Effects of selective GPER-1 agonist G1 on bone growth

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Conclusion

Our data suggest that estrogen may affect the growth plate via GPER-1 mainly by increasing chondrocyte proliferation and proliferative zone height. To clarify if this effect will translate into increased bone length, a longer treatment study would be needed.

Objective and hypothesis

We hypothesized that GPER-1 mediates estrogenic effects on growth plate cartilage.

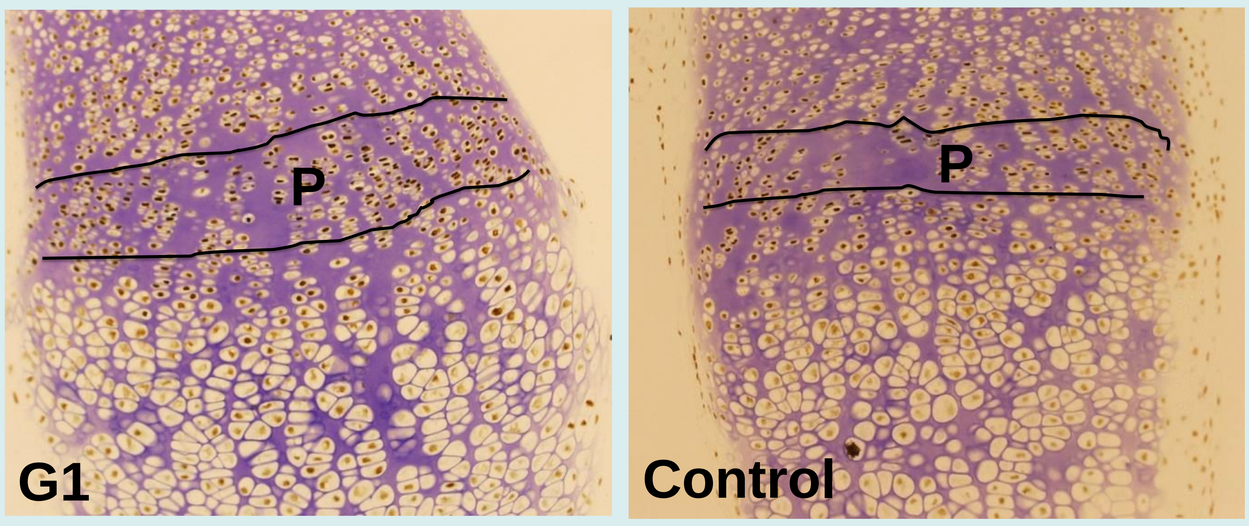

Figure 1. PCNA staining of growth plate sections from mouse metatarsal bones treated with 100 nM G1 compared to control bones. The height of the proliferative zone was significantly higher in G1-treated bones compared to controls, ***p<0.001. P=proliferative zone.

Introduction

Abnormal growth is a common problem in children. High doses of estrogen induce growth plate closure and growth cessation and therefore have been used for treatment of tall stature. However, high-dose estrogen treatment may also have severe side effects, including increased risk of cancer and reduced fertility. The expression of estrogen receptors (ER), including membrane GPER-1, has been demonstrated in growth plate cartilage in humans as well as mice.

Results

- Proliferative zone height and proliferation rate of the growth plate of the metatarsal bones treated with 100 nM of G1 in culture were increased when compared to control bones (Figs. 1 and 2B).
- Growth plate height of the metatarsal bones treated with 100 nM of G1 were longer than the control metatarsal bones (Fig. 2A).
- Animals treated with G1 had tibia lengths similar to the controls (Fig. 2C).
- The height of the proliferative zone of the tibia growth plate was not affected by G1 treatment in vivo.

