Novel insights in dopamine receptor:
The old –new receptor in endocrinology.

Essay

Submitted for the partial fulfillment of master degree in

Endocrinology and Metabolism

BY

Yara Muhammed Ahmad Eid

Msc Internal medicine-MD Internal medicine.

Supervised by

Prof.Dr.Nermin Ahmad Sheriba

Professor of Internal Medicine & Endocrinology

Faculty of Medicine-Ain Shams University

Prof.Dr. Nehad Shoukry Shoeb

Professor of Internal Medicine & Endocrinology

Faculty of Medicine-Ain Shams University

Prof.Dr. Hanan Mohamed Amer

Professor of Internal Medicine & Endocrinology

Faculty of Medicine-Ain Shams University

Ain-Shams

2014

بسم الله الرحمن الرحيم

"وَعِندَهُ مَفَاتِحُ الْغَيْبِ لاَ يَعْلَمُهَا إِلاَّ هُوَ وَيَعْلَمُ مَا فِي
الْبَرِّ وَالْبَحْرِ وَمَا تَسْقُطُ مِن وَرَقَةٍ إِلاَّ يَعْلَمُهَا وَلاَ حَبَّةٍ
فِي ظُلُمَاتِ الأَرْضِ وَلاَ رَطْبٍ وَلاَ يَابِسٍ إِلاَّ فِي كِتَابٍ مُّبِينٍ"

صدق الله العظيم

ACKNOWLEDGEMENT

At first and foremost all praises and thanks is to **"ALLAH"** who gave me the power to finish this work.

No words can ever express my deepest appreciation and gratitude to **Professor of Internal Medicine Nermin Ahmad Sheriba**, Ain Shams University, not only for her outstanding kind support, precious suggestions and continuous guidance throughout all stages of this work.

I would like to thank **Nehad Shoukry Shoeb, Professor of Internal Medicine**, Ain shams University who was very kind, supportive and helpful throughout this project.

My greatest respect and thanks to **DR. Hanan Mohamed Amer, Professor of Internal Medicine**, Ain Shams University for their moral, scientific support and continuous encouragement that helped me to finish my job smoothly.

I am also deeply grateful to my dear family, for their great support and help offered throughout this study.

CONTENTS

List of Figures
(Review of Literature)

List of Tables

Introduction
And
Aim Of The Work

BACKGROUND

Dopamine is the predominant catecholamine neurotransmitter in the human central nervous system, where it controls a variety of functions including cognition, emotion, locomotor activity, hunger and satiety, and endocrine system regulation Dopamine also plays multiple roles in the periphery as a modulator of cardiovascular and renal function, gastrointestinal motility, and the endocrine system.

Dopamine exerts its functions via its binding to dopamine receptors. In recent years, the availability of new dopaminergic compounds and new investigations into the dopaminergic system have produced novel information on the physiological role of dopamine and dopamine receptors, mainly in the endocrine system, and their implication in the management of endocrine tumors, especially regarding the hypothalamus–pituitary–adrenal axis, and the neuroendocrine system.

Although no drug has demonstrated a sufficient effectiveness in controlling cortisol secretion and inducing

tumor shrinkage in CD, the dopamine agonist bromocriptine was reported to inhibit cortisol secretion in a limited group of patients after short-term therapy, and in sporadic patients after long-term treatment .

A preliminary report of a conducted by ***(Pivonello R et al , 2004)*** study described that a short-term treatment with the potent dopamine agonist cabergoline controlled cortisol secretion in six of 10 (60%) patients with CD, suggesting that cabergoline could be more efficacious than bromocriptine in the management of this disease.

The dopamine receptor expression and function in the corticotrope pituitary tumors and adrenal tumors confirms the role of dopaminergic system in the hypothalamus–pituitary–adrenal axis, and suggests novel treatment strategies for Cushing's syndrome. In addition, the dopamine receptor expression in neuroendocrine tumors confirms the role of the dopaminergic system in the entire neuroendocrine system.

In keeping with their diverse physiological actions, dopamine receptors are distributed widely throughout

the central nervous system. Also, both D1 and D2-like receptors are (differentially) expressed in many peripheral tissues, including the kidney, the adrenals and pancreatic beta cells. New insights into the role of Dopamine showed that is involved in the control of food intake, energy expenditure, glucose and lipid metabolism, blood pressure and insulin release.

It has been proposed that bromocriptine can reverse many of the metabolic alterations associated with obesity by resetting central (hypothalamic) circadian organization of monoamine neuronal activities. The food and drug administration (FDA), on May 5-2009 , approved bromocriptine mesylate 0.8-mg tablets as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus.

