Chapter 9
Norepinephrine

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Introduction

History of Norepinephrine

Norepinephrine (NE) is a neurotransmitter of the brain that has a vital role in the modulation of cognition, arousal, attention, and stress responses. In the periphery, NE functions as a hormone as a part of the "fight or flight" response in the sympathetic nervous system [1]. NE was discovered in the peripheral nervous system (PNS), along with epinephrine. German physiologist, Otto Loewi, demonstrated that a substance released into the blood subsequent to sympathetic ganglion stimulation increased the heart rate, which was later identified as epinephrine. NE was considered an inactive precursor of epinephrine; however, Ulf von Euler, a Swedish physiologist, demonstrated that NE was also involved in the sympathetic response in 1940 [2, 3].

Marthe Vogt, in 1954, expanded the role of NE as a neurotransmitter in the central nervous system (CNS). In 1962, Falck and Hillarp applied histochemistry to brain structures, and NE was identified in both PNS and CNS. Dahlstrom and Fuxe,

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in 1964, demonstrated that locus coeruleus (LC) is the primary source of NE in the CNS through their experiments [2, 4]. Alpha-2 adrenoceptors were first identified on peripheral nerve endings in 1974 and on cell bodies and dendrites of central noradrenergic neurons in 1975 [5, 6].

Neurochemical Profile

The noradrenergic system in the brain has two primary ascending projections that arise from the brainstem: the dorsal noradrenergic bundle (DNB) and ventral noradrenergic bundle (VNB). DNB originates from LC and is mainly composed of noradrenergic neurons that project to the cerebral cortex, hippocampus, and cerebellum and intersects with the projections from the VNB to innervate the hypothalamus amygdala, and spinal cord. The VNB also innervates the midbrain and medulla along with the amygdala and hypothalamus. VNB plays a crucial role in controlling vegetative functions and endocrine regulation [7–9].

NE is released mainly from the LC in the brain. LC, a small pontine nucleus that is located in the lateral wall of the brainstem by the fourth ventricle. LC has about 20,000 neurons that produce central NE, while the medullary nuclei primarily function peripherally. Most of the noradrenergic neurons of the brain are found in LC. LC projects to most parts of the brain, forming both synaptic and nonsynaptic contacts, with projections to the forebrain, cerebellum, brainstem, and spinal cord. NE pathways have a wide innervation in the brain from olfactory tubercle to spinal cord and are shown below in Fig. 9.1 [10–12].

LC neurons produce NE from two types of NE cells, the large multipolar cells (35 μM) and smaller fusiform cells (20 μM). Their distribution in the LC is distinct—fusiform cells are located in the dorsal LC and multipolar cells in the ventral

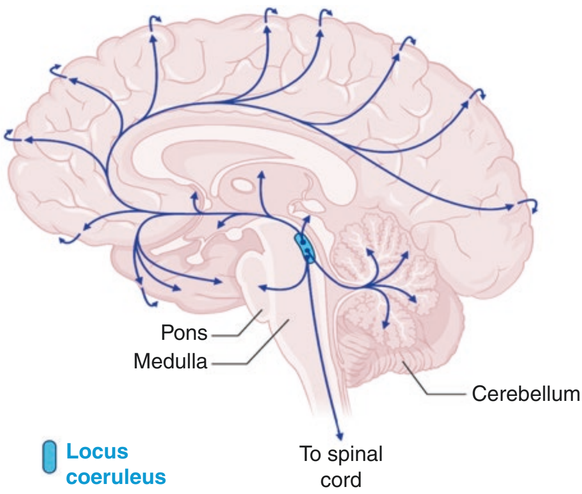


Fig. 9.1 Norepinephrine pathways in the brain

LC [13]. In addition to NE, galanin is also expressed in up to 80% of LC neurons, which is involved in regulating wake/sleep states, feeding, nociception, and parental behavior [14, 15].

The unique characteristic of LC is the diversity of projections and intense collateralization of the axons. LC projects to most parts of the brain and modulates information from various systems like sympathetic, parasympathetic, cortical, and limbic centers [12]. The sympathetic and parasympathetic nervous systems and their neurotransmitters are shown below in Fig. 9.2. The sympathetic nervous system and neuroendocrine chromaffin cells of the adrenal medulla synthesize and release NE and other catecholamines [2, 16].

