Salahaddin University

College of Education

Chemistry department

(The Role of Dopamine in the Pathophysiology of Depression)

Research Project

Submitted to the Department of Chemistry in partial fulfillment of the requirements for the degree of BSc.

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Certificate

This project has been written under my supervision and has been submitted for the award of the degree of B.Sc. in C**hemistry** with my approval as supervisor.

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Date: 30 / 3 /2024

Dedication

I dedicate this project to my family especially my mother, and my dear husband and brothers. they always support me all the time I want to thank my family from the bottom of my heart. also, I want to thank my friends.

Acknowledgment

First of all, I would like to thank God for helping and supporting me to complete my research project, am very thankful to my dear supervisor Dr. Luttfia, she tired me a lot I would like to thank my dear family and special my husband who have always encouraged and supported me during these years of study and all my teachers.

Abstract

The relationship between depression and dopamine deficiency in the mesolimbic pathway has been hypothesized for many years. The experimental studies with animal models and human studies implicate the role of the dopamine system in depression. Not only do dopaminergic receptor agonists, but also antagonists such as olanzapine exhibit antidepressant effects associated with standard antidepressants in patients with treatment-resistant depression. This paradoxical result suggests that further investigations are necessary to understand the role played by dopamine in depression

Keyword:

Dopamine (DA), dopamine deficiency, depression, dopaminergic receptor agonists, dopamine in depression.

Content:

Introduction

The monoamine hypothesis based on the deficiency of one or other monoamines is commonly evoked to explain the physiopathology of depression. This hypothesis, initially based on noradrenaline and serotonin deficiency, is extended to dopamine. The implication of dopamine was suggested earlier by clinical observations. Thus, depression is a common disturbance in schizophrenia and Parkinson's disease which are pathologies known to present with a dopamine central system dysfunction (Merschdorf, Berg et al. 2003)Moreover, there are similarities between symptoms of Parkinson's disease, schizophrenia, and depression. Some symptoms of depression such as anhedonia (inability to experience pleasure) and decreased motor activity are also observed in schizophrenia (Juckel, Sass and Heinz 2003)The symptoms of Parkinson's disease such as psychomotor retardation and diminished motivation are common in depressed patients (Brown and Gershon 1993) Biochemical evidence in patients with depression is derived from the study of Homovanillic acid, a dopamine metabolite. Reduced venoarterial plasma concentration gradients of homovanillic acid were found in depressed patients (Lambert, Johansson et al. 2000)This likely implication of dopamine in depressive illness was also proved by the technique of acute tyrosine depletion (McLean, Rubinsztein et al. 2004)Tyrosine is the precursor of dopamine synthesis and results of neuropsychological tests of healthy volunteers with a reduction in tyrosine availability to the brain paralleled those reported in previous investigations of unipolar depression. All these results are consistent with the hypothesis of a role of dopamine in depression physiopathology, Multiple sources of evidence support a role for diminished dopaminergic neurotransmission in major depression. The physiological alterations underlying reduced dopamine (DA) signaling could result from either diminished DA release from presynaptic neurons or impaired signal transduction, either due to changes in receptor number or function and/or altered intracellular signal processing. Data support each of these mechanisms, although the interpretation of previous research is confounded by issues around the study population, medication status, and technological limitations. In some patients with depression, DA-related disturbances improve by treatment with antidepressants, presumably by acting on serotonergic or - adrenergic circuits, which then affect DA function. However, most antidepressant treatments do not directly enhance DA neurotransmission, which may contribute to residual symptoms, including impaired motivation, concentration, and pleasure. Animal models of major depression show considerable responsiveness to manipulations of DA neurotransmission. Several studies, including postmortem investigations, particularly of subjects with severe depression, have demonstrated reduced concentrations of DA metabolites both in the cerebrospinal fluid and in brain regions that mediate

mood and motivation. Although the neuroimaging findings are not unequivocal, several studies support the hypothesis that major depression is associated with a state of reduced DA transmission, possibly reflected by a compensatory up-regulation of D2 receptors. These alterations in DA signaling may underlie the findings of increased "liking" or "high" feelings reported by severely depressed subjects treated with d-amphetamine compared with the response of less severely ill and normal control sub- jects. The efficacy of medications that directly act on DA neurons or receptors, such as monoamine oxidase inhibitors and pramipexole, suggests that subtypes of depression stemming from a primary DA dysfunction exist. Further research on the contribution of DA to the pathophysiology of depression is justified to improve outcomes for patients with treatment-resistant and no remitting depression.

1.1 histories

While dopamine was first synthesized in 1910, it was not until the mid-1950s that it began to emerge as a substance of importance in its own right rather than just an intermediary in the formation of noradrenaline. There are excellent reviews of the early history of dopamine by Oleh Hornykiewicz (1986; 2002), who himself played such an important role in the initial studies showing loss of dopamine in post-mortem brains from Parkinsonian patients and the subsequent use of L-DOPA in such patients (Hornyewicz, Birkmayer and Der 1961)The present account will be restricted to the key steps in the story. Herman Blaschko at Oxford, who worked on monoamine oxidase (MAO) in the early years (see also Youdim & Bakhle, this issue), was one of the first to suggest that dopamine may be physiologically significant, a view substantiated by studies showing that dopamine could lower blood pressure and this effect was potentiated by inhibition of MAO (Blaschko 1957)Incidentally, my first viva voce examination was conducted by Herman Blaschko and in such a manner that it was a factor that led me to stay in research; he also asked the first question after my first presentation at a BPS meeting. At about the same time, Kathleen Montagu (1957) and Arvid Carlsson, together with Lindqvist, Magnusson and Waldeck (Carlsson, Lindqvist et al. 1958), identified dopamine in the brain, and in 1959, the Swedish group showed that dopamine was found in the striatum in high concentrations where there was very little noradrenaline (Bertler and Rosengren 1959)These findings led to the subsequent work by Hornykiewicz on post-mortem Parkinsonian human brain (Ehringer and Hornykiewicz 1960)The next important step was the development of the fluorescence histochemical method by Hillarp & Falk for the visualization of catecholamine and indoleamine (5-HT) neurones and their pathways in the brain (for details of the methodology, see Corrodi & Johnsson, 1967). With this method, Kjell Fuxe and Annika Dahlstrom together with others, including a young Urban Ungerstedt who later played an essential role in the development of the microdialysis technique, produced the first evidence for neuronal pathways containing dopamine that

projected from the substantia nigra to the striatum and the ventral tegmental area (VTA) to the limbic areas of the rat brain (Dahlstro 1973); (Andén, Dahlström et al. 1966)This relatively simple plan of the dopamine pathways in the brain has been refined over the years with dopaminergic input to the frontal cortex being identified (see later), but the basic plan remains. It was at this point that I entered research and my PhD used the fluorescence history chemical technique to visualize dopamine and 5-HT in the ganglia ('brains') of snails and the leech.

