

THE COMPREHENSIVE GUIDE TO
PARKINSON'S DISEASE

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CONTENTS

SECTION 1		HISTORY OF PARKINSON'S DISEASE
1	1	HISTORY OF PARKINSON'S DISEASE
2	25	FAMOUS PEOPLE WITH PARKINSON'S DISEASE
SECTION 2		PREVALENCE OF PARKINSON'S DISEASE
3	47	PREVALENCE OF PARKINSON'S DISEASE
SECTION 3		BIOCHEMISTRY OF PARKINSON'S DISEASE
4	63	DOPAMINE BIOSYNTHESIS
5	67	COENZYME BIOSYNTHESIS
6	71	IRON METABOLISM
7	83	ZINC METABOLISM
8	91	MANGANESE METABOLISM
9	97	DOPAMINE RECEPTORS
10	127	G PROTEINS
11	156	DOPAMINE RECEPTOR PHOSPHOPROTEIN
SECTION 4		CYTOLOGY OF PARKINSON'S DISEASE
12	162	DOPAMINERGIC NEURONS
13	170	CYTOLOGICAL EFFECTS
SECTION 5		ANATOMY OF PARKINSON'S DISEASE
14	183	DOPAMINERGIC NEURONAL GROUPS
15	188	ANATOMICAL EFFECTS

SECTION 6 PHYSIOLOGY OF PARKINSON'S DISEASE

16 198 DOPAMINERGIC PATHWAYS

17 206 PHYSIOLOGICAL EFFECTS

SECTION 7 SYMPTOMS OF PARKINSON'S DISEASE

18 217 PRIMARY SYMPTOMS

19 222 SYMPTOM PROGRESSION

20 232 MUSCULAR SYSTEM

21 270 NERVOUS SYSTEM

22 315 ALIMENTARY SYSTEM

23 325 URINARY SYSTEM

24 329 CARDIOVASCULAR SYSTEM

25 333 RESPIRATORY SYSTEM

26 336 SKELETAL SYSTEM

27 342 INTEGUMENTARY SYSTEM

28 347 SENSORY SYSTEM

29 358 ENDOCRINE SYSTEM

30 363 REPRODUCTIVE SYSTEM

31 368 IMMUNE SYSTEM

SECTION 8 DIAGNOSIS OF PARKINSON'S DISEASE

32 372 OBSERVATIONAL METHODS

33 397 TECHNOLOGICAL METHODS

34 420 CHEMICAL METHODS

SECTION 9 CAUSES OF PARKINSON'S DISEASE

- 35 426 BIOCHEMICAL CAUSES
- 36 433 TOXIC CAUSES
- 37 464 GENETIC CAUSES
- 38 523 PHARMACOLOGICAL CAUSES
- 39 544 MEDICAL CAUSES

SECTION 10 TREATMENTS OF PARKINSON'S DISEASE

- 40 572 BIOCHEMICAL TREATMENT
- 41 582 PHARMACOLOGICAL : L-DOPA
- 42 604 PHARMACOLOGICAL : DOPAMINE AGONISTS
- 43 650 PHARMACOLOGICAL : MAO INHIBITORS
- 44 659 PHARMACOLOGICAL : COMT INHIBITORS
- 45 671 PHARMACOLOGICAL : ANTI-CHOLINERGICS
- 46 676 PHARMACOLOGICAL : NON-DOPAMINERGIC
- 47 716 SURGICAL TREATMENTS
- 48 746 NATURAL TREATMENTS
- 49 758 EXERCISE METHODS
- 50 771 TECHNOLOGICAL METHODS

APPENDIX PARKINSON'S DISEASE RESOURCES

- 1 783 PARKINSON'S DISEASE ORGANISATIONS
- 2 789 PARKINSON'S DISEASE WEB SITES
- 3 791 PARKINSON'S DISEASE NURSING

CHAPTER 1

HISTORY OF PARKINSON'S DISEASE

ORIGINS

Parkinson's Disease is primarily due to insufficient dopamine. There has been the potential for humans to have insufficient dopamine and to develop Parkinson's Disease since humans have existed. Consequently there have been descriptions and treatments of Parkinson's Disease since ancient times [1].

ANCIENT INDIA

An ancient civilisation in India practiced their medical doctrine called Ayurveda. Ayurveda is claimed to be a divine revelation of the ancient Indian creator God Lord Brahma as he awoke to recreate the universe. They described the symptoms of Parkinson's Disease, that they called Kampavata, as far back as 5000 BC [2]. To treat Kampavata they used Atmagupta, which is a tropical legume called mucuna pruriens. The seeds of mucuna pruriens are a natural source of therapeutic quantities of L-dopa [3]. Mucuna pruriens is the oldest known method of treating the symptoms of Parkinson's Disease and is still widely used to treat Parkinson's Disease. The earliest reference to bradykinesia was in 600 BC. In 300 BC Charaka described the Parkinson's Disease symptoms tremor, rigidity, bradykinesia and gait disturbances [4].

ANCIENT CHINA

The Huang di nei jing su wen, which is often known as the Su wen, is the oldest existing Chinese medical text. It was written in around 500 BC. It is composed of two texts each of 81 chapters or treatises in a question and answer format between the mythical Huang di (Yellow Emperor) and his ministers. The first text, the Suwen, which is also known as Plain Questions, covers the theoretical foundation of Chinese Medicine, diagnosis methods and treatment methods. It also describes the symptoms of Parkinson's Disease [5].

CHAPTER 2

FAMOUS PEOPLE WITH PARKINSON'S DISEASE

MUHAMMAD ALI

American boxer (1942-2016)

Muhammad Ali is a former American boxer who was three time world heavyweight champion. He became Olympic light heavyweight champion in 1960 at the Rome Olympics. In 1964 he became the youngest world heavyweight champion by beating Sonny Liston. In 1967 Muhammad Ali was stripped of his world heavyweight title for refusing to be drafted into the U.S. Army, because of his conscientious objections. He was allowed to resume boxing again in 1970. In 1974 he regained the world heavyweight title by beating George Foreman, and retained it the following year against former champion Joe Frazier. In 1978 Muhammad Ali lost the title to Leon Spinks but regained it the same year before relinquishing the title. He made a failed attempt to regain the world heavyweight title in 1980, and retired in 1981. He was diagnosed with Parkinson's Syndrome in 1984. In 1996, with Parkinsonian symptoms, he lit the flame at the Summer Olympics in Atlanta. In 1997 he set up The Muhammad Ali Parkinson Center to help people with Parkinson's Disease. In 2012, with assistance, he was a bearer of the Olympic Flag during the opening ceremonies of the London Olympics. In 2016 he was hospitalised with a respiratory condition from which he died the following day.

YASSER ARAFAT

Palestinian politician (1929-2004)

Yasser Arafat was Chairman of the Palestine Liberation Organization (PLO), President of the Palestinian National Authority (PNA), and leader and founder of the Fatah political party. He spent much of his life opposing Israel in order to try to achieve a Palestinian state. In 1994 he received the Nobel Peace Prize jointly with Yitzhak Rabin and Shimon Peres because of their peace negotiations. It was frequently speculated that Yasser Arafat had Parkinson's Disease because he exhibited the symptoms but he denied that he had it.

CHAPTER 3

PREVALENCE OF PARKINSON'S DISEASE

HISTORY OF PREVALENCE

As life expectancies have improved, the number and proportion of people with Parkinson's Disease has probably been increasing for centuries. However, in recent decades, the rate at which people with Parkinson's Disease have been newly diagnosed has been declining. The annual rate of decline is somewhere between 1% and 6%. A rate of decline of 1% was obtained when symptoms and Parkinson's Disease drugs were included. A decline of 6% was obtained when only Parkinson's Disease diagnosis was considered [1]. An assessment of the incidence rates between 1990 and 2010 found a reduction in 2000 down to 55% of what the incidence rate was in 1990. The incidence of Parkinson's Disease in 2010 was found to be only 39% of what it was in 1990. Therefore, the incidence of Parkinsonism in general, and Parkinson's Disease in particular, decreased substantially between 1990 and 2011, and is continuously declining [2]. However, in another study, there was found to be a very gradual increase in the incidence of Parkinson's Disease between 1976 and 2005 but only in men [3].

WORLD PREVALENCE

There are up to 10 million or more people in the world who have Parkinson's Disease. There may be many more than this due to the incompleteness and inconsistencies of prevalence studies, no precise definition of Parkinson's Disease, and so many people with Parkinson's Disease not being diagnosed. The actual number of people in the world with Parkinson's Disease is not known.

WORLD'S HIGHEST PREVALENCE

China is the country with the world's greatest number of people with Parkinson's Disease. In China there are probably more than 1.7 million people who have Parkinson's Disease [4].

CHAPTER 4

BIOCHEMISTRY OF PARKINSON'S DISEASE

DOPAMINE BIOSYNTHESIS

DOPAMINE BIOSYNTHESIS

Parkinson's Disease is primarily due to the insufficient formation of dopamine. Therefore, in order to treat Parkinson's Disease effectively it is essential to increase the biosynthesis of dopamine. Dopamine is biosynthesized in the dopaminergic neurons, in the brain, from L-tyrosine via L-dopa : L-tyrosine > L-dopa > dopamine.

FIRST STEP

The first step in the biosynthesis of dopamine requires L-tyrosine, ferrous iron as a cofactor, and the coenzyme tetrahydrofolic acid, for the enzyme tyrosine 3-monooxygenase, which catalyzes the formation of L-dopa [1-4]. In studies on the enzyme tyrosine 3-monooxygenase the biosynthesis of L-dopa rose or fell according to the concentrations of L-tyrosine, ferrous iron and tetrahydrofolic acid [1-4].

enzyme name : tyrosine 3-monooxygenase

enzyme classification : EC 1.14.16.2

cofactor : ferrous iron (Fe^{2+})

substrate : L-tyrosine + tetrahydrofolic acid + O_2

product : L-dopa + dihydrofolic acid + H_2O

SECOND STEP

The second step in the biosynthesis of dopamine requires pyridoxal phosphate as a coenzyme for the enzyme aromatic L-amino acid decarboxylase (dopa decarboxylase) which catalyzes the formation of dopamine from L-dopa [5-9]. In studies on the enzyme L-amino acid decarboxylase the biosynthesis of dopamine rose or fell according to the concentrations of pyridoxal phosphate [5-9].

CHAPTER 5

BIOCHEMISTRY OF PARKINSON'S DISEASE

COENZYME BIOSYNTHESIS

COENZYME BIOSYNTHESIS

Coenzymes are essential for the biosynthesis of dopamine. The coenzymes that are necessary for dopamine biosynthesis are : tetrahydrofolic acid, pyridoxal phosphate and the nicotinamide coenzymes NADP and NADPH. The vitamins folic acid, pyridoxine and nicotinamide are essential for their formation.

