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# The Effect of Sitagliptin and Liraglutide on the Lipopolysaccharide Rat Model of Parkinson's Disease

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**Committee Decision**

**This Thesis (The Effect of Sitagliptin and Liraglutide on the Lipopolysaccharide Rat Model of Parkinson's Disease) was Successfully Defended and Approved on -----**

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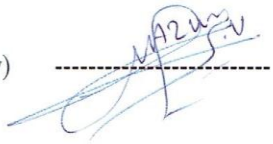
| **Dr. Yazan Jarrar**<br>(Associate Professor - Alzaytoonah University)<br>(External Member) |  <br>---------- |

# Dedication

Thanks to Allah who gives me determination to face difficulties and to succeed in passing them.

I dedicate this work to my lovely dad **Dr.Abdulghafoor Alsaidi** who believed in me and encouraged me from the first day of life to this moment.

To my beautiful mum **Suzan Ameen** for her love and continuous support for me through this period.

To my best friends and sisters (the most precious thing I have) the kind and sweetheart **Dalya**, and my beautiful little princess **Dena**.

To my brothers, the most beautiful boys **Mohammed** and **Ali**.

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# List of Symbols and Abbreviations

| The Symbol | The Mean |
|---|---|
| MPP+ | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| α-syn | Alpha-synuclein |
| BBB | Blood brain barrier |
| CSF | Cerebrospinal fluid |
| Cox-2 | Cyclo-oxygenase-2 |
| H2O2 | Hydrogen peroxide |
| OH | Hydroxyl radicals |
| Ex-4 | Exendin -4 |
| LPS | Lipopolysaccharide |
| LUHMES | Lund human mesencephalic |
| MAO-B | Monoamine oxidase-B |
| PD | Parkinson's disease |
| SNc | Substantia nigra pars compacta |
| O2- | Superoxide anion |
| TNFα | Tumor necrosis factor-alpha |
| TH | Tyrosine hydroxylase |
| Glp-1 | Glucagon-Like peptide 1 |
| SN | Substantia nigra |
| T2 DM | Type-2 diabetes mellitus |
| Treg | Regulatory T cell |

# The Effect of Sitagliptin and Liraglutide on the Lipopolysaccharide Rat Model of Parkinson's Disease

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## Abstract

Parkinson's Disease (PD), is defined as a neurodegenerative disorder that leads to the death of dopamine neuron found in the substantia nigra (SN) in the brain, resulting in movement disorders. Accordingly, current treatment strategies for PD have targeted the dopamine system. However, There is an urgent need for finding effective treatments to improve the progression of the disease and improve the quality of life; however, existing therapies can neither slow nor prevent the progression of PD. The disease is caused by a lack of dopamine (DA), so the primary therapy involves DA replacement drugs. In this paper, the effectiveness of sitagliptin and liraglutide, will be investigated both of which have Food and Drug administration's (FDA) approval for treating type II diabetes.

**Aim:**This study aims to investigate the extent to which Sitagliptin and Liraglutide are effective on lipopolysaccharide (LPS) rodent model of parkinson's disease. LPS is an endotoxin that is extracted from gram negative bacteria; as such, it functions as a potent stimulator of microglia, and researchers have used it to examine the inflammatory process of the pathogenesis of the disease. Thus, LPS can replicate two main characteristics of PD: microglia's extensive activation as well as the loss of nigrostriatal dopaminergic neurons.

**Method:** Twenty four Male rats, weighing between (250-300) g, were randomized then divided into 4 different groups of 6 rats each. Group A was the control group, group B rats were subjected to LPS alone (intracerebral injection), and group C was subjected to LPS + (s.c) Liraglutide for 14 days after intracerebral injection of LPS. Finally group D where LPS + oral Sitagliptin for 14 days after intracerebral injection of LPS. This study assessed the LPS induced lesion severity both behaviorally and neurochemically.

**Result:** Fourteen days after LPS intracerebral injection of LPS, and following an apomorphine challenge, LPS lesioned rats receiving Liraglutide or Sitagliptin showed significantly lower tight contralateral circling in comparison to LPS only group. Consistent with these findings, concentrations of the striatal tissue dopamine were significantly higher in groups C and D (LPS + Liraglutide or Sitagliptin treated rats) versus group B (LPS only group).

**Conclusion:** This study showed that Liraglutide and Sitagliptin are neuroprotective compounds that can slow and protect dopaminergic neurons and they have the capacity to alleviate the pathophysiology of Parkinson's disease (PD) because of they might to reduced the inflammatory prosses.

# Chapter One

# Introduction

## 1.1 Introduction:

Parkinson's disease is the neurodegenerative disorder which affects regulation of movements as a result of losing neurons that produce dopamine (Hackney and Earhart, 2009; Physiology, 2018).

In 1817, James Parkinson was the first to describe PD as a neurological syndrome (Goetz et al., 2014). PD is currently defined as neurological disorder with symptoms that gradually worsen because of degenerating dopaminergic neurons that are located in substantia nigra para compacta (SNpc) (Huang et al., 2017). The disease is a movement disorder, and ranks second among neurodegenerative conditions after the Alzheimer's disease (Yahalom et al., 2020; Lang, 2010; Muangpaisan and Mbbs, 2011).

PD can change the quality of life to the worse significantly after about 10 years (Ascherio and Schwarzschild, 2016). However, with time the disease get worse especially in the late stage of the disease, leading to treatment resistance (Schneider, Iourinets and Richard, 2017).

## 1.2 Prevalence of Parkinson's disease

Globally, neurological disorders are now the main source of disability, affecting persons over sixty five years who have age related neurodegenerative disorder including PD (Bill and Foundation, 2019).

According to the US Census Bureau population projections for the year 2010, estimates predicated an overall pervasiveness of PD among people aged ≥45 years to reach 572 individuals per 100,000. In fact, 680,000 people in the United States whose ages were ≥45 years had PD in the year 2010. Moreover, the projections predicted that number of people with parkinson's disease would rise to about 930,000 in 2020,

then gradually increasing to rise to 1,238,000 in the year 2030 (Marras et al., 2020). While in Jordan during the period (2007 to 2008) the crude prevalence rate of PD was estimated to be 59/100,000 (Alrefai *et al.*, 2009).

## 1.3 Signs and symptoms

The main signs of PD represent both motor and non-motor signs and symptoms. Tremors are usually the early motor symptoms of PD, followed bradykinesia in addition to postural instability and rigidity; non-motor symptoms, through include mood problems like depression, anxiety, memory problems and sleep problems (Rodriguez-oroz et al., 2009; Storstein, 2017; Chahine et al., 2018).

## 1.4 Dopamine synthesis

Dopamine synthesis begins from tyrosine the amino acid. Tyrosine can cross the BBB and converted by an enzyme called tyrosine hydroxylase (TH) to give L- DOPA (Daubner, Le and Wang, 2011; Sung and Jeong, 2016). Once formed, DOPA in the cytoplasm is immediately metabolised with another enzyme decarboxylase to dopamine, which is later transported and localized by an amine transporter mechanism, in synaptic vesicles. Once these vesicles produce their contents in the synaptic space, they form an interaction with the dopaminergic receptors located in the postsynaptic neurons (Sung and Jeong, 2016).

## 1.5 Diagnosis of Parkinson's disease

When the pathological process is advanced, the diagnosis of (PD) usually takes place once it is determined that most of the dopamine neurons have died (Sulzer et al., 2018). According to evidence, cerebrospinal fluid (CSF) and blood biomarkers both reveal prognostic and diagnostic values in the pathophysiology of PD (Parnetti et al., 2019). Biomakers include α-synuclein species, lysosomal enzymes, tau pathology, in addition to neurofilament light chain reveal. Further, different methods can be utilized to diagnose these biomarkers. These methods all invlove imaging scans that can point to a striatal dopamine damage by visual representations. Magnetic Resonance Imaging (MRI), Single Photon Emission Tomography (SPECT), Positron Emission Tomography (PET), Computed Tomograpgy (CT), and, finally,Transcranial Sonography (TCS) are all techniques with which biomakers are diagnosed (Marshall et al., 2004; Sulzer et al., 2018).

## 1.6 Pathology

The degeneration of dopaminergic neurons from the Substantia Nigra is considered a histopathological mark of the disease (Bergman, 2002), where as cellular and molecular processes contribute to neurodegeneration in PD (Zeng et al., 2018).

### 1.6.1 Molecular pathology

The pathology of PD is unknown, but it is suspected that an interaction of environmental factors and genetic could trigger the disease, or that there could be a genetic cause for being sensitive to environmental toxins (Follett, 2014). Some known genetic mutations exist which are thought to be the cause of familial PD, although those mutations only account for a small number of PD cases, leaving most cases with

an unknown pathology (Zeng et al., 2018). Some of these mutations cover four types of genes Aggregation of alpha-synuclein (α-syn), leucine-rich repeat kinase 2 (LRRK2), PARKIN and DJ-1 (Zeng et al., 2018).