1.2 definition of hormone

Hormones are chemical substances that act like messenger molecules in the body, these chemicals are secreted by special glands known as the endocrine glands, and after being made in one part of the body they travel to other parts of the body and are secreted directly into the blood. Hormones are produced by humans, animals, and plants and they play important roles, many types of hormones act on different parts of bodily functions and processes (in ***Journal of Natural Science)***

1.3 classification of hormone

Hormones can be classified into:

1. Peptide or Protein Hormones:

2. Steroid Hormones:

3. Amine Hormones:

And Dopamine is classified as an amine hormone. It is derived from the amino acid tyrosine (Macchi,et all .2004)

1.4 source of hormone

In humans, hormones are produced mainly by the endocrine glands and many other organs and tissues that contain endo echinocytes (these are cells that secrete specific hormones). However many foods, human activities, and events can also enhance or disrupt the production of many of these hormones. The various sources of hormones will be discussed below Pineal body, Pituitary, Parathyroid, Thyroid gland, Thymus, Adrenal glands, Pancreas, Ovaries, Testes, and (dopamine is the source of the pineal body (Dahlstro 1973)

1.5 dopamine (DA)

Dopamine is a neurotransmitter (or chemical messenger) found in diverse organisms ranging from invertebrates to humans. It is also a required intermediate in the formation of the neurotransmitters noradrenaline and adrenaline. Although found in several vertebrate tissues, dopamine's most important effects are due to robust expression in a relatively small number of central nervous system neurons that have widespread projections, Dopamine is a simple chemical derived from an amino acid. It belongs to a small family of related compounds known as catecholamine's, each possessing a catechol group (a benzene ring with two adjacent hydroxyl groups) and an amine group. Originally thought to serve solely as an intermediate in the biosynthesis of the catecholamine neurotransmitters noradrenaline (norepinephrine) and adrenaline (epinephrine), dopamine was not identified as a potential neurotransmitter in its own right until the late 1950s to early 1960s. With the development of new analytical procedures, it was discovered that dopamine was robustly expressed in the basal ganglia, a brain region involved in motor control, (Karam, Ballon et al. 2010) The idea that dopamine might serve as a brain neurotransmitter nevertheless met with some resistance, as neuronal signaling in the central nervous system (CNS) was still thought to be primarily electrical rather than chemical in nature. Within short order, however, it was reported that basal ganglia dopamine was severely depleted in the brains of patients dying from Parkinson's disease and that administration of the dopamine precursor L-dopa provided symptomatic relief in these patients. These seminal findings led to an explosion of dopamine-related research today we know much more about how dopamine acts as a neurotransmitter in a variety of organisms ranging from invertebrates to humans. Dopamine modulates many distinct facets of normal brain functioning and has been implicated directly or indirectly in several disorders of the nervous system. Drugs that indirectly affect dopamine neurotransmission (by affecting changes in dopamine synthesis, storage, release, or inactivation) or that directly mimic or block the actions of dopamine at its biological targets (i.e. dopamine receptors) are currently used to treat a wide range of medical disorders, thousands of scientific papers related to dopamine continue to be published each year. (Volkow, Wise et al. 2017)

*structure of dopamine

Dopamine(3,4-dihydroxyphenethylamine) molecule consists of a catechol structure and is made from tyrosine (a benzene ring with two hydroxyl side groups) with one amine group attached via an ethyl cha As such, dopamine is the simplest possible catecholamine, a family that also includes the neurotransmitters norepinephrine and epinephrine.