TETRAHYDROFOLIC ACID

The first step in the biosynthesis of dopamine requires tetrahydrofolic acid in order to turn L-tyrosine into L-dopa. Tetrahydrofolic acid cannot be administered in order to facilitate dopamine biosynthesis as it is not easily absorbed intact. Folic acid can be administered instead of tetrahydrofolic acid as it readily forms tetrahydrofolic acid [1-4] : folic acid > dihydrofolic acid > tetrahydrofolic acid

FIRST STEP

enzyme name : dihydrofolate reductase

enzyme classification : EC 1.5.1.3

substrate : folic acid + NADPH + H⁺

product : dihydrofolic acid + NADP⁺

SECOND STEP

enzyme name : dihydrofolate reductase

enzyme classification : EC 1.5.1.3

substrate : dihydrofolic acid + NADPH + H⁺

product : tetrahydrofolic acid + NADP⁺

CHAPTER 6

BIOCHEMISTRY OF PARKINSON'S DISEASE

IRON METABOLISM

FERROUS IRON COFACTOR

The first step in the biosynthesis of dopamine requires ferrous iron as a cofactor. The activity of the enzyme increases or decreases according to the concentration of ferrous iron [1-4].

enzyme name : tyrosine 3-monooxygenase

enzyme classification : EC 1.14.16.2

cofactor : ferrous iron (Fe^{2+})

substrate : L-tyrosine + tetrahydrofolic acid + O_2

product : L-dopa + dihydrofolic acid + H_2O

TRANSFERRIN BIOSYNTHESIS

The transport of iron requires the secretion of transferrin from the hepatocytes of the liver. Transferrin is biosynthesized from amino acids, which via translation first form a single chain polypeptide in the ribosomes. With the addition of two molecules of water, leader peptidase removes the signal peptide to produce transferrin in the endoplasmic reticulum. Serotransferrin glycan is added to transferrin in the golgi complex. Iron is attached to the transferrin in the plasma [5-13].

TRANSFERRIN STRUCTURE

Transferrin is a protein consisting of a chain of 679 amino acids [5]. There are two known variants of transferrin. One has isoleucine replaced by asparagine at position 378 or 381 [14]. The other has glycine replaced by arginine at position 394 [15].

CHAPTER 7

BIOCHEMISTRY OF PARKINSON'S DISEASE

ZINC METABOLISM

ZINC COFACTOR

The second step in the biosynthesis of dopamine requires pyridoxal phosphate. The biosynthesis of pyridoxal phosphate requires zinc as a cofactor. The activity of the enzyme increases or decreases according to the concentration of zinc [1, 2].

enzyme name : pyridoxal kinase

enzyme classification : EC 2.7.1.35

cofactor : zinc (Zn^{2+})

substrate : pyridoxal + ATP

product : pyridoxal 5'-phosphate + ADP

METALLOTHIONEIN BIOSYNTHESIS

The transport of zinc requires the secretion of metallothionein. Metallothionein is biosynthesized from amino acids, which via translation first form a single chain polypeptide in the ribosomes. With the addition of two molecules of water, leader peptidase removes the signal peptide to produce metallothionein in the endoplasmic reticulum [3-11]. In the golgi complex zinc is added to metallothionein to form zinc-thionein in the plasma. Zinc is then detached from apothionein in the plasma making it available to the target cells [12, 13].

METALLOTHIONEIN STRUCTURE

There are eleven forms of Metallothionein : Metallothionein MT-2, MT-3, MT-1a, MT-1b, MT-1e, MT-1f, MT-1g, MT-1h, MT-1j, MT-1k, and MT-1l.

CHAPTER 9

BIOCHEMISTRY OF PARKINSON'S DISEASE

DOPAMINE RECEPTORS

DOPAMINE SECRETION

When dopamine has been biosynthesized it is secreted from the dopaminergic neurons, and then stored in synaptic vesicles before being released to the synaptic cleft. The synaptic cleft is the gap between the dopaminergic neuron and the receptive cell whose dopamine receptors it stimulates.

DOPAMINE RECEPTOR BIOSYNTHESIS

Dopamine, via translation, stimulates the biosynthesis in the receptive cells of the dopamine receptors [1-8]. Dopamine causes amino acids to form Pre Dopamine Receptor Protein in the ribosomes. In the endoplasmic reticulum, the addition of two molecules of H₂O enables leader peptidase to remove the signal peptide of Pre Dopamine Receptor Protein. Sugars are then added in the golgi complex. Glycosylation has little effect on the activity of this type of receptor [9]. Secretory vesicles then transport the dopamine receptors to the plasma membrane [1-8].

TYPES OF DOPAMINE RECEPTOR

There are five types of dopamine receptor : D1, D2, D3, D4, D5. Dopamine receptors D1, D5 are stimulatory. Dopamine receptors D2, D3, D4 are inhibitory. The overall effect of the dopamine receptors is inhibitory because the combined effect of the inhibitory dopamine receptors (D2, D3, D4) is far more powerful than the combined effect of the stimulatory dopamine receptors (D1, D5) [10-15].

CHAPTER 10

BIOCHEMISTRY OF PARKINSON'S DISEASE

G PROTEINS

G PROTEIN STIMULATION

The dopamine receptors D1, D2, D3, D4 and D5, affect the G proteins [1, 2]. There are three types of G protein : Gs, Go and Gi. Dopamine receptors D1 and D5 stimulate the activity of the G protein Gs [3]. D1 and D5 stimulate the activity of the G protein Go [4]. D2, D3 and D4 stimulate the activity of the G protein Gi [5].

TYPES OF G PROTEIN SUBUNITS

There are three subunits in G proteins : alpha, beta and gamma. The alpha subunits of the G proteins are : Gs 1 alpha, Gi 1 alpha, Gi 2 alpha, Gi 3 alpha, Go alpha. The beta subunits of the G proteins are : beta one, beta two, beta four. The gamma subunits of the G proteins are : gamma 2, gamma 3, gamma 4, gamma 5, gamma 7, gamma 10, and gamma 11.

G PROTEIN BIOSYNTHESIS

The G proteins are formed from a combination of the three types of subunit (alpha, beta and gamma) [6]. Dopamine receptors stimulate the formation of the pro alpha, pro beta and pro gamma subunits in the ribosomes. With the addition of $2H_2O$, leader peptidase removes the signal peptide of each of the subunits to form the alpha, beta and gamma subunits in the endoplasmic reticulum [6]. The alpha subunits in the biosynthesis of the Gs, Go and Gi proteins then undergo palmitoylation by adding palmitic acid in the endoplasmic reticulum [7]. The alpha subunits of the Go [8] and Gi [9] proteins undergo myristoylation by adding myristic acid in the endoplasmic reticulum.

CHAPTER 12

CYTOLOGY OF PARKINSON'S DISEASE

DOPAMINERGIC NEURONS

STRUCTURE

The dopaminergic neurons are cells that occur in a variety of sizes and shapes [1]. Dopaminergic neurons have dendrites, which are branched projections that act to propagate electrical stimulation. Electrical stimulation is transmitted on to dendrites via synapses, which are located on the dendrites [2]. The dopaminergic neurons also have axons, which are slender projections from the neurons. They are more consistent in shape and greater in length than dendrites.

BIOSYNTHESIS

The dopaminergic neurons, unlike most cells, do not reproduce by undergoing mitosis (cell division) in adults [3, 4]. So the number of dopaminergic neurons tends to decline with age. Although it is often claimed that there is a massive loss of dopaminergic neurons in Parkinson's Disease no research has ever shown this. The study from which these claims originate assessed the enzyme levels in the dopaminergic neurons not the number of the dopaminergic neurons. Enzyme levels determine cell activity not cell loss [5].

FUNCTION

The unique function of the dopaminergic neurons is the biosynthesis and secretion of dopamine [6]. The functions of the dopaminergic neurons are otherwise similar to those of other neurons. In dopaminergic neurons, axons and dendrites are both sites of dopamine release [6]. Insufficient biosynthesis and secretion of dopamine is the primary cause of Parkinson's Disease. In Parkinson's Disease the activity of the enzymes involved in dopamine biosynthesis, not the number of dopaminergic neurons, is greatly reduced [7, 8].

CYTOLOGICAL FEATURES

Cytological features of the dopaminergic neurons are the : cytoplasm, cytosol, nucleus, nucleoli, mitochondrion, smooth endoplasmic reticulum, rough endoplasmic reticulum, ribosomes, Nissl substance, the golgi complex, lysosomes, lipofuscin, endosomes, centrosomes, neurofilaments, cytoskeleton, microtubules, vesicles, and cell membrane.

CYTOPLASM

The cytoplasm is the content of the fluid-filled space inside cells, which is a jelly-like substance. It is within the cytoplasm that most cellular activities occur, including many metabolic pathways. The concentrated inner area is called the endoplasm and the outer layer is called the cell cortex or the ectoplasm.

CYTOSOL

The cytosol is the liquid found inside cells that constitutes most of the intracellular fluid. Water forms the large majority of the cytosol. The cytosol is within the cell membrane and is part of the cytoplasm. Many of the metabolic pathways occur in the cytosol, including the biosynthesis of dopamine [9, 10].

NUCLEUS

The nucleus is a membrane enclosed organelle that contains most of the genetic material of the cells, including chromosomes composed of DNA. The nucleus maintains the integrity of these genes and controls the activities of the cell by regulating gene expression. Nucleolar damage can occur in Parkinson's Disease [11].

NUCLEOLUS

The nucleolus is the largest structure within the nucleus. It is the site of rRNA transcription and processing, and of ribosome biosynthesis and assembly. Cells require large numbers of ribosomes to meet their needs

CHAPTER 13

CYTOLOGY OF PARKINSON'S DISEASE

CYTOLOGICAL EFFECTS

CYTOLOGICAL EFFECTS

When L-dopa or dopamine is not biosynthesized properly in the dopaminergic neurons, as occurs in Parkinson's Disease, certain cytological effects can occur. This can result in the formation of Superoxide anion [PAGE 170], Neuromelanin formation [PAGE 172], Iron accumulation [PAGE 175], the accumulation of Alpha-synuclein [PAGE 176], and the formation of Lewy bodies [PAGE 179].