### 1.6.1.1 Aggregation of alpha-synuclein (α-syn)

SNCA gene is responsible for coding α-synuclein. The mutations and/or the multiplications of this SNCA are autosomal and dominant; in turn, this leads to mutations in α-synuclein protein which increases lewy bodies. This abnormality to the gene is considered one of the pathological features of the disease (Lubbe and Morris, 2013). On a related note, the misfolded aggregates of α-syn protein usually leads to increase its toxicity level to dopaminergic neurons when toxic oligomers or fibrils are formed, resulting in neuronal death (Duffy et al., 2018).

### 1.6.1.2 (LRRK2), PARKIN, and DJ-1

In addition to SNCA, there are other genes that can mutate and cause PD, including LRRK2, which gives rise to Lewy bodies. Biochemical and genetic studies reveal that the products of two genes that are mutated in autosomal recessive Parkinsonism, include Parkin and PINK1, normally work together in the same pathway to govern mitochondrial quality control, bolstering previous evidence that mitochondrial damage is involved in Parkinson's disease (Lubbe and Morris, 2013). Lastly, DJ-1 is another gene which, despite its rare subjectivity to mutatations, causes autosomal and recessive PD. It is believed to have effect on normal protein that control oxidative stress (antioxidant) and effect on mitochondrial function . All of these factors can lead to dopaminergic cell death (Lubbe and Morris, 2013; Zeng et al., 2018).

### 1.6.2 Cellular Pathways to PD

Disorder in cellular system activates to neuronal death, this include oxidative stress, mitochondrial dysfunction and neuroinflammation (Zeng et al., 2018).

#### 1.6.2.1 Oxidative stress and mitochondrial dysfunction

According to the oxidative stress theory in PD studies, the mitochondria is known to be the hub for possible degenerative progression. When defects occur to activities of complex-I in the mitochondria, they affectthe cellular ATP productions directly, which cause, in turn, cell death. α- synuclein has direct and/or indirect roles in modification processes of complex I actions. Indirectly,it modifies the action by a physical interaction with Cardiolipin, an element that is necessary for forming mitochondrial complex I, III, in addition to IV, leading, finally to disruption of electron transfers (Rocha, Miranda and Sanders, 2018). Further, a break down of the monoamines of brain, such as dopamine as well as 5-hydroxytryptamines (5-HT) by monoamine oxidase-B, (MAO-B), when O2 is added to it, results usually in forming Reactive Oxygen Species, (ROS). There is a high inclination for dopaminergic neurons, located in SNc, to produce ROS—likesuperoxide anion (O2•−), Hydroxyl Radicals (•OH) as well as Hydrogen Peroxide (H2O2 )—in metabolism processes of Dopamine. These findings further stress the significance of oxidative stress relating to PD pathogenesis (Fulda et al., 2010; Blesa et al., 2015).

### 1.6.2.2 Neuroinflammation

Neuroinflammation is among the factors that contribute to PD progressions (Poewe et al., 2017). Microglial cells constitute specific types of macrophages located in CNS. These cells were found to play a significant role in the immune system as they remove the damaged neurons; as such, these cells preservethe neurovascular integrity and, most importantly, control inflammation. However, an activation of the microglia is a feature of initial neuronal damage, which leads to a neuroinflammation through the stimulation by 6-OHDA, MPTP, and the endotoxin lipopolysaccharide (LPS). This causes several functional changes, including the death of dopaminergic neurons (Bazan et al., 2012; Caggiu et al., 2019).

## 1.7 Treatment

Treatment for PD is challenging; existing therapeutic strategies are known to only relieve clinical symptoms, improve disease progression and quality of life; however, these stratgies have failed to control PD progression ( Kriebel-Gasparro,2016; Zhao et al., 2019). According to observations of dopamine loss in the brain as a result of the death of dopaminergic neuron, a number of therapies of dopamine replacements have been developed and introduced, including dopamine agonists, (DA), Catechol-O-methyl transferase (COMT) inhibitor, Levodopa (L-DOPA), and the Monoamine oxidase–B (MAO-B) inhibitor (Olanow and Stern, 2009; Duty and Jenner, 2011). Accordingly, to find a new treatment is a critical and a challenging issue since available therapies symptomatic only ( Kriebel-Gasparro, 2016).

## 1.8 Pharmacotherapy

### 1.8.1 Levodopa (L-DOPA)

Currently, L-DOPA is among the most effective drugs for PD. It becames available in the markets in the 1960s. This drug passes the blood-brain barrier, promoting the increase in dopamine level (Olanow, Obeso and Stocchi, 2006). L-dopa is often combined with carbidopa, to prevent break down of L-dopa before it crosses in to the brain (Liu, 2019). However, long-term treatment of , L-DOPA value becomes limited because of needed dose increase and resulting induced motor fluctuations (Lewitt and Fahn, 2016; Liu, 2019).

### 1.8.2 MAO-B inhibition

MAO-B inhibition is used for alternative of dopamine in patients diagnosed with PD. The neuronal and glial MAO-B inhibition maintains stable levels of dopamine in addition to other biogenic amines located in the synaptic cleft, leading to improvements of PD symptoms (Riederer and Müller, 2018). Selegiline and Rasagiline are two MAO-B inhibitors used currently as therapy to increase dopamine concentration levels (Cereda et al., 2017).

### 1.8.3 Catechol-O-methyl transferase (COMT) Inhibition

Usually co-administered with the L-dopa to control the PD motor symptoms, COMT inhibitors are known to increase dopamine levels at CNS and (Cheong et al., 2019). Methylation of L-DOPA by the COMT to form 3-O-methyldopa presents the key metabolic pathway for L-DOPA. As COMT inhibitors are able to decrease conversion of the levodopa to 3-O-methyldopa, they can improve levodopa bioavailability in the brain, leading, as such, to an increase of dopamine levels and the treatment of PD (Teaching, Nhs and Trust, 2018). Entacapone and Tolcapone are COMT inhibitors

which are used currently to enhance L-DOPA's therapeutic effects (Cheong et al., 2019; Salamon et al., 2019).

### 1.8.4 Dopamine agonists

Dopamine agonists have also been introduced and used in the treatment of PD. They are similar to functions of L-DOPA; however, they differ from L-DOPA as they do not have to be first converted to dopamine. Apomorphine and ergot derivatives are among early discovered dopamine agonists that proved to be effective albeit with a number of worrying side effects, a matter subsequently made scientists to abandon their use (Duty and Jenner, 2011). To reduce their side effects relating to motor impediments because of patients' chronic use, dopamine agonists are administered in combination with L-DOPA; or, they are given to patients as a type of monotherapy early in the course of PD progession (Cheong et al., 2019).

## 1.9 Non-pharmacological Therapy

### 1.9.1 Surgical Therapies

In addition to pharmacological therapy, surgical therapies offer noticeable benefits for PD treatment. For example, one of the surgical procedures used to treat PD is done by creating a number of lesions in specific selected overactive areas of the brain, like the thalamus' ventral intermediate nucleus in order to treat (PD) tremors.Or, for example, targetting the globus pallidus pars interna, leading to improvements in rigidity, tremor and dyskinesias (Poewe et al., 2017). Lately, deep brain stimulations is introduced for PD treatement. This surgical procedure entials the implantation of electrical leads into specific brain areas, like globus pallidus pars interna,ventral

intermediate nucleus in the thalamus, and the subthalamic nucleus. They are connected to a subcutaneous pulse-generator which is implanted below the chest skin. The pulse generator then makes high-frequency-stimulations in a selected brain area, leading to an interference that decreases the abnormal and/or the overactive neuronal signal. This surgical method could offer important improvements of PD motor symptoms, like dyskinesias as well as motor fluctuations (Jamora and Miyasaki, 2017; Sharma, 2020).

One advantage of using deep brain stimulations, when compared to the creation of lesions, is that the generator can be reprogrammed to decrease the emerging PD symptoms. In fact, deep brain stimulations is also not damaging nor does it prevents using future therapies in the selected brain areas (Follett, 2000). Nevertheless, this procedure has adverse effects, inlcuding the possibilty of damaging the neighboring brian structures. As destructive therapy, this procedure may hinder future uses of more available and effective treatments (Olanow and Stern, 2009). To conclude, surgical and pharmacological treatments have shown to be able to target specific symptoms of PD, have side effects, and, finally,do not cure PD (Olanow and Stern, 2009; Maiti, Manna and Dunbar, 2017).

