ROLE OF DOPAMINE

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ABSTRACT

Dopamine belongs to the category of catecholamines which is synthesized from the highly essential amino acid Tyrosine. It is a catecholamine neurotransmitter found predominately in the central nervous system. Dopamine have several mechanisms in the human body due to which our stress, voluntary movements, attention hyperactivity, reward seeking process are being controlled. Dopamines have in all five different receptors which carries a certain pathways and functions in the brain.The defects in one of these pathways may leads to fatal disesase such as Parkinson, schizophrenia, disturbance in movement control which are explained further. They play several functions in the human body such as regulating prolactin secretion, learning process, movement, pleasure , reinforcement etc. If there is any abnormality in the secretion of the dopamine can results in the false functioning of the above mentioned functions.

Key words: *Dopamine, Neurotransmitter, Parkinson's disease, Neuroendocrine signaling.*

Introduction

Dopamine (abbreviated as DA), a simple organic chemical in the catecholamine family, is a monoamine neurotransmitter which plays a number of important physiological roles in the bodies of animals. In addition to being a catecholamine and a monoamine, dopamine may be classified as a substituted phenethylamine. Its name derives from its chemical structure, which consists of an amine group (NH_2) linked to a catechol structure called dihydroxyphenethylamine, the decarboxylated form of dihydroxyphenylalanine (acronym DOPA)

- Dopamine is a catecholamine neurotransmitter found predominately in the central nervous system. It is synthesized from the amino acid tyrosine, which is converted to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. Dihydroxyphenylalanine is converted to dopamine by the enzyme DOPA decarboxylase (or aromatic amino acid decarboxylase) which is found in the cytoplasm.

Dopamine is found in three major pathways in the central nervous system. A dopamine projection from the hypothalamus plays an important role in the regulation of prolactin release from the pituitary gland. Dopamine also is synthesized by neurons in the ventral tegmental area, which projects to the prefrontal cortex and the basal forebrain, including the nucleus accumbens. Another important dopamine pathway is from the substantia nigra pars compacta to the neostriatum.

