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Dopamine, from "The Molecule of More" to a Theoretical Concept of Building an Enzymatic Nanoreactor used as Treatment in Parkinson's Disease

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ABSTRACT

Dopamine is the spectacular molecule responsible for survival behavior, reproductive behavior, controlling impulses and gaining control over the surrounding environment. Between the deficit and the excess of dopamine lies balance materialized through maximizing rewards, overcoming primal instincts, using principles and values, exploring creativity and meeting one's own soul by using imagination. The dopamine metabolism has importance for neuronal redox-homeostasis and neuronal viability, because dopamine degrading processes produce reactive O2 species, while some dopamine derivates have antioxidant effects. The two enzymes involved in synthetizing dopamine: tyrosine-hydroxylase, and dopa-decarboxylase, play an important role in preventing excessive oxidative stress and so in controlling dopaminergic homeostasis. Disrupting dopamine function has important neuropsychiatric implications, making the dopaminergic system an important subject of study in neuroscience and neural-imaging and a target for the development of drugs.

Parkinson's disease appears as a consequence of a pathological change consisting of substantia nigra dopaminergic neurons degrading processes, resulting in lowered dopamine in the striatum.

There are numerous studies pertaining to attempts to treat Parkinson's disease. Administering drugs to the brain is a real challenge because of the blood-brain barrier. Nanotechnology is a continually developing domain which also consists of nano-type delivery systems (liposomes - nano-reactors). Using liposomes in cerebral pathologies can become an effective, specifically targeted delivery system through: blood-brain barrier penetrability, bioavailability, biodegradability, low levels of toxicity and the capacity to incapsulate lipophilic and lipophilic drugs. The proposed theoretical concept consists of incapsulating the 2 enzymes inside a liposome type, two-compartmented, enzymatic-nanoreactor, divided by a semipermeable synthetic membrane; each compartment having a specific protein channel. The reactions catalyzed by the two incapsulated enzymes, take place inside the liposome, the resulting dopamine being release at the neural level through the specific protein channel.

This new treatment possibility in treating Parkinson's disease has real potential through it's capacity of penetrating the blood-brain barrier, targeted therapeutic effect and minimal side effects.

ABBREVIATIONS

AADC: Aromatic Amino Acid Decarboxylase; ADH: Alcohol Dehydrogenase; ALDH: Aldehyde Dehydrogenase; AR: Aldehyde Reductase; BH4: 6 R-L-erythro-5,6,7,8-Tetrahydrobiopterin; COMT: Cathechol-o-Methyl Transferase; DOPAC: 3-4-Dihydroxyphenylacetaldehyde; GTP: Guanosine Triphosphate; GTPCH: GTP Cyclohydrolase; HVA: Homovanilic Acid; L-dopa: L-3,4-Dihydroxyphenylalanine; MAO: Monoamine Oxidase; PCR: Polymerase Chain Reaction; PET scan: Positron Emission Tomography Scan; VMAT2: Type 2 Vesicular Monoamine Transporter

"THE MOLECULE OF MORE"- DOPAMINE

Between art and science "The molecule of more" is the book written by Daniel Liberman, in which he describes the effects and implications of this spectacular molecule, dopamine, referring to two circuits of dopamine: the mesolimbic pathways, which he calls the pathway of dopaminergic desire and the mesocortical pathway which he calls the pathway of dopaminergic control. Discovered in 1975 by Katharine Montagu, dopamine was called the molecule of pleasure after studies involving drug users. Later, it became the molecule of desire, after studies which replaced drugs with food, revealing the same levels of elevated dopamine.

The desire pathway was involved in survival and reproductive behaviors, for all of our existence and triggering this pathway produces enthusiasm and hope. The control pathway involves the prefrontal cortex, being responsible for calculation and planning, administering uncontrolled impulses and allowing the gaining of control over the environment. The two pathways are opposed to each other, when desire becomes damaging, the control through will power, planning and abstraction results in imagining the long-term consequences. The opposition of the two pathways creates balance is disturbed, the effect on an individual's life are major. Self-efficacy is an important characteristic of an individual's life, but it can become pathological after drug use, such as amphetamines and cocaine, whose effect result in dopamine levels rising and the appearance of delirious grandeur ideas.

At the opposite pole lies the weakening of the dopaminergic control circuit, which leads to impulsivity and difficulties in focus, what we call hyperactive and attention deficit disorder. This disorder is found particularly in children and is explained through the delayed development of the frontal lobes, towards the end of maturity.