Dopamine D2 receptor binding is diminished in the brain of obese rodents and humans, and activation of this receptor facilitates glucose metabolism, reduces blood pressure, enhances energy expenditure and ameliorates circulating lipid profiles. It has been suggested that a reduction in dopamine D2 receptor signal transduction

contributes to the pathogenesis of various components of the metabolic syndrome in obese rodents and humans and that dopamine D2 receptor agonists may be useful for the control of these various metabolic anomalies**.**

In this context, it seems critical to unravel the mechanism(s) underlying the dopaminergic defects in the brains of obese individuals further so as to be able to design drugs that can boost the clinical impact of D2 receptor agonists in patients with obesity**.**

Aim Of the work:

To explore and review the old and new expanding role of dopamine receptors in different areas of endocrinology and their novel applications .

Review of Literature

Part One
Dopamine receptors structure and function

Dopamine is the predominant catecholamine neurotransmitter in the human central nervous system, where it controls a variety of functions including cognition, emotion, locomotor activity, hunger and satiety, and endocrine system regulation. Dopamine also plays multiple roles in the periphery as a modulator of cardiovascular and renal function, gastrointestinal motility, and the endocrine system . Dopamine exerts its functions via its binding to dopamine receptors ***(Emilien G et al., 1999)***

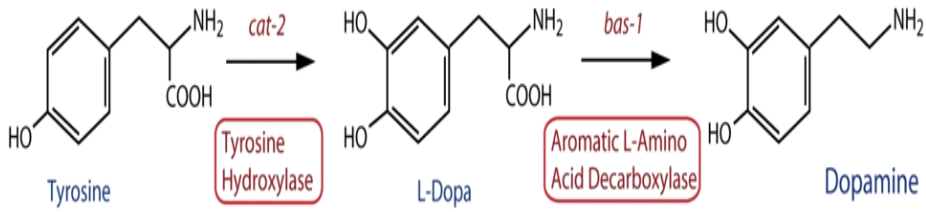
The availability of new dopaminergic compounds and new investigations into the dopaminergic system have produced novel information on the physiological role of dopamine and dopamine receptors, mainly in the endocrine system ***(Kvernmo T et al., 2006)***

Structure and function of Dopamine

Dopamine (DA) belongs to a group of neurotransmitters called catecholamines. Their distinctive structural features are the single amine group, a nucleus of catechol (a benzene ring with two adjacent hydroxyl groups) and a side chain of ethylamine or one of its derivatives . The precursor for the synthesis of DA is the aromatic amino acid tyrosine. Two reactions transform tyrosine into DA: the first

is catalyzed by the enzyme tyrosine hydroxylase (TH) which converts tyrosine into l-3,4-dihydroxyphenylalanine (L-DOPA). TH is considered the rate-limiting enzyme in this pathway . The second step is the decarboxylation of DOPA, catalysed by the enzyme aromatic l-amino acid decarboxylase (AADC), which produces DA ***(Emilien G et al., 1999)***.

Figure (1) Biochemical Structure of Dopamine



DA constitutes about 80% of the catecholamine content in the brain. Projections originating from brain areas that synthesize this neurotransmitter give rise to four axonal pathways: (1) nigro-striatal; (2) mesolimbic; (3) mesocortical; and (4) tuberoinfundibular ***(Vallone D et al., 2000).***

Projections constituting the nigrostriatal pathway arise from dopamine-synthesizing neurons of the midbrain nucleus, the substantia nigra compacta (SNc) which innervates the dorsal striatum (caudate-putamen). The nigrostriatal pathway

is involved in the control of movement and its degeneration causes Parkinson's disease, characterized by tremors, rigidity and akinesia ***(Kvernmo T et al., 2006)***.

The mesocortical pathway arises from the ventral tegmental area (VTA) and innervates different regions of the frontal cortex. This pathway seems involved in some aspects of learning and memory. The mesolimbic pathway originates from the midbrain VTA and innervates the ventral striatum (nucleus accumbens), the olfactory tubercle (OT) and parts of the limbic system. It has been implicated in influencing motivated behaviour. The tuberoinfundibular pathway arises from cells of the periventricular and arcuate nuclei of the hypothalamus . Projections of this pathway reach the median eminence of the hypothalamus where they release DA into the perivascular spaces of the capillary plexus of the hypothalamic–hypophyseal portal system. Thus, DA is transported to the anterior pituitary where it acts on the lactotrophs to inhibit the release of prolactin ***(Beaulieu JM et al., 2011).***