Factors contributing to noradrenergic transmission are the diversity of noradrenergic receptors, tonic and phasic neurotransmission, and the nonlinear relationship between innervation and performance [17]. The noradrenergic system promotes wakefulness, arousal and facilitates sensory signal detection. Most studies have shown that NE influences cognition and behavior like working memory, attention, behavioral flexibility, and long-term mnemonic processing [18].

During anxiety or stress, the released NE and epinephrine are bound to adrenergic receptors throughout the body that exert effects like dilating pupils and bronchioles, increasing heart rate and constricting blood vessels, increasing renin secretion from the kidneys, and inhibiting peristalsis. NE plays a crucial role in metabolic effects like stimulating glycogenolysis and gluconeogenesis and inducing ketogenesis and lipolysis [19, 20].

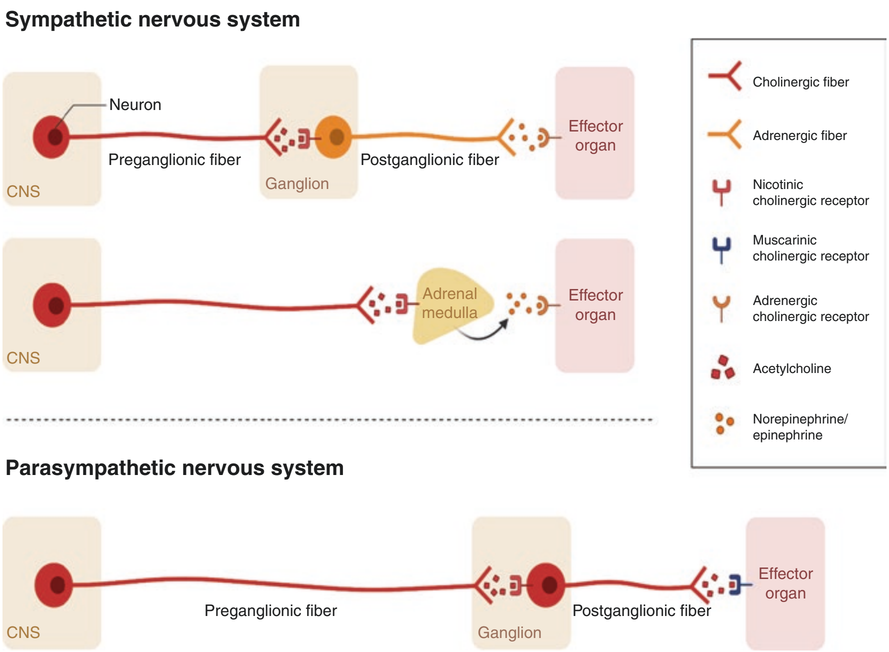


Fig. 9.2 Sympathetic and parasympathetic nervous system neurotransmitters

Norepinephrine Receptors

NE acts through alpha and beta receptors, which are α1, α2, β1, β2, β3 adrenoreceptors. The various types of α1 receptors include α1a, α1b, and α1d receptors, which are found in LC, amygdala, thalamus, cerebral cortex, olfactory bulb, and dentate gyrus. α1 receptors act through the Gq protein signaling pathway, and the receptor pathway is shown below in Fig. 9.3. NE receptor and their mechanism of action are shown below in Table 9.1 [21, 22].

Noradrenaline has an excitatory action through its post-synaptic α1 and β-adrenoreceptors and inhibitory action through presynaptic α2-adrenoreceptors [17]. α2-adrenoreceptor is commonly found in prefrontal cortical areas, and NE has the highest affinity and lower affinity for α1 and β-adrenoreceptors, respectively.