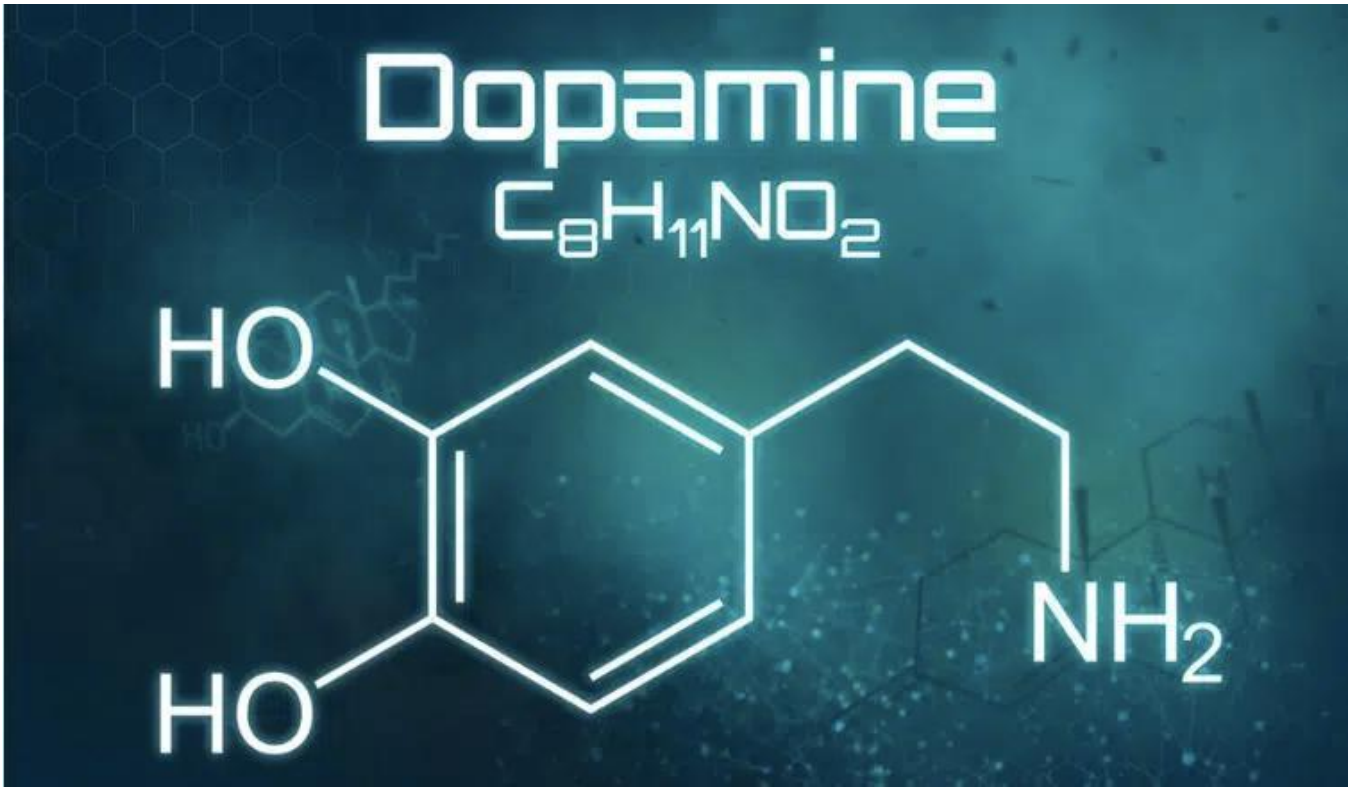


Fig 1:structure of dopamine

1.6 dopamine receptor

These receptors are divided into two Subfamilies: the D1-like receptor subtypes (D1 and D5) coupled with the Gs protein activate adenylyl cyclase and the D2-like subfamily (D2, D3, and D4) coupled with G proteins inhibit adenylate cyclase (Missale, Nash et al. 1998) D1 and D2 dopamine receptors are the most abundant subtypes in the central nervous system, but the D1 dopamine receptor is the most widespread. D1 RNA was found in the striatum, nucleus acumens, olfactory tubercula, hypothalamus, and thalamus. In other areas such as substantia nigra pars reticula with numerous binding it's for the D1dopamine receptor, no mRNA was detected ,

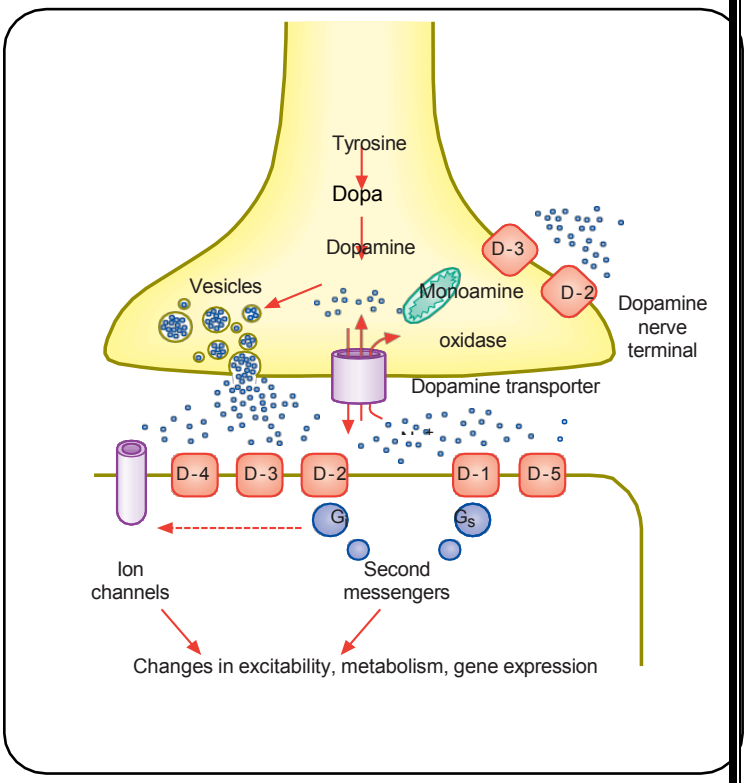


Fig:2 Receptors of dopamine

suggesting that in these areas the D1 dopamine receptor is present in projections only (Jaber, Robinson et al. 1996). The D5 dopamine receptor is expressed at a much lower level than the D1 dopamine receptor and its distribution is limited to the hippocampus and thalamus (the lateral mamillary nucleus and the Para fascicular nucleus of the thalamus). The D2 dopamine receptor is located mainly in the striatum, olfactory tubercula, nucleus acumens, the substantia nigra pars compacta, the ventral tegmental area, and the pituitary gland. D2 dopamine receptors are pre- and post-synaptic receptors contrary to D1-like receptors which are mainly post-synaptic (Jaber, Robinson et al. 1996). D4 dopamine receptors were found with a low expression in the basal ganglia and a higher expression in the frontal cortex, medulla, amygdala, hypothalamus, and mesencephalon. However, this high expression is weak in comparison with other dopamine receptors . D3 dopamine receptors are expressed in the limbic area (nucleus acumens, olfactory tubercula, and islands of Calleja) and at a lower level in the striatum (Jaber, Robinson et al. 1996). The D3 dopamine receptors exist as auto receptors that inhibit neuronal dopamine synthesis and post-synaptic receptors. These receptors by

negatively regulating dopamine neuronal activity and/or by post-synaptic action exhibit an inhibitory influence on locomotor activity (Sibley 1999) The genetic techniques for negatively modulating dopamine receptor expressions such as knockout animals and antisense technology showed that the disruption of D3, D4, D5 dopamine receptor functions involved an increase or an improvement in the behavioral activity of animals contrary to the results observed with the disruption of D1, D2 dopamine receptor functions. Although these results have to be interpreted with caution as a compensatory mechanism could develop, these observations suggest that the most abundant dopamine receptors D1 and D2 are involved in the positive regulation of behavioral activity whereas the D3, D4, and D5 receptors are inhibitory by likely negative modulation of D1 and/or D2 receptor function in some cases (Sibley 1999)

Table 1. Characteristics of Dopamine Receptor Subtypes[10,11]

	D_1 Family		D_2 Family		
Characteristic	**D_1**	**D_5**	**D_2**	**D_3**	**D_4**
Homology with D_1	100	82	45	42	42
Homology with D_2	45	50	100	75	54
Second messenger effect	Increase AC	Increase AC	Decrease AC	Decrease AC	Decrease AC
Localization	Dorsal striatum Ventral striatum Thalamus Prefrontal cortex	Hippocampus Thalamus Striatum	Dorsal striatum Ventral striatum Pituitary	Ventral striatum Islands of Calleja	Frontal cortex Midbrain Amygdala Hippocampus Hypothalamus PD 168077
Agonists*	SKF 38393 Pergolide Chloro-PB	Chloro-PB	Bromocriptine, pergolide, piribedil, pramipexole, quinpirole		Quinpirole
Antagonists	SCH 23390	SCH 23390	Sulpiride, typical antipsychotics raclopride		Clozapine PD 101387

Abbreviation: AC, adenylyl cyclase.

