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The role of dopamine and norepinephrine in CNS stimulant activity: A neuropharmacological review

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Abstract
In the brain, dopamine (DA) is a crucial neurotransmitter. It has been proved in several studies to regulate limbic and motor functioning. Cognitive abnormalities can result from selective lesions of dopaminergic neurons in rats or primates, according to experimental research. This is particularly true when the mesocorticolimbic component of the dopaminergic systems is changed. The trials' data also revealed notable changes in attentional processes, which begs the question of whether DA directly controls attention. Given that the frontal lobe and basal ganglia are the primary sites of dopaminergic impact, It has been suggested that cognitive deficiencies reflect changes in subcortical brain regions that are closely connected to cortical areas, rather than being solely due to a lack of dopaminergic transmission. Stimulant use disorders remain a significant public health concern, with no approved pharmacotherapies available. The monoamines dopamine (DA), serotonin (5-HT), and norepinephrine (NE) are all elevated at the synaptic level by stimulants. Although increased dopamine (DA) in the reward circuitry is the main cause of the pleasant effects of stimulants, DA stimulation by itself does not completely explain the rewarding qualities of stimulants. Arousal, attention, mood control, learning, memory, and the stress response are all functions of the noradrenergic system, which uses NE as its primary chemical messenger.

Keywords: Dopamine, norepinephrine, CNS stimulant, pharmacotherapy, clinical implications

1. Introduction
Cocaine and psychostimulants similar to amphetamines, such as methamphetamine and methylphenidate, influence arousal and lead to behavioral activation and reinforcing behaviors that carry a considerable risk of abuse [1]. Following the administration of a stimulant drug, there are temporary functional alterations in the brain that are thought to persist even after the drug or its metabolites are no longer present in the brain [2]. Recognizing the primary functional alterations caused by psychostimulants is essential for comprehending the subsequent homeostatic responses that account for the behavioral and subjective effects of drug consumption, which persist beyond the drug's presence in the brain [3]. Even though earlier research has provided substantial evidence that dopamine plays a crucial role in the rewarding effects of psychostimulants, the exact mechanisms by which psychostimulants alter dopamine-mediated transmission have yet to be fully elucidated. Uncovering into these processes will not only clarify the intricate mechanisms underlying psychostimulant addiction but also assist in the development of effective treatments to combat addiction to these substances [4].
The central noradrenergic and peripheral sympathetic pathways make up the noradrenergic system, which uses norepinephrine (NE) as its main chemical messenger [5]. It is essential for several brain processes, including learning, memory, emotion, arousal, attention, and stress response [6]. Norepinephrine (NE) has received minimal attention as a potential treatment option for stimulant addiction. Along with a better knowledge of the noradrenergic system's anatomical and functional complexities, new drugs that target NE via different pathways have surfaced in the past 20 years [7]. These developments sparked a resurgence of interest in developing drugs to treat stimulant addiction that target the noradrenergic system. Clinical studies to evaluate noradrenergic drugs as possible therapies for amphetamine addiction have just begun. The noradrenergic and dopaminergic systems will be briefly reviewed in this essay, along with the functions of dopamine (DA) and norepinephrine (NE) in the neurobiology of stimulants [8].

Neurotransmitters: Through many calculations, the nervous system interprets sensory data and regulates behavior. These calculations take place both inside and between cells, but the nervous system's extraordinary functional ability is derived from intercellular information processing involving intricate neural networks. Neurons are the primary cells that process information, and depending on their shape, location, connection, and chemistry, there are hundreds or even thousands of distinct cell kinds [9]. The average of 10 [11] neurons in the human brain establishes around 1,000 connections, or synapses, where communication with other neurons takes place, providing an indication of the brain's information processing capacity. Each cell has a very wide range of connections; the cerebellum's Purkinje cells may receive up to 100,000 interactions from input cells. There may be between 10 [14] and 10 [15] synaptic connections in the human brain overall. Only a tiny percentage of neurons in the neurological systems of higher animals directly regulate output cells, such as striated muscle, smooth muscle, or endocrine cells, or transduce sensory information. The large majority make up what Nauta referred to as the "great intermediate net," which is the foundation of the brain's remarkable processing capacity [10]. The intricate network of neurons that sit between input and output neurons serves as the foundation for a variety of processes, including the acquisition of intricate motor skills, cognition, emotion, "top down" behavioral control, and human abilities like language, poetry writing, and war planning. The development of therapeutic drugs intended to treat psychiatric and neurologic disorders, pain, and a variety of other ills depends heavily on neurotransmitter receptors and other proteins involved in neurotransmitter synthesis and inactivation. In addition, natural substances that mimic or interfere with the actions of neurotransmitters, such as cocaine, opiates, nicotine, ethyl alcohol, and LSD, have a significant impact on human behavior [9].