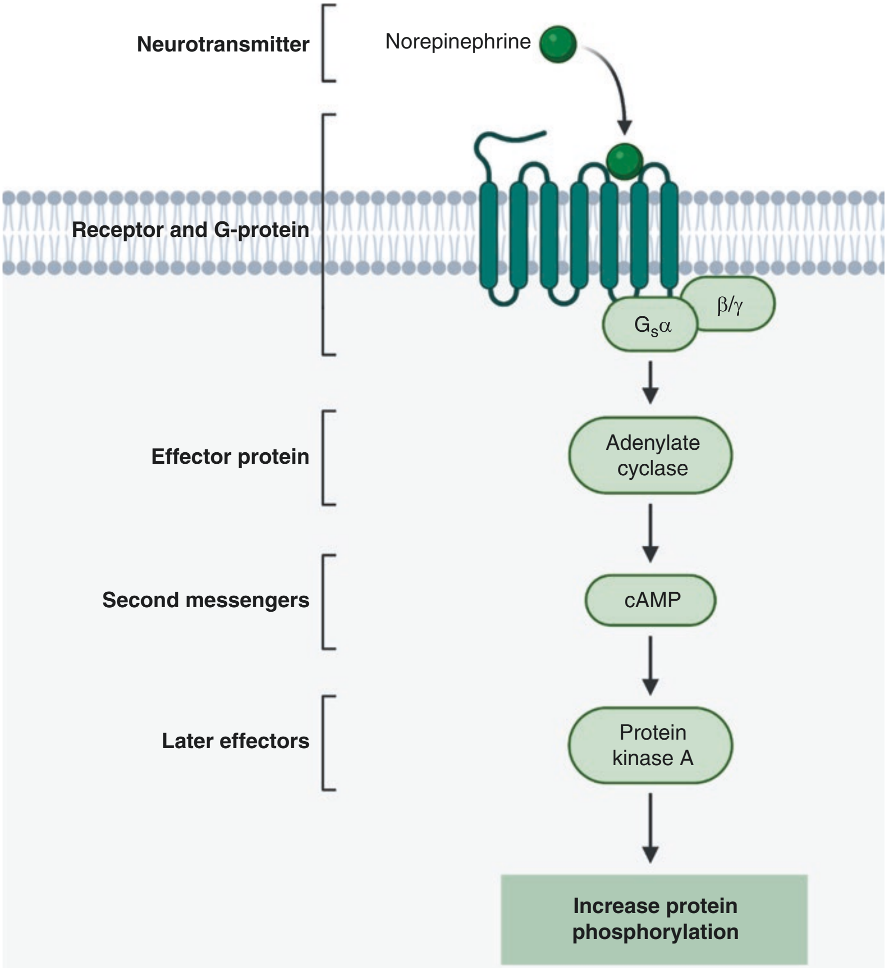


Fig. 9.3 Norepinephrine receptor pathway

Table 9.1 NE receptor, mechanism of action and their effects [21]

Receptors	Subunits	Mechanism	Effects
α-Receptor	α1—α1a, α1b, α1d	Phospholipase C is activated, that leads to the formation of IP3 and DAG—intracellular calcium ↑	Smooth muscle contraction, mydriasis
	α2—α2a, α2b, α2c	Adenylate cyclase is inactivated, which leads to a ↓ intracellular cAMP	Mixed smooth muscle effects
β-Receptor	β1	Adenylate cyclase is activated, and intracellular cAMP ↑	Increased cardiac chronotropic and inotropic effects
	β2	Adenylate cycle becomes activated through the Gs-protein-coupled receptors, ↑ intracellular cAMP. Gi protein-coupled receptors are also activated, and ↓ intracellular cAMP	Bronchodilation
	β3	Adenylate cyclase is activated, and intracellular cAMP ↑	Increased lipolysis

cAMP cyclic adenosine monophosphate, *DAG* diacylglycerol, *IP3* inositol triphosphate

Thus the distribution and relationship of adrenoreceptors are variable, with moderate levels of NE activating α2 receptors, while higher levels activate lower-affinity α1 and β-adrenoreceptors [23–25].

α1 and α2 receptors have been found to influence attention, fear, working memory, and spatial learning. β1 and β2 have been found to work on fear memory, auditory fear, memory retrieval, and spatial reference [18].

The stimulation or inhibition of these functions is dependent on the agonism or antagonism of the adrenergic receptors. The α1 and β-adrenoreceptors promote neurotransmission and plasticity, thus enhancing the stimulatory effects in the CNS. At the same time, α2 receptors have inhibitory effects in the CNS, like decreasing NE release and reducing neuronal excitability [18].

In the periphery, acetylcholine (Ach) stimulates the release of adrenaline and noradrenaline. Ach binds to nicotinic receptors on adrenal chromaffin cells that generate action potentials via voltage-gated sodium and potassium channels. Calcium influx into the cytosol leads to binding of NE vesicles to the cell membrane causing NE release into the blood [26].

