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Review

Pharmacology of cathecholamine biosynthesis and signaling

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ABSTRACT

This review summarizes the pharmacological potential of catecholamine signaling for the treatment of socially significant diseases such as depression, Parkinson's disease, hypertension, etc. The catecholamines dopamine, norepinephrine and epinephrine are released as neurotransmitters in nervous system and as hormones as well. The hormone prolactostatin is known to be biochemically dopamine and is continuously secreted by hypothalamic neurons in both sexes. Norepinephrine, as the main mediator released from postganglionic endings of sympathetic neurons, activates alpha- and beta-adrenoreceptors of target cells. In adrenal medulla, norepinephrine is a precursor for epinephrine synthesis and is released in small amounts as a hormone. Both norepinephrine and epinephrine induce stress responses by generalized sympathetic "fight-or-flight" response that increases cardiac output, blood pressure and breathing. A common therapeutic approach is usage of pharmacological substances that influence the adrenergic signaling. Additionally, treatments with drugs like reserpine, desipramine, 6-hydroxydopamine and others are useful tools for studding the role of local reuptake, *de novo* synthesis and plasma catecholamines in the regulation of physiological processes.

KEYWORDS: catecholamines, neurotransmission, dopamine, reserpine, desipramine.

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INTRODUCTION

Biogenic amines are synthesized from amino acids and contain amino groups (R-NH2). The most common biogenic amines are dopamine, norepinephrine, epinephrine, serotonin and histamine [1]. Dopamine, norepinephrine and epinephrine contain a catechol ring and an amino group; therefore, these amines are called cathecholamines [2]. Dopamine is a neurotransmitter in dopaminergic neurons in the central nervous system (CNS) and also serves as a precursor to norepinephrine in all central and peripheral noradrenergic neurons. Norepinephrine is a major mediator released from the endings of noradrenergic neurons in the brain, most of the postganglionic sympathetic neurons and the adrenal medulla chromaffin cells. It is stored in dense-core vesicles in the presynaptic terminals of the neurons. Adrenal medulla secretes mainly epinephrine and also small amounts of dopamine and norepinephrine. Postganglionic sympathetic endings however do not produce epinephrine as a neurotransmitter. In humans, the only place where epinephrine is synthesized is the adrenal medulla chromaffin cells [3, 4].

1. Biosynthesis of catecholamines

Synthesis and release of catecholamines are strictly modulated by autoreceptors on presynaptic terminals. The type of released catecholamines depends on the available enzymes in the neuron terminal. The first two steps of their synthesis are common to all catecholamines and start from the amino acid tyrosine (Figure 1). Tyrosine can be synthesized from phenylalanine by the enzyme

phenylalanine hydroxylase, but most often sufficient amount of tyrosine is supplied with the diet. It passes across the cell membrane of the catecholaminergic neurons and chromaffin cells of adrenal medulla by facilitated diffusion involving sodium-independent transporters [5]. Catecholamine synthesis in neurons is assumed to start from tyrosine synthesized from dietary phenylalanine in the liver and then is transported to neurons. Non-efficient phenylalanine hydroxylase leads to phenylketonuria, which increases phenylalanine in the body and causes severe mental deficiency but the catecholamine synthesis from tyrosine remains unchanged [3, 6].

Tyrosine is converted to L-dopa (L-dihydroxyphenylalanine) by cytosolic enzyme tyrosine hydroxylase at the axonal terminals. This is a rate-limiting step in the synthesis that requires the presence of molecular oxygen, Fe^{2+} and tetrahydrobiopterin (a cofactor for tyrosine hydroxylase and some other amino acid hydroxylases) [7]. Lack of this cofactor leads to phenylketonuria in combination with catecholamine and serotonin deficiencies. Tyrosine hydroxylation step is essential for the catecholamine synthesis, and hence its inhibition stops both the neuronal dopamine and norepinephrine synthesis as well as epinephrine synthesis in adrenal medulla [8].