2. Role of dopamine: Synthesis

Tyrosine, an amino acid found in large quantities in dietary proteins, is typically considered the initial precursor in the production of dopamine. Furthermore, phenylalanine hydroxylase in the liver and tyrosine hydroxylase in dopamine neurons both contribute to the conversion of dietary phenylalanine to tyrosine. Both high-affinity and low-affinity amino acid transporters subsequently move the amino acid from the brain's extracellular fluid into dopaminergic neurons after a low-affinity amino acid transport system takes blood-borne tyrosine into the brain [10]. The rate-limiting step in dopamine production is often the conversion of tyrosine to dihydroxyphenylalanine (L-DOPA), which is facilitated by the cytosolic enzyme tyrosine hydroxylase once it has entered the neuron [11]. In most dopaminergic neurons, tyrosine availability has no effect on the rate of tyrosine hydroxylation *in vivo* under normal circumstances. However, tyrosine levels can affect the rate of conversion to L-DOPA when the enzyme is activated or in dopamine neuronal systems with a relatively high basal firing rate (e.g., dopamine neurons projecting to the medial prefrontal cortex).

Protein kinases and perhaps alternative splicing phosphorylate the regulatory domain to short-term activate tyrosine hydroxylase [12]. It is believed that the activated version of tyrosine hydroxylase efficiently lowers end-product inhibition because it has a greater Ki for dopamine and a lower Km for its pterin cofactor. It has been proposed that different isoforms of tyrosine hydroxylase may be found in different parts of the brain or expressed differently during development or disease. In primates, as opposed to rodents, different tyrosine hydroxylase mRNAs are produced via alternative mRNA splicing from a single primary transcript [13]. Since the enzyme dihydropteridine reductase helps convert the quinonoid dihydrobiopterine back to tetrahydrobiopterine, a vital cofactor for tyrosine hydroxylase, its activity is indirectly linked to dopamine production [14]. It's also critical to emphasize that the synthesis of tetrahydrobiopterine depends on the activity of GTP-cyclohydrolase-1, another enzyme. In the cytosol, an enzyme known as aromatic amino acid decarboxylase (AADC, dopa decarboxylase) transforms L-DOPA into dopamine. Under normal circumstances, the brain has very low quantities of L-DOPA because this enzyme decarboxylates it so strongly [15]. AADC does not use D-aromatic amino acids as substrates. D-amino oxidase can transform D-DOPA into 3,4 dihydroxyphenylpyruvic acid in the periphery. L-DOPA is the end result of the reaction between transaminase and 3,4-dihydroxyphenylpyruvic acid. However, because L-DOPA was linked to fewer adverse effects, racemic DOPA therapy was stopped. The main result of the enzymatic processes described above is dopamine, but these enzymes can also make other so-called trace amines, such phenylethylamine, albeit their functions are yet unclear. Additionally, there have been fresh indications that L-DOPA may function as a neurotransmitter or neuromodulator on its own [16].

3. Storage of dopamine

In dopaminergic neurons, the neurotransmitter is transferred from the cytoplasm to certain storage vesicles. At about 0.1 M, the amine concentration in this instance is 10±1000 times higher than that in the cytosol [17]. This reserpine-sensitive synaptic vesicular monoamine transporter is distinct from the cocaine-sensitive plasma membrane transporter present on the outer membrane of the dopamine neuron. Dopamine appears to be stored in dendrites in both smooth endoplasmic reticulum and classical vesicles, despite the fact that it may be generated and released from both dendrites and terminal regions [18].

4. Release of dopamine

When an action potential begins, a change in membrane protein conformation makes it possible for calcium ions to enter the cell, which is a critical part of the stimulus that promotes the fusing of vesicles with the neuronal membrane. Vesicles use the mechanism of exocytosis to release their soluble contents into the synapse. The amount of dopamine released seems to be influenced by the pattern and speed of neuronal ringing; the increased dopamine release in response to "burst-firing" is particularly noteworthy [19].

5. Reuptake of dopamine

The transporters (uptake mechanism) found in dopaminergic terminals are vital for stopping transmitter activity and preserving transmitter homeostasis [20]. Uptake is facilitated by a high-affinity membrane carrier that can transport dopamine in either direction, depending on the current concentration gradient. To recycle dopamine released into the synaptic cleft, the transporter normally actively pumps

extracellular dopamine back into the nerve terminal [21]. According to estimates, the transporter can concentrate dopamine 100-1000 times. Currently, specialized ligands and antibodies for the dopamine plasma membrane transporter are probably the most selective markers for dopamine neurons. In addition to dopamine being taken up by dopamine neurons, glia and non-dopaminergic neurons may also absorb and metabolize extracellular dopamine to a limited extent [22].

