

Anti-dementia Acetylcholinesterase inhibitor inhibits osteoclastogenesis: Investigation of potential therapeutic effects and mechanism of actions of Alzheimer's Disease drugs in osteoporosis aiming to improve the treatment outcomes of osteoporotic patients.

Background

Alzheimer's dementia (AD) and osteoporosis (OP) are common and frequently coexist in an ageing population.

Bone is a dynamic organ which continuously undergoes bone remodelling involving balanced activities of bone forming osteoblasts and bone resorbing osteoclasts [1-3]. Bone remodelling is important for the bone architecture and the maintenance of circulating calcium levels. A disruption in the balance between osteoclasts and osteoblasts activity results in bone diseases [3]. The study of factors controlling bone cell formation and activation is essential to understand the process of bone homeostasis and provide potential therapeutic targets against debilitating diseases such as osteoporosis.

A recent study published in the Journal of Alzheimer's Disease linked low BMD with increased risk of AD [4]. It has also been found that patients with AD have increased bone turnover markers [5,6]. The study was conducted over 5 years period which assessed association between BMD and the risk of AD in 3263 patients aged 65 and over.

Acetylcholine and Acetylcholinesterase Inhibitor

Acetylcholine (ACh) is an ester of choline and acetic acid that acts as a neurotransmitter present at many nerve, synapses, and at the motor end plate of muscles in both the central and peripheral nervous system [7]. ACh is known to play an important role in learning and the functionality of memory. ACh is broken down by acetylcholinesterase to prevent excessive signalling [8]. Reduced ACh has been observed in patients with AD and has been associated with the clinical symptoms of the disease. As a result, Acetylcholinesterase inhibitors (AChEI) have been developed to treat the symptoms of patients with mild to moderate AD [9].

Reductions in levels of ACh have also been implicated in bone loss. Acetylcholine receptor (AChR) subunits and Acetylcholinesterase (AChE) are expressed in bone. Patients suffering from poliomyelitis, a viral disease that destroys the motor neurons which use ACh, have been found to have impaired bone growth in the limbs affected by the damage to nerves. Even when muscle activity recovers, patients have an increased tendency to develop osteoporosis [10]. Botulinum neurotoxin (botox) inhibits the release of ACh from motor neurons at presynaptic level. This has been associated with impairment of bone healing and decrease in bone mineral content. Again, bone density is not found to improve after the recovery of muscle function, suggesting that botulinum neurotoxin has an effect on bone tissue unrelated to muscle function [11].

Various clinical conditions that alter Acetylcholine (ACh) signalling have also been shown to affect bone function [10-14]. A recent publication has demonstrated a correlation between treatment with AChEI Donepezil and Rivastigmine, but not Galantamine, and reduction in hip fracture in osteoporotic AD patients [15]. Although studies have found that there is a link between Alzheimer's Disease and osteoporosis there have been no studies looking at the effects of current approved AChEI for Alzheimer's Disease medication in relation to osteoporosis.

Hypothesis and Aims

We hypothesised that acetylcholinesterase inhibitors (AChEI) as used in dementia management would reduce osteoclastogenesis if this was the mechanism of bone effect of ACh. We aimed to look at the effect of Donepezil, Galantamine and Rivastigmine on osteoclasts.

Methods

Bone marrow cells are seeded at the density of 6×10^3 cells/well in 96-well plate. Prior to RANKL stimulation, cultures were incubated with the drugs Donepezil and Galantamine at concentrations of 0.1, 0.5, 1.0 and 5.0 μ M. Cells without treatment and cells stimulated with RANKL are used as negative and positive control respectively.

Results

At equimolar concentrations Donepezil inhibit, whereas Galantamine had no effect on osteoclastogenesis. Donepezil inhibited osteoclastogenesis at the lowest concentration of 0.1 μ M (see Fig 1)

Discussion

This data suggests ACh may be important in bone biology. AChEI that bind to mAChR may have the additional benefit of reducing osteoclastogenesis. Donepezil and Rivastigmine both bind mAChR as well as nAChR. Galantamine, predominantly binds nAChR (Table 1). This finding is consistent with a recently published case control study confirming the protective effect of Donepezil and Rivastigmine but not Galantamine in hip fracture reduction. The potential reason is the difference in cholinergic enhancement. Donepezil has muscarinic effects as well which favours bone mass accrual. Galantamine binds Nicotinic Allosteric Potentiating Ligand (APL) only, exhibiting excessive nicotinic cholinergic enhancement, which reduces bone remodelling (see Table 1).