### 1.9.2 Gene Therapy

The use of gene therapy is grounded either on the symptomatic approach, which involves using the strategy of enzyme-replacement; or, on the disease-modifying approach which relies on neurotrophic factors (Choong, Baba and Mochizuki, 2016). For example, both glial cell-derived neurotrophic factors (GDNF) as well as neurturin (NTN) are critically significant due to their roles as survival and protection factors of dopaminergic neurons in CNS (Tenenbaum and Humbert-claude, 2017). Using adeno-

associated virus (AAV) vectors for the purpose of delivering the GDNF to particular regions in mid-brain is a noevl therapeutic approach in treatment of PD. In fact, rodent and the primate models of (PD), injected with the AAV-GDNF vectors have enhanced both nigrostriatal regenerations and locomotor activities (Choong, Baba and Mochizuki, 2016). Moreover, the use of recombinant GDNF therapy has increased TH amounts, which is the rate limiting enzyme in synthesis of dopamine (Grondin et al., 2018).

# Chapter Two

# Literature Review

## 2.1 Experimental Therapies

As mentioned earlier, inflammation is significant to the development of the disease**.** Typically, microglia are the brain's resident innate immune cells with several functions, including presenting antigens to the adaptive immune cell, debris-clearing, and, finally, surveying surrounding environments to locate any possible antigens that are foreign (Sanchez-guajardo et al., 2013). When in healthy condition, microglia usually helps preserve the anti-inflammatory environments (Wilson et al., 2014). Preventing damages to the neurons. The T cells constitute a part of the adaptive immune system; they help the innate cells repel infections. They are also responsible for sustaining the immunological memory in order to stop repeating infection (Herz, Zipp and Siffrin, 2010). In general, helper T cells are pro-inflammatory, while regulatory T cell (Treg) are anti-inflammatory. In healthy conditions, Tregs cells maintain anti-inflammatory environments of central nervous system because neurons contain the proteins and the molecules which support Tregs cells activation. But, in PD neurons get damaged and the T cells' ability to maintain an anti-inflammatory environment of the central nervous system is lessened (Neurochemistry, 2010). In fact, they further activate the microglia causing the production of high concentrations of cytokines that are pro-inflammatory, like reactive oxygen species, for example. Meanwhile, the increasing activation of the microglia as well as the infiltration of T helper cells further worsen the damage of dopaminergic neurons in the SNpc. Ultimately, this causes a chronically-activated inflammatory environment (Neurochemistry, 2010). PD symptoms develop as this process occurs gradually once 60 to 70% of the SNpc dopaminergic neurons get damaged. The state worsens later because of the absence of interdictive treatments. No treatment for PD exists (Jay and

Jackson-lewis, 2005). As such, this constitutes a dire need for extensive studies about neuroprotective and/or restorative treatments that either can stop PD before it emerges, or stop/reverse PD progression once it is detected (Stoker et al., 2018; Zhen and Chu, 2020). In fact, the absence of effective pharmaceutical therapies should encourage researchers looking to lower costs of PD treatments, to find therapies that can change PD progressions. Suggested therapies include the following: Exendin-4, Nicotine, Urocortin, Caspase's inhibitor, Dexamethasone, Glatiramer acetate (Copaxone) and Minocycline.

## 2.2 Exendin-4 (Ex-4)

The majority of studies show that diabetes is correlated with an increased risk for PD as the impairment of the signaling neuronal insulin leads to the disease (Cheong et al., 2020). Evidently, insulin signaling is crucial to neuronal survival as it prevents the neurodegeneration process. Ultimately, this has led researchers to find new therapeutic approaches for treating neurodegenerative disorders (Chao, Hu and Chau, 2020). Glucagon-like peptide 1 (GLP-1) receptor is located within both the brain and pancreatic β-cells (Kim et al., 2017). Stimulating (GLP-1) enhances neuroprotective effects of PD, which is a neurodegenerative disorder (Burcelin and Nathanson, 2011). Ex-4, a peptide agonist of GLP-1 receptor, can easily traverse BBB, thus, leading to promotion of neurogenesis (Ventorp et al., 2017). Additionally, Ex-4 preserves dopamine levels as it decreases loss of dopaminergic neurons. Ex-4 is an anti-inflammatory in the CNS, which impacts microglial cells by deactivating their functions and promoting dopaminergic neuron survival (Harkavyi, Rampersaud and Whitton, 2013; Chen *et al.*, 2018). In fact, microglial activation is important to the emergence and development of the pathogenesis of a number of neurodegenerative

disorders, like PD and AD (Aviles-olmos et al., 2013; Kim et al., 2017). Further, patient motor functions also improve when using Ex-4, a matter that makes it a valuable element for neuroprotective effects when treating neurodegenerative diseases, including PD (Harkavyi, Rampersaud and Whitton, 2013).

## 2.3 Nicotine

Undoubtedly, smoking is a main health risk factor (Piao et al., 2009). Nevertheless, evidence continues to show that smokers are less prone to have some inflammatory and neurodegenerative disorders. Actually, nicotine has the potential to act as a neuroprotective and/or anti-inflammatory agent (Ma et al., 2017; Nicholatos et al., 2018). When nicotine interacts with microglial a-7 nicotinic receptor, findings show it suppresses LPS-induced production of TNF-α (Dutta, Zhang and Liu, 2008). Nicotine, accordingly, is likely to have an anti-inflammatory role by protecting DA neurons from possible inflammatory damages (Ma et al., 2017). Certainly, micro-molar concentrations of nicotine have considerably lowered the LPS-stimulated release of TNF-α, and contributed to loss reduction of DA neurons in the cell cultures of the LPS PD model. Specifically, administering nicotine (1 mg/kg;5 times daily) has considerably lowered the TNF-α production and the damage of SNpc DA neurons when they were injected by the intranigral LPS (Dutta, Zhang and Liu, 2008).

## 2.4 Glatiramer acetate (Copaxone)

Existing PD treatments mainly target the dopaminergic symptoms of the disease, but they do not alter the progression of neurodegenerations (Vorup-jensen et al., 2017). Glatiramer acetate (GA) constitutes a group of synthetic polypeptides that have been approved for treating relapsing-remitting, multiple sclerosis (Conner, 2014). According to animal studies, GA possesses a main anti-inflammatory influence as it releases anti-inflammatory cytokines (Dutta, Zhang and Liu, 2008; Conner, 2014). GA, as such, can act as a possible therapeutic agent for treating PD when taking into account its anti-inflammatory effect (Dutta, Zhang and Liu, 2008).

## 2.5 Dexamethasone

Due to their anti-inflammatory features, Glucocorticoids are used for treatments of brain inflammation as well as spinal cord injuries (Herrero et al., 2015). Intraperitoneal injection of dexamethasone (4mg/kg) has considerably repressed the microglial activation in dopaminergic cells in the SN; thus, protected SNpc DA neurons from loss when they were induced by LPS intranigral injections (Dutta, Zhang and Liu, 2008). Evidently, these studies reveal the efficiency of dexamethasone in protecting DA neurons from inflammatory loss (Kurkowska-jastrze, 2004; Dutta, Zhang and Liu, 2008).

## 2.6 Urocortin (UCN-1)

UCN-1 is the 40-amino acid peptide, which correlats to the corticotropin-releasing factor (CRF). It is located in the brain, CRF its receptor are found on the dopaminergic neuron (Biology et al., 2015). As a result, UCN-1 plays a significant role in relation to PD pathophysiology. In fact, studies have demonstrated UCN-1 is

able to restore damage to the nigrostriatal functions (Abuirmeileh et al., 2007; Biology et al., 2015). This peptide represses cellular apoptosis and free radical damage in addition to inflammation. As such, it can have prospective effects for treating PD (Liew et al., 2012).

## 2.7 Caspases inhibitor

The activation of the Caspase-3 is an important feature in PD. It can cause neuron death by inflammation resulting from apoptosis and microglia activations (Liu et al., 2013). As a result, the inhibition of caspase lowers cell death as well as the production of the pro-inflammatory cytokine, thus, preventing PD progress (Smith et al., 2017).

## 2.8 Minocycline

Minocycline is a type of tetracycline antibiotics with anti-inflammatory potential (Cankaya et al., 2019). Its neuroprotective effect is due to repression of the LPS-stimulated-NO release, TNF-a release, and finally,Caspase-3 activation. Adminstring minocycline (45mg/kg) has reduced significantly SN microglial activation induced by an intranigral LPS injection in the Wistar rat's (Dutta, Zhang and Liu, 2008). Additionally, the LPS-induced loss of SNpc DA neuron was lowered in minocycline-dosed rats significantly (Pang et al., 2012).

## 2.9 Sitagliptin and liraglutide

### 2.9.1 Background

According to recent studies (Badawi et al., 2017, 2019). There is a high comorbidity between Type-2 Diabetes mellitus (T2DM) and neurological diseases. Developments in current research and studies demonstrate the Glucagon-like peptide 1 (GLP-1) probably has effects that transcend mere modulating of food-intake. Examples include modulation of sleep patterns as well as restricting inflammation and providing neuroprotections (Dixit et al., 2013). Currently, GLP-1 are available in the market for treating Type-2 Diabetes. They have shown neuroprotective features in animal models for studying neurodegenerative diseases. Sitagliptin and Liraglutide, accordingly, can act as potential agents for treating some types of neurodegenerative disorders (Badawi et al., 2017).