*Apomorphine is an agonist at all receptor subtypes

1.7 Synthesis of dopamine

Synthesizing dopamine involves several important steps and requires specific starting materials and chemical reactions. Here are the key steps and information involved in synthesizing dopamine, The initial step in the biosynthesis of dopamine (and the other catecholamine neurotransmitters) is catalyzed by tyrosine hydroxylase, the rate-limiting enzyme in the process. The amino acid tyrosine (like other amino acids) is actively transported across the blood-brain barrier to gain entry into the CNS, then transported again into individual brain cells. Using tyrosine and molecular oxygen as substrates, tyrosine hydroxylase catalyzes the addition of a hydroxyl group to the meta position of tyrosine, forming dihydroxyphenylalanine (DOPA; Figure 1). Although tyrosine concentrations are normally not limiting, tyrosine hydroxylase enzymatic activity can be modulated by local concentrations of a required cofactor (tetrahydrobiopterin) and the inhibitory effects of catecholamine end-products, as well as the state of enzyme phosphorylation induced by a variety of factors. See also: Blood-Brain Barrier; Enzyme Activity: Allosteric Regulation A second enzyme, aromatic amino acid decarboxylase, then catalyzes the subsequent and final step in dopamine synthesis, namely the removal of the carboxyl group from DOPA (Figure 1). The high activity of this enzyme relative to tyrosine hydroxylase means that under normal conditions little or no endogenous DOPA is found in most cells. As mentioned above, in some cells dopamine is further converted enzymatically into noradrenaline or adrenaline whereas, in many other neurons, dopamine serves as the final neurotransmitter product. See also: Adrenaline and Noradr, It's important to note that the synthesis of dopamine requires careful control of reaction conditions, as well as adherence to safety protocols due to the use of hazardous reagents and intermediates. Additionally, variations in synthetic routes may exist depending on the specific laboratory protocols and the desired purity of

the final product.

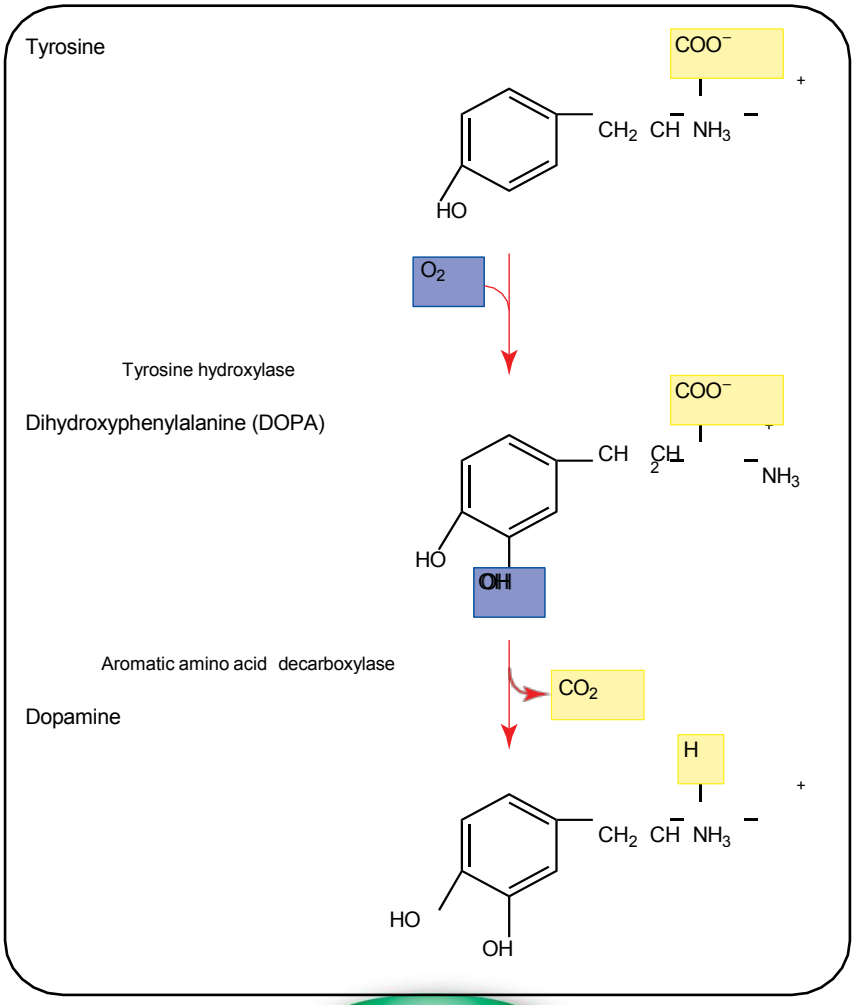


Fig 3: Biosynthetic pathway of dopamine. Tyrosine hydroxylase is the rate-limiting step