NE is removed from the synaptic cleft through presynaptic reuptake. NE transporters (NET) are found on presynaptic terminals that mediate the NE reuptake that can either be stored in the vesicles or undergo degradation [18, 27].

Norepinephrine Metabolism

NE is a monoamine neurotransmitter, and the chemical structure of Norepinephrine is shown below in Fig. 9.4. Tyrosine is an aromatic amino acid that acts as a precursor for the synthesis of dihydroxyphenylalanine (DOPA) by the action of tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting enzyme in NE and dopamine

Fig. 9.4 Chemical structure of Norepinephrine

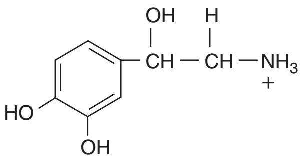
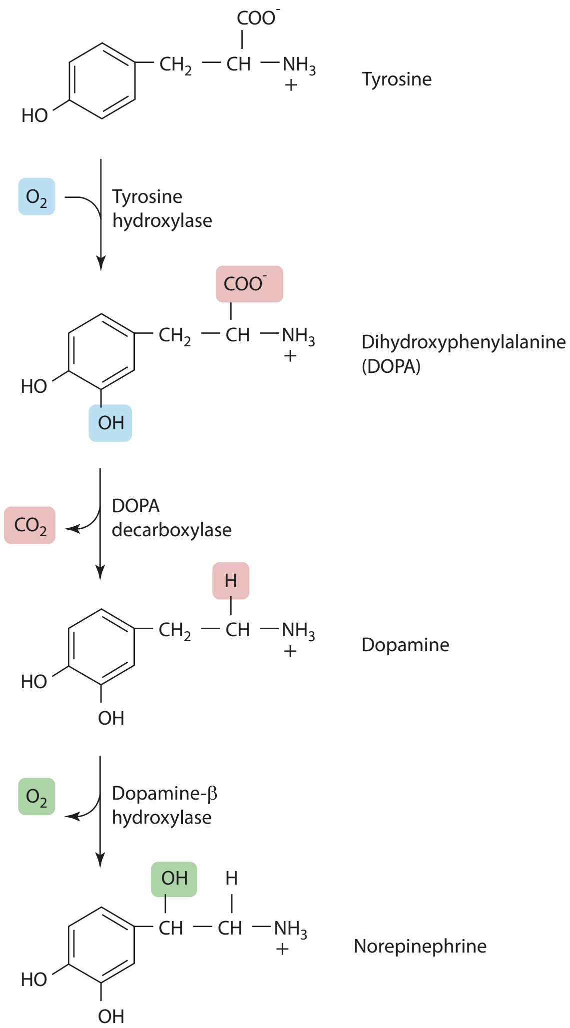


Fig. 9.5 Synthesis of Norepinephrine



synthesis. Dopamine is synthesized by the action of DOPA decarboxylase; dopamine is transported into vesicles through vesicular monoamine transporter (VMAT). Dopamine β hydroxylase (DBH) converts dopamine to NE. NE is converted to epinephrine via phenylethanolamine-*N*-methyltransferase, both in the CNS and adrenal medulla [2, 28]. The synthesis of NE is shown below in Fig. 9.5.

NE is degraded intracellularly or in the synaptic cleft by the enzymes monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT). MAO oxidizes norepinephrine, and COMT metabolizes deaminated norepinephrine by O-methylation. MAO and COMT are found in adrenal chromaffin cells, while sympathetic nerves have only MAO. MAO has two isoforms—MAO-A and MAO-B. MAO-A is mainly found in noradrenergic neurons, while MAO-B is found in serotonergic cells. COMT is found in all organs, and degradation of NE to vanillylmandelic acid (VMA), is completed in the liver [2, 7, 16, 29].

Medications Acting on the Norepinephrine System

Adrenergic drugs can bind to one or more of the receptors to produce physiological actions. Based on the specific receptor affinity, they are classified into selective or direct-acting drugs and nonselective or indirectly acting drugs [21]. Medications acting on the NE system are shown below in Table 9.2 [30]. Direct-acting drugs are bronchodilators, and vasopressors, while indirect-acting drugs are amphetamines, desipramine, atomoxetine, and phenelzine [31, 32].

