2021 Best Research Poster Award

Barwon Health

DEAKIN UNIVERSITY

Effect of Antipsychotics and Dopamine on Human Osteoclastogenesis

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INTRODUCTION

Antipsychotics target dopamine and serotonin receptors to treat psychiatric disorders such as schizophrenia. Long-term use of antipsychotics decreases bone mineral density and increases fracture risk. It is vital to elucidate how dopaminergic signaling impacts bone, with current insights into mechanism(s) limited to data from animal models. This study investigates the role of dopamine and a range of commonly prescribed antipsychotics on the process of human osteoclastogenesis, which will help inform clinical decisions to reduce possible off-target effects on bone.

OBJECTIVES

Determine the effects of dopamine and first generation antipsychotics on human osteoclastogenesis.

METHOD

The effects of dopamine, dopamine receptor agonists ropinirol, cariprazine and dopamine receptor antagonists chlorpromazine and haloperidol were assessed in a human model of osteoclastogenesis. Briefly, human cord blood mononuclear cell-derived osteoclast (OC) precursors were cultured on dentine slices in the presence of RANKL and MCSF for 14 days. Cells were fixed and stained for TRAP and dentine slices assessed for resorption.

RESULTS

Dopamine, cariprazine, chlorpromazine and haloperidol all dose-dependently inhibit OC formation and resorption (IC50 >10μM, ~10μM, ~6μM and ~10μM respectively), whereas ropinirol decreased OC number (IC50 ~100μM), which was compensated by an increase in OC size with no effect on total resorption.

Further work is ongoing to identify which of the 5 dopamine receptor subtypes and subsequent downstream signaling pathways may be involved in regulating normal human osteoclastogenesis, in addition to modes of action of first generation antipsychotics that will help to explain bone loss that results from long-term use of these drugs.

DISCUSSION/CONCLUSION

Dopamine is present in sympathetic nerves in the body, including highly innervated bone tissue, where levels up to 10μM having been reported. In this study dopamine, dopamine agonist cariprazine and antagonists all negatively-impacted on the process of human osteoclastogenesis, while ropinirol had no significant effect. This highlights the likely importance of dopaminergic signaling pathways in human osteoclastogenesis.

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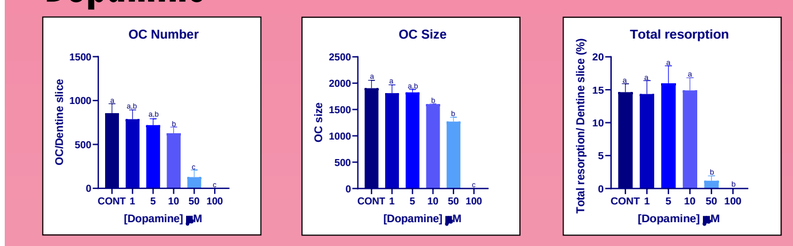
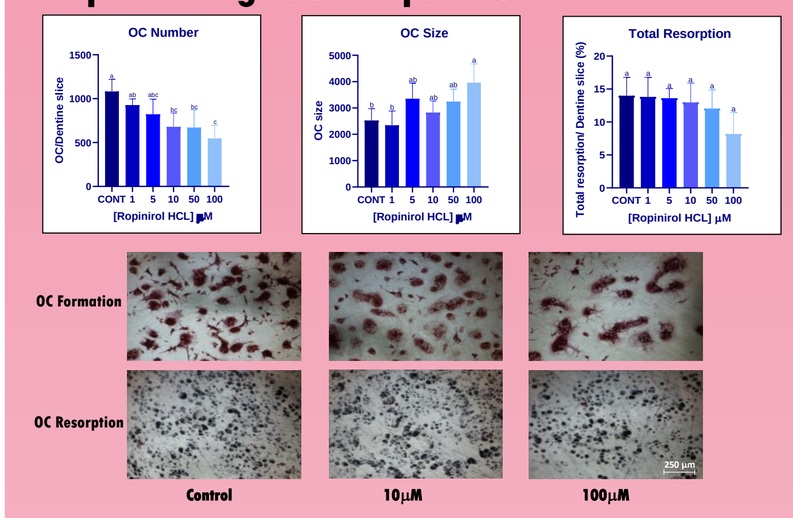
RESULTS