Another subject with dopaminergic implications is constituted by the creativity-madness balance. Excess stimulation of the desire pathway has at its basis the concept of salience, that refers to the measure in which things are important, evident or prominent. To much or to little salience at the "right" time may lead to delirious ideas, found in schizophrenia. Medication, consisting of antipsychotics targets the reduction of activity in the desire pathway. In schizophrenia, the brain attaches salience to commonplace events which should normally be ignored - a concept called lowered latest inhibition. The link between schizophrenia and creativity was made following studies based in cerebral scans of schizophrenics and people actively involved in creative processes, which revealed the same type of regional brain activity.

On the other hand, following smaller studies, using continuous current for transcranial stimulation, an acceleration of the learning processes, enhancing concentration and ever treating depression was noticed. Dopaminergic medication acts in the same way, and considering this, on Parkinson's patients it can worsen compulsive behavior or enhance creativity. Between the deficit and excess of dopamine lies the balance materialized through maximizing rewards, overcoming basic instincts using principles and values, exploring creativity and meeting one's own soul, through the use of imagination [1].

DOPAMINE-METABOLISM, RECEPTORS AND DOPAMINERGIC PATHWAYS

Dopamine metabolism

Dopamine metabolism is important for neural redox-homeostasis and neuronal viability, because degrading it produces Reactive Oxygen Species (ROS) while some dopamine derivates present antioxidative effects. The classic pathway of dopamine synthesis was postulated by Blaschko in 1939 [2]. The biosynthesis takes place inside the dopaminergic neuronal cytosol and begins with the hydroxylation of L-tyrosine by tyrosine-hydroxylase resulting in L-Dopa. This oxidation is regulated by BH4 (tetrahydrobiopterine) as a cofactor, which is synthesized from GTP (guanosine-triphosphate) by GTP cyclohydrolase (GTPCH). The next step is the decarboxylation of L-Dopa by DOPA-decarboxylase resulting dopamine. The newly synthetized dopamine is

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imported into synaptic vesicles by VMAT2 (vesicular monoamine transporter type2) through secondary active transport. Inside the vesicle, dopamine which is predisposed to oxidation, is stabilized by the slightly acidic pH [3] this prevents oxidative stress inside the cytosol [4]. Oxidative stress is additionally minimized through the association of VMAT2 with other biosynthetic enzyme- TH, AADC [5].

Dopamine which is lost from vesicle is deaminated by MAO (monoamine oxidase). During neuronal depolarization, dopamine is released in the synaptic space resulting in signal transduction. Dopamine signaling is stopped through recapture in the presynaptic neuron and recycled, or through recapture by the surrounding cells and broken down using COMT (cathecol-o-methiltransferase), MAO (monoaminoxidase), ADH (alcohol dehydrogenase), ALDH(aldehyde-dehydrogenase) and AR (alcohol reductase) in variable order. The main break down components of dopamine are DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanilic acid). The enzyme involved in dopamine homeostasis are: tyrosine hydroxylase, guanosine triphosphate hydroxylase and dopa decarboxylase. They play an important role in preventing excessive oxidative stress

Tyrosine hydroxylase: catalyzes the first step in dopamine biosynthesis and is constituted of 4 identical subunits, each catalytically active, each needing BH4, a ferrous ion and oxygen in order to oxidize tyrosine into L-dopa [7]. Regulating Tyrosine hydroxylase is achieved at a transcriptional level [8] through covalent modifications, protein-protein interaction and allosteric regulation [9].

Dopa decarboxylase: Uuses vitamin B6 as a cofactor [10] catalyzes the decarboxylation of L-Dopa into dopamine and is regulated at a transcriptional and posttranslational level [11,12] At a protein level, it is regulated through phosphorylation [13] and then stimulation of the dopamine receptors [12,14].

Dopaminergic receptors

Dopamine presents 5 subtypes of receptors coupled with protein G (GDPR): D1, D2, D3, D4, D5 [15]. These are divided into two types: D1-like-which contains the D1 and D5 subtypes and D2-like which contains D2, D3 and D4 subtypes [16]. Activating D1-like receptors results in depolarization (opening of sodium channels) or inhibition (opening of the potassium channels) of the targeted neurons, while activating D2-like receptors leads to their inhibition [16]. The dopaminergic effect depends on the type of receptor present on the neuronal membrane and the internal response of the neuron to the second messanger cAMP [16].

D1 receptors are highly concentrated in the mesolimbic, mesocortical ang nigrostriatal areas, such as substantia nigra, olfactory bulb, nucleus accumbens, caudate, putamen. They are expressed at a low level in cerebellum, hippocampus, thalamus, hypothalamus, kidney. They are involved in functions like: voluntary movements, regulate growth and development, regulation of feeling, affect, attention, reward, sleep, impulse control, reproductive behaviors, working memory, learning, control of renin in kidney. D2 receptors are expressed in high levels in: substantia nigra, olfactory bulb, caudate, putamen, Ventral Tegmental Area (VTA), nucleus accumbens. Are found in low levels in hypothalamus, septum, kidney, cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia. The functions: regulate blood pressure, renal functions, gastrointestinal motility, vasodilatation, regulate locomotion-pre-sympathetic receptors inhibit locomotion and post-sympathetic receptors activate locomotion.