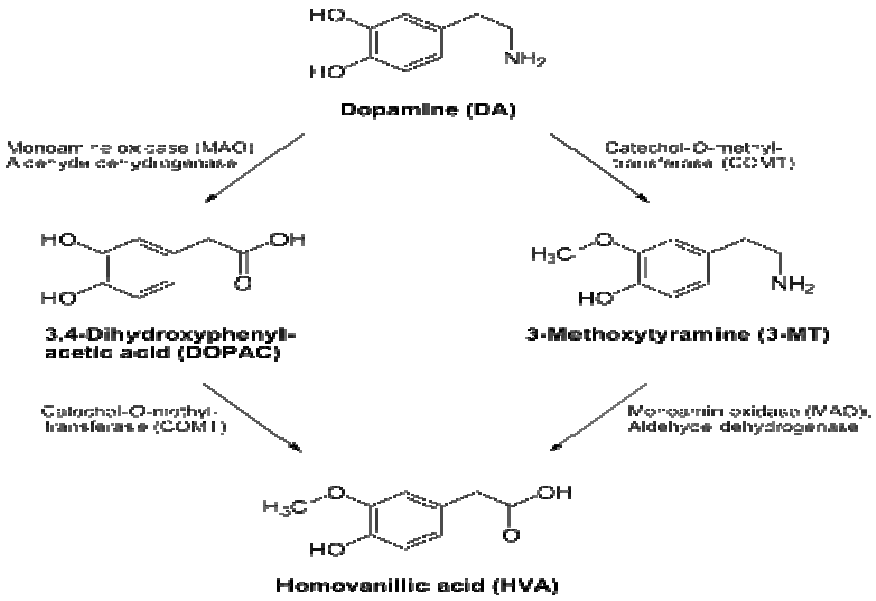


Fig.1.1 Structure of dopamine

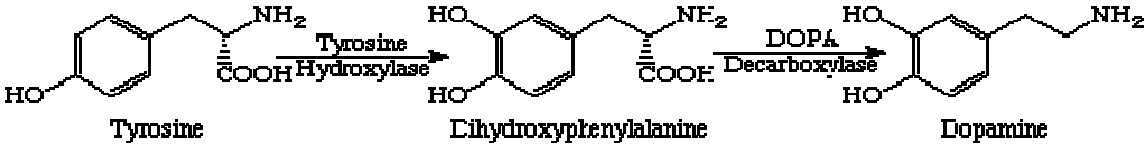


Fig.no. 1.2 Synthesis of dopamine

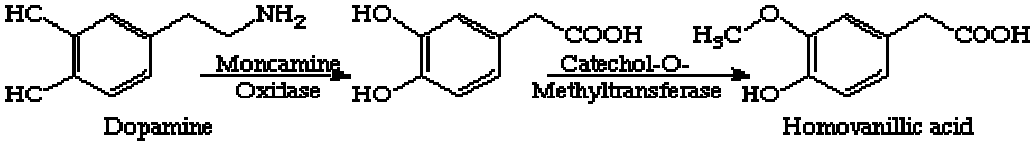


Fig.no.1.3 Dopamine synthesize Homovanillic acid

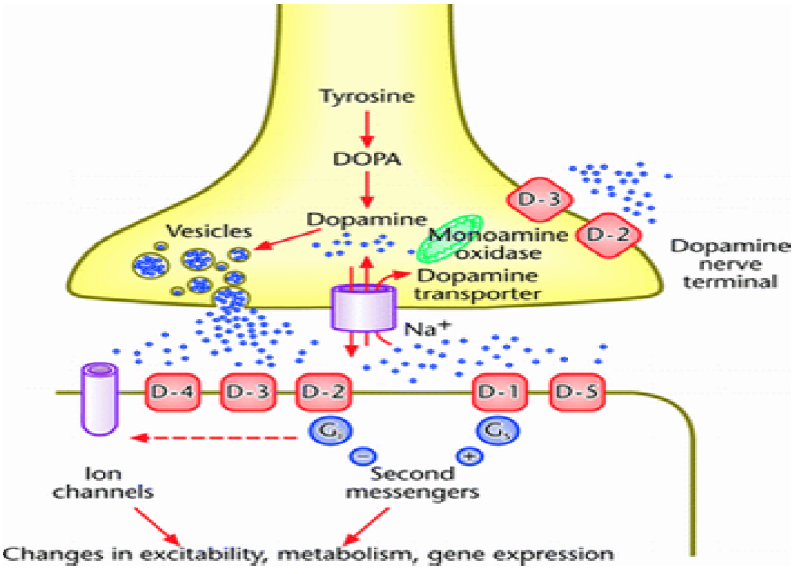


Fig.no.1.4 Synthesis of dopamine from tyrosine

Dopamine can be further metabolized to norepinephrine by the enzyme dopamine-hydroxylase, in neurons containing the enzyme. Catecholamines can be taken back up into neurons after release via the dopamine transporter, or metabolized by monoamine oxidase (to 3,4,-dihydroxyphenylacetic acid) or catechol-O-methyltransferase (to 3-methoxytyramine). These enzymes are major mechanisms for inactivation of catecholamines (and monoamines). Action by both enzymes results in the formation of homovanillic acid (3-methoxy-4hydroxy-phenylacetic acid).

Dopamine Synthesis Flow Chart

Dopamine synthesis is regulated by a rate-limiting enzyme, and its extracellular concentrations controlled by an active recapture mechanism and several metabolic enzymes. The effects of dopamine are mediated by a family of G protein coupled receptors linked to distinct intracellular signalling pathways. Brain dopamine influences learning and execution of voluntary movements, motivation, reward, attention and working memory

- In the brain, dopamine functions as a neurotransmitter - a chemical released by nerve cells to send signals to other nerve cells. The human brain uses five known types of dopamine receptors, labeled D_1, D_2, D_3, D_4, and D_5. Dopamine is produced in several areas of the brain such as **ventral tegmental area** (VTA), is a group of neurons located close to the midline on the floor of the **midbrain** (mesencephalon). The VTA is the origin of the dopaminergic cell bodies and substantia nigra which is a brain structure located in the mesencephalon (midbrain) that plays an important role in reward, addiction, and movement.

Dopamine is a neurotransmitter in the brain and elsewhere, as well as an intermediate in the biosynthesis of the neurotransmitters noradrenaline and adrenaline – hormones secreted in stress conditions. During this the blood vessels dilates and the heart rate increases. But actually the function of both the hormone is synergistic in raising the blood pressure. These also release glucose from liver and reinforce the effects of sympathetic system(best known for mediating the neuronal and hormonal stress response). In the absence of these hormones, the stress conditions are diminished.