SUPEROXIDE ANION

The first step in the formation of dopamine is the biosynthesis of L-dopa from L-tyrosine [1-4]. In Parkinson's Disease, largely due to inadequate cofactors, L-tyrosine and molecular oxygen do not completely form L-dopa. Consequently, the toxic partial reduction product of oxygen, the superoxide anion can be formed instead. Superoxide (O_2^-) is formed by the oxidation of ferrous ions (Fe^{2+}) by dioxygen (O_2) [5].

enzyme name : tyrosine 3-monooxygenase

enzyme classification : EC 1.14.16.2

cofactor : ferrous iron (Fe^{2+})

substrate : L-tyrosine + O_2 + Fe^{2+}

product : L-tyrosine + O_2^- + Fe^{3+}

Superoxide is the origin of most reactive oxygen species. It undergoes a chain reaction in cells playing a central role in the reactive oxygen species system. Increased oxidative stress on an organism causes damage to cells [6]. The Superoxide anion is a major inducer of neurodegenerative damage in Parkinson's Disease. There is a high

CHAPTER 14

ANATOMY OF PARKINSON'S DISEASE

DOPAMINERGIC NEURONAL GROUPS

DOPAMINERGIC NEURONAL GROUPS

The term dopaminergic neuronal groups refers to collections of neurons in the central nervous system that have been found to contain dopamine. Ten dopaminergic neuronal groups have been recognised. They are classified as groups A8 to A17. The cell aggregations (A8, A9 and A10) are in the mesencephalon [1]. The cell aggregations (A11, A12, A13 and A14) are in the diencephalon [2, 3]. A single group of dopaminergic neurons (A15) has been found in the hypothalamus [4, 5]. A single group of dopaminergic neurons (A16) has been found in the olfactory bulb [6]. A single group of dopaminergic neurons (A17) has been found in the retina [7].

MESENCEPHALON

The mesencephalon (the midbrain) comprises the tectum (corpora quadrigemina), the tegmentum, the cerebral aqueduct (ventricular mesocoelia), the cerebral peduncles, and several nuclei and fasciculi. It is near the centre of the brain, below the cerebral cortex and above the hindbrain. Prominent cell groups of the mesencephalon include the motor nuclei of the trochlear and oculomotor nerves, the red nucleus, and the substantia nigra. Three dopaminergic cell aggregations (A8, A9 and A10) are in the mesencephalon. They are the main dopaminergic neuronal groups [1].

GROUP A8

Group A8, which is part of the mesencephalic reticular formation, is located in the retrorubral field [1]. It is also known as the substantia nigra pars lateralis [8].

CHAPTER 15

ANATOMY OF PARKINSON'S DISEASE

ANATOMICAL EFFECTS

ANATOMICAL EFFECTS

Most of the anatomical effects in Parkinson's Disease originate from the insufficient formation of dopamine. When there is insufficient dopamine, there is often an effect on each of the anatomical structures that dopamine normally stimulates via the various dopaminergic pathways.

NERVOUS SYSTEM

The dopaminergic neurons are one of only four cell types that can not reproduce in adults. However, when compared to people of a similar age, there is hardly any difference in the number of dopaminergic neurons in people with Parkinson's Disease [1]. There is also no difference in the volume of the relevant part of the brain either [1]. The volume of the part of the brain in which dopaminergic neurons are common does not decline as Parkinson's Disease gets worse as it would if there was a loss of these cells. People with Parkinson's Disease do not differ in this way from those people who do not have Parkinson's Disease [2].

Although it is often claimed that there is a massive loss of the dopaminergic neurons in Parkinson's Disease, no studies have ever shown this to be true. Studies making such claims have measured the enzyme activity of the dopaminergic neurons instead of the loss of the dopaminergic neurons [3]. Enzyme activity determines the activity of the cells not the number of cells. Research has always shown that there is a major reduction in cell activity in people with Parkinson's Disease rather than an actual major loss of the cells involved in Parkinson's Disease.

CHAPTER 16

PHYSIOLOGY OF PARKINSON'S DISEASE

DOPAMINERGIC PATHWAYS

DOPAMINERGIC PATHWAYS

Dopaminergic pathways, which are sometimes called dopaminergic projections, are neural pathways in the brain that transmit dopamine from one region of the brain to another. The neurons of the dopaminergic pathways have axons that run the entire length of the pathway. The major dopaminergic pathways in the brain are : the nigrostriatal pathway, the mesocortical pathway, the mesolimbic pathway, the tuberoinfundibular pathway, the diencephalospinal pathway, the incertohypothalamic pathway, neuroendocrine pathways, the olfactory pathway, and the visual pathway.

NIGROSTRIATAL PATHWAY

Pathway : In the substantia nigra, A9 dopaminergic neurons form the nigrostriatal pathway [1]. The functional activity of the nigrostriatal pathway is also modulated by A8 dopaminergic neurons [2]. The nigrostriatal pathway transmits dopamine from the substantia nigra pars compacta (SNc), which is located in the midbrain, to the caudate nucleus and putamen, which are located in the dorsal striatum [3].

Functions : The primary effect of the dopaminergic neurons via the nigrostriatal pathway is the maintenance of muscle tone in skeletal muscles by reducing muscle contraction [4, 5, 6]. The nigrostriatal pathway is necessary for efficient motor performance [6, 7]. Dopamine, via the nigrostriatal pathway, also acts on smooth muscle [8, 9].

[1] Proceedings, National Academy of Sciences, U.S.A. [2009] 106 (36) : 15454-15459 (M.Biagioli, M.Pinto, D.Cesselli, M.Zaninello, D. Lazarevic, P.Roncaglia, R.Simone, C.Vlachouli, C.Plessy, et al)

CHAPTER 17

PHYSIOLOGY OF PARKINSON'S DISEASE

PHYSIOLOGICAL EFFECTS

PHYSIOLOGICAL EFFECTS

Most of the physiological effects in Parkinson's Disease are due to the insufficient formation of dopamine. When there is insufficient dopamine, there is a reduction in each of the physiological functions that dopamine normally stimulates via the various dopaminergic pathways.

MUSCULAR SYSTEM

The muscular system includes skeletal, smooth muscles and cardiac muscles. Skeletal muscles are attached to the skeleton. The skeletal muscles enable movement of the body and the maintenance of posture.

The primary dopaminergic effect via the nigrostriatal pathway is the reduction of muscle contraction in the skeletal and smooth muscles. Consequently, reduced dopaminergic stimulation, as occurs in Parkinson's Disease, causes excessive contraction of the skeletal and smooth muscles.

Acetylcholine affects muscle contraction via the five cholinergic receptors : m1, m2, m3, m4, and m5. The receptors m1, m3 and m5 are stimulatory. The receptors m2 and m4 are inhibitory. The combined stimulatory effect of m1, m3 and m5 is more powerful in total than the combined inhibitory effect of m2 and m4. So the overall effect of acetylcholine is to stimulate muscle contraction.

Dopamine affects muscle contraction via the five dopamine receptors : D1, D2, D3, D4, and D5. The receptors D2, D3 and D4 are inhibitory. The receptors D1 and D5 are stimulatory. The combined inhibitory

CHAPTER 18

SYMPTOMS OF PARKINSON'S DISEASE

PRIMARY SYMPTOMS

TYPES OF SYMPTOMS

The symptoms of Parkinson's Disease differ from person to person, over time, and in their severity. Muscular symptoms, such as rigidity, tremor, bradykinesia (slowness of movement) and walking difficulties are the most apparent and characteristic symptoms of Parkinson's Disease. However, Parkinson's Disease can eventually affect every system in the body : the muscular, nervous, alimentary, urinary, cardiovascular, respiratory, skeletal, integumentary, sensory, endocrine, reproductive, and immune systems.

Instead of being due to Parkinson's Disease, some of the symptoms commonly experienced in Parkinson's Disease, such as dyskinesia, can be caused by Parkinson's Disease drugs, especially when the Parkinson's Disease is more advanced.

There are other symptoms, such as dementia, that are not due to Parkinson's Disease but often coincide with Parkinson's Disease, especially when the Parkinson's Disease is more advanced.

MOST PREVALENT SYMPTOMS

EARLIER PARKINSON'S DISEASE

The most common symptoms in earlier Parkinson's Disease are rigidity (stiffness), tremor, bradykinesia (slowness of movement), freezing, falling, micrographia (reduced handwriting size), reduced arm swing, mirror movements, dysarthria (speech difficulties), hypomimia (reduced facial expression), depression, apathy, fatigue, anxiety, pain, sleep disturbance, constipation, dysphagia (swallowing difficulty),

CHAPTER 19

SYMPTOMS OF PARKINSON'S DISEASE

SYMPTOM PROGRESSION

EARLIEST SYMPTOMS

Many people have already had Parkinson's Disease for years by the time they are diagnosed with Parkinson's Disease or have had symptoms that were progressing towards it.

A comparison was made between those symptoms before diagnosis and their subsequent diagnosis. At 10 years before diagnosis the incidence of tremor was many times higher and constipation was higher in those who went on to develop Parkinson's Disease. At 5 years before diagnosis those who went on to develop Parkinson's Disease had a much higher incidence of tremor, a higher incidence of imbalance, constipation, hypotension, and a slightly higher incidence of erectile dysfunction, urinary dysfunction, dizziness, fatigue, depression, and anxiety. At 2 years before diagnosis the incidence of all studied features except neck pain and stiffness were higher in people who went on to develop Parkinson's Disease. A range of symptoms can therefore be detected years before diagnosis of Parkinson's Disease, with tremor being especially common prior to diagnosis [1].

Whether somebody is right handed or left handed can greatly affect on which side Parkinson's Disease symptoms initiate and which symptoms they initially have. Out of those people with Parkinson's Disease 92% were right handed. Nearly 62% of them had an initial onset of symptoms on the right hand side. Out of those people with Parkinson's Disease 8% were left handed. Around 75% of them had an initial onset of symptoms on the left hand side. Out of those people with Parkinson's Disease who were right handed 77% had Parkinson's Disease symptoms that were dominant on the right hand side. Out of those people with Parkinson's Disease who were left handed 58% of them had Parkinson's Disease symptoms that were dominant on the left hand

CHAPTER 20

SYMPTOMS OF PARKINSON'S DISEASE

MUSCULAR SYSTEM

MUSCULAR SYSTEM

The muscular system consists of skeletal, smooth and cardiac muscles. Skeletal muscles are attached to the skeleton. They are called voluntary muscles because the muscles can be controlled. The muscular system enables movement of the body and the maintenance of posture.

PRIMARY SYMPTOMS

In Parkinson's Disease there are symptoms that can affect the muscles generally. These include rigidity [PAGE 233], tremor [PAGE 234], hypokinesia (reduced movement) [PAGE 237], bradykinesia (slowness of movement) [PAGE 238], akinesia (loss of movement) [PAGE 239], dyskinesia (abnormal involuntary movements) [PAGE 240], akathisia (motor restlessness) [PAGE 243], and dystonia (abnormal involuntary postures) [PAGE 244].

Those muscular symptoms that can specifically affect the lower limbs are : shuffling (when walking) [PAGE 245], freezing (feeling unable to walk forwards) [PAGE 246], festination [PAGE 249], falling [PAGE 250], and restless legs syndrome [PAGE 254].

