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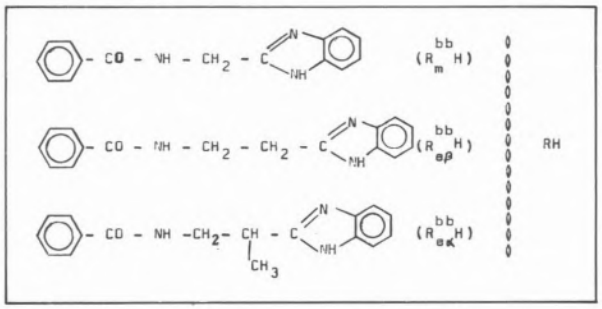
SYNTHETIC, STRUCTURAL AND ANTIBACTERIAL SCREENING STUDIES OF Co(II), Ni(II) AND Cu(II) COMPLEXES WITH BENZIMIDAZOLE DERIVATIVES

Recently several benzamido benzimidazoles have been synthesised and some of the compounds are found to be active against gram +ve microorganisms [1] whereas corresponding sulphonamido benzimidazoles which can function as chelating agents [2] are active against gram -ve microorganisms [3]. Now metal complexes of the type $M(RH)_2Cl_2$ [M = Co(II), Ni(II) and Cu(II)] have been prepared and characterized by IR, PMR and electronic spectra, conductivity and magnetic moment data.



All the Cu(II) complexes show low magnetic moment values at room temperature which suggests antiferromagnetic interaction between two Cu(II) centres bridged by chloride [4,5]. The presence of chlorine bridged structure is indicated by IR data. Magnetic moment data and electronic spectra of Co(II) complexes support tetrahedral structure [6,7]. $Ni(R_m^{bb}H)_2Cl_2$ and $Ni(R_{e\beta}^{bb}H)_2Cl_2$ are polymeric in nature and possess octahedral stereochemistry. Due to the presence of a CH_3 group in $R_{e\alpha}^{bb}H$, polymerisation is sterically hindered and $Ni(R_{e\alpha}^{bb}H)_2Cl_2$ is assumed to be in octahedral $\rightleftharpoons$ planar equilibrium and low magnetic moment value is observed [8].

These metal complexes are active against gram +ve and gram −ve microorganisms and the activity is more than the free ligand or metal ion. Co(II) complexes are found to be more active than Ni(II) and Cu(II) complexes.

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PS6.19 — TH

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EFFECTS OF COBALT IONS ON THE SYNOVIAL PRODUCTION OF NEUTRAL PROTEINASES AND PROSTAGLANDIN E_2

INTRODUCTION

Artificial joint replacements contain much metal. For a number of years the metal of choice has been an alloy based on cobalt, although newer prostheses are being made from titanium. The major cause of failure of these devices is aseptic loosening. Recent evidence suggests that loosening is secondary to a localized loss of bone in the area which surrounds the implant. Examination of the femoral component of failed artificial hip joints reveals the presence of a membrane growing at the surface where the surrounding bone meets the cement used to secure the prosthesis [1]. This membrane bears striking histological and cellular similarities to the synovial membrane which lines all articulating joints. Furthermore, it secretes collagenase and prostaglandin E_2 (PGE_2) in culture, thus implicating this pseudo-synovial membrane in the localized osteolysis that promotes aseptic loosening. If so, it is important to identify the local stimuli that provoke the production of collagenase and PGE_2 by cells of the synovial type. Working on the hypothesis that metal ions released by the prosthesis may be responsible, we are engaged in screening various implant metals for their ability to stimulate the production of PGE_2 and three neutral proteinases, including collagenase, by synovial cell cultures. Here we report the effects of Co^{2+}.

METHODS

Synovia were obtained from human or lapine knee joints and cultured by standard methods [2]. Sterile, aqueous solutions of $CoCl_2$ were added to confluent cultures to give final metal ion concentrations from 0 to 10^{-3} M. After 3 days further incubation, the conditioned media were assayed for their neutral proteolytic activity, using ^{3}H-collagen, -gelatin or -casein as substrates and aminophenylmercuric acetate (1 mM) as activator. Prostaglandin E_2 levels were measured by radioimmunoassay.

RESULTS AND DISCUSSION

The production of all three neutral proteolytic activities was stimulated by Co^{2+}. For lapine cells, the maximum stimulation of 10-30 fold occurred in the presence of 10^{-7} M Co^{2+} (Table 1). Human cells required 10^{-4} to 10^{-5} M Co^{2+} to achieve a maximum stimulation of 10-15 fold. Production of PGE_2 by lapine cells was elevated 1.5-2 fold at concentrations of Co^{2+} that maximally provoked enzyme release, whereas all concentrations of Co^{2+} slightly depressed the synthesis of PGE_2 by human synovial cells.

Table 1
Production of neutral proteinases and PGE_2 by lapine synovial cells in response to Co^{2+}

Metal Ion Added	Enzymic Activity (Units/day/10^6 cells*)			
	Collagenase	Gelatinase	Caseinase	PGE_2 (ng/culture)
None	0.40	0.27	0.050	193
Co^{2+} (10^{-7} M)	13.23	3.96	0.613	285

* 1 Unit of neutral proteinase activity degrades 1μg of the appropriate substrate per min at 37°C.

Suitable control experiments confirmed that Co^{2+} mediated its apparent effects on the production of these neutral proteinases by stimulating the cellular synthetic machinery. Concentrations of Co^{2+} that maximally enhanced apparent enzyme production had no effect when added directly to the proteinase assays. In addition, dialysis of control conditioned media against various concentrations of Co^{2+} failed to stimulate the enzymes' activity post-synthetically. Furthermore, cells whose pro-