ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 04, April-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

CATECHOLAMINES EFFECTS ON CARDIOMYOCYTE MITOCHONDRIAL AND OXIDATIVE PHOSPHORYLATION ENZYMES

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Abstract: This review outlines the pharmacological possibilities of catecholamine signaling for the management of socially important disorders like hypertension, Parkinson's disease, and depression. Dopamine, norepinephrine, and epinephrine, the catecholamines, are released as hormones and as neurotransmitters in the nervous system. Prolactostatin, a hormone that is biochemically dopamine, is constantly released by hypothalamic neurons in both sexes. Norepinephrine activates the alpha and beta adrenoreceptors of target cells as the principal mediator released from the postganglionic endings of sympathetic neurons. Norepinephrine is released in little quantities as a hormone in the adrenal medulla, where it serves as a precursor to epinephrine production. Both norepinephrine and epinephrine trigger stress reactions through a generalized sympathetic "fight-or-flight" response, which raises cardiac output, blood pressure, and respiration.It is now crucial in cardiology to determine the mechanisms of adaptation to disturbances seen during hyperactive sympathetic nervous system activity in order to create effective treatments for cardiovascular disease.

Key words: Catecholamines, adrenaline, enzymes, beta adrenoreceptors, biogenic amines

Sympathetic hyperactivation naturally leads to an increased production of both enzymatic and non-enzymatic products due to the enzymatic metabolism of catecholamines. This can result in alterations to the activity of mitochondrial and cytosolic enzymes, which in turn affects the levels of bioenergetic adaptation, antioxidant system protection, and the synthesis of intercellular modulators like AMP and adenosine [1]. It is well established that the catecholamines adrenaline and norepinephrine raise blood glucose levels by inhibiting insulin-mediated glucose uptake into adipose and muscle tissues, enhancing glucagon secretion, and stimulating glycogenolysis and gluconeogenesis via activation of hepatocyte α- and β-receptors. 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] Norepinephrine is more affected monoamine oxidase [8]. But, released by the nervous endings or when administering sympathomimetics, norepinephrine may also be affected COMT. In turn, catecholamines through beta-adrenergic receptors without the participation of cAMP can have activating effect on COMT [3]. There are two types of mitochondrial monoamine oxidases - A and B types of MAO [7]. Aldehydes, formed during oxidative deamination

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catecholamines, can accelerate the apotomic pathway oxidation of glucose due to activation of glucose-6- phosphate dehydrogenase and transketolase, as well as reduce cardiac gamma-amylase activity [5]. In a number cases, aldehydes can react condensation with non-deaminated molecules monoamines, having a hepatotoxic effect [8]. With immobilization stress against the background of high catecholamine levels revealed transformation of MAO to adenyl deaminase [6]. Close localization of MAO with enzymes of the mitochondrial respiratory chain showed the presence of a functional relationship between these biocatalytic systems [4]. Studies on quinoid oxidation catecholamines and the biological significance of the resulting products served as the basis for creating the concept of functional significance of exchange of exchange regulators [7]. During quinoid oxidation of catecholamines the corresponding quinones are formed, one of which is adrenochrome. It was found [3] that perfusion isolated rat heart with Krebs-Henseleit solution containing adrenochrome (25 or 50 mg/l) caused contractile failure and necrosis myocardium. Beta receptor blocking drugs propranolol and practolol effectively protect the heart from necrotic damage caused adrenochrome, and partially prevent contractile insufficiency. Quinoid oxidation catecholamines can be catalyzed by many enzymes (cytochrome c oxidase, catechol oxidase, ceruloplasmin). Oxidation of norepinephrine in under oxygen-free conditions, the reductone complex promotes: adenine-Cu++ [9]. In the presence of peroxidase aminosine accelerates the oxidation of catecholamines to corresponding aminochromes [3] and forms with adrenochrome complex is more stable than acetylcholine-adrenochrome complex [8]. Seduxen (diazepam), phenothiazine drugs reduce activity of this enzyme [9]. The first indication of the presence of a specific the enzyme that oxidizes adrenaline into adrenochrome was implemented [3]. Enzyme that oxidizes norepinephrine to noradrenochrome in the presence acetylcholine, hydrogen peroxide and cyanide, was found in the blood serum of patients with schizophrenia [2]. Working in an innovative psychiatric environment, Hoffer A and Humphrey F. formulated in 1952 adrenochrome hypothesis of the biogenesis of schizophrenia [7]. It was found that with thyroid toxicosis, with myocarditis, the level of quinoids increases products in the heart, and when the temperature rises body there is an increase in the excretion of adrenochrome c urine [4].Adrenochrome and adrenoxyl have hemostatic and hemolytic effects . 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 Mg2+-dependent mechanism. Reserpine and other chelators of Mg2+ inhibit this process and hence norepinephrine is rapidly deaminated in the cytosol and the amount of transmitter decreases [10]. 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 βblockers such as betaxolol and atenolol (selective β1 blockers), propranolol (non-selective βreceptor antagonist), and many others . 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 α1-blocker which ceases the transmission of nerve impulses from autonomic nervous system, reduces vascular resistance and thereby blood pressure [8]. Agonists

eISSN: 2349-5715 pISSN: 2349-5707

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of α2- adrenoreceptors such as guanabenz and methyldopa, also called central adrenergic inhibitors, stop the release of norepinephrine from sympathetic endings.

Catecholamines have non-uniform effects on cardiomyocyte mitochondrial and oxidative phosphorylation enzymes. These effects are compounded by the presence of metabolites from the quinoid and monoamine oxidase pathways, which convert adrenaline and norepinephrine. The ability of catecholamine metabolites, along with intact catecholamine molecules, to alter the enzyme activity of the respiratory chain is a key factor in regulating tissue respiration and oxidative phosphorylation. Metoprolol, a β1 blocker, reduces the intensity of animals' stress reactions caused by the injection of adrenaline. The β1-blocker metoprolol can be used to correct enzyme dysfunctions in purine metabolism and antioxidant defense observed during hyperadrenalinemia and oxidative stress of different origins.

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