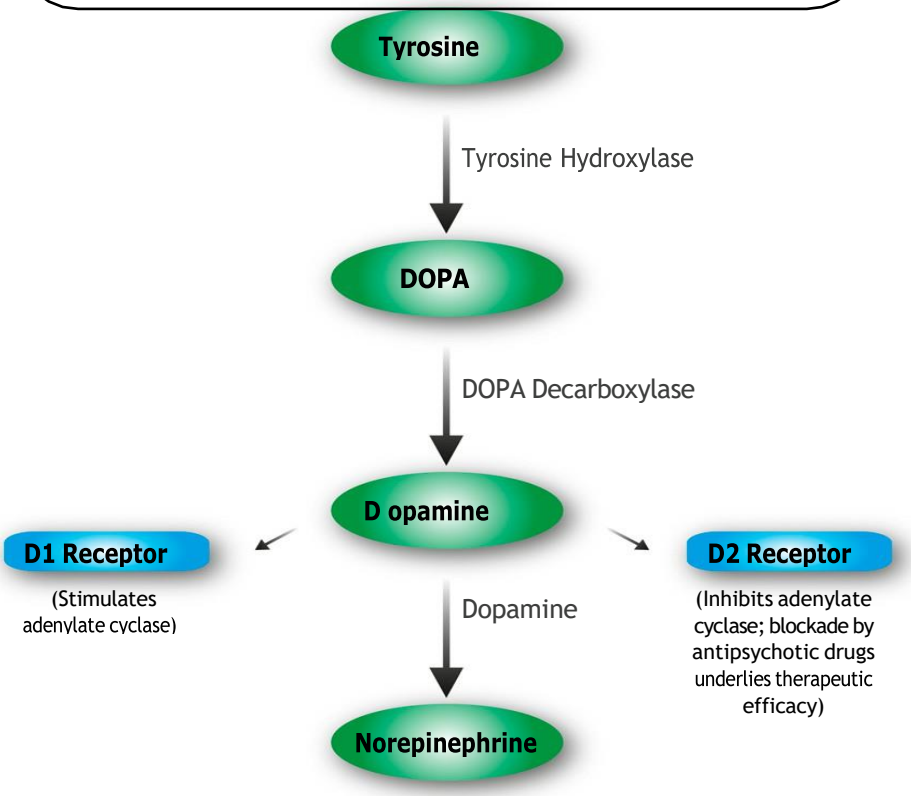


Fig 4:Biosynthesis and receptor actions of dopamine

1.8 metabolic of DA

The enzymatic breakdown of DA to its inactive metabolites is carried out by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) .This degradative action can be performed by the MAO isoforms MAO-A and MAO-B. It should be noted that COMT is predominantly expressed by glial cells. In neurons, this enzyme is either missing or found at very low levels. MAO-B is mainly found in astrocytes, whereas MAO-A predominates in catecholaminergic neurons like the cells of the SN. MAO breaks down dopamine to 3,4-dihydroxyphenylacetaldehyde (DOPAL), which in turn is degraded to form 3,4-dihydroxyphenylacetic acid (DOPAC) by the action of the enzyme aldehyde dehydrogenase (Figure5) 191.

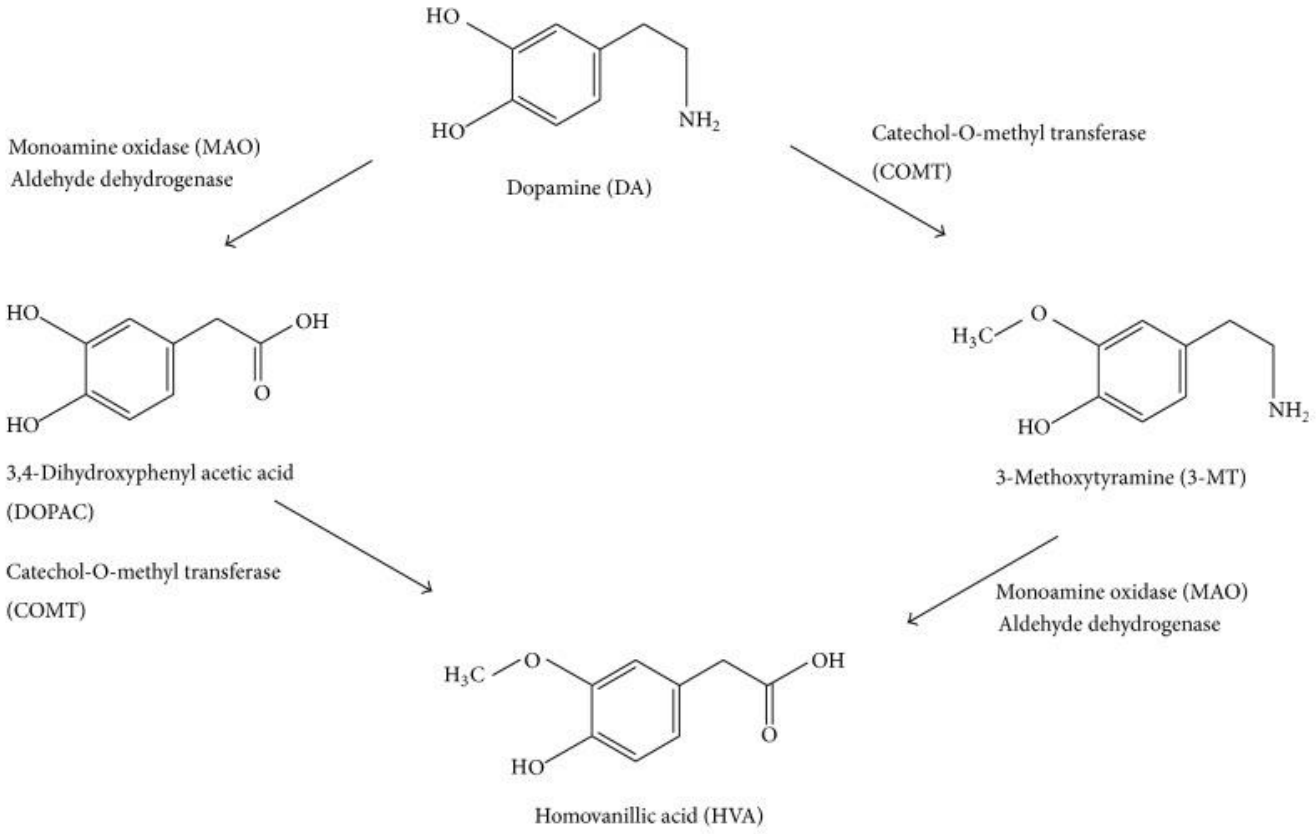


Fig 5: Dopamine metabolism:

Another pathway for the metabolism of DA involves the enzyme COMT, which converts it to 3-methoxytyramine (3-MT). Then, 3-MT is reduced by MAO to HVA and eliminated in the urine. As a result, the inhibition of monoamine oxidase has been considered as an adjunctive therapy in

neurodegenerative disorders such as Alzheimer's and Parkinson's disease (PD(D Mousseau and B Baker 2012)However, MAO inhibitors are used to increase DA levels and not to decrease hydrogen peroxide production. Neurons have different antioxidant systems, for example, catalase and glutathione, to cope with H202 production. Furthermore, the MAO-derived DOPAC metabolite is probably much more toxic than H202. The inactivation of DA in the brain, striatum, and basal ganglia is mediated by reuptake via DAT followed by enzymatic action of MAO, which breaks it down to DOPAC. Nevertheless, there are few DATs in the frontal cortex, and this leads to the breakdown of DA via another pathway that involves the norepinephrine transporter (NET) on neighboring norepinephrine neurons, proceeded by the enzymatic action of COMT that breaks DA down to 3-MT (Grace and Bunney 1984), which may be a way to design therapies against neurological disorders. The velocity of DA degradation is usually faster in the DAT pathway than in NET. In mice, DA is degraded in the caudate nucleus via the DAT pathway within 200 milliseconds, in comparison with 2,000 milliseconds in the frontal cortex 111J. Nondegraded DA is repackaged by VMAT, in the vesicles for reuse. Dopaminergic neurons are found principally in the VTA of the midbrain, the substantia nigra pars compact, and the arcuate nucleus of the hypothalamus. The axons of these neurons project to different areas of the brain through major pathways known as neocortical, mesolimbic, and nigrostriatal pathways (Prasad and Pasterkamp 2009)The mesolimbic pathway connects the VTA to the nucleus acumens. The somata of the neurons originate in the VTA, and, from there, DA is transported to the nucleus acumens through the amygdala and the hippocampus. The nigrostriatal pathway joins the substantia nigra with the neostriatum. The neuronal somata are located in the substantia nigra, and the axons of these neurons are ramified into the caudate nucleus and putamen. This pathway is also connected to the basal ganglia motor loop. All of the innervations originating from these pathways explain many of the effects produced when the DA system is activated (Cho, Song et al. 2006)For instance, the VTA and the nucleus acumens connected through the mesolimbic pathway are central to the brain reward system (Deutch and Roth 1991)The modulation of extracellular DA levels occurs by two mechanisms, designated as tonic and phasic DA transmission. The former takes place when a small amount of DA is discharged independent of neuronal activity. This type of discharge is usually regulated by the activity of neurons and neurotransmitter reuptake (Szczypka, Rainey et al. 1999)The latter occurs when DA is released by the activity of DA-containing cells. Schultz et al. in a study carried out in monkeys reported that this activity is characterized by the irregular peacemaking activity of single spikes and rapid bursts of typically 2-6 spikes in quick succession (Schultz, Apicella and Ljungberg 1993), while Brozoski et al. affirmed that concentrated bursts of active result in a greater

increase of extracellular DA levels than would be expected from the same number of spikes distributed over a longer period of time (Brozoski, Brown et al. 1979) as a consequence of dopamine metabolism.

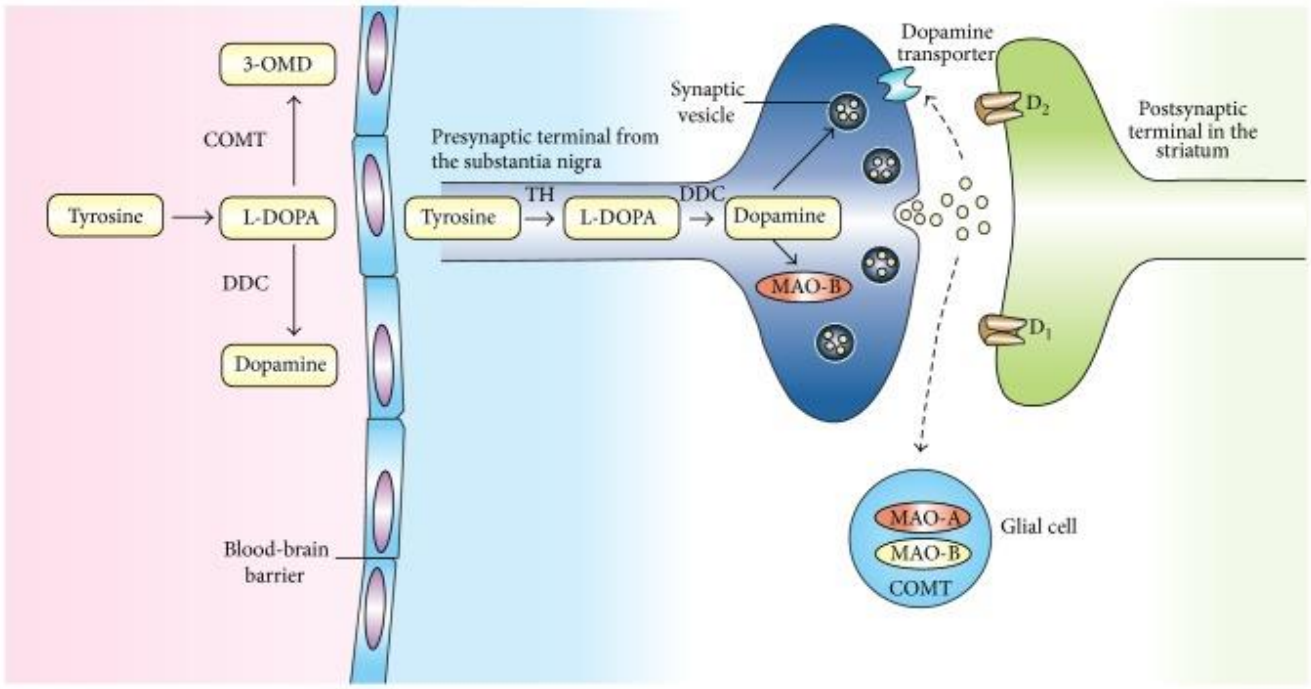


Fig 6: Dopamine metabolism pathways:

1.9 functions of dopamine:

1. Neurotransmission
2. Movement Regulation
3. Reward and Pleasure
4. Mood Regulation
5. Cognition
6. Decision-Making
7. Endocrine Regulation
8. Motor Control Disorders
9. Addiction
10. Stress Response

1.10 Dopamine deficiency

Refers to a condition in which there is an insufficient amount of dopamine in certain parts of the brain or in the body overall. This deficiency can lead to various neurological and psychiatric symptoms, depending on the extent and location of the deficiency. Some conditions associated with dopamine deficiency include:

1. Parkinson's disease: Parkinson's disease is characterized by progressive degeneration of dopamine-producing neurons in the substantia nigra region of the brain. This leads to a significant reduction in dopamine levels in the basal ganglia, resulting in motor symptoms such as tremors, rigidity, bradykinesia (slowed movement), and postural instability.
2. Depression: While the exact role of dopamine in depression is complex and not fully understood, some research suggests that imbalances in dopamine neurotransmission may contribute to depressive symptoms. Low levels of dopamine or dysregulation of dopamine signaling pathways may be associated with feelings of low mood, lack of motivation, and anhedonia (loss of pleasure).
3. Attention Deficit Hyperactivity Disorder (ADHD): ADHD is believed to involve dysfunction in the dopamine system, particularly in the prefrontal cortex, which is associated with attention, impulse control, and executive function. Individuals with ADHD may have lower dopamine levels or alterations in dopamine receptor activity.
4. Drug Addiction: Drugs of abuse, such as cocaine, amphetamines, and opioids, exert their effects in part by increasing dopamine levels in the brain's reward pathway. Prolonged substance abuse can lead to downregulation of dopamine receptors and decreased dopamine release, contributing to addiction and withdrawal symptoms.
5. Schizophrenia: Dopamine dysregulation is implicated in the pathophysiology of schizophrenia. While the exact nature of dopamine abnormalities in schizophrenia is complex and not fully understood, excessive dopamine activity in certain brain regions is associated with positive symptoms such as hallucinations and delusions

2. Depression:

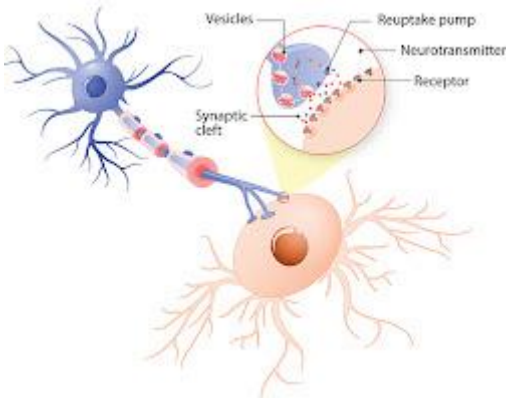
Depression or major depressive disorder is a common but serious mood disorder that extends far beyond regular feelings of sadness. It significantly disrupts a person's quality of life, affecting their thoughts, emotions, behaviors, and overall well-being. Depression can manifest differently in each individual, making it crucial to watch out for persistent changes in mood and functioning, and Depression is a common debilitating, and potentially lethal disorder.' This is a standard opening to many a scientific paper on depression. And it is often followed by some very grim statistics. Over 300 million people in the world are estimated to live with depression, and the disorder is ranked by who as the single largest contributor to global disability. There is also evidence that depression has increased over the last decade (2012, 2014). Most worryingly, adolescents with major depressive disorder are up to 30 times more likely to commit suicide. Yet, what exactly is depression? Do all 300 million depressed people in the world suffer from the same thing And, more practically, should we be treating all, The variable symptoms of Major Depressive Disorder (MDD), indicate that depression is a heterogeneous disorder . Individuals who experience depression may suffer from a number of possible symptoms, and the duration of these symptoms may range from a few weeks to years. Increasingly, the chronic and recurrent nature of depression has been recognized, and efforts at treatment and prevention have been emphasized ,Depression also exacts a heavy toll on society; the direct and indirect annual costs associated with the United States (Greenberg et al., 1999) have been estimated at $14.4 billion and $33 billion and MDD in Canada (Stephens & Joubert, 2001), respectively. Researchers have predicted that by the year 2020 depression will be second only to ischemic heart disease in terms of cost to society (Keller & Boland, 1998; Lecrubier, 2001) .

2.1What Couse to depression

There isn't one single cause of depression. It's a complex mental health disorder likely stemming from a combination of factors. Here's a breakdown of the key contributors:

1. **Brain Chemistry:**

Neurotransmitter Imbalance: Key neurotransmitters like serotonin, dopamine, and norepinephrine help regulate mood. Imbalances in these chemicals can play a significant role in depression(Cervo, Grignaschi and Samanin 1990).



2. Genetics:

Family History: If you have close relatives with depression, your risk of developing it increases. While genes don't guarantee you'll have depression, they suggest a predisposition (Laasonen-Balk, Kuikka et al. 1999)

3. Life Events and Stress

Trauma: Adverse childhood experiences, abuse (physical, sexual, or emotional), or significant loss can create lasting vulnerabilities for depression.

Chronic Stress: Prolonged difficult situations, such as financial strain, relationship problems, or work conflicts, can overwhelm coping mechanisms and trigger depressive episodes.

4. Medical Conditions:

Chronic Illness: Chronic pain, and severe diseases like cancer, diabetes, or heart disease can lead to depression, both due to the illness itself and the associated stress{Russo, 2013 #104}.

5. Other Factors:

Personality Traits: Low self-esteem, perfectionism, negative thinking patterns, and sensitivity to criticism can increase susceptibility to depression.

Substance Misuse: Alcohol and drug use can worsen or trigger depression,{Essex, 1987 #103} even if they seem to alleviate symptoms temporarily.

Medication: Certain medications may have depression as a side effect.

3. Dopamine Dysregulation in Depression:

3.1 Reward Processing and Anhedonia

Anhedonia, or the inability to experience pleasure from activities usually found enjoyable, is a hallmark symptom of depression. Research indicates that anhedonia is associated with dysfunction in the brain's reward system, particularly in regions rich in dopamine. Studies using functional MRI have shown altered activity in the nucleus acumens, a key component of the reward system, in depressed individuals. (Cho, Song et al. 2006)

3.2. Motivation and Apathy

Depression is often accompanied by a profound lack of motivation, making even simple tasks feel insurmountable. Dopamine plays a critical role in motivation, driving goal-directed behavior.{Russo, 2013 104} Evidence suggests that depressed individuals may have alterations in dopaminergic transmission, leading to reduced motivation and increased apathy.