Those muscular symptoms that can specifically affect the upper limbs are : impaired finger dexterity [PAGE 258], micrographia (small handwriting) [PAGE 258], reduced arm swing [PAGE 260], mirror movement [PAGE 261], and frozen shoulder syndrome [PAGE 263].

Those muscular symptoms that can specifically affect the head and neck are hypomimia (reduced facial expression) [PAGE 264], reduced blinking [PAGE 265], dysarthria (difficulty speaking) [PAGE 266], dysphonia [PAGE 268], and neck rigidity [PAGE 268].

CHAPTER 21

SYMPTOMS OF PARKINSON'S DISEASE

NERVOUS SYSTEM

NERVOUS SYSTEM

The nervous system is made up of the brain, the spinal cord, the nerves, and the sense organs, such as the eye and the ear. The nervous system receives, interprets, and responds to stimuli from inside and outside the body.

PRIMARY SYMPTOMS

In Parkinson's Disease there can be an increased likelihood of depression [PAGE 270], dementia [PAGE 276], pain [PAGE 281], sleep disturbance [PAGE 286], excessive daytime sleepiness [PAGE 289], fatigue [PAGE 294], apathy [PAGE 296], anhedonia [PAGE 299], bradyphrenia [PAGE 301], alexithymia [PAGE 303], neuropathy [PAGE 304], anxiety [PAGE 305], hallucinations [PAGE 307], compulsions [PAGE 311], vertigo [PAGE 313]. The most prominent, prevalent or troubling of these symptoms are depression, dementia, pain, fatigue and sleep disturbance.

DEPRESSION

Symptoms : Dopamine is involved in the control of behaviour. So its deficiency can cause emotional depression and slowness of thinking. Symptoms of depression can be evident in people with Parkinson's Disease at the time of diagnosis and might develop in the pre-motor stage of the disease [1, 2]. Depression made Parkinson's Disease as much as four times more likely to develop [3-9]. Depressive features did not differ according to whether or not people also had Parkinson's Disease [10]. Depression has been shown to contribute to an increased rate of decline of both cognitive and motor function, profoundly impacting on the patient's quality of life [11-13].

CHAPTER 22

SYMPTOMS OF PARKINSON'S DISEASE

ALIMENTARY SYSTEM

ALIMENTARY SYSTEM

The Alimentary System includes all the body structures involved in eating food, preparing food for absorption, digesting food and the excretion of waste products. This includes the : oral cavity, pharynx, oesophagus, stomach, small intestine, large intestine (colon), rectum and anus.

PRIMARY SYMPTOMS

In Parkinson's Disease there can be an increased likelihood of constipation [PAGE 315], dysphagia (swallowing difficulty) [PAGE 317], sialorrhea (excessive saliva and drooling) [PAGE 319], intestinal bacterial overgrowth [PAGE 320], gastroparesis (slow gastric emptying) [PAGE 321], and obesity [PAGE 322]. The most common symptoms of these in Parkinson's Disease are constipation, which occurs in most people, followed by dysphagia, then sialorrhea, both of which occur in a large minority of people.

CONSTIPATION

Symptoms : Constipation refers to bowel movements that are infrequent or hard to pass. Constipation is a common cause of painful defecation. Severe constipation can progress to bowel obstruction.

Prevalence : Most people with Parkinson's Disease suffer from constipation [1-10]. Severe constipation is associated with the time since diagnosis and the severity of Parkinson's Disease [6]. Severity of constipation is associated with a future diagnosis of Parkinson's Disease [11, 12]. Constipation is more common when Parkinson's

CHAPTER 23

SYMPTOMS OF PARKINSON'S DISEASE

URINARY SYSTEM

URINARY SYSTEM

The urinary system consists of the two kidneys, ureters, the bladder, and the urethra. The urinary system is the primary means of eliminating liquid from the body.

PRIMARY SYMPTOMS

In Parkinson's Disease there is often nocturia (frequent urinating at night) [PAGE 325], urinary incontinence (loss of urinary control) and increased urinary frequency [PAGE 326], and urinary retention [PAGE 326]. Urinary symptoms occur in between 27% and 85% of people with Parkinson's Disease [1-8].

NOCTURIA

Symptoms : Nocturia is the need to often urinate at night. Most people with Parkinson's Disease have nocturia, which is the most common urinary symptom that people with Parkinson's Disease experience [2, 4, 7, 8, 9, 10, 11].

Prevalence : More than a third of people with Parkinson's Disease are diagnosed with nocturia [8, 12]. Those people who had Parkinson's Disease who were 70 years old and older were more likely to have both nocturia and nocturnal polyuria, which is the passing of an excessive quantity of urine - 72% instead of 55% for those younger than 70. Men had nocturia more frequently - 33% for men and 20% for women [7]. However, in another study, only 15% of men had nocturia [13]. Asian and Indian males were especially at a significantly greater risk of nocturia than other ethnicities [12]. Symptoms of nocturia were not

CHAPTER 24

SYMPTOMS OF PARKINSON'S DISEASE

CARDIOVASCULAR SYSTEM

CARDIOVASCULAR SYSTEM

The cardiovascular system, also known as the circulatory system, is an organ system that encompasses the heart and blood vessels of the body. The cardiovascular system carries blood, oxygen, and nutrients to organs and tissues of the body, and carries waste and carbon dioxide from these tissues for removal from the body.

PRIMARY SYMPTOMS

Cardiovascular dystautonomia usually occurs in Parkinson's Disease and can include a variety of cardiovascular symptoms. Certain Parkinson's Disease drugs can increase the likelihood of heart failure, in which breathlessness, feeling very tired and ankle swelling are the main symptoms.

CARDIOVASCULAR DYSAUTONOMIA

Symptoms : Cardiovascular dystautonomia includes signs or symptoms of impaired autonomic regulation of circulation and are often affected in Parkinson's Disease [1]. Over a period of three years there is progression of an impairment of sympathetic and parasympathetic control of the cardiovascular functions in people with Parkinson's Disease [2]. Cardiovascular autonomic function, especially orthostatic hypotension, is often affected in Parkinson's Disease [1, 3, 4, 5]. Mild impairment of autonomic cardiovascular control occurred early in the course of Parkinson's Disease [6]. Latent cardiac and vasomotor sympathetic dysfunction but not parasympathetic dysfunction is already present early in Parkinson's Disease, even without orthostatic hypotension [7]. There is a cardiovascular dysfunction, which occurs

CHAPTER 25

SYMPTOMS OF PARKINSON'S DISEASE

RESPIRATORY SYSTEM

RESPIRATORY SYSTEM

The respiratory system includes the nasal passages, larynx, trachea, bronchial tubes, diaphragm and the lungs. Muscles are involved in facilitating the function of the respiratory system. The respiratory system enables a person to breathe and exchange oxygen and carbon dioxide throughout the body.

PRIMARY SYMPTOMS

Respiratory muscle dysfunction usually, but not always, occurs in Parkinson's Disease. Respiratory muscle dysfunction makes respiratory diseases such as pneumonia more dangerous due to the reduced respiratory capacity it causes.

RESPIRATORY MUSCLE DYSFUNCTION

Symptoms : Repetitive ventilatory tasks can be limited and contribute to respiratory muscle fatigue. Consequently, the breathing rate can not be sustained as well and breathing efficiency is reduced [1]. There is often abnormal ventilatory control despite normal lung volumes and flows [2]. Respiratory muscle strength and endurance are also decreased [3]. Due to the reduced respiratory capacity, people with Parkinson's Disease are more prone to the effects of pneumonia, which occurs more commonly than expected in Parkinson's Disease, but not because of Parkinson's Disease [4, 5, 6]. Consequently, pneumonia is the most common cause of death associated with Parkinson's Disease [7-13]. However, death certificates indicated that pneumonia was a substantial contributor to the cause of death in only 20% of people with Parkinson's Disease [13]. Asthmatics, especially those people with

CHAPTER 26

SYMPTOMS OF PARKINSON'S DISEASE

SKELETAL SYSTEM

SKELETAL SYSTEM

The skeletal system includes all of the bones and joints in the body. The skeleton acts as a scaffold by providing support and protection for the soft tissues that make up the rest of the body. The skeletal system also provides attachment points for muscles to allow movements at the joints.

PRIMARY SYMPTOMS

In Parkinson's Disease there can be an increased likelihood of osteoporosis [PAGE 337] and osteopenia [PAGE 337]. The postural deformities can include scoliosis [PAGE 338], Pisa syndrome [PAGE 338], and camptocormia [PAGE 339].

Postural deformities can be frequent and disabling complications of Parkinson's Disease [1]. The prevalence of skeletal problems is higher in people with Parkinson's Disease. Around two thirds of people with Parkinson's Disease have them. Only just over a quarter of people with Parkinson's Disease answered that their musculoskeletal problems were recovering. Musculoskeletal problems tended to receive less treatment when people had Parkinson's Disease. The most common sites of musculoskeletal problems are the lower back, in nearly half of people, and the shoulder and knee, which were affected far less [2].

[1] Lancet Neurology [2011] 10 (6) : 538-549 (K.M.Doherty, B.P.van de Warrenburg, M.C.Peralta, L.Silveira-Moriyama, J.P.Azulay, O.S. Gershanik, B.R.Bloem)

[2] Parkinsonism & Related Disorders [2013] 19 (7) : 666-669 (Y.E. Kim, W.W.Lee, J.Y.Yun, H.J.Yang, H.J.Kim, B.S.Jeon)

CHAPTER 27

SYMPTOMS OF PARKINSON'S DISEASE

INTEGUMENTARY SYSTEM

INTEGUMENTARY SYSTEM

The integumentary system is the skin and its associated glands, including the sweat glands, as well as the hair and nails. The skin protects the body from various kinds of damage such as loss of water or abrasion from outside.

PRIMARY SYMPTOMS

In Parkinson's Disease there is an increased likelihood of melanoma [PAGE 342], which is a form of skin cancer; hyperhidrosis [PAGE 344], which is increased sweat secretion; and seborrhea [PAGE 345], which is increased sebum secretion.

MELANOMA

Symptoms : Melanoma is a type of skin cancer that forms from the melanocytes. Most melanomas present as a dark, mole-like spot that spreads and, unlike a mole, has an irregular border.

Prevalence : There is a higher than expected frequency of melanoma in people with Parkinson's Disease [1-8], which is not due to L-dopa [5, 9, 10, 11]. Melanoma was over three times more likely in people with Parkinson's Disease after they have been diagnosed but was not more likely before diagnosis. The risk of melanoma could sometimes be as much as four to nine times higher in Parkinson's Disease [12, 13]. There was no relationship between Parkinson's Disease and other skin cancers [14].