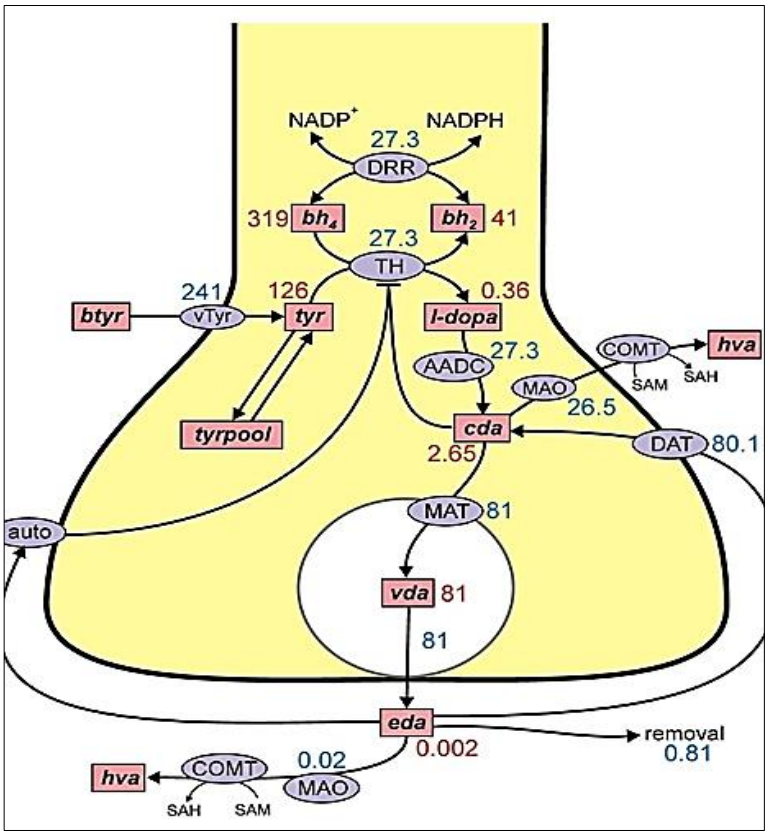

Fig 1: dopamine synthesis, release and reuptake.

6. Regulation of dopamine release

the reliance on dopamine D2 auto receptors, striatal acetylcholine, and action potential firing. These parameters have one thing in common: they significantly alter the dopamine vesicle fusion step's effectiveness. However, the basic molecular processes are still unknown. Action potentials strongly stimulate dopamine release. Using reverse dialysis of tetrodotoxin in the striatum to stop action potential firing during microdialysis reduces extracellular dopamine levels by about 70%. But the quantity of dopamine released by each action potential varies. Short-term plasticity is a key illustration of this: dopamine neuron release is severely suppressed during a brief action potential train because of the high initial release 220 probability, and the depression lasts for tens of seconds after firing. Long periods of quiescence prior to action potential firing are probably positively connected with the quantity of dopamine produced by an action potential, and the tonic firing of dopamine neurons at 0.2-10 Hz suggests that dopamine neurons are depleted [23]. Dopamine release can occasionally occur without the firing of somatic action potentials. Independent of ascending action potentials from midbrain dopamine neuron somata, stimulation of β2-containing nAChRs located on dopamine axons significantly triggers dopamine release. The tonically firing striatal cholinergic interneurons may have a significant impact on dopamine signaling [24]. Another example that may be connected is reward expectancy, which occurs when striatal dopamine levels progressively rise without an increase in dopamine cell activity [25]. Therefore, it will be critical to discover and evaluate the functions of local striatal processes in dopamine signalling, as these mechanisms cause increases in extracellular dopamine independent of somatic dopamine neuron action potentials [26]. Additionally, not all action potentials from somatic dopamine neurons may reach the dopamine varicosities. Axons of dopamine are widely arborized and unmyelinated. Because it necessitates activating membrane conductance over broad axonal surfaces, action potential propagation is expensive, and modelling suggests that propagation failures may be frequent in these intricate axons. A recent study showed that shunting can block action potential propagation when potassium conductance is open in a specific area [27]. The Gi-coupled D2 autoreceptors expressed by dopamine axons are responsive to both phasic and tonic dopamine. Dopamine synthesis is inhibited, dopamine uptake is increased, and VMAT2 expression is regulated when these autoreceptors are activated [28]. D2 receptors and GIRK potassium channels are connected at the soma, and dopamine neuron firing is inhibited when these channels are activated [29]. It's intriguing to wonder if activating D2 receptors and other axonal GPCRs can directly control elements of the active zone, such as dopamine release sites. These locations would be predestined as molecular substrates for regulation since dopamine release necessitates them and a number of active zone proteins are controlled by GPCR signalling, for instance through protein kinase. Alternatively, or in addition to controlling particular sites, it may be possible to control the total number of axonal release sites [30]. Since only around 30% of dopamine vesicle clusters are linked to secretory sites at baseline, this might be a very effective method of regulating dopamine release [31].