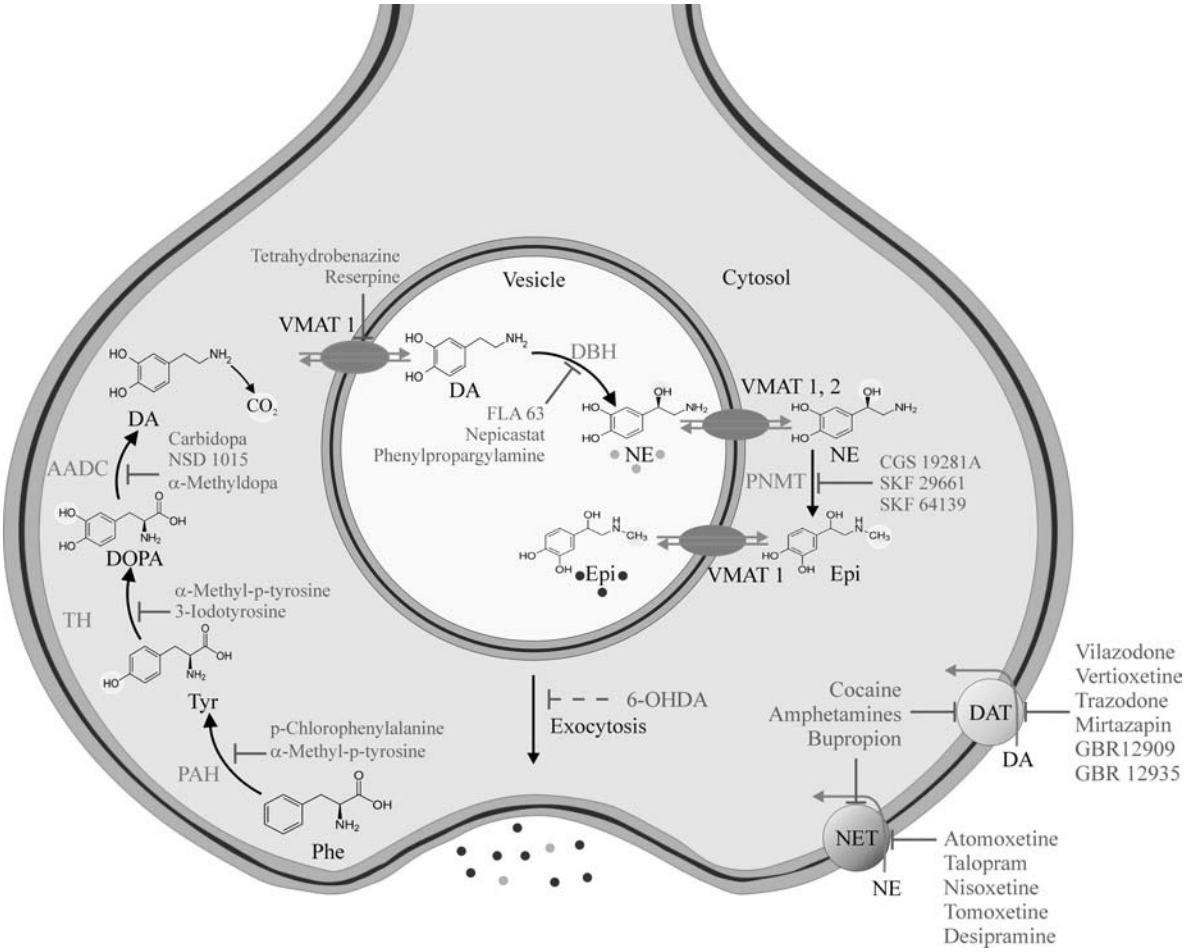

Figure 1. Biosynthesis of catecholamines. Some of common inhibitors are labelled with "├". AADC – aromatic L-amino acid decarboxylase, DA – dopamine, DAT – dopamine transporter, DBH – dopamine-β-hydroxylase, DOPA – L-3,4-dihydroxyphenylalanine, Epi – epinephrine, NE – norepinephrine, NET – norepinephrine transporter, PAH – phenylalanine-4-hydroxylase, Phe – phenylalanine, PNMT – phenylethanolamine N-methyltransferase, TH – tyrosine-3-hydroxylase, Tyr – tyrosine, VMAT – vesicular monoamine transporter.

The next step is the transformation of L-DOPA to dopamine catalysed by DOPA-decarboxylase. It is about 100 times faster, so endogenous DOPA is virtually non-detectable in the CNS. This enzyme uses pyridoxal phosphate (vitamin B6) as a cofactor and because of its low substrate specificity is also known as L-aromatic amino acid decarboxylase. Reactions of tyrosine hydroxylation and L-DOPA decarboxylation occur in the cytosol of catecholaminergic neuron endings. Then dopamine is transported to storage vesicles. More than 75% of dopamine is stored in large dense vesicles at the dopaminergic neuron terminals and released by the common calcium-dependent mechanism. Reserpine and tetrabenazine impeded transport of dopamine to the vesicles, resulting in decreased amount of all cathecholamines. They also prevent the re-inclusion of dopamine in vesicles following its reuptake. Remaining in the cytosol, dopamine is rapidly deaminated by the monoamine oxidase (MAO). In general, in the neurons where dopamine deposition in vesicles is blocked, active release of dopamine and amines is not achieved [6].

In norepinephrinergic neurons vesicles, dopamine is converted to norepinephrine with the participation of membrane-bound enzyme dopamine-β-hydroxylase. All enzymes and factors are stored in vesicles in neuron body and then undergo axoplasmic transport. Under normal conditions due to the high affinity of the DOPA-decarboxylase and dopamine-β-hydroxylase to their substrates, neither L-DOPA nor dopamine accumulates in the norepinephrinergic nerve endings. Dopamine β-hydroxylase may also become a rate-limiting enzyme as a result of treatment with L-DOPA in Parkinson's disease (dopamine concentration in the nerve endings is greatly increased) [6].