Table 9.2 Medications acting on NE system [30]

Receptor	Drugs	Action	Indication
Agonists			
α1	Phenylephrine	Vasoconstriction	Hypotension and nasal congestion
α2	Clonidine Brimonidine	↓ Blood and intraocular pressure	Hypertension and glaucoma
β1	Dobutamine	↑ Cardiac output	Cardiogenic shock
β2	Albuterol, terbutaline, ritodrine	Relaxes smooth muscle in lung and uterus	Asthma and premature labor
Indirect acting	Amphetamine	CNS stimulant	Narcolepsy, hyperactivity
Indirect acting	Desipramine, atomoxetine	Blocks NE reuptake	Depression, ADHD
Indirect acting	Phenelzine	Inhibits NE metabolism by MAO	Depression
Antagonists			
α1	Prazosin, terazosin	Vasodilation	Hypertension, benign prostatic hypertrophy
α2	Mirtazapine	Antidepressant	Depression
B1, β2	Propranolol, timolol	↓ cardiac output and intraocular pressure	Hypertension, glaucoma, angina, migraine, tremors, and anxiety
B1	Atenolol, metoprolol	↓ Cardiac output	Hypertension

Selective Drugs

Alpha-1 Receptor Drugs

Phenylephrine, an alpha-1 receptor agonist, is commonly used as a decongestant and vasopressor in cases of hypotension due to septic shock. Another drug, oxymetazoline, is used as a decongestant and to treat rosacea. Common side effects include reflex bradycardia [33, 34].

Alpha-1 receptor antagonists like prazosin and terazosin are used in the treatment of hypertension and benign hypertrophy of the prostate because of their vasodilatory effect [30].

Alpha-2 Receptor Drugs

Clonidine, an alpha-2 receptor agonist, is used to treat hypertension and attention deficit hyperactivity disorder (ADHD). Nonapproved indications include post-traumatic stress disorder (PTSD), sleep disorders, anxiety, hot flashes associated with menopause, restless leg syndrome, and other illnesses. Methyldopa is a centrally acting sympatholytic and is used in the treatment of hypertension and gestational hypertension. It decreases the adrenergic outflow by alpha-2 agonistic action from CNS, thus reducing the total peripheral resistance and systemic blood pressure. As alpha-2 agonistic activity does not affect the cardiac output or renal blood flow, it is preferred in hypertensive patients with renal insufficiency. Dexmedetomidine is used in the intensive care unit for sedation, which does not induce respiratory depression. Common adverse effects of alpha-2 agonists include dry mouth, sedation, hypotension, respiratory depression, and somnolence [35, 36].

Alpha-2 receptor antagonists like mirtazapine are used as an antidepressant. It is a noradrenergic and specific serotonergic antidepressant, which acts by antagonizing both alpha-2 autoreceptors and heteroreceptors and also blocks the 5-HT2 and 5-HT3 receptors [30].

Beta-1 Receptor Drugs

Beta-1 receptors are commonly found in cardiac myocytes, cardiac nodal tissues, cardiac conduction pathways, and kidneys. Dobutamine is a beta-1 receptor agonist that is indicated in the treatment of cardiogenic shock and heart failure. Common side effects include hypertension, tachycardia, palpitations, anxiety, and tachyarrythmias [37, 38].

Beta-1 blockers: Cardio-selective blockers include atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol. They are clinically used for hypertension, heart failure, chronic stable angina, post-myocardial infarction, and decreased left ventricular function after myocardial infarction. They are also used in the treatment of arrhythmias, glaucoma, migraine prophylaxis, anxiety, and essential tremor [21, 39]. Common adverse effects include hypotension, bradycardia, heart failure, decreased exercise capacity, and atrioventricular nodal block. Noncardiac side effects include headache, fatigue, dizziness, nausea, vomiting, abdominal discomfort, dry mouth and eyes, sexual dysfunction, confusion, and memory loss.

