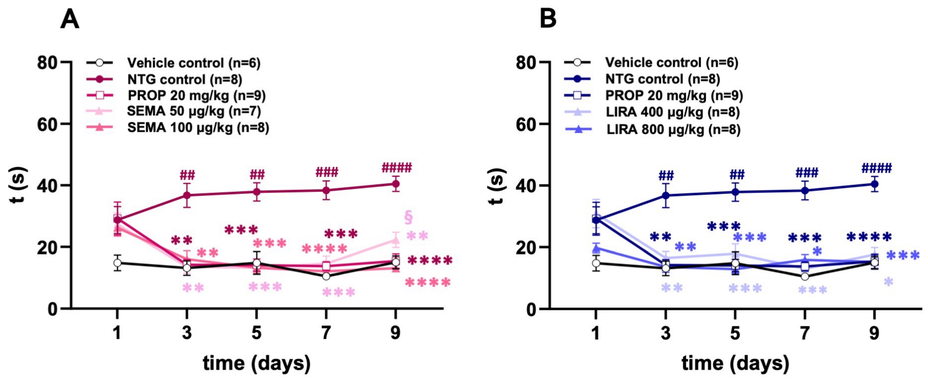
Migraine stands as **the second leading cause of global disability**, particularly affecting **females under 50**.[1] Nearly **70% of migraine sufferers are dissatisfied with conventional prophylactic therapies**,[2] prompting exploration into alternative treatment approaches.

Recent preclinical investigations have shown that liraglutide, a **GLP-1 receptor agonist**, is effective against mechanical hypersensitivity associated with chronic migraine.[3,4]



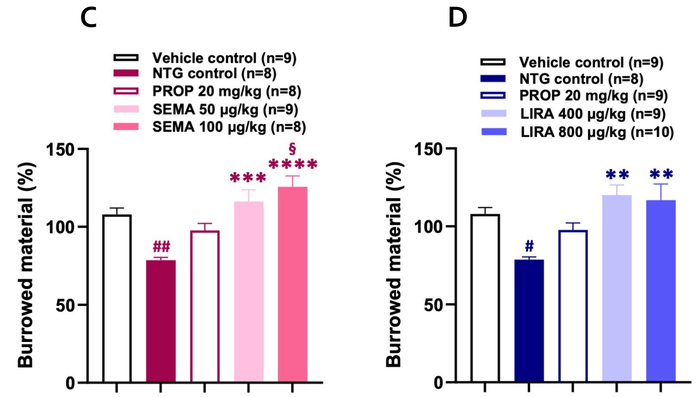
To add on existing knowledge, we aimed to investigate **the effects of semaglutide and liraglutide**, both long-acting GLP-1 receptor agonists, through an **extended battery of antinociceptive tests** including well-being assessment in a **murine model of chronic migraine.**

RESULTS



In **the orofacial glutamate test**, prophylactic repeated administration of semaglutide in both doses (SEMA; s.c.) (A), liraglutide in both doses (LIRA; s.c.) (B), as well as propranolol (PROP; i.p.), **significantly reduced the development of chemical pain hypersensitivity** in female mice with NTG-induced chronic migraine, characterized by a decrease in total time spent in nociceptive behavior.

##p < 0.01; ###p < 0.001; ####p < 0.0001 vehicle control vs. NTG control ; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001
NTG control vs. treatment groups; §p < 0.05 PROP vs. GLP-1 agonists;
Two-way repeated measures ANOVA (Tukey *post hoc* analysis)



In **the burrowing test**, prophylactic administration of semaglutide in both doses (SEMA; s.c.) (C) and liraglutide in both doses (LIRA; s.c.) (D), contrasting the reference drug, statistically **significantly increased the amount of burrowed material** in comparison with the NTG control.

#p < 0.05; ##p < 0.01 vehicle control vs. NTG control ; **p < 0.01; ***p < 0.001; ****p < 0.0001
NTG control vs. treatment groups; §p < 0.05 propranolol (PROP) vs. GLP-1 agonists;
One-way ANOVA (Tukey *post hoc* analysis)

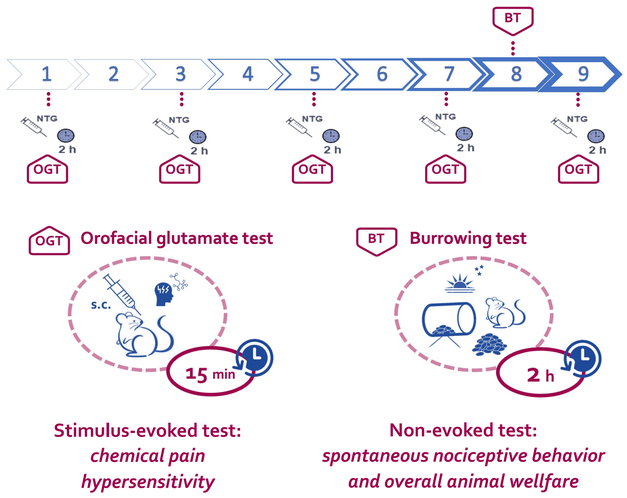
METHODS

A model of chronic migraine was established by **repeated intraperitoneal (i.p.) administration of nitroglycerin** (NTG; 10 mg/kg; every second day **over 9 days**) in female C57BL/6 mice.

Semaglutide (50 and 100 µg/kg/day, s.c.), **liraglutide** (400 and 800 µg/kg/day, s.c.), and **propranolol** (20 mg/kg/day, i.p.; positive control) were given **daily** all over the study course.

To evaluate pain hypersensitivity and the antinociceptive effects of treatments, both **stimulus-evoked and non-evoked nociceptive tests** were used.

The experiments were approved by the Institutional Animal Care and Use Committee and were carried out in compliance with the EU Directive 2010/63/EU.



CONCLUSION

- The presented results showed that **GLP-1 receptor agonists, semaglutide and liraglutide, attenuated provoked pain-like behavior** in a comparable manner to propranolol, the referent drug, in the chronic migraine model in female C57BL/6 mice.
- Unlike propranolol, **GLP-1 receptor agonists beneficially affect spontaneous pain-like behavior and animal well-being**.
- Assuming the high predictive value of the employed chronic pain model, **semaglutide and liraglutide might represent useful alternatives for chronic migraine prophylaxis**. (Further exploration of GLP-1 agonists in clinical settings is essential to ascertain their potential applicability.)

References:

[1] Steiner, T. et al. (2020) The Journal of Headache and Pain, 21.
[2] Pascual, J. et al. (2023) The Journal of Headache and Pain, 24(1).
[3] Jing, F. et al. (2021) The Journal of Headache and Pain, 22(1).
[4] Jing, F. et al. (2023) Neuroscience Letters, 812.

No conflict of interest.

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