Norepinephrine, like dopamine, is stored in large, dense-core vesicles which are accumulated in varicosities of sympathetic nerves [7]. They contain ATP, proteins, divalent metal ions and norepinephrine at a concentration 10^4 to 10^6 times higher compared to that in cytosol. So norepinephrine is moved into vesicles by secondary active transport *via* vesicular monoamine transporters (VMATs). VMATs mediate the exchange of one norepinephrine molecule against two H^+ using the H^+ electrochemical gradient. It is believed that either the binding or transfer of the first H^+ increases the affinity of the transporter to norepinephrine and the binding of the second H^+ actually triggers its transfer [6]. Thus, a sufficient amount of the transmitter is stored in the vesicles ready to be released; the neuron is protected from the potentially toxic effects of excess cytoplasmic norepinephrine, and a concentration gradient facilitating the norepinephrine reuptake is maintained.

Two types of VMATs have been identified that transport dopamine, norepinephrine and epinephrine (serotonin and histamine) from cytosol to the secretory vesicles. They are distinguished on the basis of their distribution and sensitivity to reversible inhibitors (tetrabenazine), amphetamines and histamine but both are blocked by reserpine [5]. In rats, VMAT1 is detected in the adrenal medulla, but not in the neural tissue, whereas VMAT2 is found only in neurons. In other species, the tissue diversity is not so distinct. The release of norepinephrine in the synaptic cleft is again by a calcium-dependent mechanism.

The dopamine and norepinephrine released into the synaptic cleft is removed by neuronal re-uptake into the presynaptic terminals. Both transporters are similar but not identical allowing specific inhibition: for example, nomifensine influences dopamine transporter but only slightly affects norepinephrine transporter [6]. The norepinephrine transporter is a Na-Cl co-transporter. Na^+ and norepinephrine bind to the extracellular side of the carrier and open an internal "door" channel in the transporter by conformational changes. This allows the passage of norepinephrine from the extracellular space into the cytosol of the neuron. Inhibition of reuptake is a major mechanism of cessation of neurotransmitter signaling that prolongs and increases norepinephrine effects. Thus, some effective antidepressants are inhibitors of amine reuptake [9]. After re-uptake of norepinephrine by presynaptic terminals it is transported back into the vesicles through a Mg^{2+}-dependent mechanism. Reserpine and other chelators of Mg^{2+} inhibit this process and hence norepinephrine is rapidly deaminated in the cytosol and the amount of transmitter decreases [7].

In humans, phenylethanolamine-N-methyltransferase presents only in the cytosol of adrenal chromaffin cells. In these cells, norepinephrine moves out of the vesicle into the cytosol where phenylethanolamine-N-methyltransferase transfers a methyl group to norepinephrine thereby creating

epinephrine. The newly synthesized epinephrine is transported back in the vesicles for storage *via* the same VMAT1 catecholamine-H^+ carrier [4].

Reserpine reversibly inhibits H^+-ATPase and thus reduces the vesicular neurotransmitter storage in the neuronal terminals. Normal function of the neuron is restored only after the delivery of new vesicles from the cellular body. Some amphetamine derivatives such as methylenedioxymethamphetamine (MDMA) act also as a substrate for this transport mechanism and competitively inhibit the norepinephrine entering the vesicle [7]. Another way to inhibit transport is by scattering the H^+ gradient across the vesicle membrane (p-chloramphenicol acts in this way) [10]. In the vesicles, norepinephrine and epinephrine are associated with ATP and chromogranins A or B. Two steps of epinephrine synthesis are controlled by other stress hormones: (1) adrenocorticotropic hormone stimulates the DOPA and norepinephrine synthesis; (2) cortisol stimulates PNMT in the chromaffin cells [11, 12]. As a result, a synergetic interaction occurs between the hypothalamus-pituitary-adrenal gland and the sympathetic-epinephrine axis.

2. Receptors and signal transduction

Norepinephrine and epinephrine interact with α- and β-adrenoreceptors, regardless of whether they are released as neurotransmitters or as hormones. They are G-protein coupled receptors but pharmacologically divided into several subtypes – α_1- and α_2-subtype and β_1-, β_2- and β_3-subtype, respectively. In addition, α_1 receptors are a heterogeneous group and subdivided into three subtypes [13].

Norepinephrine and epinephrine, secreted by the adrenal medulla, show a difference in their interaction with α- and β-receptors. Norepinephrine stimulates mainly α-receptors, but to a small extent, it also activates β-receptors. The epinephrine interacts in equal affinity with both type of adrenoreceptors. Dopamine itself interacts with five types of D_1-D_5 receptors, which are also G-protein coupled receptors.