Causes of symptoms : The melanocytes in the skin produce melanin,

CHAPTER 28

SYMPTOMS OF PARKINSON'S DISEASE

SENSORY SYSTEM

SENSORY SYSTEM

The sensory system consists of the olfactory system (for olfaction, which is the sense of smell), the gustatory system (for the sense of taste), the visual system (for visual perception), and the auditory system (for the sense of hearing).

PRIMARY SYMPTOMS

In Parkinson's Disease there can be an increased likelihood of anosmia (which is a loss of the sense of smell) [PAGE 347], rhinorrhea (which is nasal discharge) [PAGE 349], visual disturbance [PAGE 350], retinal thinning [PAGE 351], hypogeusia (which is impaired sense of taste [PAGE 354], and hearing loss [PAGE 356]. Visual disturbances and anosmia are particularly prominent.

OLFACTORY SYSTEM

The olfactory system is the sensory system used for olfaction, which is the sense of smell. Odorants are inhaled through the nose where they contact the main olfactory epithelium. The olfactory epithelium contains olfactory receptors, which turns receptor activation for a variety of smells into electrical signals in neurons, which is where the stimulus is perceived.

ANOSMIA

Symptoms : A loss of the sense of smell (anosmia) and reduced sense of smell (hyposmia) often occur in Parkinson's Disease [1-11]. Those people with mild cognitive impairment are often unaware of it [12].

CHAPTER 29

SYMPTOMS OF PARKINSON'S DISEASE

ENDOCRINE SYSTEM

ENDOCRINE SYSTEM

The endocrine glands include the pineal gland, pituitary gland, thyroid gland, thymus, adrenal gland, pancreas, parathyroid gland, ovaries, testes, and hypothalamus. The endocrine system refers to glands that secrete hormones directly into the circulatory system to be carried towards target organs.

PRIMARY SYMPTOMS

In Parkinson's Disease there is an increased likelihood of hyperprolactinemia [PAGE 358] in the pituitary gland, blunted circadian rhythms [PAGE 359] in the pineal gland, hypothyroidism [PAGE 360] in the thyroid gland, and catecholamine deficiency [PAGE 362] in the adrenal gland.

PITUITARY GLAND

The pituitary gland (hypophysis) is a small endocrine gland in the brain. It is a protrusion off the bottom of the hypothalamus at the base of the brain. The pituitary gland produces a number of hormones including prolactin.

HYPERPROLACTINEMIA

Symptoms : Hyperprolactinemia is the increased secretion of prolactin from the pituitary gland. It affects the reproductive functions.

Prevalence : In most people with Parkinson's Disease the levels of prolactin are raised [1, 2, 3], but in some people with Parkinson's

CHAPTER 30

SYMPTOMS OF PARKINSON'S DISEASE

REPRODUCTIVE SYSTEM

REPRODUCTIVE SYSTEM

The reproductive system is a system of sex organs which work together for the purpose of sexual activity and sexual reproduction. Many non-living substances such as fluids, hormones, and pheromones are important accessories for the proper functioning of the reproductive system.

PRIMARY SYMPTOMS

Parkinson's Disease can cause sexual dysfunction in men and women. Sexual dysfunction is common in Parkinson's Disease, with over 40% of people with Parkinson's Disease being affected in this way [1]. Over two thirds of people with Parkinson's Disease had decreased sexual activity [2]. Nearly two thirds of people with Parkinson's Disease had a loss of sex drive [3, 4]. Sexual dissatisfaction is experienced by 37% of people [5]. Associated illnesses, use of medications, and advanced stage of Parkinson's Disease contributed to sexual dysfunction [6]. Sexual dysfunction was not otherwise related to age or age of onset [1] or duration [7] of Parkinson's Disease. Perception of sexual functioning is also considerably influenced by depression [8]. The neurological features that were most associated with a greater loss of sex drive and sexual activity were autonomic dysfunction, aging, depression, female gender and severer Parkinson's Disease [4, 9].

MALE REPRODUCTIVE SYSTEM

The male reproductive system can be grouped into three categories. The first category is the production and storage of sperm. This takes place in the testes, which are inside the scrotum. Immature sperm travel

CHAPTER 31

SYMPTOMS OF PARKINSON'S DISEASE

IMMUNE SYSTEM

IMMUNE SYSTEM

The immune system is a diffuse network of interacting cells, cell products, and cell-forming tissues. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, macrophages, lymphocytes, antibodies and lymphokines. The immune system protects the body from pathogens and other foreign substances, destroys infected and malignant cells, and removes cellular debris.

PRIMARY SYMPTOMS

Neuroinflammation commonly, but not always, occurs in Parkinson's Disease [PAGE 368]. There is a greater likelihood of CNS infections occurring in Parkinson's Disease after diagnosis, and also before being diagnosed with Parkinson's Disease [PAGE 370].

NEUROINFLAMMATION

Symptoms : Neuroinflammation is a defence mechanism associated with the restoration of the normal structure and function of the brain [1]. People with Parkinson's Disease who have neuroinflammation present with all of the classical features of inflammation including phagocyte activation, complement activation, increased synthesis and release of proinflammatory cytokines [2]. In people with Parkinson's Disease activated microglial cells and T lymphocytes have been detected in the substantia nigra concomitantly with an increased expression of pro-inflammatory mediators [3]. Under conditions of increased glucocorticoids, the elevated prolactin that occurs in Parkinson's Disease functions physiologically to maintain the survival and function of T-lymphocytes [4].

CHAPTER 32

DIAGNOSIS OF PARKINSON'S DISEASE

OBSERVATIONAL METHODS

DIAGNOSIS

Diagnosis is usually based on physical observation and questioning of the patients. The most commonly used symptom questionnaire is the Unified Parkinson Disease Rating Scale (UPDRS). Assessments can also involve the SPECT or PET scans, which are the most accurate methods of diagnosing Parkinson's Disease.

MISDIAGNOSIS

Misdiagnosis in Parkinson's Disease is very common. The average accuracy of diagnosing Parkinson's Disease is only 80% [1]. For clinical diagnosis performed by non-experts the accuracy is even less, at 73% [1]. Accuracy of clinical diagnosis performed by movement disorders experts rose from 79% at the initial assessment to 84% after a follow-up assessment [1]. However, initial diagnoses of Parkinson's Disease made by general neurologists were only infrequently changed [2]. They were incorrect in 18% to 35% of cases [1, 2, 3]. This means that many people have been treated for Parkinson's Disease without ever having had Parkinson's Disease. In people taking Parkinson's Disease drugs Parkinsonism was confirmed in only 74% of cases and only 53% of them had probable Parkinson's Disease. Over a quarter of the people diagnosed with Parkinson's Disease did not benefit from Parkinson's Disease drugs [3, 4]. More than 1 in 3 people with tremor were misdiagnosed as having Essential Tremor when most of them actually had Parkinson's Disease [5]. From 17% to 26% of people with tremor disorders were wrongly diagnosed as having tremor dominant Parkinson's Disease [6]. From 6% to 20% of people with tremor dominant Parkinson's Disease were wrongly diagnosed as having other tremor disorders [6]. The accuracy of diagnosing Parkinson's Disease had not significantly improved in the previous 25 years [1].

- [1] Neurology [2016] 86 (6) : 566-576 (G.Rizzo, M.Copetti, S.Arcuti, D.Martino, A.Fontana, G.Logroscino)
- [2] Archives of Neurology [2000] 57 (3) : 369-372 (J.Jankovic, A.H. Rajput, M.P.McDermott, D.P.Pperl)
- [3] Lancet Neurology [2006] 5 (1) : 75-86 (E.Tolosa, G.Wenning, W. Poewe)
- [4] Age and Ageing [1999] 28 (2) : 99-102 (J.Meara, B.K.Bhowmick, P.Hobson)
- [5] Archives of Neurology [2006] 63 (8) : 1100-1104 (S.Jain, S.E.Lo, E.D.Louis)
- [6] Journal of Neurology, Neurosurgery and Psychiatry [2010] 81 (11) : 1223-1228 (N.P.Bajaj, V.Gontu, J.Birchall, J.Patterson, D.G.Grosset, A.J.Lees)

OBSERVATIONAL METHODS OF DIAGNOSIS

Besides the Unified Parkinson Disease Rating Scale (UPDRS) [PAGE 373], less common means of assessment are : the Hoehn and Yahr [PAGE 384], which grades patients according to five stages of severity; the MDS-UPDRS [PAGE 385], which is a revision of the UPDRS; the modified Rankin Scale (mRS) [PAGE 386], which assesses the level of disability; the PDQ-39 [PAGE 387] and the PDQL [PAGE 390], which assess the quality of life; the Schwab and England Activities of Daily Living [PAGE 392]; and the Webster disability rating scale [PAGE 393].

UNIFIED PARKINSON DISEASE RATING SCALE (UPDRS)

The most commonly used symptom questionnaire is the Unified Parkinson Disease Rating Scale (UPDRS). The UPDRS was developed to address the need for a comprehensive Parkinson's Disease measurement tool. It includes scoring by a clinician, based on motor examination, and a historical report of mental functioning and activities of daily living obtained by questioning the patient. It enables the

CHAPTER 33

DIAGNOSIS OF PARKINSON'S DISEASE

TECHNOLOGICAL METHODS

DIAGNOSIS

Diagnosis is usually based on physical observation and questioning of the patients. The most commonly used symptom questionnaire is the Unified Parkinson Disease Rating Scale (UPDRS). Assessments can also involve the SPECT or PET scans, which are the most accurate methods of diagnosing Parkinson's Disease.

MISDIAGNOSIS

SWEDD (scans without evidence for dopaminergic deficit) refers to somebody assumed to have Parkinson's Disease but whose scan shows the absence of dopamine deficiency. Most SWEDD cases are due to a misdiagnosis of Parkinson's Disease but a small proportion may still have Parkinson's Disease because of : a positive L-dopa response, clinical progression, imaging and genetic evidence [1].

[1] Journal of Neurology, Neurosurgery and Psychiatry [2016] 87 (3) : 319-323 (R.Erro, S.A.Schneider, M.Stamelou, N.P.Quinn, K.P.Bhatia)

TECHNOLOGICAL METHODS OF DIAGNOSIS

Besides the SPECT scan [PAGE 398] and the PET scan [PAGE 400], less common technological methods that are available or in development include : dysphonia measures [PAGE 402], eye brain tracker [PAGE 403], Gaitrite [PAGE 403], laryngeal electromyography [PAGE 404], magnetic resonance imaging [PAGE 405], P3a wave [PAGE 406], Parkinson's Kineti Graph [PAGE 406], sensory pen [PAGE 407], smartphones [PAGE 408], smartwatch [PAGE 408], transcranial doppler sonography [PAGE 409], transcranial sonography [PAGE 410], ultrasound elastography [PAGE 413], vestibulography [PAGE 413], and wearable sensors [PAGE 414].