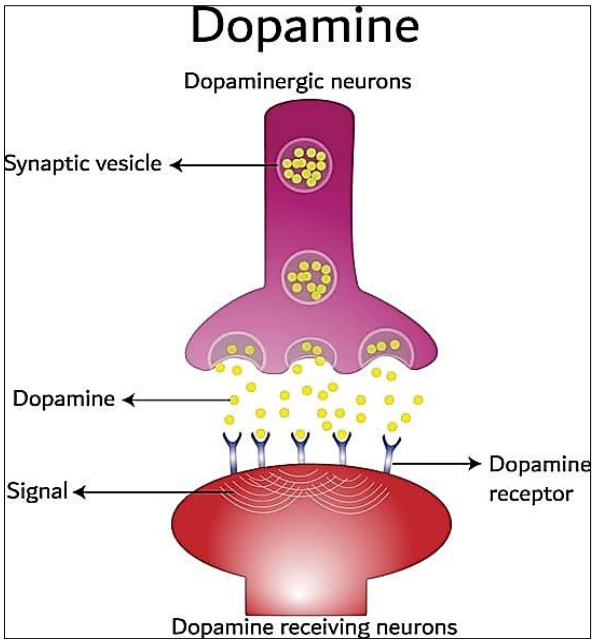

Fig 2: Dopamine release

7. Different pathways of dopamine

The brain's dopaminergic system is divided into three main pathways:

Nigro-stiatal pathway: Fibers from the substantia nigra (pars compacta) project rostrally to become broadly dispersed throughout the basal ganglia (caudate nucleus and putamen) through the nigro-stiatal Pathway. Dopamine has a major role in movement (the regulation of motor function and the acquisition of new motor abilities) in this route. Parkinson's disease is brought on by nigrostriatal system degeneration. This region's pars compact division contains dopamine cell bodies that affect motor control by sending ascending projections to the dorsal striatum, particularly to the caudate and putamen. Antipsychotic medications' extrapyramidal effects are believed to be caused by blocking these striatal dopamine receptors [32].

Mesolimbic pathway: The mesolimbic pathway is where dopaminergic projections begin in the ventral tegmental region and go to the pyriform cortex, amygdala, nucleus accumbens, lateral septal nuclei, and other areas. Dopamine is important for the brain's reward and emotion systems. In particular, pleasure is controlled by the mesolimbic dopamine pathway. It is released under enjoyable circumstances and encourages one to pursue enjoyable hobbies or careers. Furthermore, dopamine is a key player in this route of addictions. Drug addiction is believed to be caused by plastic alterations in the mesolimbic pathway, which is activated by all known drugs of abuse [33].

Mesocortical pathways: Dopaminergic fibers in the Mesocortical Pathway extend to the frontal cortex and septohippocampal areas from the A10 region, which is also called the ventral tegmental area. Emotional and cognitive behaviors are influenced by mesocortical dopamine. The levels of dopamine in the brain, especially in the prefrontal cortex, play a crucial role in enhancing our working memory and focus. This is a fine balance, though, as memory deteriorates when levels rise or fall to abnormal levels. Antipsychotic medications exacerbate negative symptoms of schizophrenia by inhibiting the mesocortical pathway's dopamine receptors [34].

8. Dopamine receptors

Table 1: summary of dopamine receptors, locations and functions [35].

Receptors	Locations	Functions
D1	It is abundant in the mesolimbic, nigrostriatal, and mesocortical regions, including the striatum, caudate, putamen, nucleus accumbens, olfactory bulb, and substancia nigra. Low amounts are found in the kidney, thalamus, hypothalamus, hippocampus, and cerebellum.	Regulations of voluntary movements, growth and development, nutrition, emotion, attention, reward, sleep, impulse control, reproductive behaviors, working memory, learning, and kidney rennin control.
D2	The olfactory bulb, substantia nigra, cuadate, putamen, nucleus accumbens, and ventral tagemental area (VTA) all have high levels. The hypothalamus, septum, kidney, heart, blood arteries, sympathetic ganglia, gastrointestinal tract, and adrenal glands all have low amounts.	Working memory, reward-motivation processes, blood pressure, renal function, gastrointestinal motility, vasodilatations, and locomotion are all regulated by these systems. Presynaptic receptors prevent movement, whereas post-synaptic receptors stimulate it.
D3	This is expressed solely within the central nervous system (CNS), specifically located in the nucleus accumbens of the olfactory bulb.	Taking part in the modulation of endocrine function, thoughts, emotions, and movement control.
D4	The lowest dopamine receptors in the central nervous system can be found in several key areas, including the thalamus, hypothalamus, kidneys, frontal cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia, globus pallidus,	Blood pressure, vasodilation, gastrointestinal motility, renal function regulation, and cognitive function modulation.

	hippocampus, amygdala, and substantia nigra.	
D5	substantia nigra, hypothalamus, hippocampus, dental gyrus, kidney, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia.	Engaged in the pain process, emotional functions, and the hormonal roles of dopamine.