### 2.9.2 Function of sitagliptin and liraglutide

GLP-1 is an incretin hormone mainly secreted from the intestinal L cells. GLP-1 has favorable effects: for glucose homeostasis, stimulating the proliferation and differentiation of β-cell, and well as inhibiting β-cell apoptosis (Dixit et al., 2013). GLP-1-based therapies include GLP-1 receptor agonist (Liraglutide) and the inhibitor of dipeptidyl peptidase-IV (DPP-IV), Sitagliptin which regulates DPP-IV activities and increases levels of active GLP-1. Both therapies have been developed for treating type-2 diabetes (Mk- et al., 2005; Ferreira et al., 2010; Hansen et al., 2016). Further, GLP-1 is produced in the brain, and possesses neuroprotective and neurogenic actions on different brain regions. Additionally, GLP-1 and GLP-1 analogs pass freely through the blood-brain barriers (Badawi et al., 2017). Anti-inflammatory action of both sitagliptin and liraglutide was evident on different diseases relating to chronic

inflammations in peripheral and/or central tissues. Thus, Sitagliptin and Liraglutide can be beneficial for treating chronic inflammatory diseases, such as neurodegenerative diseases and disorders. This study is designed to illustrate the therapeutic potentials of both Sitagliptin and Liraglutide as anti-Parkinsonian treatments.To do so, there will be focus on their anti-inflammatory anti-apoptotic-dependent mechanisms to be observed on LPS induced parkinsonism in rats (Badawi et al., 2017, 2019).

### 2.9.3 Uses as Novel Therapy

Several studies have examined possible relation between pro-inflammatory cytokines and programmed nigral neuronal death in PD models. Where the Sitagliptin and Liraglutide can inhibit the inflammatory degenerative process because they have neuroprotective effect (Badawi et al., 2017). Moreover, Sitagliptin and Liraglutide are promising therapies to mitigate PD progression due to their anti-inflammatory, anti-apoptotic, neurotrophic, and neurogenic mechanistic activities and features (Badawi et al., 2019). In sum, Sitagliptin and Liraglutide can be promising therapies to PD. This study offered experimental evidence for an ability of GLP-1-based therapies (analog Liraglutide and enzyme-inhibitor sitagliptin) for alleviation of the pathophysiology of PD. Similarly, their encouraging outcomes clinical trial experiment of GLP-1 to produce drugs for treating neurodegenerative diseases, one of which is PD (Hansen et al., 2016; Nader et al., 2017; Badawi et al., 2019).

## 2.10 Models of Parkinson disease

To understand the pathology of PD, and to develop effective therapeutic agents for management, it is important to produce relevant disease models (Duty and Jenner,

2011). There are many models of PD, these can be divided to in-vivo and in-vitro models (Blandini and Armentero, 2012).

### 2.10.1 In vitro models

Dopamine neuron-derived cell lines are useful for illustrating neuronal death mechanisms in PD, and for studying novel pharmacological agents (Shimohama et al., 2003).

#### 2.10.1.1 SH-SY5Y cell line

In 1973, scientists were able to isolate the human neuroblastoma SH-SY5Y cell line from a girl's metastasis biopsy (Popova, Karlsson and Jacobsson, 2017). The cell line is able to produce dopamine because of existing dopaminergic markers, like tyrosine hydroxylase, dopamine transporter, and dopamine- β-hydroxylase. As such, this cell line is utilized as replacement for dopaminergic neurons in studies of PD (Martins et al., no date; Xicoy, Wieringa and Martens, 2017). Treating of SH-SY5Y cells with differentiation agents of Brain-Derived Neurotrophic Factor (BDNF) and Retinoic Acid (RA). Causes alterations to cellular morphology which develops cytoplasmic projection (Martins et al., 2010). Further, this differentiation mechanism causes a phenotype which resembles neurons that show increases in the appearance of several synaptic function genes, such as DNM1 and CLTC (Cells et al., 2000).

#### 2.10.1.2 LUHMES cell line

LUMES is the tetracycline sub-clone, isolated from an 8-week-old fetus ventral mesencephalic brain tissues (Neurochemistry, 2011). Dissimilar to SH-SY5Y, the over-expression of dopamine markers necessitates a differentiation marked by adding

both neurotrophins and antibiotics. Following the differentiation, the dopamine release increases, resulting in cells becoming similar to neurons (Zhang, Yin and Zhang, 2014; Zuberek et al., 2018). On a related note, positively charged of 1-methyl-4-phenylpyridinium (MPP+) are frequently used to create cytotoxic PD models in this examined cell line (Ste and Pgam, 2015).

### 2.10.2 In vivo models

For the past four decades, animal models of PD have been used to study its pathogenesis and pathophysiology (Blandini and Armentero, 2012). However, these models have also demonstrated effectiveness while searching for new treatments for PD motor incapacities (Duty and Jenner, 2011). Available rodent models include acute pharmacological models—such as haloperidol or reserpine-managed rats with PD symptoms, models showing destructive nigro-striatal pathway of dopamine—such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) (Koprich, Kalia and Brotchie, 2017; Zeng, Geng and Jia, 2018). Furthermore, although administration of the pesticides, parquet and rotenone toxic models of nigro-striatal degradation assist in studying the pathogenesis of disease, but not for improvements of PD drugs (Shimohama et al., 2003). Poisons used to produce rodent PD models and in trials of neuroprotective agents have action mechanisms that mimic the pathogenesis of PD, including inflammogens such as LPS, proteasomal inhibitor like epoximycin, mitochondrial complex I inhibitors like MPTP and ROS producer as 6-OHDA (Deng et al., 2020).

### 2.10.3 PD Model: lipopolysaccharide (LPS)

For a closer examination of PD pathogenesis, a number of animal models were developed; one of which is the Lipopolysaccharide (LPS) neurotoxin model, which was discovered first and termed by Richard Friedrich Johannes Pfeiffer (Dutta, Zhang and Liu, 2008). Neuro-inflammation causes the loss of the nigrostriatal dopaminergic (DA) pathway, which is the pathological source of movement disorders in PD (Liu and Bing, 2011; Hoban et al., 2013). Neuro-inflammation is characterized by active brain glial cells, specifically, the microglia and the astrocytes, both of which release a number of soluble factors, such as free radicals (reactive oxygen and nitrogen species), cytokines as well as lipid metabolite. LPS, meanwhile, is considered to be an extensively used glial activator to induce inflammatory DA neurodegeneration. LPS endotoxin is present in bacterial cell wall and is extremely very toxic to the human body (Catorce and Gevorkian, 2016; Deng et al., 2020). A single LPS injection to the SN regions in rats models has shown to lead to a marked loss of SNpc DA neuron (50–85%) (Ribeiro et al., no date; Dutta, Zhang and Liu, 2008). LPS Injection to the substantia nigra region causes advanced, preferential and permanent loss of SNpc DA neurons, which were observed after 2 weeks during which LPS was delivered (Kong et al., 2019). The degenration of SNpc-DA neurons started within 2-4 weeks (Dutta, Zhang and Liu, 2008).

# Chapter Three

# Materials and Methods

## 3.1 Materials:

Table 3.1 below illustrates the used material in this research.

**Table 3.1: Used Materials**

| **Used Material** | **Purchased from** |
|---|---|
| Liraglutide (Victoza) | Sigma-Aldrich (Pool, UK) |
| Sitagliptin powder | Sigma-Aldrich (Pool, UK) |
| Desipramine hydrochloride | Sigma-Aldrich (Pool, UK) |
| Pargyline | Sigma-Aldrich (Pool, UK) |
| Apomorphine | Sigma-Aldrich (Pool, UK) |
| LPS | Sigma-Aldrich (Pool, UK) |
| White phosphate-buffered saline | Sigma-Aldrich (Pool, UK) |
| Crystalline l-ascorbic acid | Sigma-Aldrich (Pool, UK) |
| Perchloric acid | Fulltime (China) & Lab Chem. (NJ, USA) |
| Water (HPLC grade) | Fulltime (China) & Lab Chem. (NJ, USA) |
| Methanol | Chem.-Lab Analytical (Belgium) |

## 3.2 Methods:

### 3.2.1 Description of rat Groupings and the Experimental Design:

Male Wistar rats (n=24), each weighing (250-300 g), were acquired from the Jordan University of Science and Technology (JUST). The selected rats were divided into 4 groups (6 rats per cage) in a hygienic house with adequate supplies of food and water. During the experiments, the room temperature was kept at (22˚C) during a 12-hr light/12-hr dark (LD) cycle. All experiments followed the ethical guides for use of experimental animals.

The mice groups were divided into the following:

• **Group A** (Control): This group is used for the comparison to the other three experimental groups of treated mice (n=6).