- Disturbances in dopamine neurotransmission have been implicated in a number of CNS disorders, but shown most conclusively in Parkinson disease and drug abuse. The drugs which modify CNS dopamine neurotransmission play a role in treating a variety of disorders including Parkinson disease [disorder of the brain that leads to shaking and difficulty with walking, movement, and coordination], schizophrenia [Schizophrenia is a mental disorder that makes it hard to: tell the difference between what is real and not real, think clearly, have normal emotional responses, act normally in social situation], attention deficit hyperactivity disorder, sleep disorders, and nausea [is a sensation of unease and discomfort in the upper stomach with an involuntary urge to vomit].

- Dopamine receptors outside of the CNS are targets in the medical treatment of excessive pituitary hormone release, certain gastrointestinal disorders, and cardiovascular shock.

- Dopamine plays a major role in the brain system that is responsible for reward-driven learning. Every type of reward that has been studied increases the level of dopamine transmission in the brain, and a

variety of highly addictive drugs, including stimulants such as cocaine and methamphetamine, act directly on the dopamine system. There is evidence that people with extraverted (reward-seeking) personality types tend to show higher levels of dopamine activity than people with introverted personalities.

Materials and methods

As we know, dopamine is a neurotransmitter (or chemical messenger) found in diverse organisms ranging from simple invertebrates to humans, t shows various modes of action in certain process as follows:

- **Act as an intermediate in the synthesis of adrenaline and non-adrenaline:** It is required as an intermediate in the formation of the neurotransmitters noradrenalin and adrenaline. It was earlier known to be an intermediate in the formation of non adrenalin but the recent studies have proved the importance of dopamine as a neurotransmitter itself in the brain. Such neurotransmitter controls the movement and the attention deficit hyperactivity disorder. Dopamine also has a social importance as the neurotransmitter that plays a central role in the mechanism of action of the major substances of abuse and, in particular, those associated with dependence and addiction.(Marsden 2009)

- **The effects of dopamine on membrane currents and synaptic transmission**: are complex and depend of the nature and distribution of the postsynaptic receptors. At the single cell level in the in vitro rat preparation, DA has been found to either increase or decrease the excitability of neurons, through the modulation of specific sets of sodium, potassium and calcium currents.

While the exact nature of the modulation is still not understood properly, it is likely to depend on the opposing contributions of the D1/D5 and D2/D3 family of dopamine receptors that are respectively positively and negatively coupled with adenylate cyclase.[2]. Dopamine modulates excitatory and inhibitory synaptic transmission. While the nature of neuro-modulation of inhibitory transmission is still debated, it appears that in both the cortex and the striatum.

- **Dopamine acts selectively in a form of stimulus–reward learning:** In individuals with a propensity for this form of learning, reward cues come to powerfully motivate and control behavior. Individuals make choices and prioritize goals using complex processes that assign value to rewards and associated stimuli. During learning, previously neutral stimuli that predict rewards can acquire motivational properties, becoming attractive and desirable incentive stimuli.(Shelly et.al. , paul et.al. 2011)

In recent years significant progress has been made delineating the psychological components of reward and their underlying neural mechanisms. Here we briefly highlight findings on three dissociable psychological components of reward: '*liking*' (hedonic impact), '*wanting*' (incentive salience), and *learning* (predictive associations and cognitions). A

better understanding of the components of reward, and their neurobiological substrates, may help in devising improved treatments for disorders of mood and motivation, ranging from depression to eating disorders, drug addiction, and related compulsive pursuits of rewards.(Berridge 2009)

In your brain, dopamine plays a big role in two important areas - motor skills and focus. It's also low in people with Parkinson's Disease (primarily in the motor skills area) and ADD/ADHD.(primarily in the mental focus area) - Attention deficit/hyperactivity disorder (commonly referred to as ADD or ADHD – though AD/HD is the technically correct abbreviation) is a neurologically based condition characterized by problems with attention, impulse control, and hyperactivity which occurs in childhood, but can persist into adolescence and adulthood. Without appropriate identification and treatment, ADHD can have serious consequences including chronic under-achievement, school/work failure, problematic and strained relationships, lowered self-esteem and can result in increased risk for depression, anxiety and substance abuse.