9. Clinical implication of dopamine

Role in addiction: Dopamine plays a key role in drug addiction by significantly impacting the brain's reward system. Drugs of abuse trigger massive surges of dopamine, leading to feelings of intense pleasure and reinforcing the desire to repeat drug use. This process, coupled with the brain's adaptation to reduced dopamine response, drives compulsive drug seeking behaviour, even when the initial pleasurable effects diminish [36]. Drugs of abuse hijack the brain's natural reward system, which is primarily driven by dopamine. This system reinforces behaviours essential for survival, like eating and socializing, by releasing dopamine when these activities are performed [37]. Drugs however cause a much rapid surge of dopamine, creating a powerful sense of pleasure and motivating the individual to repeat the drug-taking behaviour. The intense dopamine surge associated with drug use reinforces the connection between the drug, the pleasure experiences, and the cues surrounding that experiences. Even after the immediate effects of the drug have worn off, these signals can cause strong cravings because they are linked to its rewarding benefits. This learning effects contributes to the progress of habits and compulsions related to drug use [38]. When the brain is repeatedly exposed to drugs, it starts to adapt in some pretty significant ways. This includes a decrease in the number of dopamine receptors and a reduced ability for dopamine to trigger the reward system. This leads to tolerance, meaning that a person has to consume more of the drug to feel the same pleasurable effects. Long-term drug use can really mess with the brain's ability to feel pleasure from things that usually bring joy, like enjoying a good meal, having sex, or connecting with friends. This happens because the brain's reward system becomes less responsive to these natural rewards [39]. Dopamine is also implicated in the motivational aspects of drug use, particularly in the experience of craving. Even in the absence of the drug's immediate effects, conditioned stimuli linked to drug use can stimulate dopamine secretion and create strong cravings to seek the substance. This can leads to compulsive drug-seeking behaviour, where the individual prioritizes drug use over other important goals and activities. Loss of control over drug usage and compulsive drug-taking behavior can result from alterations in the brain's reward system and other brain areas, including the prefrontal cortex, which is involved in decision-making and impulse control. These adaptations can also affect learning, judgment, memory, and stress responses [40].

Role in ADHD: Neuronal motor control, cognition, emotion, vascular function, and event prediction are all significantly influenced by DA. Dysfunction of the brain's dopaminergic system has been implicated in several neuropsychological conditions, including Parkinson's disease, Tourette's syndrome, ADHD, addiction, and schizophrenia [41]. Chromosome 5q35.1 contains the dopamine D1 receptor gene (DRD1). It is the most predominant subtype in the brain and couples with heterotrimeric G proteins Gs and Gq to regulate phosphoinositide hydrolysis and adenylyl cyclase activation. Due to the high expression of DRD1 in the striatum and prefrontal cortex (PFC), a number of neuropsychological investigations indicate that PFC dysfunction may be largely responsible for the basic challenges of ADHD, and those with impaired PFC exhibit behaviors similar to those of ADHD [42]. The PFC's D1 receptor is found in both pyramidal neurons and GABAergic interneurons, forming a feedforward inhibition microcircuit to control working memory, which is closely linked to attention and significantly compromised in ADHD patients [43]. In an attempt to explore the relationship between ADHD and these genetic variations, several population studies looked at DRD1 genetic variations, including single nucleotide polymorphisms (SNPs) in D1.7 maker (rs686) located in the 3′-untranslated region, D1P.6 maker (rs265981) located in the 5′-untranslated region, and D1P.5 maker (−1251 G/C) located ~0.2 kb upstream of one of two promoter regions. Every result came back negative [44].

The final cloned DA receptor is the dopamine D5 receptor gene (DRD5), which is located on chromosome 4p15.3. Large aspiny neurons in the neostriatum of monkeys, which are normally cholinergic interneurons, only express D5 receptors at the cellular level [45]. D5 receptors can be found in various parts of the neuron, particularly in the proximal dendrites and the cell body, or perikarya. They also appear here and there in the neuropil of the olfactory bulb, cerebral cortex, superior colliculus, and the molecular layer of the cerebellum. D5 DAR is functionally linked to adenylate cyclase activation and interacts with Gamma-aminobutyric acid receptor subunit Gamma-2 (GABRG2), indicating that it may modify GABAA receptor-mediated activity via direct receptor-receptor interaction as well as second messenger pathways [46]. Clewing its inhibitory influence on locomotion, D5R-absent mice exhibit more exploratory activity and lower baseline locomotor exploration activity compared to their broad type littermates. The D5 receptor has been linked to regulating hypothalamus activity based on antisense oligonucleotide research and some types of motor control [47].

The dopamine D2 receptor gene, located on chromosome 11q23.1, undergoes alternative splicing to produce two distinct transcript variants encoding the D2L and D2S isoforms. Research has shown that deletion of the DRD2 polymorphism leads to increased locomotor hyperactivity and a significant rise in reward-seeking behavior in a mouse model of ADHD. Additionally, carriers of the DRD2 A1 allele exhibit significantly reduced glucose metabolism in several brain regions including the putamen, temporal, frontal, central, prefrontal, orbital, and occipitotemporal cortices as revealed by positron emission tomography (PET) analysis using fluorodeoxyglucose [48].