D3 receptors are expressed only in the central nervous system, in the olfactory bulb and nucleus accumbens. Functions: involved in endocrine function cognitions, motions, regulations of locomotor functions and modulates endocrine functions. D4 receptors are expressed in substantia nigra, hippocamps, amygdala, thalamus, hypothalamus, kidney, frontal cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia, globulus pallidum. They have the lowest concentration in the CNS. Regulation of the renal functions, gastrointestinal motility, vasodilatations, blood pressure, modulation of cognitive functions. D5 receptors are expressed in the substantia nigra, hypothalamus, hypothalamus, dental gyrus, kidney, blood vessels, adrenal glands, gastrointestinal tract and sympathetic ganglia. Functions: involved in pain process, affective functions, endocrine functions of dopamine [17].

Pathways of the dopaminergic system

Mesostriatal pathway- the fibers emerge from the substantia nigra(pars compacta) and is projected rostaly to be widely distributed in the basal ganglia(caudate nucleus and putamen).

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Here, dopamine plays an important role in movement, controlling the motor functions and is involved in the learning of new motor abilities. The degeneration of this pathway causes Parkinson's disease [18,19]. Mesolimbic pathway - the fibers emerge from the ventral tegmental area and spread to the amygdala, piriform cortex, the lateral septal nuclei and accumbens nucleus. Here, dopamine functions are tied to the emotional state and the reward system. Dopamine mediates pleasure and is released in pleasant situations and urges to seek pleasant reactions, especially in areas of the brain like the accumbens nucleus and frontal cortex, while also having an important role in addiction. Antipsychotic medication reduces the positive symptoms of schizophrenia, it acts by blocking dopamine receptors in the mesolimbic system [20-22].

Mesocortical pathway- the fibers emerge from the ventral tegmental area and are projected to the frontal cortex in the septohippocampal region. Here, dopamine mediates cognitive and emotional behavior , at the frontal cortex level and contributes to improving memory and attention. Antipsychotic medication aggravate the negative symptoms of schizophrenia by blocking these receptors. Tuberoinfundibular pathway- the fibers emerge from the arcuate nucleus and are projected towards the pituitary gland(median eminence). Here, dopamine inhibits prolactin release. Antipsychotic medication that block hypophysary receptors uninhibiting prolactin, causing galactorrhea, dopamine being the main neuroendocrine inhibitor of prolactin in the anterior hypophysary glande. Disturbing dopamine functions has serious neuropsychiatric consequences, marking the dopaminergic system a key point in neuroscientific and neuroimaging study and a target for the development of medication [23-25]. Currently PET scans are used for evaluating the dopaminergic system on healthy brains and pathological ones and also om evaluating medication effects. The development of radiotracers will increase our understanding of regulation mechanisms with all their effects [26].

Dopamine in parkinson's disease

Parkinson's disease appears as a consequence of pathological changes that consist of the neuron degradation in the substantia nigra, which leads to lowered dopamine levels. It appears frequently in elders, progresses slowly, is manifested through static tremors, muscular rigidity and bradykinesia [27,28] and reduces quality of the life significantly. Studies have suggested multiple factors possibly being involved in the process of neuron degeneration, such as: oxidative stress, environment factors, the aging process and genetical factors. The biosynthesis of dopamine begins with the enzyme tyrosine hydroxylase which catalyzes the forming of L-dopa, a stage of limiting the speed dopamine biosynthesis., so the disease could be considered a tyrosine hydroxylase deficit syndrome [29].

A study determining the relative expression of TH-mRNA in the brain of rats using PCR tests [30]. The results showed that the relative expression of TH-mRNA was lower in lab mice with Parkinson's disease compared to those with healthy brains, linking TH-mRNA relative expression with Parkinson's disease. Considering this the natural treatment strategy is based on correcting the deficit through administering L-dopa, dopaminergic agonists, inhibitors of dopamine metabolism or cerebral graft which expresses TH. Treatments have as a purpose elevating dopamine levels and may be beneficial at the beginning, their efficacy decreases with time, and the side effects monopolize the patients status. There are studies regarding gene therapy, which has as a purpose offering neuronal cells the tools to produce dopamine. An example of such a study was realized using the gene which codifies AADC, delivered in the putamen of patients with Parkinson's. Because AADC is an essential enzyme in transforming L-dopa into dopamine its decrease may lead to lowering the effectiveness of L-dopa and its increase to a greater L-DOPA effectiveness [31]. The therapy's efficiency depends on mode of delivery, administering of the medication, the brain having the blood-brain barrier, in this case convection-enhanced delivery being used.