This is the thing to blame for the mental fog that leads to burners left on, keys locked in your house, and not being able to remember the chapter you just read. It's also what's responsible for rigid muscles, shaking or tremors, and falling down.(Goldman-Rakia et.al. , Muly et.al. 2000)

Dopamine receptors

Dopamine receptors play an important role in the neurological processes of pleasure, motivation, cognition, learning, memory, and movement, among others. Any impairment in the normal function of these receptors can have a mild to severe effect on a person's physical and mental well-being.

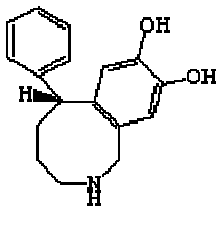
Dopamine receptors are a class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS). The diverse physiological actions of dopamine are mediated by at least five distinct G protein-coupled receptor subtypes.

The neurotransmitter dopamine is the primary endogenous ligand for dopamine receptors. Dopamine receptors have key roles in many processes, including the control of motivation, learning, and fine motor movement, as well as modulation of neuroendocrine signaling. Abnormal dopamine receptor signaling and dopaminergic nerve function is implicated in several neuropsychiatric disorders. Thus, dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors.(Missale et.al. , Caron et.al. 1998)

- **Types of receptors**: There are five types of dopamine receptor - D1, D2, D3, D4 and D5, and their variants.The D1 and D5 receptors are members of the D1-like family of dopamine receptors, whereas the D2, D3 and D4 receptors are members of the D2-like family. There is also some evidence that suggests the existence of possible D6 and D7 dopamine receptors, but such receptors have not been conclusively identified.

These five subtypes of dopamine receptor have been cloned. The D1 and D5 receptors are closely related, and couple to Gsalpha and stimulate adenylyl cyclase activity. In contrast, the D2, D3 and D4 receptors couple to Gialpha and inhibit the formation of cAMP. SKF-38393 is a selective D1/D5 agonist. D1 receptors are found within the neostriatum, nucleus accumbens and substantia nigra. SCH-23390 is a potent D1 antagonist.(Biol 1991)

D2 receptors are found in the pituitary, striatum, limbic system and the substantia nigra. Both bromocriptine and apomorphine mimic the action of dopamine at D2 receptors. Dopamine receptors are involved in neurological disorders such as Parkinson's disease and schizophrenia. The ability for a group of chemically unrelated compounds to act as sedatives and thus provide treatment for schizophrenia has been attributed to their ability to block dopamine receptors.



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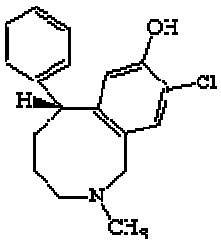

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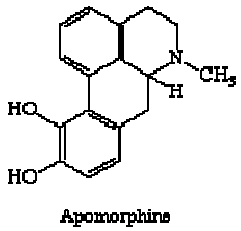

Apomorphine

Dopamine Receptors					
	D1	D2	D3	D4	D5
Antagonists	SCH-23390	-	-	-	SCH-23390
Agonists	SKF-38393	-	-	-	SKF-38393
G protein	Gαs	Gαi/o	Gαi/o	Gαi/o	Gαs
Intracellular response	Adenylyl cyclase stimulation	Adenylyl cyclase inhibition	Adenylyl cyclase inhibition	Adenylyl cyclase inhibition	Adenylyl cyclase stimulation

D1-like family

Activation of D1-like family receptors is coupled to the G protein Gas, which subsequently activates adenylyl cyclase, increasing the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP). Increased cAMP in neurons is typically excitatory and can induce an action potential by modulating the activity of ion channels.(Sunahara 1991 , Tiberi and Caron 1994)

D1 (DRD1)

D5 (DRD5)

D2-like family (inhibitory)

D2-like activation is coupled to the G protein Gai, which subsequently increases phosphodiesterase activity. Phosphodiesterases break down cAMP, producing an inhibitory effect in neurons.