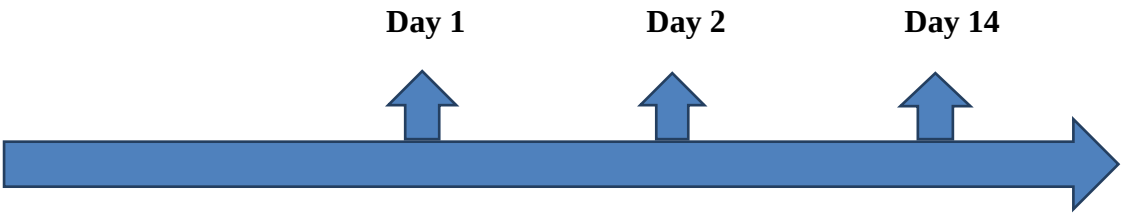
• **Group B** (Injected with LPS only): This group demonstrates LPS effects on the dopaminergic cells, allowing for comparisons to the other groups of treated mice (n=6).

• **Group C (**LPS injection, followed by a (50 μg/kg) Liraglutide (s.c) treatment) (Badawi *et al.*, 2019): Each rat was injected once daily for the duration of 14 days. This group will demonstrate if the selected treatment will decrease LPS induced-damages to the dopaminergic neurons (n=6).

• **Group D** (LPS injection, followed by (30 mg/kg) oral Sitagliptin treatment) (Badawi *et al.*, 2019): Each rat was injected once daily for the duration of 14 days. This group demonstrated if the selected treatment can reduce LPS induced-damages to dopaminergic neurons (n=6).

The table 3-2, shows the study of protocol of the work and its sequence of events.

**Table 3-2: The study protocol and its sequence of events.**




| | | | |
|---|---|---|---|
| **Group A** | **Vehicle** | **Vehicle** | **Apomorphine + killing** |
| **Group B** | **LPS only** | | **Apomorphine + killing** |
| **Group C** | **LPS** | **Start Liraglutide (s.c)** | **Apomorphine + killing** |
| **Group D** | **LPS** | **Start Sitagliptin(oral)** | **Apomorphine + killing** |

**Table 3-2: The Flow diagram illustrates the study protocol and its sequence of events. On the second day of the experiments, Liraglutide was administered to Group C; while Sitagliptin was given to Group D. On the 14$^{th}$ day of the experiments, both Apomorphine rotation test and killing were conducted.**

## 3.3 Stereotaxic surgery

Using stereotaxic surgery, mice in groups B, C, and D were injected with LPS through the following steps: First, rats were anesthetized with isoflurane (3% for induction purposes and 1-1.5% for maintenance), which was purchased from Hikma pharmaceuticals company (Amman, Jordan). The animals, then, were placed on a vernier stereotaxic frame. Using a scalpel blade, an incision was made along the longitudinal midline of the rat's scalp, swapped with iodine solution.

Using a marker, the bregma was located then drilling the skull and later injecting it with 2µl (2µg/1µl) LPS dissolved in normal saline by a micro syringe (10µl) into SN (from bregma A 2.2mm, L 5.3mm, V 8.3mm), The solution was placed in dark place on ice until injection. Finally, the syringe was kept in the drilled skull for additional five minutes before it was slowly withdrawn in order to block any backflow.

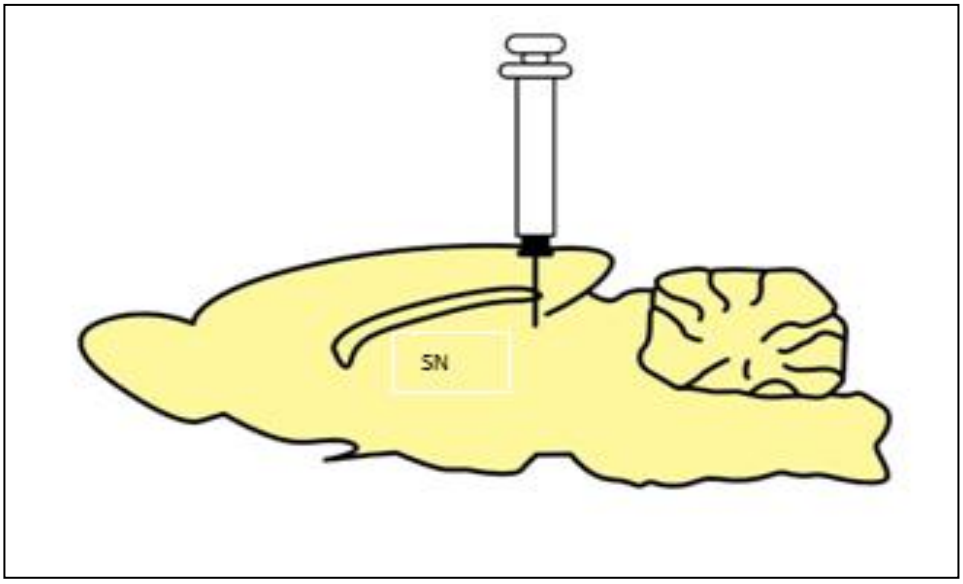



**Figure 3-1: An illustration of the study's experimental design which identifies the site of the stereotaxic injection.**

## 3.4 Administering Sitagliptin and Liraglutide Treatments

Sitagliptin-treated animals were subjected to (30 mg/kg) for 14 days orally, Liraglutide-treated animals were subjected to (50μg/kg) for 14 days (s.c), these drugs were scheduled for administration on the second day of surgery.

## 3.5 Tissue dopamine assay

On day 14, after having finished all treatments and behavioral estimations, the rat was decapitated and its skull was carefully removed and placed in dry-ice. The brains were then stored in an -80 (Haier Biomedical) freezer for later analyses, using a High-Performance Liquid Chromatography-Electrochemical Detector (HPLC-ECD). On the designated day of tissue analyses, the striatum was dissected, ice-bathed, and, later, homogenized by using (1 ml) of cold phosphate-buffer.

Using a Hettich universal 30 RF cold centrifuge (Wiltshire, UK), homogenates were twice centrifuged at 10000 rpm for the duration of 10 minutes at (4˚C). After that, 35μl of the supernatant was prepared with 15 μl (0.2 M per chloric acid) to remove cell debris and centrifuged again. Finally, were put into 1 ml-Eppendorf tube and HPLC was used for tissue dopamine evaluations.

## 3.6 HPLC System Components

Dionex Ultimate 3000 HPLC, manufactured by Thermo Fisher Scientific (Germany), was utilized in this study for its renowned optimal and high-performance simultaneous dopamine assays. This HPLC-ECD system consisted from the following parts: (1) An auto-sampler/model-WPS-3000, (2) a delivery pump/model-ISO-3100BM, and, finally, (3) an electrochemical detector /model-ECD-3000RS. The

detector is fitted with VTO3 cell (Vcell +625mV, filtered to 5; range was set at 0.5 nA/volt for a deflection of full-scale deflection). Chromatographic separation, meanwhile, was conducted on a Venusil XBP (L) C18 (5μm particle size; 4.6×250 mm) reverse-phase-column, manufactured by Agela Technologies in Torrance, USA.

The column was kept at temperature of 4˚C, while the auto-sampler's temperature was set at (25˚C). The mobile phase was made up from the following: 35mM citric acid, (90mM) sodium acetate tri-hydrate, 0.34mM EDTA, 0.06Mm of an ion paring reagent 1-octane-sulfonic acid sodium salt, 5.5% methanol, and pH was adjusted to 4.2 by citric acid. The flow rate, meanwhile, was kept at 0.65ml/min with a 20μl sample-injection-volume.

## 3.7 Apomorphine rotation test

After 14 days of the conducted surgery, all selected rats were injected with Apomorphine (0.5 mg/kg) in order to identify possible lesion severities as well as motor defects that appeared in brain regions between right and left hemispheres. 15 minutes after being injected, the rats were placed in a circular test. A two-minute full rotation was recorded by using a stop-watch.

## 3.8 Statistical Analysis

The purpose of the statistical analyses was to determine the effectiveness of the treatments given to the rat group for comparisons to each other as well as to the control group. For comparisons, One-way ANOVA tests were completed. They were followed later by a Bonferroni correction post-hoc test for multiple comparisons which were completed by using Prizm 5 software (GraphPad Software, Inc., La Jolla, CA). Values were expressed as the (mean ± standard error of mean). $P < 0.05$ was considered statistically-significant.

# Chapter four

# Results

## 4.1 Introduction

This study sought to investigate the neuro-protective effects of Sitagliptin and Liraglutide drugs on the LPS rat model. In this chapter, data were obtained from neurochemical and behavioral evaluations. Each group was subject to analysis to identify the total number of dopaminergic neurons; also, data were obtained from the Apomorphine-induced rotation.

## 4.2 The External Standard:

In this study, the analytical technique of HPLC-ECD for dopamine was used to compare the device's retention time with dopamine standards. The peak area ratio value was then measured by software to quantify it. All values were connected to a specific amount of dopamine.