CHAPTER 34

DIAGNOSIS OF PARKINSON'S DISEASE

CHEMICAL METHODS

DIAGNOSIS

Diagnosis is usually based on physical observation and questioning of the patients. The most commonly used symptom questionnaire is the Unified Parkinson Disease Rating Scale (UPDRS). Assessments can also involve the SPECT or PET scans, which are the most accurate methods of diagnosing Parkinson's Disease.

CHEMICAL METHODS OF DIAGNOSIS

Chemical methods of diagnosing Parkinson's Disease that are either available or are in development include : biomarkers [PAGE 420], a breath test [PAGE 421], saliva gland test [PAGE 422], and several types of smell test [PAGE 422].

BIOMARKERS

Technology : A biomarker is a substance used as an indicator of a biological state or illness [1]. These have included a selection of blood-borne autoantibody biomarkers with a higher prevalence in early Parkinson's Disease used to facilitate the diagnosis of early Parkinson's Disease. Antibodies are proteins produced by a person's immune system that allows their body to distinguish between "self" and "non-self" proteins [2].

Efficacy : A systematic review was undertaken to determine which biomarkers for disease progression in Parkinson's Disease exist. The sensitivity of the tests was an average of 71%, which is insufficient for Parkinson's Disease diagnosis. The range in sensitivity was between 51% and 86% showing that some of the methods were nearer to having

CHAPTER 35

CAUSES OF PARKINSON'S DISEASE

BIOCHEMICAL CAUSES

BIOCHEMICAL REACTIONS

Almost all biochemical reactions require the presence, in optimal quantities, of specific enzymes, substrates, coenzymes and cofactors. Consequently, the concentrations of those enzymes, substrates, coenzymes and cofactors determine the rate at which the biochemical reactions take place.

DOPAMINE BIOSYNTHESIS

Parkinson's Disease is primarily due to the insufficient biosynthesis of dopamine. The primary methods of treating Parkinson's Disease are based on this fact. So when the enzymes, substrates, coenzymes and cofactors required for dopamine biosynthesis are deficient the biosynthesis of dopamine is greatly reduced. The insufficient biosynthesis of dopamine causes Parkinson's Disease.

ENZYMES

Enzymes enable biochemical reactions to take place. Almost all biochemical reactions require an enzyme for the biochemical reaction to be completed. The level of activity of the enzyme determines the rate at which the biochemical reaction occurs. However, unless the enzymes have genetic errors, which is a rare occurrence, the enzymes will be present.

In people with Parkinson's Disease, the activity of the enzymes required for dopamine biosynthesis are substantially reduced, to very low levels in some people [1-6]. However, the activity of the enzymes can be greatly increased with the use of the substrate, coenzymes, and cofactors for those enzymes [7-15].

CHAPTER 36

CAUSES OF PARKINSON'S DISEASE

TOXIC CAUSES

TOXIC CAUSES

A small proportion of cases have a toxic cause as the sole or a partial cause of Parkinson's Disease. The toxic exposure usually has to be acute or chronic. Symptoms normally develop when the toxic exposure occurs or soon after, or gradually increase over time when the exposure persists. Symptoms do not develop years later as is sometimes claimed. Avoidance of the source of toxicity can lead, in most cases, to a reduction in the symptoms but with some toxins this can take years.

Toxic causes of Parkinson's Disease include : Annonaceae [PAGE 433], Carbon disulfide [PAGE 435], Carbon monoxide [PAGE 436], Copper [PAGE 438], Cyanide [PAGE 439], Cycad seeds [PAGE 440], Dieldrin [PAGE 445], Hydrocarbons [PAGE 446], Lead [PAGE 447], Maneb [PAGE 448], Manganese [PAGE 450], Mercury [PAGE 452], MPTP [PAGE 453], N-hexane [PAGE 454], Nitrogen dioxide [PAGE 455], Octenol [PAGE 455], Organophosphorus pesticides [PAGE 456], Paraquat [PAGE 457], Rotenone [PAGE 460], Toluene [PAGE 462] and Trichloroethylene [PAGE 463]. No studies have proven Agent Orange to be a cause of Parkinson's Disease.

ANNONACEAE

Chemistry : Annonaceae is a family of flowering plants that is also called the custard apple family. Some annonaceae species produce edible fruits. Annonaceae contain acetogenins.

Common sources : In Guadeloupe, Annonaceae are consumed as herbal teas and fruits, especially soursop [1-8].

Means of toxicity : Annonacin, which is the most abundant acetogenin,

CHAPTER 37

CAUSES OF PARKINSON'S DISEASE

GENETIC CAUSES

GENETIC CAUSES

A small proportion of cases of Parkinson's Disease have a genetic cause. Most genetic causes make Parkinson's Disease more likely rather than make it inevitable. Genetic disorders normally occur due to inheritance, either autosomal recessive (from both parents) or autosomal dominant (from one parent), but can arise spontaneously. Having relatives with Parkinson's Disease does not mean that it has been inherited. Relatives can have similar environmental factors as each other that causes their Parkinson's Disease. Most but not all genetic causes are identified by a PARK number.

Genetic causes of Parkinson's Disease with a PARK number include : PARK 1 (Alpha-Synuclein) [PAGE 465], PARK 2 (Parkin) [PAGE 469], PARK 3 (Lewy body) [PAGE 475], PARK 5 (UCHL1) [PAGE 476], PARK 6 (Pink 1) [PAGE 477], PARK 7 (DJ-1) [PAGE 479], PARK 8 (LRRK2) [PAGE 480], PARK 9 (ATP13A2) [PAGE 482], PARK 10 (USP24) [PAGE 485], PARK 11 (GIGYF2) [PAGE 487], PARK 12 [PAGE 489], PARK 13 (HtrA2) [PAGE 490], PARK 14 (PLA2G6) [PAGE 491], PARK 15 (FBXO7) [PAGE 493], PARK 16 [PAGE 494], PARK 17 (VPS35) [PAGE 495], PARK 18 (EIF4G1) [PAGE 497], PARK 19 (DNAJC6) [PAGE 497], PARK 20 (SYNJ1) [PAGE 498], PARK 21 (DNAJC13) [PAGE 499], PARK 22 (CHCHD2) [PAGE 501], PARK 23 (VPS13C) [PAGE 502].

Genetic causes of Parkinson's Disease without a PARK number include : Tyrosine Hydroxylase [PAGE 503], Dopa decarboxylase [PAGE 505], ADORA1 [PAGE 506], CYP2D6 [PAGE 507], DRD2 [PAGE 508], DRD3 [PAGE 509], GLIS1 [PAGE 510], HLA [PAGE 510], LINGO1 [PAGE 512], MAPT [PAGE 513], NR4A2 [PAGE 515], PDE8B [PAGE 516], PITX3 [PAGE 517], PTRHD1 [PAGE 518], RAB39B [PAGE 519], RIT2 [PAGE 520], STH [PAGE 521], TMEM230 [PAGE 522].

PARK 1

Gene : Alpha-Synuclein (SNCA) [1]

Chromosome : 4 (q21-q23) [1-5]

Biochemical function : Alpha-Synuclein appears to be involved in dopamine biosynthesis, storage, release, and uptake [6].

Type of inheritance : Autosomal dominant [1, 7-14]

Symptoms : Increased risk of developing Parkinson's Disease [15-30], at an early age of onset [31]. Over half of the cases had early-onset parkinsonism and non-motor features, such as dysautonomia, rapid eye movement sleep behaviour disorder (RBD), hallucinations (usually visual) and cognitive deficits leading to dementia [32].

Prevalence : China [15, 18, 19, 21, 23, 26, 31, 33, 34, 35], Taiwan [16], Iran [17], India [20], Italy [22, 36], Australia [31], Poland [37], Tunisian Berbers [38], Japan [39], Korea [40], Mexican Mestizos [41]

Genetic tests : PARK1 Parkinsonism (by Centogene AG), SNCA Complete sequencing (by Instituto de Medicina Genomica Paterna), SNCA MLPA testing (by Instituto de Medicina Genomica Paterna), Parkinson disease type 1 (by Bioarray), Parkinson disease 1/4 (by CGC Genetics), CSingle gene testing SNCA (by CeGaT GmbH) [42]

[1] Annals of Neurology [1998] 44 (3 Supplement 1) : S63-S64 (M.H. Polymeropoulos)

[2] Movement Disorders [2000] 15 (6) : 1075-1083 (M.Farrer, T. Destée, E.Becquet, F.Wavrant-DeVrièze, V.Mouroux, F.Richard, L. Defebvre, S.Lincoln, J.Hardy, P.Amouyel, M.C.Chartier-Harlin)

[3] Annals of Neurology [1999] 46 (3) : 374-381 (K.Markopoulou, Z.K.Wszolek, R.F.Pfeiffer, B.A.Chase)

[4] Neurology [1998] 50 (1) : 270-273 (J.J.Higgins, I.Litvan, L.T.Pho, W.Li, L.E.Nee)

CHAPTER 38

CAUSES OF PARKINSON'S DISEASE

PHARMACOLOGICAL CAUSES

PHARMACOLOGICAL CAUSES

A small proportion of cases of Parkinson's Disease have a pharmacological cause. To varying extents some drugs can also be a partial cause or the sole cause of Parkinson's Disease. The use of the drugs must usually be persistent in order to cause Parkinson's Disease. The withdrawal or gradual reduction of the dosage of these drugs can lead, in most cases but not with all drugs, to the reduction in the Parkinson's Disease symptoms they cause or contribute to.

The drugs that can cause or worsen Parkinson's Disease symptoms include : Amiodarone (an anti-arrhythmic agent) [PAGE 523], Amphetamines and methamphetamines [PAGE 524], Aripiprazole (an anti-psychotic) [PAGE 525], Benzamides [PAGE 526], Calcium channel blockers [PAGE 527], Dopamine antagonists [PAGE 531], Ephedrone (which is manganese containing) [PAGE 533], Estrogen (an oral contraceptive) [PAGE 535], Lithium [PAGE 536], Phenothiazines (drugs with anti-psychotic effects) [PAGE 538], Trimetazidine (an anti-ischaemic agent) [PAGE 540], Valproic acid (a drug used for the treatment of a variety of psychiatric and neurological disorders including epilepsy) [PAGE 541], and Zolpidem [PAGE 543].

AMIODARONE

Pharmacology : Amiodarone is the most widely used anti-arrhythmic agent [1]. Use of Amiodarone causes a marked increase in the duration of transmembrane action potential [2].

Adverse effects : Use of Amiodarone is associated with Parkinsonism [3-6], which can revert after withdrawal of Amiodarone [6].