D2 (DRD2): There is a short version of D2 (D2Sh) and a long version of D2 (D2Lh):

1 The D2Sh are pre-synaptic situated, having modulatory functions (called autoreceptor, they regulate the neurotransmission by feed-back

mechanisms, i.e., synthesis, storage and release of dopamine into the synaptic cleft.(Griffan 1995)

2. The D2Lh may have the classic function of a post-synaptic receptor, i.e., keep going on the neurotransmission (excitatory or inhibitory) once blocked by a receptor antagonist or stimulated by the endogenous neurotransmitter itself or a synthetic full or partial agonist.(Sakolog 1990)

D3 (DRD3): Maximum expression of dopamine D3 receptors is noted in the islands of Calleja and nucleus accumbens.(Audinot et.al. 1998)

D4 (DRD4): The D4 receptor has the following variants D4.2, D4.3a, D4.3b, D4.4a, D4.4b, D4.4c, D4.4d, D4.4e, D4.5a, D4.5b, D4.6a, D4.6b, D4.7a, D4.7b, D4.7c, D4.7d, D4.8, D4.10. These variants differ in a variable number tandem repeat domain present within the coding sequence of exon 3. Some of these alleles are associated with greater incidence of certain diseases. For example, the D4.7 alleles have an established association with attention-deficit hyperactivity disorder.(Bristow 1997 , Kulagowaski 1996)

- A dopamine agonist is an interesting medication that is most useful in early treatment of Parkinson's disease and in conditions like restless legs syndrome (RLS). Its mechanism of action is to work on dopamine receptors so that they are stimulated. This is different than adding dopamine to the body, which would stimulate the receptors, and it's also distinct from preventing the body from taking up (reuptake) free dopamine so there is more in use. Instead, it's something like a substitute for dopamine that can fool dopamine receptors into working, even when the body lacks a good supply of this neurotransmitter.(Kholi 1993)

- A receptor antagonist works by binding itself to dopamine receptors. In doing so, the drug dampens or blocks the ability of the receptors to receive dopamine. In other words, it effectively turns down dopamine activity. This disruption to the normal function of the receptors can be used to treat various disorders, such as schizophrenia, which is often associated with an overactive dopamine system. A dopamine antagonist can treat conditions resulting from drug abuse through the blocking of dopamine receptors and the inhibiting of the reuptake of dopamine by these receptors.

The Dopamine pathways

Dopamine is the neurotransmitter used by the reward pathway (also called the mesolimbic pathway, which is closely associated with the mesocortical pathway). But there are two other important pathways in the brain that utilize dopamine: the nigrostriatal pathway and the tuberoinfundibular pathway. Generally, drugs that affect dopamine levels in the brain affect all three of these dopamine pathways.

Fig.1.5. Structure explaning Dopamine pathways

Name	Description	Disorders
mesolimbic pathway	The mesolimbic pathway transmits dopamine from the ventral tegmental area (VTA) to the nucleus accumbens. The VTA is located in the midbrain, and the nucleus accumbens is in the limbic system. The "meso-" prefix in the word "mesolimbic" refers to the midbrain, or "middle brain", since "meso" means "middle" in Greek.	schizophrenia
mesocortical pathway	The mesocortical pathway transmits dopamine from the VTA to the frontal cortex. The "meso-" prefix in "mesocortical" refers to the VTA which is located in the midbrain, and "cortical" refers to the cortex.	schizophrenia
nigrostriatal pathway	The nigrostriatal pathway transmits dopamine from the substantia nigra to the striatum. This pathway is associated with motor control.	Parkinson's disease
tuberoinfundibular pathway	The tuberoinfundibular pathway transmits dopamine from the hypothalamus to the pituitary gland. This pathway influences the secretion of certain hormones, including prolactin. "Infundibular" in the word "tuberoinfundibular" refers to the infundibulum out of which the pituitary gland develops.	hyperprolactinaemia

Dopamine Functions

Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement, motivation and reward, inhibition of prolactin production (involved in lactation), sleep, mood, attention, and learning, regarding to the sites at which dopamine pathways are associated. Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are present chiefly in the ventral tegmental area (VTA) of the midbrain, the substantia nigra, and the arcuate nucleus of the hypothalamus (is an aggregation of neurons in the mediobasal hypothalamus).

- **Dopamine function in reward prediction-** (related to the mesolimbic and mesocortical pathway). It has been hypothesized that dopamine transmits reward prediction error, although this has been questioned. According to this hypothesis, the phasic responses of dopamine neurons are observed when an unexpected reward is presented. These responses transfer to the onset of a conditioned stimulus after repeated pairings with the reward.