Chromosome 3q13.3 contains the dopamine D3 receptor gene, which, in the right expression systems, couples to Gi/Go to inhibit adenylyl cyclase. D3 receptors are primarily involved in incentive-based learning and the reward system of addictive behaviors. D3 receptors, which control DA-related prefrontal neurocognition, have been linked to impulsive personality and addictive behaviors, which are key characteristics of adult obesity and ADHD. Additionally, there is a wealth of data supporting the D3 receptor's inhibitory influence on motor response.

Furthermore, anatomical research revealed that the D3 receptor plays a part in motivation and motor behavior. Its placement in the ventral striatum suggests that it may be able to control movement more so than attention. Limbic distribution also played a role in emotion regulation and motivation. In particular, there was a clear and substantial correlation between DRD3 and ADHD in a study of the Chinese Han population, and a subsequent investigation similarly found a connection between DRD3 and the emergence of hyperactive/impulsive symptoms of ADHD [49].

10. Role of norepinephrine: Synthesis

Norepinephrine is a catecholamine neurotransmitter and hormone synthesized primarily in neurons of the sympathetic nervous system and adrenal medulla. It is produced via a sequence of enzymatic processes from the amino acid tyrosine. Tyrosine is obtained from the diet or synthesized from phenylalanine, is transported into the neuron's cytoplasam. The enzyme tyrosine hydroxylase transforms tyrosine into L-DOPA. Since it is the slowest stage and controls the total synthesis rate, it is known as the rate limiting step. The enzyme DOPA decarboxylase then decarboxylates L-DOPA to produce dopamine [50].

11. Storage and release of norepinephrine

Norepinephrine is stored in small, specialized vesicles located at the axon terminals of neurons. The vesicular monoamine transporter (VMAT) plays a key role by actively transporting norepinephrine into these vesicles. When a nerve impulse also known as an action potential arrives, it triggers the vesicles to fuse with the cell membrane, releasing their contents into the synaptic cleft, the gap between neurons [51]. Once released, norepinephrine diffuses across the synapse and binds to specific receptors on the postsynaptic neurons, triggering a response. Afterward, it can either be reabsorbed by the presynaptic neurons or broken down by enzymes such as monoamine oxidase (MAO) [52].

12. Regulation of norepinephrine release

Norepinephrine release is regulated through a complex interplay of presynaptic mechanisms, as well as enzymatic pathways and neuronal activity.

Autoreceptors: These α2-adrenergic autoreceptors can be found on the presynaptic neuron, typically at the axon terminals. When norepinephrine is released into the synaptic cleft, a portion of it attaches to these presynaptic α2-adrenergic autoreceptors. This binding triggers G-protein-coupled signaling pathways, ultimately leading to a reduction in calcium influx and inhibition of further norepinephrine release. By acting as a negative feedback mechanism, it prevents excessive norepinephrine release. This autoregulation protects postsynaptic targets from overstimulation and helps maintain homeostasis. It represents a crucial mechanism for regulating noradrenergic transmission [53].

Heteroreceptors: Through presynaptic heteroreceptors, other neurotransmitters such as dopamine, serotonin, and acetylcholine can influence the release of norepinephrine. These neurotransmitters can either inhibit or promote norepinephrine release by binding to their corresponding heteroreceptors on the presynaptic terminal. This heteroreceptor-mediated control enables cross-talk between neurotransmitter systems, allowing for complex modulation of noradrenergic activity. Such modulation may be essential for integrating inputs across multiple brain regions and systems [54].

Calcium-dependent release

When an action potential reaches the presynaptic terminal of a noradrenergic neuron, voltage-gated calcium channels open. Calcium ions flow into the presynaptic terminal, increasing the intercellular calcium concentration. The increase in calcium causes norepinephrine-containing vesicles to fuse with the presynaptic membrane, resulting in the exocytosis of norepinephrine into the synaptic cleft. Proteins like synaptotagmin act as calcium sensors, detecting the calcium increase and initiating the vesicle fusion process. The rate of norepinephrine released is directly proportional to the amount of calcium-dependent release a key point for regulating the strength of noradrenergic transmission [55].

Reuptake mechanism

The norepinephrine transporter (NET) returns norepinephrine to the presynaptic neuron after it has been released into the synaptic cleft. This sodium-dependent transporter reabsorbs norepinephrine in combination with sodium and chloride ions. The reuptake mechanism quickly terminates the signal and limits the duration of norepinephrine's action on postsynaptic receptors. Once back in the presynaptic neuron, norepinephrine can either be broken down by enzymes such as monoamine oxidase (MAO) or packaged into vesicles for later release [56].