2.1. G_S and $G_{I/O}$-protein-mediated signaling pathways

All β-adrenoreceptors and α_2-adrenoreceptors affect the adenylate cyclase → protein kinase A pathway but they are coupled to different G-proteins that activate or suppress their activity (Figure 2). β-receptors are coupled to G_s-protein and activate adenylate cyclase thereby increasing the concentration of cAMP and activating protein kinase A downstream [13, 4]. Protein kinase A phosphorylates a number of target proteins depending on the cell type. In contrast, α_2-receptors activate $G_{i/o}$-proteins that suppress adenylate cyclase and lower cAMP concentration. As a result, the activity of protein kinase A decreases. Furthermore, after phosphorylation of the receptor by activated protein kinase A, β_2 may switch from G_s- to G_i-signaling [14]. In this way, the signal is highly localized in the cell, unlike β_1-receptors, which couple only to the G_s-proteins and have diffusive effects [15]. The ultimate physiological effect of epinephrine and norepinephrine on the relevant organ depends on the receptor type with which they interact.

D_1 and D_5 receptors, similar to the β-adrenoceptors, activate G_s-proteins and subsequently adenylate cyclase pathway. The remaining three dopamine $D_{2\text{-}4}$ receptors suppress the same pathway by G_i-proteins [16].

2.2. $G_{Q/11}$-protein-mediated signaling pathway

The α_1-receptor subtype affects qualitatively different signaling pathway (Figure 3). It is coupled with a $G_{q/11}$-protein that activates the membrane-bound enzyme phospholipase C. It degrades phosphatidylinositol 4,5-bisphosphate to diacylglycerol and inositol-(1,4,5)-trisphosphate. Each of these secondary messengers induces corresponding cellular responses. Diacylglycerol activates protein kinase C, which itself phosphorylates different target proteins. Inositol-(1,4,5)-trisphosphate opens calcium channels on the membrane of the endoplasmic reticulum and induces calcium ions release. All three subtypes of α_1-adrenoceptors follow this signaling pathway [17].

3. Parkinson's disease

Parkinson's disease is a long-term progressive degenerative disorder affecting about 1% of people over the age of 55. In the patient brain suffering from Parkinson's disease, substantia nigra loses its pigmentation and becomes brighter due to the loss of dopaminergic neurons [18].