Further, dopamine neurons are depressed when the expected reward is omitted. Thus, dopamine neurons seem to encode the prediction error of rewarding outcomes. In nature, we learn to repeat behaviors that lead to maximize rewards. Dopamine is therefore believed to provide a teaching signal to parts of the brain responsible for acquiring new behavior. Temporal difference learning provides a computational model describing how the prediction error of dopamine neurons is used as a teaching signal.

The reward system in insects uses octopamine, which is the presumed arthropod homolog of norepinephrine, rather than dopamine. In insects, dopamine acts instead as a punishment signal and is necessary to form aversive memories.

- **Movement:** Dopamine plays a role in smooth, controlled body movements. In the brain, the pathways of dopamine form important links between various parts, allowing the organ to function more smoothly as a whole. Cognition depends on access of information from other areas of the brain to the frontal cortex, which occurs along paths of dopamine transmission. Low levels of dopamine have been associated with Parkinson's disease, which is characterized by uncontrolled and shaky body movements.Insufficient dopamine biosynthesis in the dopaminergic neurons can cause Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

- **Regulating prolactin secretion: (**Related to the tubueroinfundibulum pathway). Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin.

- **Motivation, pleasure and Reinforcement:** (related to mesolimbic and mesocortical pathway). Dopamine is commonly associated with the pleasure system of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and prefrontal cortex) by naturally rewarding experiences such as food, sex, drugs, and neutral stimuli that become associated with them. Recent studies indicate that aggression may also stimulate the release of dopamine in this way. This theory is often discussed in terms of drugs such as cocaine, nicotine, and amphetamines, which directly or indirectly lead to an increase of dopamine in the mesolimbic reward pathway of the brain. Dopamine activity in the nucleus accumbens (NAC) appears to play a major role in the positive reinforcement of conditioned, goal-directed behaviors and the experience of pleasure(Harvitz 2000), as well as salient non-reward events and arousal-producing environmental changes.(Liberzon et.al. , Taylar et.al. 2003)

- **Dopamine, learning, and reward-seeking behavior-** (related to nigrostriatal pathway) Dopamine is closely associated with reward-seeking behaviors, such as approach, consumption, and addiction. Recent researches suggest that the firing of dopaminergic neurons is a motivational substance as a consequence of reward-anticipation. This is based on the evidence that, when a reward is greater than expected, the firing of certain dopaminergic neurons increases, which consequently increases desire or motivation towards the reward. This

finds the reward neurons predominate in the ventromedial region in the substantia nigra as well as the ventral tegmental area. Neurons in these areas project mainly to the ventral striatum and thus might transmit value-related information in regard reward values.

DA also plays a critical role in incentive learning produced by rewarding stimuli. Using DA as the link, these results suggest that psychosis in schizophrenia can be understood from the point of view of excessive incentive learning. Incentive learning is mediated through the non-declarative memory system and may rely on the striatum or medial prefrontal cortex depending on the task. Hyperfunction of brain dopamine (DA) systems is associated with psychosis in schizophrenia and the medications used to treat schizophrenia are DA receptor blockers.

- **Processing of pain** - Dopamine has been demonstrated to play a role in pain processing in multiple levels of the central nervous system including the spinal cord, thalamus, basal ganglia etc. Accordingly, decreased levels of dopamine have been associated with painful symptoms that frequently occur in Parkinson's disease. Abnormalities in dopaminergic neurotransmission have also been demonstrated in painful clinical conditions, including burning mouth syndrome, fibromyalgia, and restless legs syndrome. In general, the analgesic capacity of dopamine occurs as a result of dopamine D2 receptor activation, in which dopamine D1 receptor activation attenuates pain presumably via activation of neurons involved in descending inhibition. In addition, D1 receptor activation in the insular cortex appears to attenuate subsequent pain-related behavior.

- **Behavior disorders** - Deficient dopamine neurotransmission is implicated in attention-deficit hyperactivity disorder, and stimulant medications used to successfully treat the disorder increase dopamine neurotransmission, leading to decreased symptoms. Consistent with this hypothesis, dopaminergic pathways have a role in inhibitory action control and the inhibition of the tendency to make unwanted actions.

