بسم الله الرحمن الرحيم

شبكة المعلومـــــات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

﴿ قـــســـم ﴾

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لم ترد بالأصـــل

BLADDER DYSFUNCTION IN PARKINSON'S DISEASE CLINICAL AND URODYNAMIC STUDIES

THESIS

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TO

The memory of
Professor Doctor Omar El Garem
A great Pioneer
teacher and Founder
of
Neuropsychiatry department
Alexandria University

LIST OF ABBREVIATIONS

- **MPPP** : -1- methyl -4- phenyl -4- proprion oxypiperidine .
- **MPTP** : -1- mythyl -4- phynyl -1,2,3,6 tetrahydropyridine .
- **MAO-B** : Monoamin oxidase - B-
- **MPDP** : 1- methyl - 4 - phenyl - 2, 3, dihydropyridinium
- **MPP** : 1- methyl - 4 - phenyl - pyridinium
- **TIQ** : tetra-hydroisoquinoline
- **IPD** : Idiopathic parkinson's disease
- **ISO** : -iso prenaline
- **-PET** : Positron emmission tomography .
- **-PSP** : Progressive supranuclear palsy
- **DA** : dopamine
- **NE** : Norepinephrine
- **AAAD** : aromatic amino acid decarbocxylase
- **D_1** : dopamine -1- receptor
- **-D_2** : dopamine -2- receptor
- **COMT** : catecholamine -o- methyl - transferase
- **CSF** : Cerebrospinal fluid .
- **-3- OMD** : 3-methyl dopa
- **SNPC** : Substantia nigra pars compacta

CONTENTS

INTRODUCTION

HISTORICAL CONSIDERATIONS

Our knowledge and concepts of parkinson's disease have gradually evolved over the past 177 years . It was first clinically recognized by the English physician and geologist James Parkinson. He provided the first clear description of the disorder that now bears his name in a brief monograph (An Essay on the Shaking Palsy) published in 1817 .[1] The lack of widely accepted earlier descriptions suggests that perhaps parkinson's disease is a consequence of the industrial revolution and raises the speculation that industrial toxins released into the environment may contribute to the causation of this disorder .[2]

Lewy bodies in neurons were described in 1912 . Lesions in the substantia nigra were not recognized until 1919 . The involvement of other brain stem pigmented neurons was appreciated in 1953 .[3]

The modern era of correlating striatal dopamine deficiency with parkinsonism was unfolded in 1960 .[4] High dosage levodopa therapy was used by Cotzias et al in 1967 .[5] Since then, improvements in pharmacotherapy have been made with the use of peripheral decarboxylase inhibitors and direct acting dopamine receptor agonists .[6]

ETIOLOGY OF PARKINSON'S DISEASE

I. Toxic theory :-

Parkinson's disease is usually a slowly progressive sporadic disorder associated with old age . The development of acute parkinsonism in a cluster of young addicts suggested exposure to a toxin. These patients abused drugs and had in fact obtained the potent narcotic 1-methyl-4-phenyl-4-proprionoxypiperidine (MPPP) from the same source .[7] Modifications in the synthesis of MPPP had apparantly produced the contaminant 1- Methyl - 4 - Phenyl - 1,2,3,6 - tetrahydropyridine (MPTP) which causes subacute parkinsonism in humans and other primates due to selective destruction of dopaminergic neuromelanin- containing substantia nigra compacta neurons .[8] In contrast to other drug induced parkinsonism states eg. neuroleptics, the syndrome produced by MPTP did not resolve. As in idiopathic parkinson's disease, treatment with L-dopa alleviated the symptoms but only briefly, with the subsequent development of on-off phenomena and other disabling dyskinesia as side effects .[9]

Pathologically, the MPTP syndrome also showed great similarity to the idiopathic disorder [10], with less extensive lesions in the ventral tegmental area and locus coeruleus in addition to the more severe damage of the substantia nigra . MPTP even produces oesinophilic inclusions reminascent of Lewy bodies .[11]

Although MPTP injures dopaminergic projections to the caudate more than the putamen and idiopathic parkinson's disease preferentially affects the putamen, MPTP model provides an

excellent test of the different lines for treatment and in particular for understanding the cause of Parkinson's disease .[12] The mechanism of MPTP neurotoxicity has been worked out . Being highly lipophilic, it enters the brain, where it is metabolized by mono amine oxidase-B located in glial cells to produce 1- methyl - 4 - phenyl - 2, 3, dihydropyridinium (MPDP), which in turn is converted to 1- methyl - 4 - phenyl - pyridinium (MPP^{+}) . MPP^{+} which is taken into dopamine neurons by the dopamine reuptake mechanism where it persists, perhaps due to an interaction with neuromelanin. Subsequently, MPP^{+} is actively accumulated by mitochondria where it acts by inhibiting complex I (NADH Co O reductase) of the respiratory chain, leading to a depletion of ATP and the initiation of cell death .[13]

The absence of MPTP in cases of idiopathic parkinson's, raises the possibility that toxins other than MPTP may be the cause.[14] The nucleus of MPTP responsible for its toxicity is a common chemical moiety which may exist in many other substances such as the B-carbolines which occur naturally in the brain as a derivative of indolamines metabolism and with a similar structure to MPP. Gradual accumulation over life time can inhibit mitochondrial oxygen consumption and may produce neural degeneration of late onset .[15] Another compound structurally related to MPP namely tetrahydroisoquinoline (TIQ) also occur in the brain.TIQ apparently undergoes metabolism by a cytochrome P450 isoenzyme that varies in activity in different animal strains and human population..[16].