Nonselective beta-1 blockers include propranolol, timolol, sotalol, and nadolol. Beta-1 blockade decreases heart rate, myocardial contractility by slowing AV conduction and suppresses automaticity. Beta-2 blockade reduces peripheral vascular resistance and can cause bronchospasm and hypoglycemia. Propranolol is used in hypertension, myocardial infarction, angina, idiopathic hypertrophic subaortic sclerosis, migraine, and vascular headaches. It also used for anxiety and in improving tremors by blocking the peripheral beta-2 adrenergic receptors. Common side effects include hypotension, bradycardia, dizziness, depression, memory loss, impotence, and rebound hypertension with sudden withdrawal. It is contraindicated in asthma, bradycardia, and heart failure [21, 40].

Beta-2 Receptor Drugs

Beta 2 receptors are commonly found in airway smooth muscles and cardiac muscles, uterine muscles, alveolar type II cells, mast cells, mucous glands, epithelial cells, vascular endothelium, eosinophils, lymphocytes, and skeletal muscles [41]. Short-acting Beta-2 agonists (SABAs) are albuterol, levalbuterol, metaproterenol, and terbutaline. Beta-2 agonists that act as bronchodilators are indicated for the treatment of obstructive lung diseases, such as COPD, asthma, or emphysema [41, 42].

Other uses of SABAs like albuterol are in the treatment of hyperkalemia, and terbutaline is used to postpone preterm labor and in the management of vascular extravasation. Long-acting B2 agonists (LABAs) are used in the maintenance treatment of patients with COPD, chronic bronchitis, and emphysema. Common LABAs include salmeterol, formoterol, and arformoterol. Olodaterol is an ultralong-acting beta-2 agonist used in the management of COPD and asthma [43, 44]. Adverse effects include anxiety, tachycardia, tremors, palpitations, nausea, vomiting, constipation, dizziness, and fatigue [37].

Beta-3 Receptor Drugs

Beta-3 receptors are located in the gallbladder, urinary bladder, and brown adipose tissue. They enhance lipolysis in adipose tissue and promote thermogenesis in skeletal muscle. They cause relaxation of the urinary bladder, thus preventing urination. Mirabegron is used in the treatment of overactive bladder (urinary incontinence, urinary frequency) [21].

Indirect Acting Agonists

Atomoxetine is a selective noradrenaline reuptake inhibitor, which is used as a first-line alternative when unresponsive to stimulants or in tic disorders that are aggravated by stimulants. As atomoxetine does not affect the dopamine level associated with motor activity, hence they do not worsen Tourette's or tics. As it has a sedative effect, the dose is split for the evening to improve sleep symptoms, and it has a 24-h duration of action that can take up to 4–6 weeks to see the clinical benefit [45, 46].

Nonselective Drugs

Norepinephrine is used for the treatment of shock and hypotension. Epinephrine (adrenaline) is used in the treatment of cardiac arrest, anaphylaxis, and croup, while dopamine is used in the treatment of hypotension, bradycardia, and cardiac arrest. Isoprenaline is used in treating bradycardia and heart block [40].

Carvedilol and labetalol are nonselective and have both beta-receptor and alpha-blocking activity. Beta-1 blockade decreases heart rate, myocardial contractility by slowing AV conduction and suppresses automaticity. Beta-2 blockade reduces peripheral vascular resistance and can cause bronchospasm and hypoglycemia. Alpha-1 receptor blockade causes arterial smooth muscle relaxation and vasodilatation. Carvedilol is used in hypertension and heart failure and reduces cardiovascular mortality after myocardial infarction. It is also used in the treatment of migraine and vascular headaches [21].

Other Clinical Aspects

LC neuronal loss is the most commonly seen early feature in many neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, and progressive supranuclear palsy.

Alzheimer's Disease

Alzheimer's disease is the most common neurodegenerative dementia that is characterized by progressive loss of memory and cognition. Although the disease pathology is considered multifactorial, the main factor might be the interaction between noradrenaline and acetylcholine. Proposed mechanisms of disease development and progression are tau protein hyperphosphorylation assembles into neurofibrillary tangles, which accumulate in LC, causing neurodegeneration and cell death. The rostral cortically projecting neurons are widely affected, leading to impaired cognition and dementia. Alzheimer's disease is seen as a cholinergic dysfunction due to nucleus basalis of Meynert (nbM) degeneration. However, there is a significant loss of LC neurons and is directly correlated with the severity of the disease. Other factors include decreased NE levels that affect the anti-inflammatory and neuroprotective effects within the CNS. Impaired transmission of NE within the hippocampus leads to hyperphosphorylated tau protein and noradrenergic axonal degeneration [47, 48].