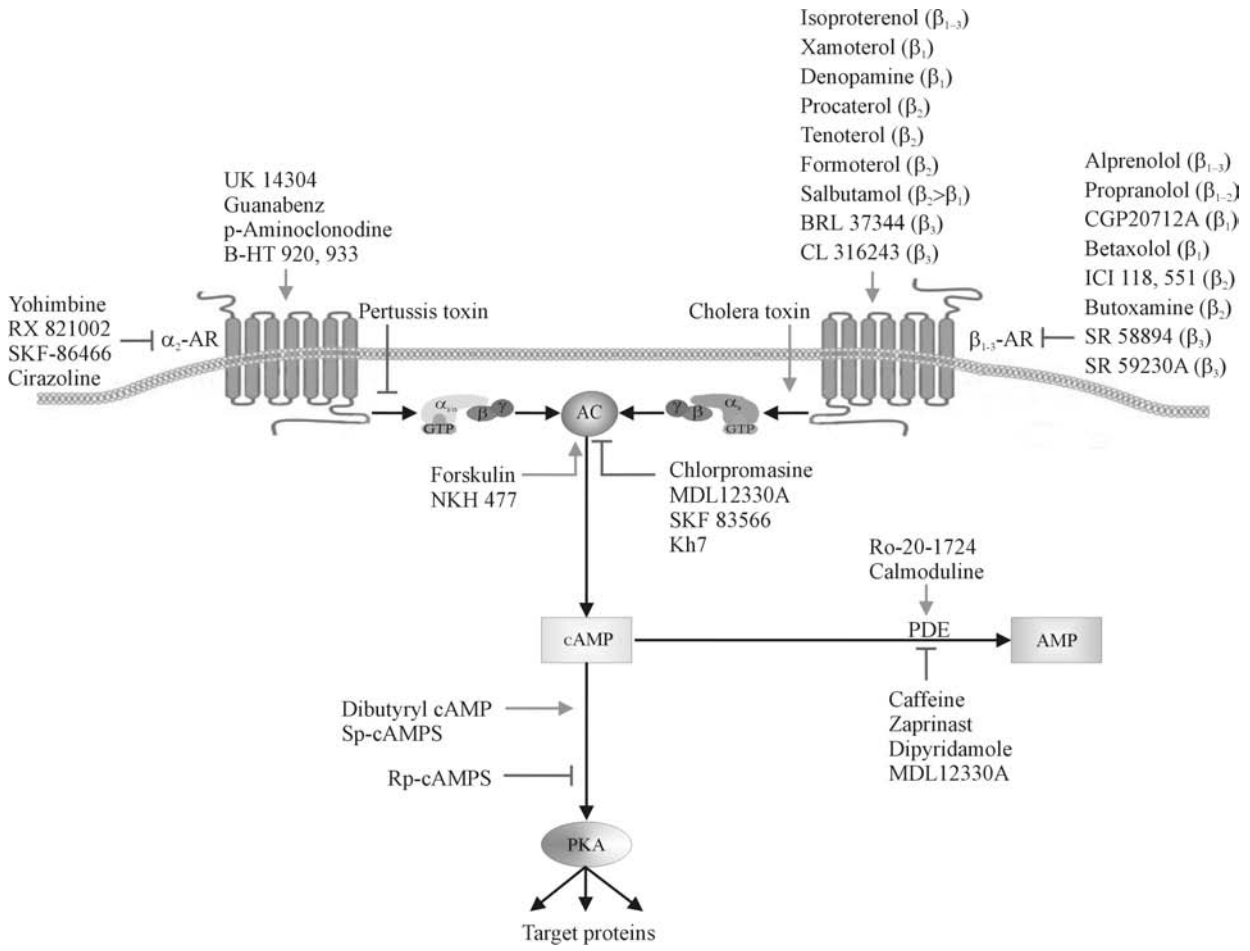

Figure 2. α_2- and β-adrenoreceptors signaling through G_s and $G_{i/o}$. Blockers are labelled with "┣", and agonists – with "→". α_2-AR – α_2-adrenoreceptor, $\beta_{1\text{-}3}$-AR – $\beta_{1\text{-}3}$-adrenoreceptor, AC – adenylate cyclase, AMP – adenosine monophosphate, cAMP – cyclic adenosine monophosphate, PDE – phosphodiesterase, PKA – protein kinase A.

The degeneration of dopaminergic nigrostriatal pathway leads to loss of dopamine in the striatum. Symptoms include: slowness of movements (bradykinesia) to complete loss of ability to move (akinesia); muscle stiffness and rigidity; limb tremors, especially at rest, but not during sleep [19]. These symptoms result in a trembling gait, inability to make movements like turning, writing and stationary standing posture.

Because it is a relatively specific degeneration of a particular neuronal pathway and the loss of a certain neurotransmitter, it allows the use of substances with specific toxic effects on these neurons such as 6-OHDA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to create convenient experimental models of Parkinson's disease. 6-OHDA enters the neuron terminals through the catecholamine reuptake system, then oxidizes and forms several cytotoxic substances (such as free radicals), increases oxidative stress and induces apoptosis. It also depolarizes mitochondrial membrane and suppresses mitochondrial respiratory chain. Administration of a norepinephrine reuptake blocker prior to 6-OHDA preserves norepinephrinergic neurons and destroys only the dopaminergic neurons [20]. Another more specific neurotoxin for dopaminergic neurons is MPTP which destroys only dopaminergic neurons in the same way by the mechanism of reuptake. This substance is not pharmacologically active but has to be metabolized to the active form. In the brain MPTP is oxidised by MAO_B first to 1-methyl-4-phenyl-2,3-dihydropyridine