NANOTECHNOLOGY AND PROPOSING A THEORETICAL CONCEPT OF TREATING PARKINSON'S DISEASE USING ENZYMATIC NANOREACTORS

Administering medicine to the brain is a real challenge because of the blood-brain barrier. Nanotechnology is a continually developing domain which has lead to the development of nanomedicine and its medical applicability *in vivo* and *in vitro* [32]. Nano-type delivery systems consist of small nanometric scale vesicles (20-200nm). Vesicles used as nanoreactors to

deliver medication are lipidic suspensions, which incapsulate compounds in aqueous phase(enzymes, hormones, medication) . Uniquely or multi-compartmented, they contain lipidic bilayers, with a central hydrophilic nucleus. The nucleus is an aqueous environment and can incapsulate soluble compounds, stored in the vesicle. By incorporating functional proteins in its outer layers of the vesicle, these can act as channel for the containing compounds, between the vesicle nucleus and its surrounding environment. They can also act as receptors which help the vesicle attach to specific cell membranes, this confers the nanoreactor permeability. Nanoreactors are carriers for incapsulated components (enzymes) and their reaction products, which are gradually released through a specific vesicular receptor thus controlling the process [33]. The enzymes using this particular delivery system in the medical field are: peroxidase, hexokinase, glucose-6-phosphate-dehidrogenase, glucose oxidase, streptokinase, butyryl-cholinesterase, superoxide dismutase [34-39].

Nanotechnology using liposomes in cerebral pathology can constitute a potential delivery system at specific sites [40]. By penetrating the blood-brain barrier, through its bioavailability, reducing biodegradability significantly, through its low toxicity and capacity of incapsulating hydrophilic and lipophilic medication [41]

My proposition has at its basis the theoretical concept of building an enzymatic nanoreactor, creating a method of targeted therapy, through which TH and AADC can be delivered to specific brain cells to increase intracellular dopamine levels in Parkinson's disease.

The concept proposes incapsulating the two enzymes into a liposome type enzymatic nanoreactor. For an increased efficiency, the nucleus zone can be divided by a semipermeable membrane, into two compartments each having a specific protein channel. In the first compartment TH is located, which transforms the substrate tyrosine into L-dopa. L-dopa makes its way through the semipermeable membrane, thanks to the concentration gradient, where it becomes substrate for the second enzyme, AADC. The resulting dopamine will be released through a cerebral specific protein channel (Figure1).

The mechanism will be regulated through negative feed-back with the participation of the enzymes responsible for degrading dopamine.

The proposed concept envisions a new possibility treating Parkinson's disease which has real potential, through its capacity of penetrating the blood-brain barrier, targeted therapeutic effect and the minimization of adverse effects.

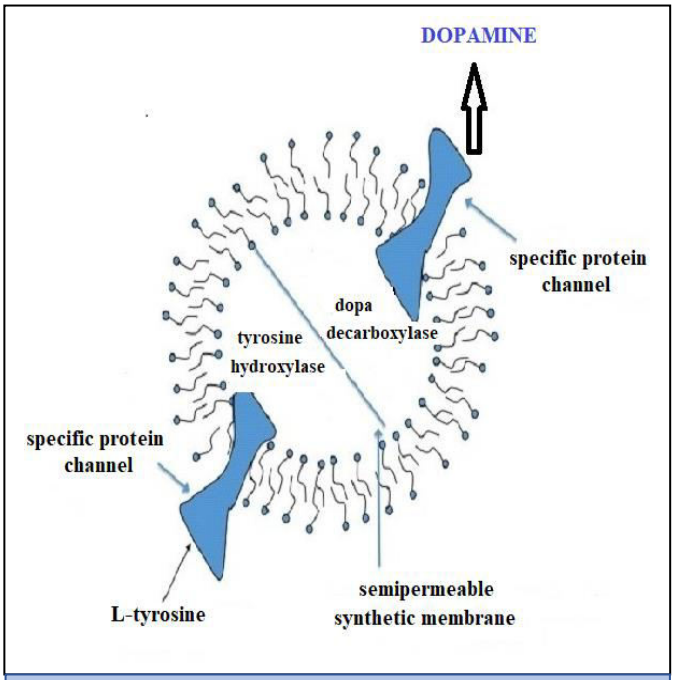

Figure 1: Theoretical concept of the dopaminergic enzymatic nanoreactor.

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