13. Norepinephrine receptors

The α1, α2, and β families of adrenergic receptors influence the effects of NE. Most members of the α1-adrenergic family are excitatory and postsynaptic. Gq proteins mediate vascular smooth muscle contraction and elevate blood pressure by linking α_1-adrenergic receptors to phospholipase C and phosphoinositide second messenger pathways. α_1 receptors are found in both neurons and glial cells in the central nervous system and are associated with motor control, fear, memory, and learning [57]. Both pre- and post-synaptically, the α2-adrenergic family's α2A, α2B, and α2C subtypes are present. Alpha2-adrenergic receptors are linked by Gi/o proteins to the second messenger adenylate cyclase, which alters the amounts of cyclic adenosine monophosphate (cAMP) [58]. Among the many actions of alpha2A receptors are drowsiness, hypothermia, analgesia, and regulation of noradrenergic activity. Alpha2B receptors mediate vascular contraction [59]. Although its exact role is unknown, α2C receptors may have an impact on memory, mood, and motor behavior. β1, β2, and β3 beta-adrenergic receptors are Gs-coupled to adenylate cyclase. Increased cardiac contractility and heart rate are the results of activating β1-adrenergic receptors. Vasodilation and bronchial relaxation are encouraged by activating smooth muscle's β2-adrenergic receptors. Although their functions are unclear, these receptor subtypes are also found in the brain [60].

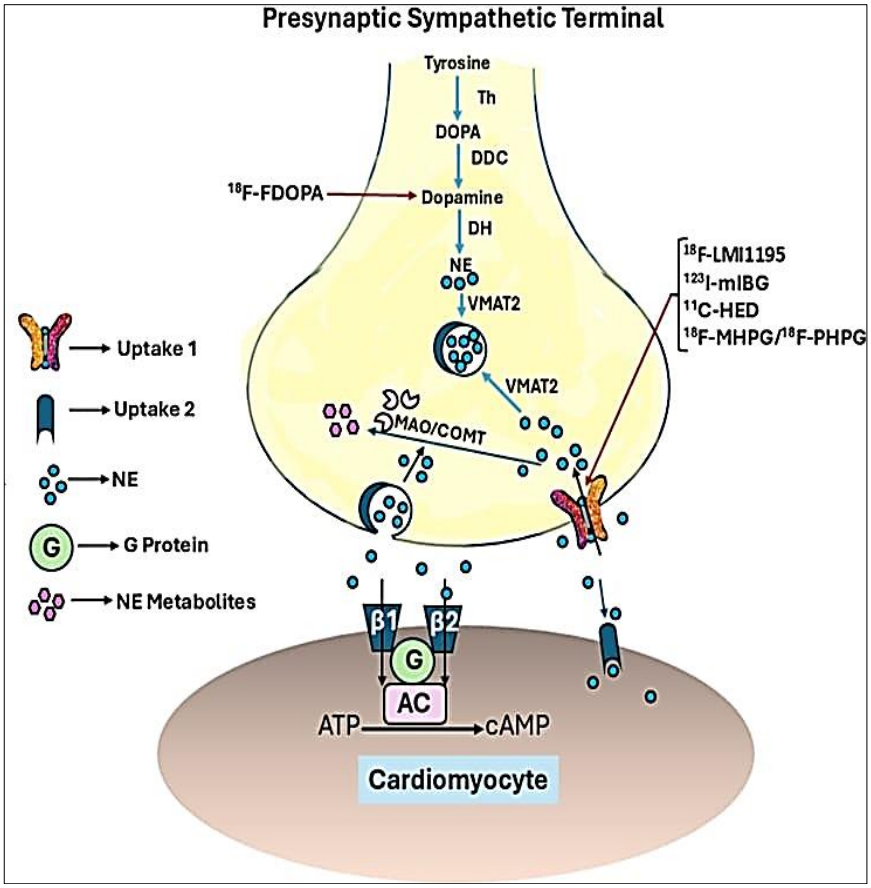

Fig 3: Norepinephrine synthesis, release and reuptake.

14. Mechanism of CNS stimulants

Cocaine: It binds firmly to the dopamine transporter (DAT) and blocks it, causing dopamine to accumulate in the synapse and prolonging and intensifying the activation of dopamine receptors on the nearby cell [61]. A key brain circuit that regulates motivation, reinforcement, and pleasure is the mesolimbic dopamine system, also known as the reward pathway. Strong sensations of euphoria and pleasure are produced when dopamine levels significantly increase in regions such as the nucleus accumbens. Cocaine elevates norepinephrine levels and contributes to its sympathomimetic effects by blocking the norepinephrine transporter (NET) [62].