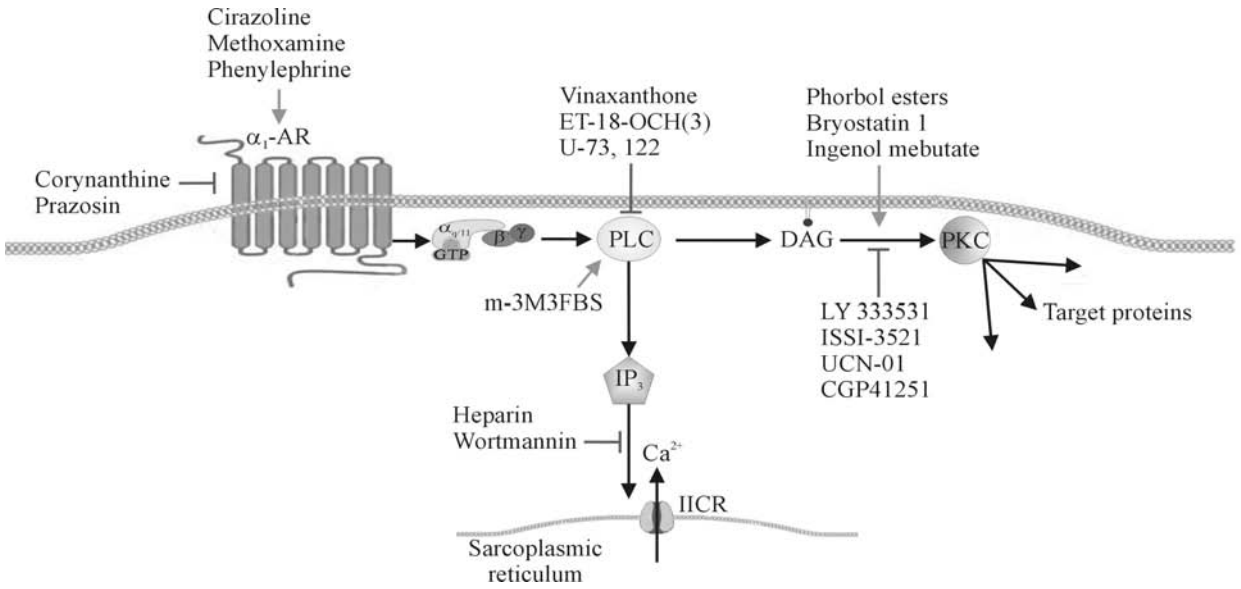

Figure 3. α_1-adrenoreceptor signaling through $G_{q/11}$. Blockers are labelled with "┣", and agonists – with "→". α_1-AR - α_1-adrenoreceptor, DAG – diacylglycerol, IICR - inositol trisphosphate-induced calcium release, IP_3 - inositol 1,4,5-trisphosphate, PKC – protein kinase C, PLC – phospholipase C.

(MPDP+) and this rearranges to form the stable metabolite 1-methyl-4-phenylpyridine (MPP+). Within the neurons the MPP+ enters mitochondria where it inhibits energy metabolism by blocking oxidative phosphorylation. In MPTP-induced Parkinson's disease models caffeine and its derivate relieve the symptoms by blocking adenosine receptors type 2A or by forming complexes between methylxanthines and all MPTP intermediate metabolites [21]. The preferred experimental models for evaluation of the drug effects are primates instead of rodents, as they show the typical symptoms of the Parkinson's disease.

There is no treatment for Parkinson's disease. All therapeutic procedures are aimed at alleviating symptoms primarily to improve the function of dopaminergic synapses in the striatum. Dopamine levels in synapses can be increased in several ways: by introducing its precursor L-DOPA (its left form); by blocking its reuptake; by inhibiting the degradation (MAO_B and COMT inhibitors). Dopamine receptors may also be stimulated by appropriate D_2 or D_1 receptor agonists.

Dopamine cannot be used directly for treatment of the Parkinson's disease because it does not cross the blood-brain barrier and is fast metabolized by MAO and COMT in gastrointestinal tract and liver. Levodopa is a substrate only for MAO but not for COMT and cross blood-brain barrier and then is converted to dopamine in striatal neurons. So its use as a replacement therapy in Parkinson's disease is a great success in neurology. The exogenous levodopa may still increase dopamine in the striatum even after almost complete degeneration of neurons in nigrostriatal pathway as a result of the disease [6]. But levodopa increases dopamine not only in the striatum but also elsewhere in the brain, and therefore side effects such as vomiting, dyskinesia (involuntary movements), some psychoses and decreased prolactin secretion are observed. Unfortunately, levodopa has a very short half-life, in addition, only 30% enters in the circulation and less than 10% crosses the blood-brain barrier [22].

In order to improve the effectiveness of levodopa, it is combined with extracerebral decarboxylase inhibitors (carbidopa and benserazide). In this way peripheral degradation of levodopa is reduced to allow greater amounts to reach the brain as well as reduce the effective dose and side effects [23].

Inhibitors of dopamine reuptake such as nomifensine, vilazodone, vortioxetine and trazodone (block the

dopamine transporter) and selegiline, rasagiline, safinamide as specific inhibitors of MAO_B, all of them prolong the action of dopamine in synaptic cleft [24]. Dopamine level increases with time but it has opposite effect due to presynaptic activation of autocrine receptors and inhibition of dopamine release. Considering these problems and the progressive degeneration of dopamine neurons, it is not surprising that these substances have weak effect and provide some improvements in the early stages of the Parkinson's disease. COMT inhibitors (entacapone, tolcapone) have insignificant effect on dopamine degradation but considerably elongate the action of levodopa by preventing its catabolism.

Since there is no reduction in the number of postsynaptic dopamine receptors in Parkinson's disease, dopamine agonists could be used in the disease treatment. They cross the blood-brain barrier, interact directly with the receptors without turning into dopamine and can be long-acting. In theory, they seem to have some advantages over levodopa treatment, but virtually they are a little disappointing. Dopamine agonists ropinirole, rotigotine, pramipexole and apomorphine are effective only when some endogenous dopamine is available. Studies of Parkinson's disease marmoset model show that after inhibition of central DOPA decarboxylase (blocking the synthesis of dopamine in the striatum), the specific D_1 and D_2 agonists were ineffective when introduced separately and less effective in a combination unless given in high doses, which is clinically inappropriate [6].

4. Schizophrenia

Schizophrenia is defined as a progressive disorder of personality and its relation to the world as a whole. The main symptoms include: (1) auditory hallucinations (voices dictating the human's thoughts and actions); (2) mental disorders (patients believe that others can read and control their thoughts); (3) physical catatonia (ability to maintain unusual postures for hours, periods of psychomotor immobility often alternate with periods of uncontrollable physical activity); (4) emotional problems (isolation, reduced emotionality and responses, difficulty speaking). The first three refer to the so-called "Positive" symptoms of the disease. The fourth concerns the "negative" symptoms - social apathy and isolation caused by positive symptoms [6].