CHAPTER 39

CAUSES OF PARKINSON'S DISEASE

MEDICAL CAUSES

MEDICAL CAUSES

There are other medical disorders that can cause symptoms, some of which coincide with those of Parkinson's Disease. In most cases the medical disorder is called a Parkinsonism. Somebody that has one of these medical disorders can be wrongly diagnosed with Parkinson's Disease due to some of the symptoms resembling those of Parkinson's Disease. Muscular injury and muscular strain can also cause symptoms similar to those of Parkinson's Disease but only in the affected muscles and whilst the muscular injury or muscular strain lasts.

These medical disorders can include : Acquired hepatolenticular degeneration [PAGE 544], Cerebellar Thoracic Outlet Syndrome [PAGE 546], Corticobasal Degeneration [PAGE 547], Creutzfeldt-Jakob Disease [PAGE 548], Encephalitis Lethargica [PAGE 549], Fahr's Syndrome [PAGE 550], FTDP-17 [PAGE 551], FXTAS [PAGE 552], Gaucher's Disease [PAGE 554], Hallervorden-Spatz Disease [PAGE 556], Head trauma [PAGE 557], HIV/AIDS [PAGE 560], Hydrocephalus [PAGE 560], Hypothermia [PAGE 562], Multiple System Atrophy [PAGE 562], Phenylketonuria [PAGE 564], Progressive Supranuclear Palsy [PAGE 565], Rett Syndrome [PAGE 566], Vascular Parkinsonism [PAGE 567], Wilson's Disease [PAGE 569], and X-Linked Dystonia-Parkinsonism [PAGE 570].

ACQUIRED HEPATOLENTICULAR DEGENERATION

Pathophysiology : Repeated episodes of liver failure or chronic liver cirrhosis may cause acquired hepatocerebral degeneration [1]. Acquired hepatolenticular degeneration is also known as "Parkinsonism in cirrhosis" [2 - 5]. Liver transplantation is usually effective. Reports of

CHAPTER 40

TREATMENTS OF PARKINSON'S DISEASE

BIOCHEMICAL TREATMENT

INCREASING DOPAMINE BIOSYNTHESIS

Parkinson's Disease is primarily due to the insufficient biosynthesis of dopamine. The primary methods of treating Parkinson's Disease are based on this fact. The biosynthesis of dopamine can be increased, without causing side effects or after effects, by taking the substrate, coenzyme precursors and cofactors that are necessary for dopamine biosynthesis.

ESSENTIAL FACTORS

The optimal biosynthesis of dopamine requires the following substances as the substrate, coenzyme precursors and cofactors : L-tyrosine, pyridoxine, folic acid, nicotinamide, ferrous iron, zinc, and manganese.

L-tyrosine : L-tyrosine is essential for the biosynthesis of L-dopa via the enzyme Tyrosine 3-Monooxygenase.

Folic acid : Folic acid is essential for the biosynthesis of the coenzyme tetrahydrofolic acid, which is essential for the biosynthesis of L-dopa from L-tyrosine.

Pyridoxine : Pyridoxine is essential for the biosynthesis of the coenzyme pyridoxal phosphate, which is essential for the formation of dopamine from L-dopa.

Nicotinamide : Nicotinamide is essential for the biosynthesis of the nicotinamide coenzymes. Dopamine biosynthesis requires coenzymes whose biosynthesis is dependent on the biosynthesis of the nicotinamide coenzymes.

CHAPTER 41

PHARMACOLOGICAL TREATMENTS
OF PARKINSON'S DISEASE

L-DOPA

PHARMACOLOGY

Dopamine is not able to enter the brain. However, L-dopa can enter the brain and then form dopamine in the dopaminergic neurons via the enzyme aromatic-L-amino-acid decarboxylase (EC 4.1.1.28) : L-dopa >>> dopamine + CO₂. However, L-dopa reduces the formation of the body's own dopamine. Consequently, L-dopa can initially be effective in treating Parkinson's Disease, but its effects wear off and its long term use leads to the disorder becoming gradually and progressively worse.

FORMS OF L-DOPA

L-dopa is widely used to treat Parkinson's Disease. Sinemet, in immediate release [PAGE 583] and controlled release [PAGE 584] versions, is combined with the dopa decarboxylase inhibitor carbidopa in order to maintain the effect of L-dopa. Madopar, in immediate release [PAGE 588] and controlled versions [PAGE 589], is combined with the dopa decarboxylase inhibitor benserazide in order to maintain the effect of L-dopa. Rytary [PAGE 589] and Numient [PAGE 589] are versions of L-dopa and carbidopa in which the immediate release and controlled versions are combined.

Other means of administering L-dopa that are available or being developed are : Duodopa [PAGE 591], which is L-dopa and carbidopa in a gel that is administered using a portable pump; Parcopa [PAGE 595], which is orally disintegrating L-dopa and carbidopa; L-dopa inhaler [PAGE 595]; a combination of β-asarone [PAGE 597] and L-dopa as a means of improving Madopar; AcuForm [PAGE 598]; L-dopa prodrug [PAGE 599]; melevodopa [PAGE 599], which is a methyl ester of L-dopa; subcutaneous L-dopa [PAGE 601]; mucuna pruriens [PAGE 602] and fava beans [PAGE 603] which are L-dopa containing vegetables.

SINEMET

Brand names : Sinemet, Atamet, Carbilev

Pharmacology : Sinemet is L-Dopa combined with carbidopa, which is a peripheral decarboxylase inhibitor. Carbidopa helps to maintain the levels of L-dopa until it is used, by inhibiting peripheral metabolism of L-dopa. Carbidopa is also available as Lodosyn, which is taken simultaneously with L-dopa.

Efficacy : In two-thirds of people taking Sinemet a good to very good improvement was obtained in the treatment of the symptoms of Parkinson's Disease [1]. Atamet was no different in its effects to Sinemet [2]. Patients who responded well to Sinemet were considerably younger than those who failed to respond [3]. After three years of treatment the response to Sinemet declined [3]. After seven years of treatment about 60%-65% of the patients had shown improvement even though to a lesser degree than during the first and second year of therapy [4]. Sinemet has been found to have little effect on many of the non-motor symptoms of Parkinson's Disease including fatigue, excessive sweating, insomnia, akathisia, anxiety, and constipation [5]. Protein intake can alter the efficacy because some of the amino acids in protein compete with L-dopa for entry in to the brain. A lack of protein can increase the effect of L-dopa, requiring a reduction in L-dopa intake. A high protein intake can prevent the effect of L-dopa [6]. Large quantities of pyridoxine (vitamin B6) can reduce the effect of L-dopa [7], but the interaction does not occur when taking a decarboxylase inhibitor as there is in Sinemet [8].

Adverse effects : The most troublesome side effects of Sinemet are dyskinesia, hypotonia, gastrointestinal symptoms, and also psychotic symptoms in 10% of people [1, 3]. Other common side effects are nausea (34%), postural hypotension (22%), and "on-off" phenomena in 12% of patients [3]. Patients discontinued treatment mostly because of psychoses, nausea, dyskinesia or exacerbation of urinary incontinence [3]. Sinemet worsened bladder overactivity [9].

CHAPTER 42

PHARMACOLOGICAL TREATMENTS OF PARKINSON'S DISEASE

DOPAMINE AGONISTS

PHARMACOLOGY

Dopamine agonists are drugs that mimic dopamine by stimulating the dopamine receptors (D1, D2, D3, D4, D5) via translation. Although there are five dopamine receptors, dopamine agonists only significantly stimulate some of them. Besides the side effects they cause, dopamine agonists cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms.

TYPES OF DOPAMINE AGONISTS

Those dopamine agonists that are presently being used for the treatment of Parkinson's Disease are apomorphine [PAGE 604], bromocriptine [PAGE 609], cabergoline [PAGE 617], lisuride [PAGE 619], pardoprinox [PAGE 623], pergolide [PAGE 624], piribedil [PAGE 631], pramipexole [PAGE 633], ropinirole [PAGE 639] and rotigotine [PAGE 644]. Some of these dopamine agonists are taken by different means of administration, including orally, subcutaneous, intranasally, and sublingually.

APOMORPHINE

Brand names : Apokyn, Uprima, APO-Go, APO-Go Pen

Pharmacology : Apomorphine is a non-specific dopamine agonist with a strong action on D2, D3, D4 receptors [1, 2]. It has weaker action on D1 and D5 receptors [1, 2]. Apomorphine is administered in single subcutaneous injection, or in continuous subcutaneous infusion if more than 7 to 9 single injections are required daily [1]. The subcutaneous administration of apomorphine has effect within 10 minutes [1, 3, 4] but wears off within 40 to 90 minutes [1, 3] or within 2 hours [4].

CHAPTER 43

PHARMACOLOGICAL TREATMENTS
OF PARKINSON'S DISEASE

MAO INHIBITORS

PHARMACOLOGY

MAO inhibitors help to maintain dopamine levels by inhibiting the enzyme Monoamine Oxidase (EC 1.4.3.4), which has two forms : MAO-A and MAO-B. Monoamine oxidase metabolizes dopamine :
 $\text{Dopamine} + \text{H}_2\text{O} + \text{O}_2 \gg \text{Dihydroxyphenylacetic acid} + \text{H}_2\text{O}_2$

TYPES OF MAO INHIBITOR

The main MAO inhibitors in use are Selegiline [PAGE 650], Rasagiline [PAGE 655] and Safinamide [PAGE 657]. Zelapar [PAGE 653] is a form of Selegiline designed for absorption in the mouth. Safinamide is believed to have both dopaminergic and non-dopaminergic actions, including the inhibition of monoamine oxidase B (MAO-B) and inhibition of glutamate release.

SELEGILINE

Common brand names : Selegiline, Selegilin, Deprenyl, Eldepryl, Jumex, Jumexil, Sefmex, Elepril, Niar, Antiparkin, Selegelina

Pharmacology : Selegiline is a MAO-B inhibitor [1]. To some extent Selegiline is also a MAO-A inhibitor [2].

Efficacy : Selegiline caused a significant improvement in Parkinson's Disease symptoms [3-14], and a reduced need for L-dopa [1, 4, 5, 6, 8, 12, 13, 15, 16]. However, the improvement was only moderate or minimal [17]. When added to the use of L-dopa, selegiline was not impressive with regard to preventing the future progression of Parkinson's Disease [1, 18]. Consequently, selegiline is sufficient on its

CHAPTER 44

PHARMACOLOGICAL TREATMENTS
OF PARKINSON'S DISEASE

COMT INHIBITORS

PHARMACOLOGY

COMT inhibitors help to maintain dopamine levels by inhibiting Catechol-O-methyl transferase (COMT) (EC 2.1.1.6), which is an enzyme that metabolizes dopamine : Dopamine + S-adenosyl-L-methionine >>> S-adenosyl-L-homocysteine + 3-Methoxytyramine.

