2022 Best Research Poster Award

Barwon Health

DEAKIN UNIVERSITY

ANTIPSYCHOTICS AND HUMAN OSTEOCLASTOGENESIS

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Introduction

Antipsychotics primarily target dopamine and serotonin receptors to treat psychiatric disorders such as schizophrenia. Long-term use of antipsychotics decrease bone mineral density and increases fracture risk [1,2]. As antipsychotics target dopamine, serotonin and adrenergic receptors it is important to elucidate how dopaminergic, serotonergic and adrenergic signalling pathways impact bone, where current insights into the mechanism(s) are limited to data from animal models.

Objective

This study investigates the role of dopamine, serotonin, noradrenaline and a range of commonly prescribed antipsychotics on the process of osteoclastogenesis, which will help inform clinical decisions to reduce possible off-target effects on bone.

Methods

Dopamine, serotonin and adrenergic receptor expression and osteoclastic genes; cathepsin K and NFATC1 expression were assessed using quantitative real time PCR. The effects of selected antipsychotics were assessed in a human model of osteoclastogenesis. Colony forming unit - granulocyte macrophage (CFU-GM) cells derived from human cord blood mononuclear cells (hCBMC) were cultured on dentine slices in the presence of receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor for 14 days. The cells were fixed and stained for tartrate-resistant acid phosphatase (TRAP) and dentine slices assessed for resorption.

Results

Osteoclastic genes cathepsin K (mediate bone resorption) and NFATC1 (master regulator of osteoclast differentiation) expression peaked on Day 7. Dopamine receptor expression was not detected while serotonin receptor 2B ($5HT_{2B}$) and beta 2 adrenergic receptor (ADRB2) expression were highest on day 7 (Fig.1). All tested antipsychotics dose-dependently inhibited OC formation and resorption where the DR antagonists chlorpromazine and haloperidol both have inhibitory effects on OC formation at IC_{50} ~6µM and ~7µM, respectively. Whereas, dopamine and serotonin antagonists olanzapine, dopamine partial agonist cariprazine and dopamine agonist ropinirole show IC_{50} ~15µM, ~4µM and ~51µM, respectively (Fig.2).

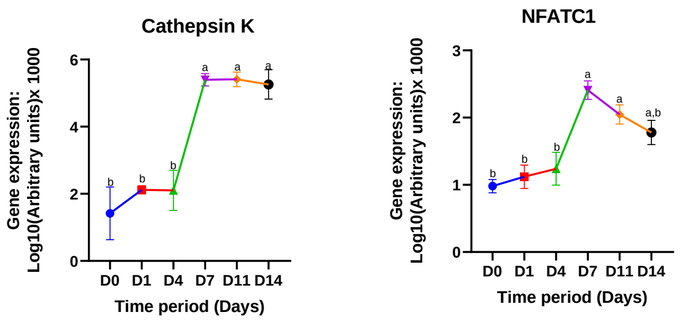

Figure 1: Cathepsin K, NFATC1, $5HT_{2B}$ and ADRB2 expression profiles in OC. Data presented as Mean± SEM; n=3. Differences between groups were assessed using one-way ANOVA with Tukey's multiple comparisons test with the statistical significance at $P<0.05$. Groups with different superscript are significantly different.

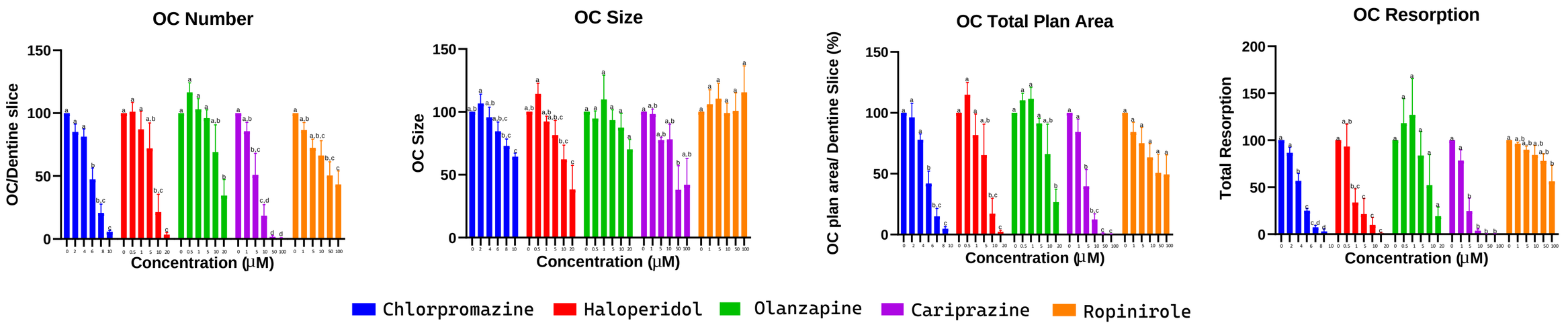

Figure 2: OC differentiation from CFU-GM-derived osteoclast precursors. Data presented as mean ± SEM, n=4 dentine slices/group ($p<0.05$; One-way ANOVA with Tukey multiple comparison test. Groups with different superscript are significantly different.

Discussion and Conclusion

In this study, each antipsychotic inhibited the process of human osteoclastogenesis. There was no detectable dopamine receptor expression throughout the process of osteoclast formation, whereas expression of $5HT_{2B}$ and ADRB2 receptor peaked at day 7. This highlights the likely importance of investigating serotonin and adrenergic signalling pathways in order to understand the effects of human osteoclastogenesis as they are known to affect osteoclast function. Moreover, The most potent inhibitor of osteoclastogenesis from the tested antipsychotics was cariprazine followed by chlorpromazine, haloperidol and olanzapine while ropinirole had the lowest inhibitory effects.

REFERENCES

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2. Paschou, S.A., P. Mentzelopoulos, and I. Lambrinoudaki, Antipsychotic therapies and bone health. Case reports in women's health, 2019. 25: p. e00160-e00160.