Heat and light cause dopamine instability, which leads, in turn, to increasing degradation rates. This main problem impacts results. Therefore, all fresh solutions were prepared in optimum condition by working in a dark and cold room. Also, all solutions were enclosed by aluminum foil to protect them from light.

Fig (4-1) shows a demonstrative dopamine sample; X-axis demonstrates the run time/minutes, identifying the retention time within (7-8) minutes. Y-axis demonstrates concentrations identified based on peak-area. Chromeleon software (ver. 6.8) was utilized in making the Chromatogram. Figure 4-2: shows a Beer-Lambert's Calibration Curve of Dopamine Concentrations vs. the Peak Area.

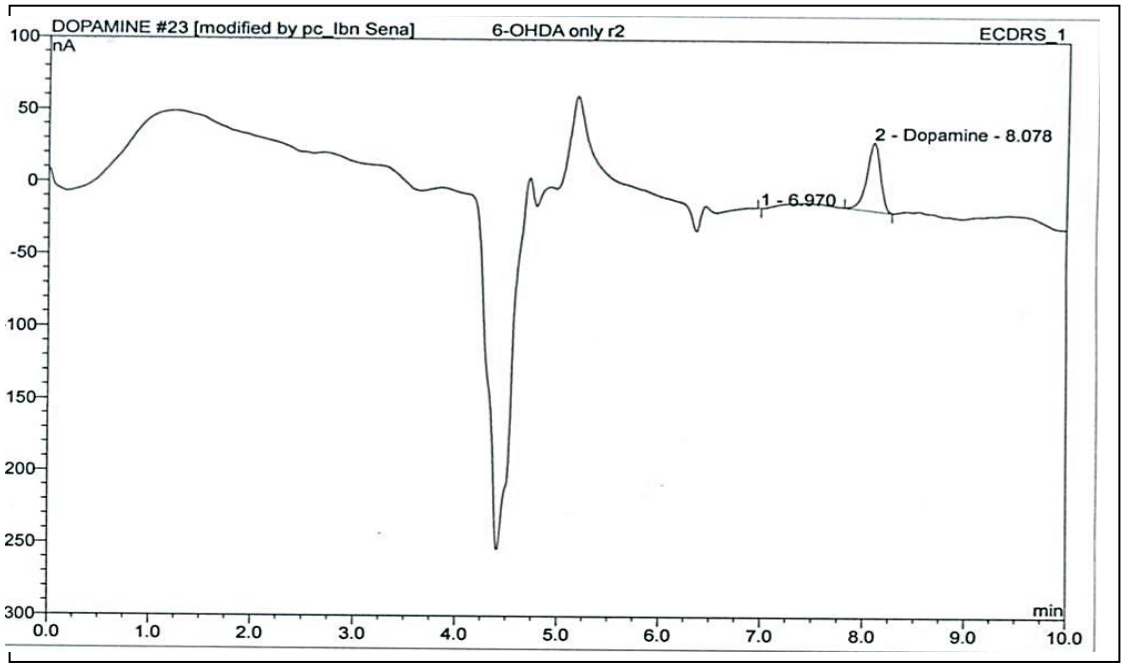



**Figure (4-1) illustrates a demonstrative typical chromatogram of striatum samples by using the HPLCED.**

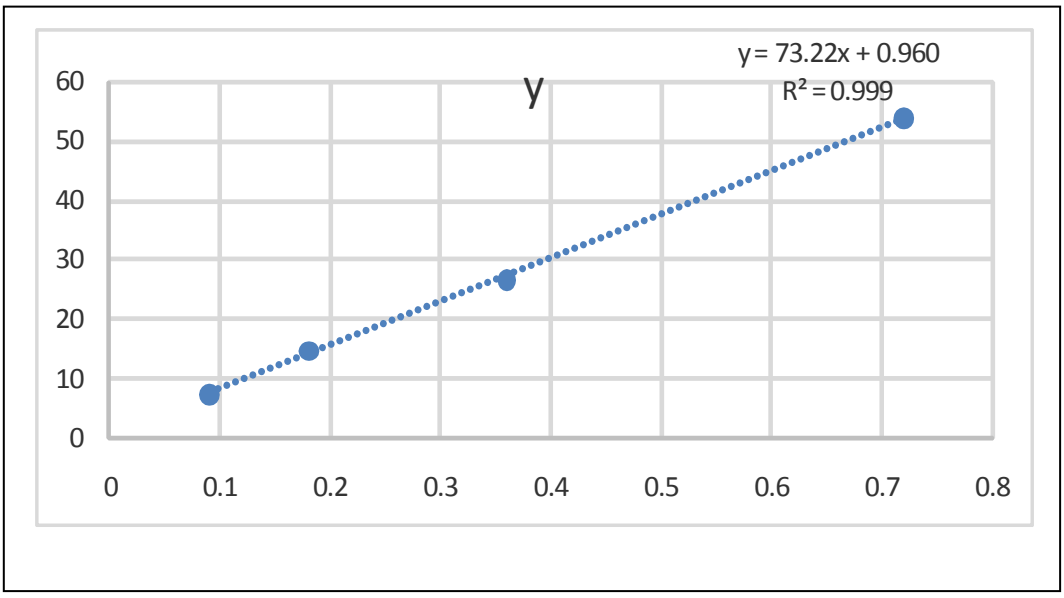



**Figure 4-2: Beer-Lambert's Calibration Curve of Dopamine Concentrations vs. the Peak Area**

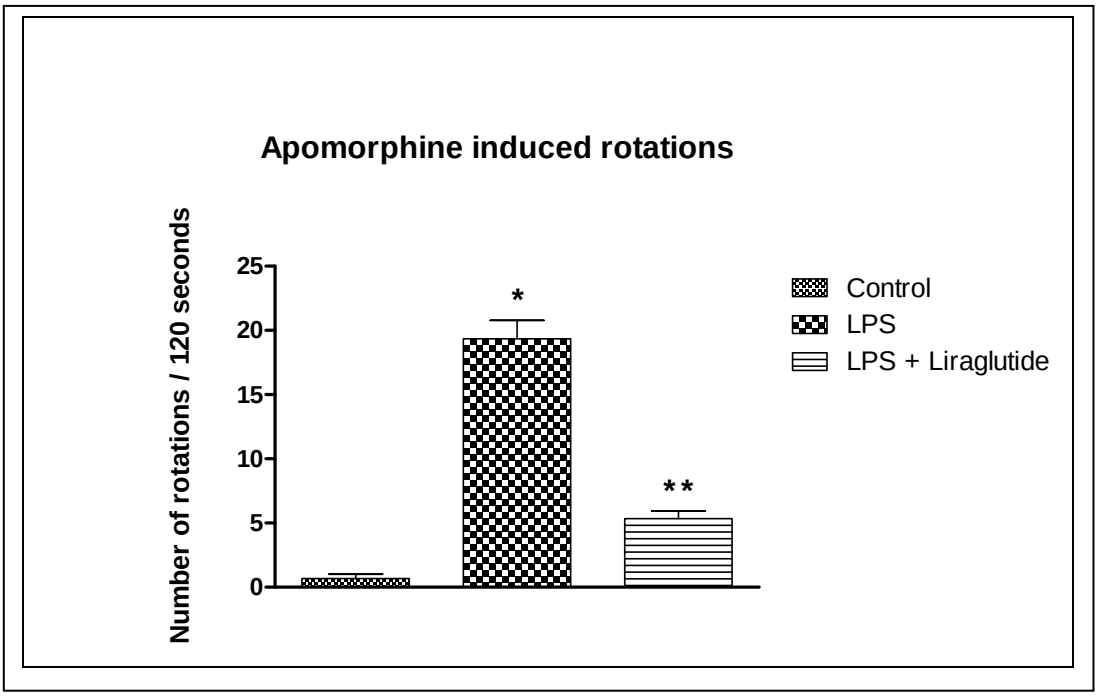
The following equation resulted from analysis of the dopamine's calibration curve: y=73.227x+0.9609, with R2=0.9992.