3.3. Cognitive and Emotional Regulation

Dopamine is also involved in regulating emotions and cognitive functions, including attention and executive function. Dysregulation of dopaminergic neurotransmission can contribute to the cognitive and emotional symptoms of depression, such as difficulties in concentrating, making decisions, and regulating emotions(Jaber, Robinson et al. 1996)

4. Relationship between dopamine and depression:

Increasing evidence from human and animal studies suggests a relationship between dopamine transmission in the central nervous system and depression. In depressed patients, a compensatory up-regulation of D2 receptor density was observed in the basal ganglia/ cerebellum in comparison with healthy subjects according to the hypothesis of an association between depression and a deficiency of dopamine transmission (D'haenen and Bossuyt 1994)Surprisingly, an up-regulation of dopamine transporter which results in a more effective reuptake of dopamine into the pre-synaptic neurons was found in depressed patients (Laasonen-Balk, Kuikka et al. 1999)The expected result was a down-regulation of dopamine transporter in depressed patients to compensate for the deficiency of dopamine transmission. The authors explain this unexpected result by alteration of dopamine transporter which would be primary to the compensatory mechanism and would lead to low intra synaptic dopamine concentration. Anhedonia is a frequent symptom of depression and it is commonly hypothesized that anhedonia is associated with a dysfunction of the dopaminergic reward system (Heinz, Schmidt and Reischies 1994)Indeed, this system is functionally and anatomically closely connected with the dopamine mesolimbic pathway. A dysfunction of both ascending dopaminergic pathways is therefore expected to cause anhedonia. However, this hypothesis is not supported by experiments showing that dopaminergic dysfunction is associated with a disorder of motivation rather than anhedonia (Berridge and Robinson 1998)The animal models of depression also suggest an implication of dopamine in the physiopathology of depression. The forced swimming test in an animal model was used to predict the antidepressant activity of drugs. With this model, (Cervo, Grignaschi and Samanin 1990) showed that the mesolimbic dopaminergic system has a permissive role in the effect of desipramine, as the antidepressant-like effect of desipramine was reduced after the administration of sulphiride bilaterally into the nucleus acumens. An indirect effect of the dopaminergic system in the antidepressant sent-like activity of selective serotonin reuptake inhibitors was also.(Renard, Fiocco et al. 2001) as the antidepressant-like effect of selective serotonin reuptake inhibitors was modulated by agonists and antagonists of dopamine receptors. Chronic mild stress-induced anhedonia is another animal model of depression. The behavioral and biochemical changes associated with chronic mild stress are a decrease in D2/D3 receptor binding in the nucleus acumens (Papp, Klimek and Willner 1994)and a functional sub sensitivity to the rewarding and locomotor stimulant effects of the D2/D3 agonist quinpirole administered systemically or within the nucleus acumens (Willner, Muscat and Papp 1992) Other studies in rodents demonstrated that exposure to stress decreases levels of brain-derived neurotrophic factor in brain regions associated with depression (Duman 2004)Moreover, a link exists between the

dopamine system and brain-derived neurotrophic factor, as it appears that the brain-derived neurotrophic factor controls the expression of the D3 receptor gene (Sokoloff, Guillin et al. 2002)These results suggest the neurotrophic hypothesis of depression implicates also the dopaminergic system

5. Therapeutic Implications and Treatments

5.1. Pharmacological Interventions

Current antidepressants primarily target the serotonin and norepinephrine systems, but these medications are not effective for all patients. There is growing interest in developing treatments that directly modulate dopaminergic activity. Dopamine agonists and medications that increase dopamine availability have shown promise in treating depression, particularly in patients with significant anhedonia and motivational deficits (Kennedy, 2016)

5.2. Non-Pharmacological Therapies

(Papp, Klimek and Willner 1994)Beyond medications, therapies such as cognitive-behavioral therapy (CBT) and physical exercise have been shown to affect dopaminergic activity positively. These interventions may help normalize dopamine function and alleviate depressive symptoms, especially when combined with pharmacological treatments

5.3. Future Directions in Treatment

Emerging research is exploring novel therapeutic targets within the dopaminergic system, such as dopamine receptors and dopamine-related genes. Personalized medicine approaches, which consider individual differences in dopaminergic functioning, may lead to more effective treatments for depression. (Papp, Klimek and Willner 1994)

5.4. Role of Diet and Microbiota

Emerging research suggests that diet and the gut microbiome may influence depression risk through effects on the dopaminergic system. Certain dietary patterns and nutrients have been associated with changes in dopamine levels and function, potentially impacting mood and behavior. Furthermore, the gut microbiota interacts with the central nervous system through the gut-brain axis, influencing dopamine metabolism. Nutritional interventions and probiotics could offer new avenues for modulating the dopaminergic system and treating depression. (Papp, Klimek and Willner 1994)

5.5. Dopaminergic System and Neuroplasticity

Depression is associated with alterations in brain structure and function, including reduced neuroplasticity. The dopaminergic system plays a key role in neuroplasticity, influencing neuronal growth, survival, and connectivity. Treatments that enhance dopamine function may improve neuroplasticity and, by extension, depressive symptoms. This highlights the potential for dopaminergic agents to not only alleviate mood symptoms but also address underlying neurobiological changes in depression. (Rush, 2006)

5.6. Personalized Medicine in Dopaminergic Treatment

Given the variability in dopaminergic dysfunction among individuals with depression, personalized medicine approaches hold promise. Genetic variations affecting dopamine receptors and metabolism can influence response to dopaminergic medications. Pharmacogenomics testing may help identify individuals who are more likely to benefit from certain dopaminergic treatments, optimizing therapeutic outcomes. Moreover, integrating biomarkers of dopaminergic activity with clinical characteristics could enable more tailored treatment selections. (Renard, Fiocco et al. 2001)

6. CONCLUSION

This review indicates that the dopamine system plays a role in the physiopathology of depression and constitutes one of the potential targets of antidepressants. However, the therapeutic strategy which would consist to correct a dopamine deficiency by dopamine receptor agonist could not be efficient in all the forms of depression. A previous case report illustrates this idea. The addition of bromocriptine 2.5–5 mg/day with imipramine improved the depressive symptoms of a patient with refractory depression but the clinical status returned to the original level when dose was increased to 15 mg/day. Thus, an overstimulation of the dopamine system could also be detrimental for depressive patients. This suggestion is only based on the results of a case report but emphasizes that further investigations are necessary to understand the exact role played by dopamine in depression

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