Conclusion

This study may have important implications for osteoporosis management in older populations with osteoporosis and dementia. Agents that have the dual benefit to both ageing bone (senile osteoporosis) and ageing brain (dementia) may be a useful future strategy to improve compliance and reduce polypharmacy. If the difference between Acetylcholinesterases in terms of effect on bone is real, this may influence drug choice in those with both conditions.

Figure 1

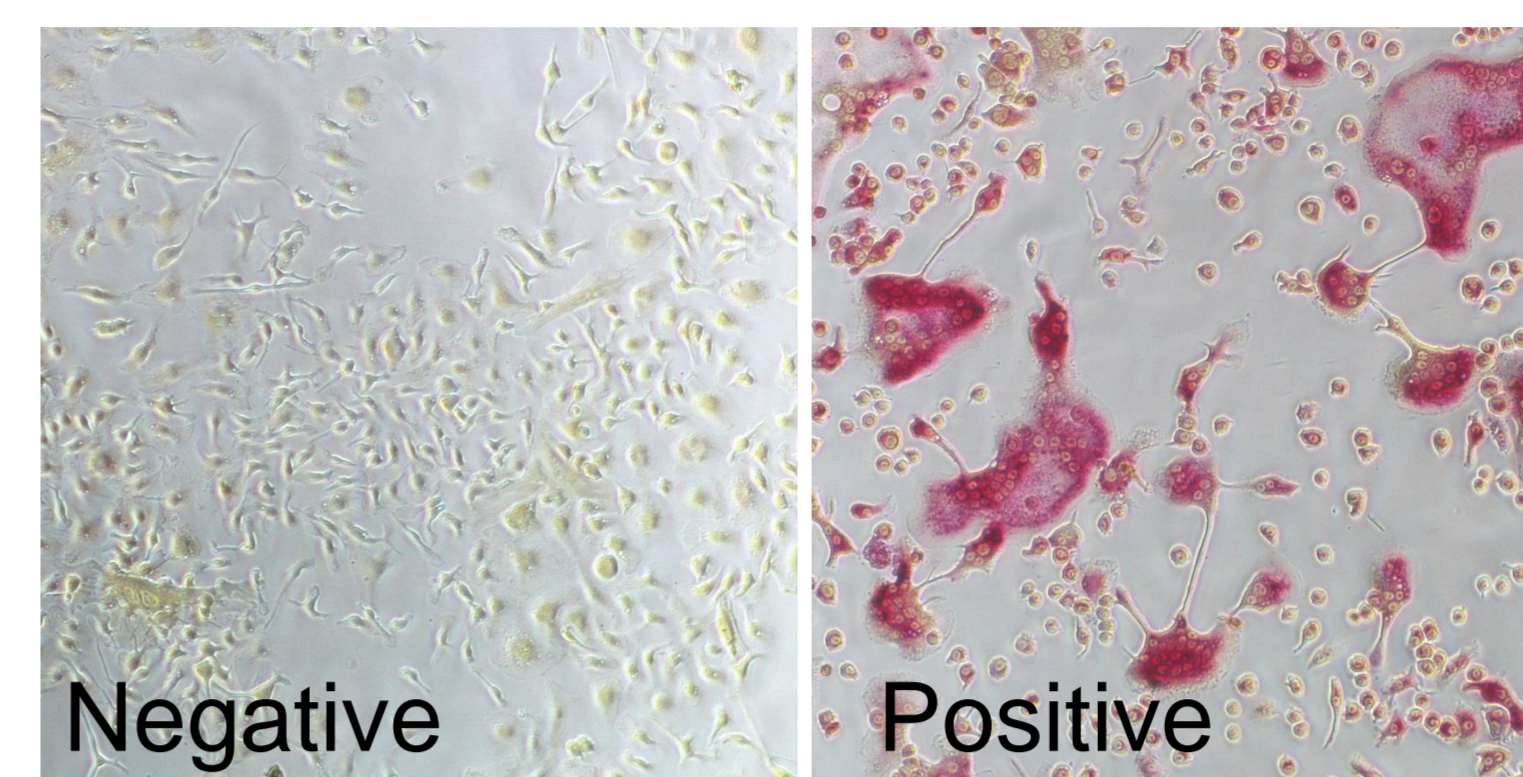


Figure 1: Representative images (100X) of osteoclasts formed from bone marrow monocytes in the presence of Donepezil and Galantamine at the stated concentrations.