In Alzheimer's disease pathogenesis, noradrenaline plays a crucial role as a neuroinflammatory moderator through microglial activation. Furthermore, it negatively affects the transcription of the inflammatory gene in microglia and astrocytes, which express adrenergic receptors [49].

Patients with Down's syndrome and Alzheimer's disease and patients with Down's syndrome who later on develop Alzheimer's disease have decreased levels of noradrenaline metabolites, which correlate with behavioral and psychological signs and symptoms of dementia [50, 51].

Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease and a movement disorder that is characterized by bradykinesia, rigidity, tremor, postural instability, and cognitive decline in late stages. Loss of the dopaminergic nigrostriatal neurons is the main neuropathological abnormality that underlies the motor symptoms of the disease. In addition to the dopaminergic system, the noradrenergic system is also involved in the impairment of cognitive and emotions seen in Parkinson's disease. The pathogenesis involves noradrenergic neuronal degeneration in LC and alpha-2 autoreceptor losing its protective effects on both noradrenergic and dopaminergic systems. Within LC, alpha-synuclein accumulates, leading to low NE levels and nigrostriatal pathway degeneration due to loss of NE neuroprotective effects [47].

Lewy body pathology is the unique feature of Parkinson's disease, which occurs commonly in substantia nigra pars compacta and LC, that is associated with cell loss. Furthermore, Lewy body pathology in substantia nigra is preceded by the pathology in LC, indicating the dysfunction of noradrenaline even before affecting the dopaminergic systems in Parkinson's disease [48, 52, 53].

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a neurobehavioral disorder characterized by inattention, hyperactivity, and impulsivity, affecting 8% to 12% of children worldwide [54, 55]. The proposed mechanism involved in ADHD is an imbalance in dopaminergic and noradrenergic systems metabolism and neurotransmission in the prefrontal cortex and other subcortical regions. The deficiency in phosphoinositide 3-kinase (PI3K-gamma) enzyme causes an imbalance in norepinephrine/dopamine ratio and synaptic plasticity dysregulation. Impaired NET function and prefrontal dysfunctional noradrenergic transmission is involved in inattention and hyperactivity [56].

For parents of preschool children, a parent training program (PTP) is recommended. For moderately severe symptoms of ADHD in school-age children, consider PTP for parents and cognitive behavioral therapy (CBT) or social skills training, while CBT should be considered for adolescents [46]. Stimulants are the first-line agents in their treatment because of their rapid onset of action, safety, and efficacy in both children and adolescents [56]. Methylphenidate is the first-line therapy with a response rate of 60–80%. Atomoxetine is used if the child is intolerant to methylphenidate or has tics and anxiety.

Schizophrenia

Schizophrenia is a chronic mental illness characterized by both positive and negative symptoms, which include inattention, delusions, hallucinations, blunted affect, and disorganized thoughts. Alterations in the signaling of the dopaminergic and glutaminergic system appear to be the main cause, and there is evidence of noradrenergic system involvement as increased NE levels in CSF and blood in patients with paranoia and elevated NE markers in the post-mortem of schizophrenic patients [47].

Noradrenergic drugs can either treat or worsen the symptoms of schizophrenia. Blockage of alpha-1 adrenoceptors decreases the positive symptoms, while alpha-2 adrenoceptors blockage has been found to decrease the negative and cognitive symptoms [57]. Clonidine, methyldopa, and propranolol reduce the positive symptoms in schizophrenia by reducing the NE transmission in the brain. Desipramine and methylphenidate are found to worsen positive symptoms by increasing NE levels [47].

Depression

Depression is a common disorder that affects thoughts, mood, cognition, and behavior. The most common clinical symptoms include depleted energy, sadness, guilt, hopelessness, impaired concentration, and suicidal ideality [58, 59]. NE levels are elevated among other biomolecules in the periphery. Tyrosine hydroxylase expression was found to be increased in the LC, and levels of urinary NE were also increased [60].

Acknowledgments All the pictures in this chapter were prepared using BioRender premium software. The tables were redrawn using information from the reference article mentioned alongside them.

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