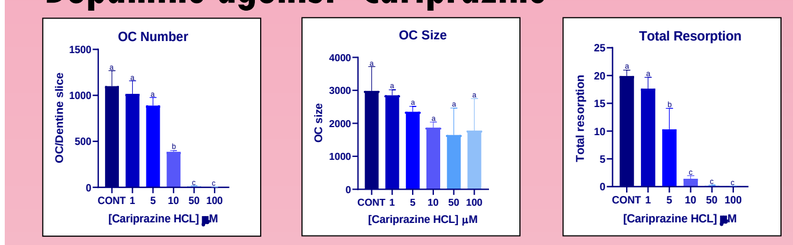
Dopamine



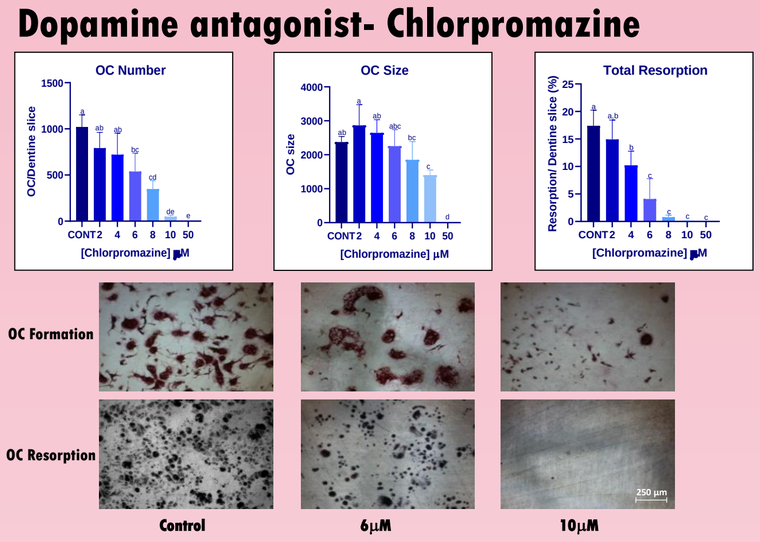
Dopamine agonist- Ropinirol



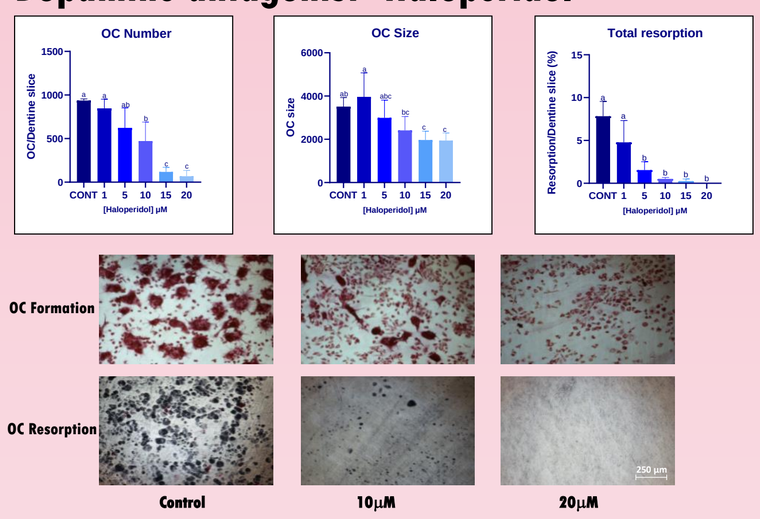
Dopamine agonist- Cariprazine



Dopamine antagonist- Chlorpromazine



Dopamine antagonist- Haloperidol



OC differentiation from human cord blood mononuclear cell derived CFU-GM. Data shown as mean ± SD, n=4 dentine slices/group ($P<0.05$; One-way ANOVA with Tukey multiple comparison test). Representative images for TRAP staining of OC formation and corresponding resorption pits (10X) are also presented with each group.