Amphetamine: Similar to other catecholamines, amphetamine enters presynaptic nerve terminals through a transport mechanism involving one chloride ion and two sodium ions. Amphetamine-ion complexes are actively transported by monoamine reuptake transporters. The more amphetamine present, the more it is taken up, as it competes with endogenous monoamines. As amphetamine enters the presynaptic terminal, it disrupts vesicular monoamine transporter 2 (VMAT2) function, displacing other monoamines and allowing neurotransmitters to be released into the synapse through a process known as reverse transport [63]. In the d-isomer, this neurotransmitter-releasing pathway is approximately four times more efficient at releasing dopamine. The inhibition of reuptake and monoamine oxidase complements amphetamine's mechanism of action, resulting in a significant increase in monoamine levels. Amphetamine is a weak dopamine reuptake inhibitor, a moderate noradrenaline reuptake inhibitor, and a very weak serotonin reuptake inhibitor because of its competitive substrate rather than inhibitory action. This particular activity indicates that the l-isomer is significantly weaker. Lastly, it is known that amphetamine inhibits the mitochondrial enzyme MAO, which breaks down any excess neurotransmitters. Since amphetamine is a weak MAO inhibitor, this mode of action is usually disregarded, although it cannot be ruled out [64].

Caffeine: It is a methylxanthine derivative, caffeine is structurally similar to adenosine, competitively binds to these receptors without activating them, effectively blocking adenosine from exerting its inhibitory effects. Thia blockade leads to increased neurotramitters, including norepinephrine, dopamine, acetylcholine, serotonin, and glutamate, all of which play roles in arousal, alertness, mood and coagnitive function. Caffeine is aweak inhibitor of phosphodiesterase enzymes, which are responsible for breaking down cyclic adenosine monophosphate (cAMP). At higher doses this inhibition leads to increased intracellular cAMP levels, which can trigger various physiological responses including increased alertness and neurotransmitter release [65].

15 Clinical implications

Role in addiction: Additionally, norepinephrine is important in drug addiction, especially when it comes to stress-induced relapse and withdrawal symptoms. Stress is a major cause of relapse in those in recovery from addiction, and NE plays a significant role in the body's stress response. Under stressful conditions, NE release is increased, which can activate reward and craving-related brain areas and cause a relapse. Medications that target NE receptors, like α2-adrenergic agonists, have shown promise in reducing stress-induced drug cravings and relapse. During withdrawal

from many drugs of abuse, NE levels tend to be elevated. This heightened NE activity contributes to the unpleasant physical and psychological symptoms of withdrawal, such as anxiety, tremors, and increased heart rate [66]. Medications that lowers NE activity, such as α2-adrenergic agonists (like clonidine) or α1-adrenergic antagonists, can help alleviate these withdrawal symptoms. NE involved in reinforcing effects of drugs and reinstatement of drug-seeking behaviour. For example, NE has been implicated in drug sensitization, discrimination, and the resumption of drug-seeking following a period of abstinence in animal models. Further altering drug-seeking behavior, norepinephrine can alter dopamine release in reward and motivation-related brain areas. NE interacts with other neurotransmitters, particularly dopamine and serotonin, in the brain. This interplay influences the reward response, salience of drug-related cues, and the development of compulsive drug-seeking behaviours. Dysregulation of NE can exacerbate cravings, stress responses, and the likelihood of relapse. The involvement of NE in addiction makes it a potential target for therapeutic interventions. Medications that modulate NE signaling, such as α1-adrenergic antagonists or α2-adrenergic agonists, are being explored as potential treatments for various substance use disorders [67].

Role in ADHD: The PFC's capacity for working memory is strongly impacted by the quantity of catecholamines it secretes. Abnormal catecholamine receptor activation causes unique modifications in the PFC's cognitive functions. Maintaining healthy prefrontal cortical activities requires a moderate level of NE. NE enhances PFC function by specifically acting on α2 A receptors found on postsynaptic to NE terminals. Tonic and phasic arousal, generalized awareness, and the activation of acute responses like startle reaction to abrupt environmental changes are all regulated by NE. It also plays a part in carrying out essential components of learning, thinking, and problem-solving. These activities are mediated by α1 and β1 receptors, and an excess of NE impairs prefrontal functioning. Working memory and attention control are changed when NE levels are low overall or in the PFC. Since the NE transporter (NET) protein is involved in the reuptake of NE, its presence also affects the strength and duration of signal transduction mediated by NE. A disrupted level of NE is frequently the result of abnormalities in NET functioning, which are frequently linked to ADHD [68].

Conclusion

The important roles that dopamine and norepinephrine play in CNS stimulant action, as well as their clinical implications in ADHD and drug addiction, have been emphasized in this study. The CNS-stimulating properties of numerous pharmaceutical drugs depend heavily on dopamine and norepinephrine. These neurotransmitters modulate key processes like reward, motivation, arousal, and locomotion. CNS stimulants such as amphetamines, methylphenidate, and modafinil exert their effects primarily by enhancing the synaptic availability of dopamine and norepinephrine, thereby increasing neural excitability and improving cognitive and behavioural performance. Elevated dopaminergic and noradrenergic activity underlying the stimulants' propensity for misuse and negative consequences, even though it also helps them treat diseases like ADHD and narcolepsy. Developing safer and more targeted stimulant-based medications requires an understanding of the complex interactions between dopamine and norepinephrine circuits. To maximize therapeutic outcomes and minimize the risks associated with CNS stimulant use, future research should focus on deepening our understanding of these pathways.

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