Dopamine Dysfunctions: A number of human disorders have been associated with a primary or a secondary impairment or by dysfunctions of one or several of the dopaminergic pathways. Among disorders associated with a primary impairment of dopaminergic transmission are Parkinson's disease, striatonigral degeneration, progressive supranuclear palsy, and possibly schizophrenia. Diseases of secondary dopaminedysfunction are chiefly represented by Huntington's disease in which dopaminergic transmission is being interrupted by progressive loss of the striatal neurons bearing the postsynaptic D1- and D2-dopamine receptors.(Corlsson 1987)

The original dopamine (DA) hyperactivity hypothesis of schizophrenia,(Giuliano et.al. 2001) although undergoing revisions and reformulations remains a pivotal neurochemical hypothesis of the illness that is yet to be fully confirmed or refuted. Multiple components of dopaminergic neurotransmission may cause dopaminergic overactivity, including

increased DA synthesis, release, receptor number and/or affinity, and DA-mediated postsynaptic effector mechanisms.(Giuliano et.al. 2001)

- **DA dysfunction and impulsive behaviors in animals:** Recent evidence suggests that the NAC, well innervated by DA neurons, plays an important role in impulsive choice in rats[23] Aggressive and impulsive behaviors in rodents are modulated, in part, by DA activity at D1 and D2 receptors. (Harnykiewicz 1986)

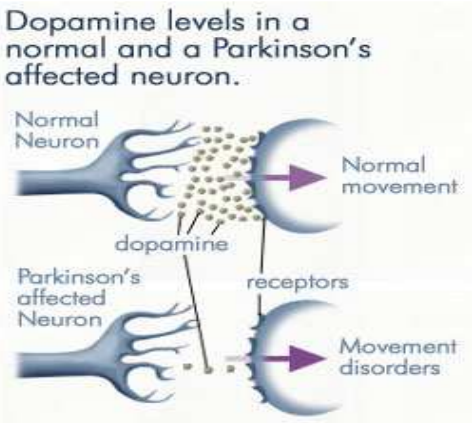

Fig.1.6 structural difference between normal dopamine secretion and schizophrenia

- **DA dysfunction leading to Parkinsons disease:** Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular events that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction and oxidative stress, may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons.(Bowen 2003)
- **DA dysfunctions causing Schizophrenia and Alcoholism:** Dysfunction of central dopaminergic neurotransmission has been implicated in the pathogenesis of schizophrenia as well as drug and alcohol dependence. Different drugs of abuse stimulate dopamine release in the ventral striatum and thus reinforce drug consumption. Increased subcortical dopamine release has also been associated with the pathogenesis of positive symptoms in schizophrenia and may be driven by a prefrontal dopaminergic dysfunction. These seemingly heterogeneous findings may be explained by recent research in non-human primates. According to these studies, reward anticipation but not anticipated reward consumption is accompanied by a phasic dopamine release in the striatum and prefrontal cortex. In the striatum, phasic dopamine release primarily affects motivation, psychomotor activation and reward craving, while in the prefrontal cortex, dopaminergic stimulation is involved in the activation of working memory and reward anticipation. In alcoholism, previously neutral stimuli that have been associated with alcohol intake can become conditioned cues which activate phasic dopamine release and reward craving. In schizophrenia, stress-

induced or chaotic activation of dopamine release may attribute release of irrelevant stimuli and thus be involved in the pathogenesis of delusional mood and other positive symptoms.(Bowen 2003)

- **Dopamine when is not released due to autosomsal recessive mutation:** The neurotransmitter dopamine is synthesised from tyrosine by the enzyme tyrosine hydroxylase, which uses tetrahydrobiopterin (BH4) as a cofactor. A mutation in the gene GCH1, which encodes the enzyme GTP cyclohydrolase I, disrupts the production of BH4, decreasing dopamine levels (hypodopaminergia). This results in autosomal-dominant DRD. Mutations in the genes for tyrosine hydroxylase and result in autosomal-recessive forms of the disease. When the latter enzyme is affected, the condition tends to be more severe. The activity of dopaminergic neurons in the nigrostriatal pathway normally peaks during the morning and also decreases with age until after age 20. Dopamine-responsive dystonia (DRD), also known as hereditary progressive dystonia, Segawa's disease, or Segawa's dystonia. Characteristic symptoms are increased muscle tone and Parkinsonian features, typically absent in the morning or after rest but worsening during the day and with exertion

- **DA dysfunction in prolactin secretion:** Dopamine serves as the major prolactin-inhibiting factor or brake on prolactin secretion. Dopamine is secreted into portal blood by hypothalamic neurons, binds to receptors on lactotrophs, and inhibits both the synthesis and secretion of prolactin. Agents and drugs that interfere with dopamine secretion or receptor binding lead to enhanced secretion of prolactin.