## 4.3 Apomorphine challenges in each group

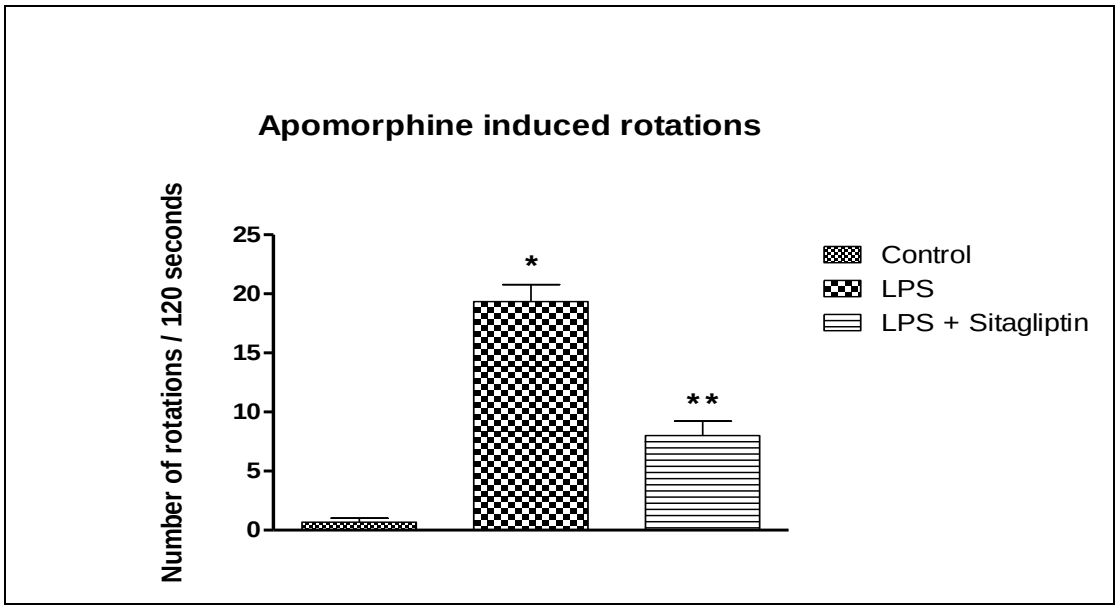
Conducting Apomorphine tests helps with detecting both lesion extents as well as motor deficits in the selected rat model. In fact, 14 days after intracerebral LPS injections, rats exhibited rotational behaviors in the direction of the opposite side of the induced lesion after following apomorphine injection. These observations were made, during a tight contralateral circling of around 21 turns in 2 minutes for the LPS model.

As shown in Figure (4-3), the control group rats showed no rotations; but, the LPS group, when compared to Group A (Control), displayed a rotational behavioral injection of Apomorphine at around 21 turns. Additionally, our data indicates the difference between the LPS-models group treated with (s.c) Liraglutide and the LPS group administered with oral Sitagliptin drug.

Figure (4-3/A) shows a decreased sensitivity of rotations to Apomorphine challenge in the groups which was treated with Liraglutide (s.c) + LPS. Similarly, the group that was given Sitagliptin (Orally) also demonstrated noticeable reductions in rotation responses following Apomorphine challenges figure (4-3/B). Shows reduction in rotation responses in Groups C and D in comparison to Group B of the LPS lesioned-rats.




(A)




(B)

**Figure 4-3: Effects of (s.c) Liraglutide +LPS (A) and oral Sitagliptin +LPS (B) on Apomorphine-induced rotational behavior in rats.**

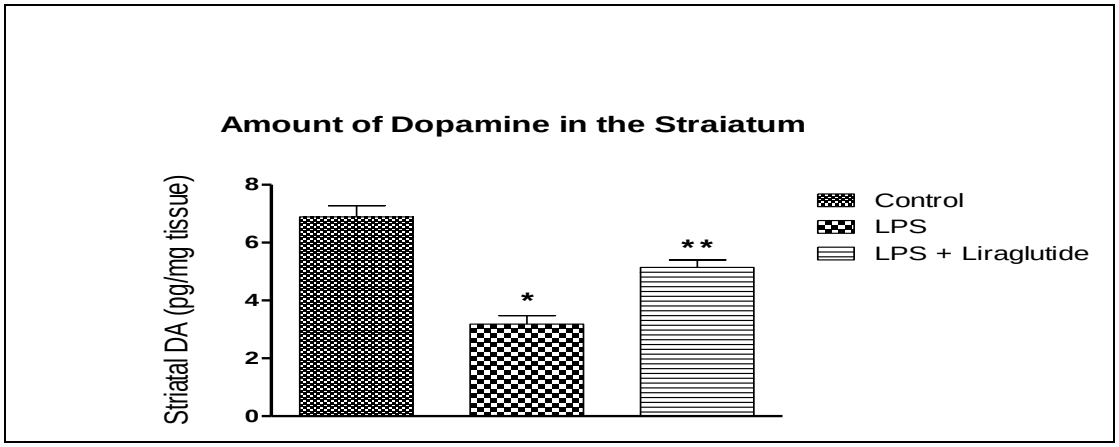
**Animals were tested for denervation super-sensitivity by administration of subcutaneous Apomorphine (0.5µg/kg) in lesioned-rats where Y axis shows the number of rotations.**

**Liraglutide (50 µg/kg) s.c (A) was administered once daily for 14 days after surgery done to LPS group. Oral Sitagliptin (30 mg/kg) (B) was administered once daily for 14 days after surgery was done to LPS group. Measuring of circling was made following 14 days of toxin injections which lasted for 120 seconds. This procedure was conducted 15 minutes after apomorphine injections. Statistical analysis was carried out using one-way ANOVA followed by Bonferroni post hoc test for multiple comparisons (n = 6 rats per group) * indicates a difference than the control group. **indicates differences than the control as well as LPS groups ($p < 0.05$, n =6 per group).**

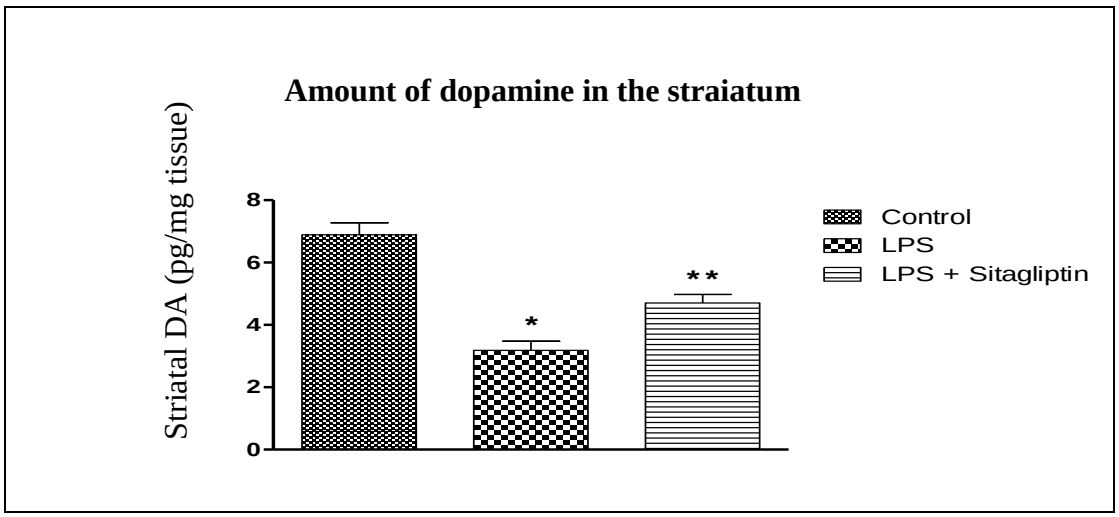
## 4.4 Determination of tissue dopamine concentrations

Injection of LPS with a dose of 2µl resulted in the loss of dopaminergic neurons, when compared to the control group. Figure (4-4) represents striatal tissue dopamine contents with (s.c) Liraglutide (50µg/kg for each rat) for 14 days or oral Sitagliptin (30 mg/kg for each rat) for 14 days.

Figure (4-4, A), (4-4, B) administration of Sitagliptin and Liraglutide to LPS treated rats showed a significantly reduced levels of dopamine induced by LPS. Which are significantly different than both the control group and the untreated LPS group.




(A)




(B)

**Figure (4-4): Shows differences of dopamine levels among the treatment groups.**

**Control group was only treated with vehicles, while the LPS treated groups were subjected to (50µg/kg/day) (s.c) Liraglutide (A) for 14 days and oral Sitagliptin (30 mg/kg /day) (B) for 14 days. Statistical analysis was carried out using one-way ANOVA followed by Bonferroni post hoc test for multiple comparisons (n = 6 rats per group). * Demonstrates a difference than the control group. ** demonstrates significant differences than both the control and the LPS groups.**

# Chapter Five

# Discussion

Parkinson's Disease (PD) is a neurodegenerative disorder with motor and non-motor symptoms, leading to the disability of affected individuals (Storstein, 2017; Zhao et al., 2019). An exact PD etiology is still unidentified; nevertheless, a number of probable causes are recognized. Genetic mutations in addition to exposure to environmental toxins, like herbicides (Liu et al., 2015; Caggiu et al., 2019) may create pro-inflammatory environments in the brain regions. Despite the lack of a precise PD etiology, scientists work relentlessly to find PD treatments.

Existing PD treatments manage to treat its symptoms only. But there is an increasing interest in examining the extent to which inflammation plays a role in the PD pathophysiology. This line of examination paves the way for finding treatments to reduce and/or end PD progression (Huang et al., 2017; Zhao et al., 2019). According to previous studies, a reduction in brain inflammation can slow or halt neuronal loss in LPS rat models (Catorce and Gevorkian, 2016). Building on this work, we used LPS model in establishing the neuro-protective effects of Sitagliptin and Liraglutide in relation to each other.