Some drugs reduce the positive symptoms and thus decrease the propensity for social isolation (positive effect on the negative symptoms). When positive symptoms are well-tolerated by drugs, it is defined as schizophrenia type I whereas type II are cases with true negative symptoms which are resistant to drug treatment.

Although schizophrenia is not a neurodegenerative disease a general neuropathology is observed. In addition, there is evidence of genetic predisposition. In the brains of almost all schizophrenics, there are no specific lesions, but pathologies such as decrease in the brain size or some small lesions, partially in the amygdala, the hippocampus and the prefrontal cortex and decreased blood supply in these areas are observed [19]. Surprisingly, these changes mainly occur on the left side. There is also evidence of increased cerebral ventricular size, especially in patients with severe negative symptoms.

Schizophrenia requires lifelong treatment with neuroleptics which are antagonists of dopamine receptors and reduce the dopamine effects, even when symptoms have subsided. Amphetamines cause hallucinations similar to schizophrenia. More and more evidence supports the dopamine hypothesis that schizophrenia is a result of increased dopaminergic activity in the brain. There is a wide range of neuroleptics today, but the most effective are antagonists of dopamine D_2 receptors. A post-mortem examination of schizophrenia patients' brains showed extremely high dopamine receptor expression but no change in total dopamine level or its inhibitory control of plasma prolactin. In addition, neuroleptics themselves, such as dopamine antagonists, cause an increase in the number of dopamine receptors [7].

The increased dopamine function is probably not the real cause of schizophrenia and its symptoms are simply mediated by normally functioning dopamine systems. It seems that is the result of overactivity due to the loss of some counteractions or other neurotransmitters. There is no reliable evidence for participation of other neurotransmitters, but serotonin and glutamate are believed to be

related to schizophrenia, as some antagonists of D_1 and 5-HT_2 receptors have shown good results in the treatment of schizophrenia [25, 26].

There are four major classes of neuroleptics: phenothiazines, butyrophenones, thioxanthenes and benzamides. They are all dopamine antagonists, predominantly D_2 receptors and their antipsychotic action is a result of blocking dopamine receptors in the brain. As a result, they reduce the positive symptoms of schizophrenia but very poorly affect the negative symptoms. They are capable of inducing extrapyramidal adverse effects because their effectiveness depends on the receptor affinity. Their long use causes unusual muscle movements and tremor. It is a mechanism of action of typical neuroleptics as chlorpromazine (phenothiazine) and haloperidol (butyrophenones). Clozapine and some other atypical neuroleptics have less side effects, have a significant effect on negative symptoms and help 30% of patients in whom conventional medications have no effect. However, clozapine causes agranulocytosis as a side effect in 1% of patients and they should perform regular blood tests at 1-2 weeks. Some of the new antipsychotic agents (risperidone, olanzapine), do not indicate a risk of agranulocytosis but have other side effects [6].

5. Depressive disorders

Depression is an emotional disorder where the patient has a feeling of melancholy, a terrible sense of sadness, hopelessness, pessimism, loss of interest in life, and emotional instability. It is one of the most common mental disorders that lead to disability to perform daily activities such as learning, work and social communication. Depressed people are 18 times more likely to commit suicide than healthy people. Annually, severe depression affects 5% of the population over age of 18. Fortunately, 80% of patients respond to drugs, psychotherapy or both. In some severely depressed patients, electroconvulsive therapy may be helpful.

Depression arises from many causes: biological (including genetic), psychological, external factors or a combination of these. Stroke, hormonal disorders, antihypertensive agents and contraceptives may also play a role. Physical symptoms include disorders of sleep, sexuality, appetite and digestion. Some of these symptoms are related to a disturbance of the delicate hormonal feedback system along the hypothalamus-pituitary-adrenal gland axis.

Most antidepressants correct the increased amount of norepinephrine and serotonin in the brain or inhibit the signals that control mood, thoughts, pain and other sensations. Initially MAO inhibitors were used as antidepressants [7]. They prevent the degradation of serotonin, norepinephrine and dopamine, allowing them to remain active longer in the synaptic cleft. The first MAO inhibitor in use was iproniazide, which induces hyperactivity in experimental animals. First, it was used in treatment of tuberculosis, but caused euphoria and was identified as a psychotic stimulant. Iproniazide is a reversible MAO inhibitor. Inhibition of this enzyme initially results in an increased concentration of the cytosol soluble mediator since only cytoplasmic monoamines have access to it. Subsequently, this leads to an increased storage of the vesical-bound mediator, the form under which the mediator is released by impulse-evoked mechanism [6]. To date, other MAO-inhibitors have been developed such as isocarboxazid, phenelzine and tranylcypromine.

A different approach in the depression treatment is the use of tricyclic antidepressants which block the reabsorption and inactivation of serotonin and norepinephrine to varying degrees. The popular drug fluoxetine (Prozac) is the first of the new class serotonin reuptake inhibitors. It also blocks the reabsorption and inactivation of serotonin but keeps it active in certain brain circles. This probably restores overall serotonin activity to a more normal condition and relieves depression [19].

