Salwa Akl

بسم اللّه الرحمن الرحيم

مركز الشبكات وتكنولوجيا المعلومات

قسم التوثيق الإلكتروني

Salwa Akl

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم باللّه العظيم أن المادة التي تم توثيقها وتسجيلها

علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

Salwa Akl

بعض الوثائق الأصلية تالفة
وبالرسالة صفحات لم ترد بالأصل

Ultrastructural Study of the Effect of Cyclosporin A on Parotid Gland in Rats

Thesis

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بسم الله الرحمن الرحيم

" و ما توفيقي إلا بالله عليه
توكلت و إليه أنيب"

--هود ٨٨

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INTRODUCTION

Introduction

Cyclosporin A (CyA) is a unique, powerful immunosuppressive agent of fungal origin. Compared with conventional immunosuppressives CyA lacks myelotoxicity "destruction to bone marrow" (Laupacis et al. 1982). It represents the first of a new generation of immunosuppressive agents that are capable of selective rather than broad-spectrum immunosuppression (Miach 1986). CyA not only acts on T-lymphocytes and reduces their production of lymphokines, but also affects T-helper far more than T-suppressor cells, resulting in a net imbalance in favour of suppressor action or immunosuppression (Laupacis et al. 1982, Daley and Wysocki 1984).

Being introduced in immunosuppressive protocols, CyA has been shown to have a profound effect on clinical transplantation worldwide, not only in terms of improved organ and patient survival but also in improving public attitudes towards transplantation (Holt et al. 1994).

Although CyA appears to be beneficial in the treatment of a wide variety of disorders, its use might result in a number of side effects. The most important of these are the nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension as well as gingival hypertrophy (Kahan 1989). Interestingly, many of these side effects were thought to be reversible. Some authors reported that these side effects are reversible after drug withdrawal (Powles et al. 1980, Laupacis et al. 1982). On the other hand Myers et al. 1984 claimed that when CyA was given at high dosage it could induce severe irreversible nephrotoxicity in heart

transplant recipients. After cessation of its long term therapy, CyA has been shown to be stored in fat, liver, lung, spleen as well as lymph nodes, slowly redistributed into the blood and maintained a low serum concentration for an unknown length of time before the drug would be completely eliminated from the body (Atkinson et al. 1982).

REVIEW OF LITERATURE

Review of literature

The Immunosuppressive agents:

Modification of the immune function by pharmacological agents emerges as a major area of therapeutics. Immunosuppressive drugs act on various components of the immune system causing selective inhibition and suppression. Drugs used for this purpose include corticosteroids (mainly, prednisone and prednisolone), azothioprine and more recently Cyclosporin A (Seymour and Haesman 1988).

Immunosuppressive agents are used as an anticancer drugs as well as in treatment of some autoimmune diseases (Spreafico and Anaclero 1977, Schniden and Levamisole 1981). Recently, many of these immunosuppressive agents have been used widely to prevent transplant rejection following organ transplantation (Seymour and Haesman 1988).

Cyclosporin A (CyA):

CyA is a novel powerful immunosuppressive agent of fungal origin. Its main effect is directed against the T-helper cells. Thus, CyA represents the first of a new generation of immunosuppressive agents that are capable of selective rather than broad-spectrum immunosuppression (Miach 1986).

After being discovered by Borel at Sandoz laboratories in 1972, CyA was thought to become extremely valuable in prevention of

transplant rejection as well as in treatment of some autoimmune diseases (Laupacis et al. 1982).

Structure and pharmacokinetics of CyA:

CyA is a cyclic endecapeptide, composed of 11 amino acids of molecular weight 1202.6 D. It was obtained from the fermentation broth of two fungi, *Trichoderma polysporum* and *Cylindrocarpon lucidum* (Borel et al. 1977). Commercially, CyA is produced as a metabolite from submerged cultures of the fungal species *Tolypocladium inflatum Gams* (Borel et al. 1976). Its peptide is neutral, rich in hydrophobic amino acids, and thus insoluble in water, but soluble in lipids and in many other organic solvents (Borel 1991). Being extremely lipophilic, CyA doesn't dissolve readily in standard intravenous preparation, however, Sandoz has produced an intravenous preparation of CyA that contains Cremophor as solubilizing agent (Laupacis et al. 1982). After its oral administration, CyA is absorbed from the gastrointestinal tract with marked individual variations. Peak plasma concentration occurs after 3-4 hours, and the drug has a serum half-life of between 17-40 hours (Beveridge et al. 1981). CyA is extensively metabolized in the liver and most of its metabolites are excreted via the bile ducts into the faeces. Only 10% of its metabolites are eliminated through the kidney (Button and Palacios 1982). To maintain immunosuppression, oral therapeutic doses of about 10-20 mg/kg body weight/day that result in a serum concentration of between 100-400 ng/ml are required (Atkinson et al. 1982, Laupacis et al. 1982). CyA has little effect at serum concentrations below 100ng/ml and patients usually exhibit significant side effects at serum concentrations greater than 400ng/ml (Laupacis et al. 1982).

Mechanism of action:

CyA exerts its therapeutic effect on a specific component of the immune system, while sparing the remainder. This action is unlike all other known immunosuppressive agents which affect the entire immune system (Daley and Wysocki 1984).

Bunjes et al. 1981 and Button and Palacios 1982 reported that CyA exerts its selective immunosuppressive effect in at least three different ways. Firstly, it inhibits the activation of macrophages and therefore interferes with the synthesis of interleukin-1. Secondly, it inhibits the synthesis of interleukin-2 as well as production of interleukin-1 receptors on the surfaces of T-helper cell. Finally, it prevents the production of interleukin-2 receptors on undifferentiated T-cells and therefore blocks the production of more T-helper cells, T-suppressor cells and T-killer cells.

Thus, CyA appears to be selective in its action on T-lymphocytes. T-suppressor cells seem to be resistant to CyA, whereas T-killer and T-helper cells are sensitive. These differential effects of CyA on various subsets of T-lymphocytes pertains to its selective cell binding properties (Hess and Colombani 1987). It has been postulated that resistance or sensitivity of T-lymphocytes to CyA may be related to the proportionate intracellular concentrations of calmodulin (a 17 KD calcium dependant protein) and cyclophilin (a 16 KD protein) (Hess and Colombani 1987). The binding of CyA to both of these proteins is calcium dependant (Colombani et al. 1985). Although the function of cyclophilin is unknown, calmodulin binds to CyA within T-lymphocytes and is