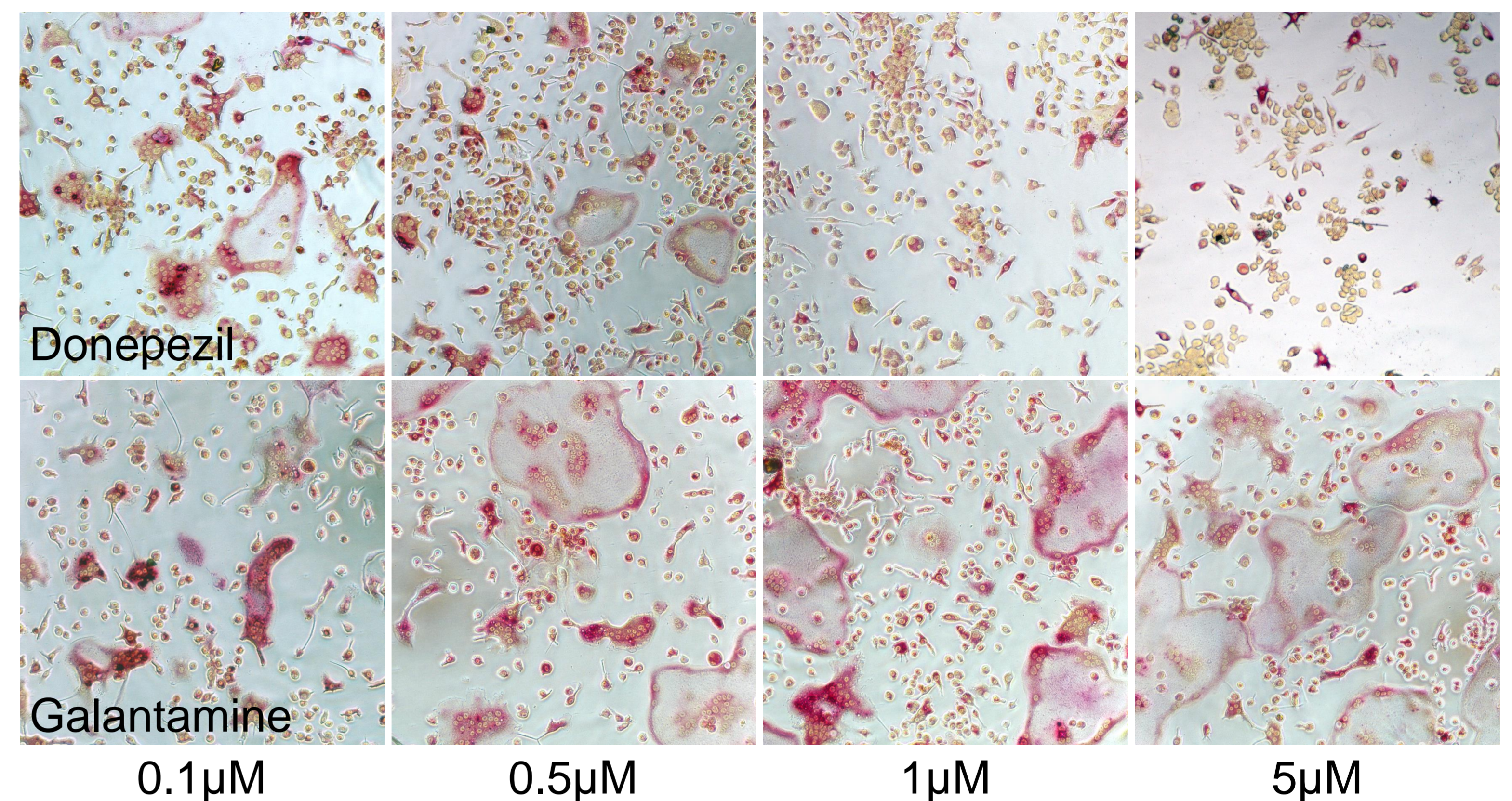


Table 1

DRUG	mAChER binding	nAChER binding	OC - Bone Effect
Donepezil	+	+	+
Galantamine	-	+(exclusively)	-

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