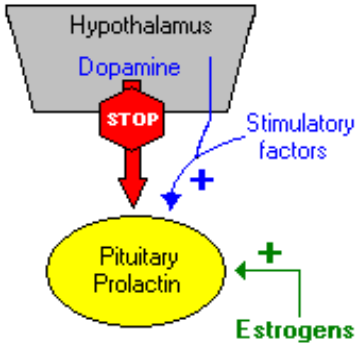

Fig.1.5. Controlled secretion of prolactin by dopamine

Excessive secretion of prolactin - hyperprolactinemia - is a relatively common disorder in humans. This condition has numerous causes, including prolactin-secreting tumors and therapy with certain drugs.

Common manifestations of hyperprolactinemia in women include amenorrhea (lack of menstrual cycles) and galactorrhea (excessive or spontaneous secretion of milk). Men with hyperprolactinemia typically show hypogonadism, with decreased sex drive, decreased sperm production and impotence. Such men also often show breast enlargement (gynecomastia), but very rarely produce milk. This happens due to loss of the function of dopamine which could not able to control the secretion of prolactin in the body.

- BPD is characterized by: (1) emotional dysregulation; (2)impulsivity; (3)

cognitive-perceptual impairment; and (4) disturbed relationships.(Gurvits et.al. , Siever et.al. 2000)

Research on the biological basis of BPD has focused primarily on the relationships between impulsive aggression and serotonin dysfunction. To a lesser degree, emotional dysregulation has been correlated with imbalances in noradrenergic neurotransmission. A recent integration of the biological, psychosocial, and clinical findings in BPD does not mention a potential role of DA dysfunction in the disorder(Schmahl et.al. , Bremner et.al. 2002).DA modulates emotional responses to salient positive and negative events and arousal producing stimuli modulates working memory and cognition. There is evidence that CSF HVA levels may be related to impulsive behavior in patients with BPD Therefore, this review evaluated data relevant to the hypothesis that DA dysfunction in specific neural pathways is associated with one or more of the behavioral dimensions of BPD.

DA dysfunction in psychotic features of BPD: Psychotic features in subjects with BPD respond well to antipsychotic agents and are induced in some subjects with BPDDA dysfunction in nonpsychotic cognitive symptoms of BPD: Neuropsychological testing demonstrates nonpsychotic cognitive deficits in BPD, including impairments in reasoning, learning, memory, and executive functions. Neuroimaging studies in subjects with BPD indicate structural and functional changes in brain regions critical to cognitive activity, such as decreases in frontal lobe, and changes in frontal lobe glucose metabolism. Tebartz van Elst et al (2001) report a significant reduction of N-acetylaspartate concentration (a proposed measure of neuronal integrity) in the dorsolateral prefrontal cortex (DLPFC) measured in patients with BPD compared to controls. Evidence suggests that nonpsychotic cognitive disturbances in schizophrenia and normal subjects and in schizotypal personality disorder are due to hypodopaminergic activity**.** DA dysfunction is involved in all symptoms in each of the three dimensions of BPD. For example, the identity disturbance commonly observed in individuals with BPD may be regarded as a cognitive-perceptual impairment.

Conclusion and discussion

Dopamine is a monoamine neurotransmitter found in diverse organisms from simple invertebrate to humans and also intermediate in the formation of the neurotransmitter nonadrenaline and adrenaline. It plays a major role in two important area i.e motor skill and in brain. It's receptor play important role in many processes including the control of motivation, learning, and fine motor movement as well as modulation of neuroendocrine signalling. Each receptor is related to adenyl cyclase activity. As discussed above the drug that affect the level of dopamine in brain affects all the dopamine pathway including nigrostriatial and tuberoinfundibular pathway. Each pathway is related to disorder like schizophrenia, parkinson's disease and hyperprolactinemia. As it is discussed, dopamine is prolactin inhibitor because the lactotrope cells that produce prolactin are absent in dopamine. It has many such effect on emotion salient event arousal-producing stimuli. Its receptor plays important role in working in memory

and cognition. Dopamine also play the activity on NMDA receptor. Parkinson's disease and schizophrenia are the disorders which are related due to dopamine dysfunction. Hence the all above is the synthesis, function, dysfunction and disease related to dopamine which plays major role as neurotransmitter.

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