The inhibition of microglia activation in the brain's regulatory T cell population can reduce the number of dopaminergic neurons that are damaged because of LPS intoxication. Therefore, LPS injection into the striatum induces neurotoxicity, which illustrates the important role for neuro-inflammation in the degeneration of the nigrostriatal dopaminergic (DA) pathway. This, in fact, constitutes the pathological basis of the prevailing movement disorder of Parkinson's disease (Hoban et al., 2013). Typically, microglia are of innate immune brain cells with specific functions: they present antigens to the adaptive immune cells; they clear cell debris, and, finally, they search for any foreign antigens in the environment. In a healthy state, microglia should help maintain anti-inflammatory environment (Sanchez-guajardo et al., 2013).

Which, therefore, should not cause any damage to neuron. In PD, however, these roles can change.

In PD, further activation of microglia by increasing the number of pro-inflammatory cytokines, like reactive oxygen species, for example. This PD-induced microglial activation, coupled with infiltrating T helper cells, further damages dopaminergic neurons in SNpc. The result is a chronically-activated inflammatory environment (Neurochemistry, 2010). PD symptoms start to emerge when (60-70 %) of dopaminergic neurons in SNpc are totally destroyed (Jay and Jackson-lewis, 2005).

Research continues to investigate new treatments and therapeutic approaches to slow and prevent neuronal degeneration and death. Specifically, scientists are looking for PD therapies with neuroprotective elements that can traverse the BBB to achieve desired outcomes with minimal adverse side-effects. As stated earlier, both Sitagliptin and Liraglutide are promising neuroprotective compounds with anti-inflammatory features. Moreover, both can pass through the BBB, a matter that compels scientists to seriously consider their effective use in PD treatments (Badawi et al., 2017).

Chapter four clarifies the positive results of the two drugs (Sitagliptin, Liraglutide). LPS-induced lesions caused phenotypic behaviors. Fourteen days after LPS lesions in PD rat models, apomorphine-induced rotations increased towards the lesioned side (Ribeiro et al., no date; Huang et al., 2018). This quantitative test is used to evaluate dopaminergic neuronal deficits and treatment effectiveness (Huang et al., 2018). Results of this study, Fig (4-3), revealed that a daily administration of Sitagliptin or Liraglutide for a period of 14 days has led to significant reductions in LPS induced-behavioral deficits (Badawi et al., 2019). Similarly, Badawi et al. found experimentally that the treatment with Sitagliptin or Liraglutide showed significant improvement in the behavioral activity (Badawi *et al.*, 2019).

Studies have examined the relation between nigral neuronal death in the LPS rat models and pro-inflammatory cytokines. However, Sitagliptin and Liraglutide were understudies for their efficacy to inhibit the inflammatory degenerative process as both have neuroprotective effects (Badawi et al., 2017). As shown in Fig (4-4), Sitagliptin and Liraglutide are able to reverse effects of LPS and to alleviate PD progression possibly due to their anti-inflammatory, anti-apoptotic neurotrophic and neurogenic features. Referring to our previous argument, this notion is supported by Badawi et al. The ability of Sitagliptin and Liraglutide to reverse effects of LPS (Badawi *et al.*, 2019). In the present work, it is observed that the oral administration of Sitagliptin, or Liraglutide in LPS-induced nigrostriatal lesions significantly induced a decrease in key indicators of nigrostriatal neurodegeneration. These indicators include the restoration of severe reductions of dopamine contents in the striatal tissues in addition to the restoration, or preservation, of the nigral TH positive cell bodies when damage is detected.

This is likely due to enhancing the cell neurogenesis associated with a dopaminergic recovery of TH activity (Badawi et al., 2019). Significantly, Sitagliptin or Liraglutide are effective when given for a period of 14 days after lesion induction. Figure (4-4) clearly illustrates how using both compounds lead to ameliorate the effect of LPS on dopamine level in striatum. This, accordingly, exemplifies that Sitagliptin and Liraglutide actually decrease the effect LPS in the nigrostriatal pathway.

## Conclusions

As hypothesized earlier, both Sitagliptin and Liraglutide have promising aspects for their neuroprotective effects to alleviate PD symptoms. To conclude, this study showed that Sitagliptin and Liraglutide are neuroprotective compounds that can slow and protect dopaminergic neurons. Liraglutide and Sitagliptin have the capacity to alleviate the pathophysiology of Parkinson's disease might be done of their "anti-inflammatory, anti-apoptotic, neurotrophic and neurogenic potentials." Hence, these encouraging results should motivate scientists to conduct future the clinical trials of GLP-1R-based therapy for treating several neurodegenerative diseases, one of which is PD.

## Future work

1- To assess effect of Sitagliptin and Liraglutide on other neurotransmitters systems.

2- To evaluate other behavioral test and biomarkers assessment.

3- Correlates final results of this study to real life.

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# تأثير السيتاجلبتين و الليراجلوتيد في الليبوبولي سكاريد في نموذج الفئران لمرض الشلل الرعاشي

**اعدت من قبل**

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## الملخص

**المقدمة :** يعرف مرض الباركنسون، بأنه اضطراب تنكسي عصبي يؤدي إلى موت عصبون الدوبامين الموجود في المادة السوداء في الدماغ، مما يؤدي إلى اضطراب الحركة. وفقاً لذلك، استهدفت استراتجيات العلاج الحالية لمرض الباركنسون نظام الدوبامين. ومع ذلك، مع مرور الوقت يتفاقم المرض خاصة في المرحلة المتأخرة من المرض، مما يؤدي إلى مقاومة العلاج. هناك حاجة ملحة لإيجاد علاجات فعالة لتحسين تطور المرض وتحسين نوعية الحياة، ومع ذلك،لا يمكن للعلاجات الحالية أن تبطئ أو تمنع تطور شلل الرعاش. ينتج المرض عن نقص الدوبامين، لذا فإن العلاج الأساسي يشمل الأدوية البديلة للدوبامين. في هذه الرسالة، سيتم التحقيق في فعالية سيتاجلبتين وليراجلوتايد، وكلاهما يتمتع بموافقة إدارة الغذاء والدواء لعلاج مرض السكري من النوع الثاني.

**الهدف :** تهدف هذه الدراسة إلى تحقيق من مدى فعالية سيتاجلبتين وليراجلوتايد في نموذج القوارض لعديد السكاريد الدهني لمرض الباركنسون. عديد السكاريد الدهني هو ذيفان داخلي يتم استخارجه من البكتيريا سالبة الجرام، على هذا النحو، فهو يعمل كمحفز قوي للخلايا الدبقية الصغيرة، وقد استخدمه الباحثون لفحص العملية

الالتهابية لتسبب في المرض. وبالتالي، يمكن ان يكرر العديد السكاريد الدهني خاصيتين رئيسيتين لمرض الباركنسون: التنشيط الواسع للخلايا الدبقية الصغيرة وكذلك فقدان الخلايا العصبية الدوبامينة.

**منهجية البحث** : تم اختيار 24 من ذكور الجرذان، وزنها ما بين (250-300) جرام، بصورة عشوائية ثم قسمت إلى 4 مجموعات مختلفة كل منها 6 فئران. كانت مجموعة (أ) هي المجموعة الضابطة، وتعرضت فئران المجموعة (ب) إلى العديد السكاريد الدهني وحده، وتعرض المجموعة (ج) لـ ليراجلوتايد تحت الجلد + العيدد السكاريد الدهني لمدة 14 يوماً بعد العملية الجراحية. اخيرا"، المجموعة (د) حيث اعطى سيتاجلبتين عن طريق الفم + العديد السكاريد الدهني لمدة 14 يوما" بعد العملية الجراحية. قمنا في هذه الدراسة بتقييم شدة الآفة التي يسببها العديد السكاريد الدهني على الصعيدين السلوكي والعصبي.

**النتائج** : بعد 14 يوماً من الحقن لعديد السكاريد الدهني، وبعد تحدي الأبومورفين، أظهرت الفئات المصابة بـ عديد السكاريد الدهني التي تلقت الليراجلوتايد أو سيتاجلبتين دوراناً مقابلاً ضيقاً أقل بكثير مقارنة بمجموعة العديد السكاريد الدهني فقط. تمشياً مع هذه النتائج، كانت تركيزات الدوبامين في الأنسجة القاتلة أعلى بكثير في المجموعتين ج و د (عديد السكاريد الدهني + الليراجلوتايد أو سيتاجلبتين) مقابل مجموعة ب ( مجموعة عديد السكاريد الدهني فقط).

**الخلاصة :** أظهرت هذه الدراسة أن الليراجلوتايد وسيتاجلبتين من المركبات الواقية للأعصاب التي يمكن ان تبطئ وتحمي الخلايا العصبية الدوبامينية ولديها القدرة على تخفيف الفيزيولوجيا المرضية لمرض الباركنسون بسبب امكاناتها المضادة للالتهابات ومضادات موت الخلايا المبرمج والتغذية العصبية .