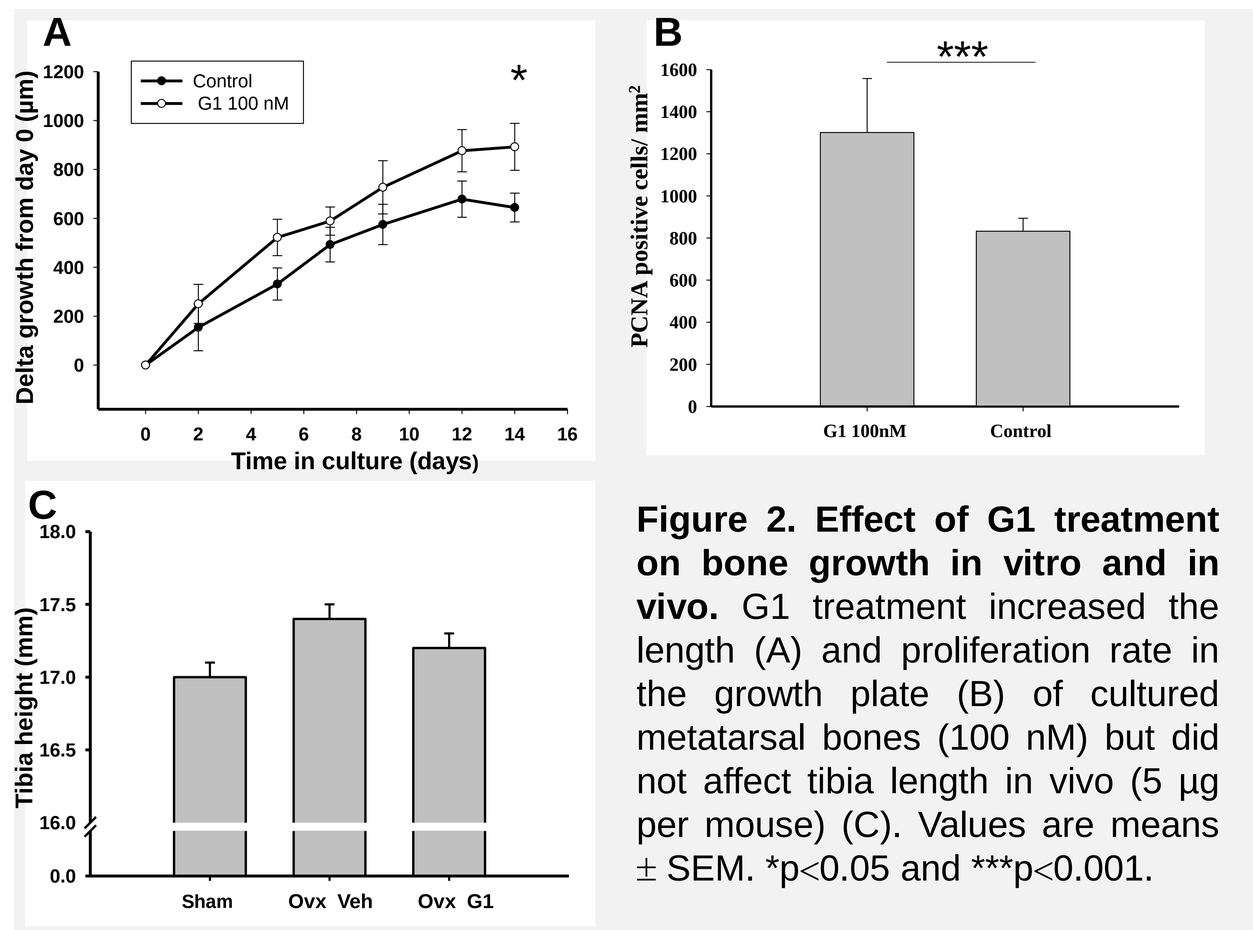

Figure 2. Effect of G1 treatment on bone growth in vitro and in vivo. G1 treatment increased the length (A) and proliferation rate in the growth plate (B) of cultured metatarsal bones (100 nM) but did not affect tibia length in vivo (5 µg per mouse) (C). Values are means ± SEM. *p<0.05 and ***p<0.001.

Materials and Methods

Twelve-week old ovariectomized (OVX) female C57BL/6 mice were injected 5 days per week for 4 weeks with G1 (5 µg per mouse). Tibia and femur lengths and growth plate morphology were evaluated after sacrifice.

Metatarsal bones of 4 day-old mice were treated with 1, 10, 100 or 300 nM of the GPER-1 agonist G1 for 14 days. Growth plate height was measured. Proliferation was evaluated by PCNA staining.

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