TYPES OF COMT INHIBITOR

The most commonly used COMT inhibitor is Entacapone [PAGE 659]. Entacapone is often taken as Stalevo [PAGE 663], which combines L-dopa, carbidopa and entacapone. A new format of Stalevo, ODM-101 [PAGE 665], is being developed. Other COMT inhibitors being used or assessed for the treatment of Parkinson's Disease are tolcapone [PAGE 666], opicapone [PAGE 669], and nebicapone [PAGE 670].

ENTACAPONE

Brand names : Comtan, Stalevo (combined with L-dopa and carbidopa)

Pharmacology : Entacapone is a COMT inhibitor.

Efficacy : Entacapone efficacy was considered by physicians to be "very good" or "good" in 77% of patients [1]. Entacapone moderately increases "on" time [2-18], moderately improves Activities of Daily Living [18], moderately improved Clinical Global Impression of Change (CGIC) [19-21] and Quality of Life [19, 20], led to a moderate reduction in the L-dopa dose [1, 4, 7, 8, 17, 20, 22-25], led to a moderate reduction in dyskinesia [1], led to a moderate improvement in Parkinson's Disease symptom scores and motor fluctuations [25, 26],

CHAPTER 45

PHARMACOLOGICAL TREATMENTS OF PARKINSON'S DISEASE

ANTI-CHOLINERGICS

PHARMACOLOGY

Anticholinergics are classified according to the receptors they affect. Antimuscarinic agents affect the muscarinic acetylcholine receptors. Antinicotinic agents affect the nicotinic acetylcholine receptors. Most anticholinergic drugs are anti-muscarinics.

Acetylcholine affects muscle contraction via the five muscarinic receptors : m1, m2, m3, m4, and m5. The receptors m1, m3 and m5 are stimulatory. The receptors m2 and m4 are inhibitory. The combined stimulatory effect of m1, m3 and m5 is more powerful in total than the combined inhibitory effect of m2 and m4. So the overall effect of acetylcholine is to stimulate muscle contraction.

The excessive muscle contraction in Parkinson's Disease is caused when the cholinergic function, which increases muscle contraction, is more powerful than dopaminergic function, which decreases muscle contraction.

Instead of increasing dopaminergic effect which is what most pharmacological treatments of Parkinson's Disease aim at achieving, anti-muscarinics increase dopaminergic effect by reducing cholinergic function. Anticholinergics are now uncommonly used because of their limited efficacy and widespread adverse effects.

TYPES OF ANTI-CHOLINERGIC

The anti-cholinergics used for Parkinson's Disease include benztropine, which is anti-muscarinic and anti-histaminergic [PAGE 672], and biperiden [PAGE 673], procyclidine [PAGE 674], and trihexyphenidyl [PAGE 674], which are all anti muscarinic.

CHAPTER 46

PHARMACOLOGICAL TREATMENTS
OF PARKINSON'S DISEASE

NON-DOPAMINERGIC

PHARMACOLOGY

There are drugs being used for Parkinson's Disease or being developed for Parkinson's Disease that do not act by directly increasing the activity of dopamine. They are intended for use either in the treatment of Parkinson's Disease by other biochemical means [PAGE 676], or are normally used for other medical disorders [PAGE 691], or are for use in medical disorders that are associated with Parkinson's Disease [PAGE 701].

NON-DOPAMINERGIC DRUGS

PART 1 : THOSE USED FOR PARKINSON'S DISEASE

Those drugs being used or assessed for the treatment of Parkinson's Disease that do not act by directly increasing the activity of dopamine are : adenosine receptor antagonists (tozadenant, preladenant, istradefylline, caffeine) [PAGE 676], calcium channel blockers (isradipine) [PAGE 681], glutamate antagonists (perampanel, amantadine, dipraglurant, mavoglurant) [PAGE 683], neurotrophic factors (cogane) [PAGE 687], nicotine agonists (nicotine) [PAGE 687], and noradrenaline precursors (droxidopa) [PAGE 689].

ADENOSINE RECEPTOR ANTAGONISTS

Adenosine receptor antagonists are drugs that act as an antagonist of one or more adenosine receptors. Those adenosine antagonists that are presently being assessed for their use in the treatment of Parkinson's Disease include tozadenant, preladenant, istradefylline and caffeine.

CHAPTER 47

SURGICAL TREATMENTS
OF PARKINSON'S DISEASE

BIOCHEMISTRY

Surgical methods of treating Parkinson's Disease aim to have effect by different means. These include : stimulating the dopaminergic neurons, inserting new dopamine containing cells, delivering genes for the formation of dopamine, repairing damaged dopaminergic neurons, destroying certain parts of the brain by surgery or radiation, and increasing the levels of GABA.

SURGICAL TREATMENTS

Deep Brain Stimulation is the most effective surgical treatment for Parkinson's Disease [PAGE 716]. Other forms of treating Parkinson's Disease involving surgery are Acupuncture [PAGE 726], Extradural cortical stimulation (ECS) [PAGE 727], GDNF [PAGE 728], Gene Therapy [PAGE 729], Neurturin [PAGE 730], NTCELL [PAGE 731], Pallidotomy [PAGE 731], ProSavin [PAGE 736], Retinal Cell Therapy [PAGE 737], Spinal cord stimulation [PAGE 738], Stem cell therapy [PAGE 739], and Stereotactic radio surgery (SRS) [PAGE 741], Subthalamotomy [PAGE 742], and Thalamotomy [PAGE 743].

DEEP BRAIN STIMULATION (DBS)

Method : Deep Brain Stimulation (DBS) involves the use of electrodes that are implanted into the brain and connected to a small electrical device called a pulse generator that can be externally programmed. DBS uses a surgically implanted, battery-operated medical device called a neurostimulator, which is similar to a heart pacemaker and approximately the size of a stopwatch. It delivers electrical stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause tremor and Parkinson's Disease

CHAPTER 48

NATURAL TREATMENTS
OF PARKINSON'S DISEASE

BIOCHEMISTRY

Natural treatments aim to improve Parkinson's Disease without the side effects that usually accompany drug treatments of Parkinson's Disease. They attempt to do this by intending to assist the natural biochemical processes purported to be involved in Parkinson's Disease. However, some of the natural treatments of Parkinson's Disease have pharmacological effects.

NATURAL TREATMENTS

Natural treatments of Parkinson's Disease are largely nutrients, and the use of natural substances. The nutrients and natural substances include cannabis [PAGE 747], coenzyme Q10 [PAGE 748], creatine [PAGE 749], curcumin [PAGE 750], glutathione [PAGE 751], GM1 ganglioside [PAGE 751], inosine [PAGE 752], mannitol [PAGE 753], mitoquinone [PAGE 754], molecular hydrogen water [PAGE 754], herbal medicines [PAGE 755], thiamine [PAGE 755] and vitamins A, C, E [PAGE 756]. Another option in Parkinson's Disease is to remain untreated.

UNTREATED

The symptoms of those people with Parkinson's Disease that remained untreated did not deteriorate in their symptoms over the two years after their diagnosis [1]. However, those people with Parkinson's Disease that did start treatment within the first year actually had higher symptom scores than those people that remained untreated [1]. Some people with Parkinson's Disease reported that their motor functions got better and came nearer to their "on" level after the effect of L-dopa wears off [2].

CHAPTER 49

EXERCISE METHODS FOR PARKINSON'S DISEASE

PHYSIOLOGY

Parkinson's Disease causes excessive muscle contraction. Although the initial effect of exercise is to increase muscle contraction, the after effect of exercise is to reduce muscle contraction. This has the same type of effect on the muscles as most Parkinson's Disease drugs. However, exercise does not raise dopamine levels and thereby improve other Parkinson's Disease symptoms.

EXERCISE METHODS

Forms of exercise that have been used to try to lessen the muscular effects of Parkinson's Disease include general exercise [PAGE 758], progressive resistance exercise training [PAGE 760], treadmill training [PAGE 761], balance training [PAGE 764], physiotherapy [PAGE 765], cycling [PAGE 766], dancing [PAGE 766], the traditional practice of Qigong [PAGE 768], the Chinese martial art of Tai Chi [PAGE 768], and the Hindu discipline Yoga [PAGE 769].

GENERAL EXERCISE

Method : Exercise is physical activity that maintains physical fitness. General exercise usually involves repeating the physical action and concentrating on particular muscles during each exercise. The exercises most relevant to Parkinson's Disease concern the muscles, because the prominent symptoms of Parkinson's Disease are muscular [1, 2].

Efficacy : In people with Parkinson's Disease, exercise can improve physical performance [3-8], and the quality of life [9]. Different means of exercising can be beneficial [10], including exercise as part of training for sports [11, 12, 13]. In Parkinson's Disease there was a

CHAPTER 50

TECHNOLOGICAL METHODS FOR PARKINSON'S DISEASE

PHYSIOLOGY

Technological devices are being used to try to improve Parkinson's Disease without the necessity for drugs or surgery. They aim to have effect by means that include : stimulating the brain, the spinal cord, or weak muscles, or stimulating the body generally, destroying abnormal neurons, using light exposure to raise dopamine levels, or to provide visual information.

TECHNOLOGICAL METHODS

The technological methods being used or developed in order to improve Parkinson's Disease include Focused Ultrasound [PAGE 771], Functional electrical stimulation [PAGE 772], Google Glass, [PAGE 773], Laser devices [PAGE 774], Light Therapy [PAGE 775], Magnetic therapy [PAGE 775], Nexalin Therapy [PAGE 776], Spinal cord stimulation [PAGE 776], STIMband [PAGE 777], Transcranial direct current stimulation [PAGE 778], Transcranial magnetic stimulation [PAGE 779], and Whole body vibration [PAGE 781].

FOCUSED ULTRASOUND

Technology : Focused ultrasound is an incisionless method of thalamotomy for people who are not candidates for surgery or who do not want to undergo an invasive procedure. The procedure is performed with the patient awake and involves no anaesthesia, no incisions in the scalp, no burr holes through the skull or insertion of electrodes into the brain. Multiple intersecting beams of ultrasound energy are focused with a high degree of precision and accuracy on the target in the thalamus to heat and destroy the abnormal neurons without harming adjacent tissue. During treatment the target is visualised in real time

APPENDIX 1

PARKINSON'S DISEASE ORGANISATIONS

WORLDWIDE

World Parkinson Disease Association
<http://www.wpda.org>

NORTH AMERICA

U.S.A.

American Parkinson Disease Association
<http://www.apdaparkinson.org>

National Parkinson Foundation
<http://www.parkinson.org>

The Parkinson's Disease Foundation
<http://www.pdf.org>

The Michael J.Fox Foundation
<https://www.michaeljfox.org>

CANADA

Parkinson Canada
<http://www.parkinson.ca>

OCEANIA

AUSTRALIA

Parkinson's Australia
<http://www.parkinsons.org.au>

New ZEALAND

Parkinson's New Zealand
<http://www.parkinsons.org.nz>