6. Cardiovascular disorders

Worldwide cardiovascular diseases are one of the primary reasons for death. These include all diseases of the heart and blood vessels. The most common is hypertension and related complications.

6.1. Hypertension

Hypertension treatment is very complex and includes preparations of many drug groups such as

renin inhibitors, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics and a wide range of α- and β-adrenoreceptor antagonists as well as α-adrenoreceptor agonists. The most commonly prescribed drugs are β-blockers such as betaxolol and atenolol (selective β1 blockers), propranolol (non-selective β-receptor antagonist), and many others [27]. All of them decrease the heart rate and the strength of heart contraction. Thereby they reduce the stroke volume and cardiac output and decrease arterial pressure. Prazosin is a α_1-blocker which ceases the transmission of nerve impulses from autonomic nervous system, reduces vascular resistance and thereby blood pressure [28]. Agonists of α_2-adrenoreceptors such as guanabenz and methyldopa, also called central adrenergic inhibitors, stop the release of norepinephrine from sympathetic endings. Guanabenz acts as a direct α_2-adrenoceptor agonist [29] whereas methyldopa affects blood pressure in two different ways. It inhibits DOPA decarboxylase from the catecholamine synthesis pathway and restricts dopamine and adrenergic neurotransmission. On the other hand, methyldopa is converted to α-methylnorepinephrine by dopamine-β-hydroxylase which is an agonist for presynaptic α_2-adrenoceptors. The activation of these receptors in the brainstem leads to decrease in sympathetic activity and lowering of blood pressure [30].

6.2. Anaphylactic shock

Anaphylactic shock is an acute, potentially deadly, multi-organ syndrome that occurs because of the release of circulatory factors from adipose cells and basophils. Released inflammatory factors such as histamine lead to contraction of smooth muscles in bronchi but at the same time, it relaxes the vessel smooth muscles. Stimulation of the vagal pathways causes intense vasodilatation and greatly suppresses cardiac activity. The administration of epinephrine and β-agonists is the first step in case of anaphylaxis that affects adrenergic signaling pathways in smooth and cardiac muscle cells [31]. Epinephrine is often used to weaken the allergic reaction in several aspects. α-receptors increase peripheral vascular resistance and consequently improve blood pressure and perfusion of coronary vessels. Stimulation of β_1-adrenoreceptors has a positive chronotropic and inotropic effect on the heart. Activation of β_2-adrenoceptors leads to bronchodilation and reduces the release of inflammatory factors from adipose cells and basophils. Some β-agonists such as albuterol (salbutamol) are also used to further improve breathing [32].

7. Respiratory diseases

Adrenergic signaling is pharmacologically targeted for treatment and alleviation of the respiratory disease symptoms. They are applicable to both chronic (asthma and chronic obstructive pulmonary disease) and acute (colds and flu) respiratory diseases. Short-acting and depot medications are used in the treatment of these diseases. Another group of pharmaceutical substances is applied as decongestants.

7.1. Long-term acting

The long-term acting preparations are taken daily to control asthma and reduce the risk of acute asthma attacks as well as to relieve the symptoms of chronic bronchitis in chronic obstructive pulmonary disease. This group includes inhalation form of β_2-agonists such as salmeterol and formoterol, whose action continues for up to 12 hours [33]. Indacaterol is an ultra-long-acting β_2-agonist with effect up to 24 hours. It is applicable to chronic obstructive pulmonary disease patients but not for the asthma treatment [34].

They have a long lipophilic side chain that binds to the extracellular side of the adrenoceptors and allows the active part to bind and unbind repeatedly from the receptor. However, these types of β2-agonists are not recommended in acute conditions as they act too slowly. In addition, they must be used in combination with corticosteroids to prevent chronic inflammation and severe asthma attacks [35].

7.2. Short-term acting

β_2-agonists (salbutamol, terbutaline) are used for fast, short-term relief of the severe, life-threatening asthma attack symptoms [34]. They can also be used before physical exercise under medical prescription. The world anti-doping agency forbids their use by athletes (S3 group), but a small number of dishonest athletes circumvent this prohibition by showing false

medical evidence that they have been diagnosed with asthma [36].

7.3. Decongestants

Decongestants serve to unblock the upper respiratory tract. Their active ingredients are α_1-agonist such as phenylephrine, xylometazoline, nafazoline or epinephrine-releasing agents, such as ephedrine and pseudoephedrine. All of them ultimately lead to activation of the intracellular signal pathway of α_1-adrenoreceptors and vasoconstriction of the nasal mucosa, throat and sinuses. This effect reduces the inflammation and the mucus formation there [37].

Thus, the pleiotropic effects of adrenergic signaling in health and disease make it an important target for various effective pharmacological treatments with a great potential for improving the human wellbeing.

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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