

## Review Article

# Dopamine: a modulator of circadian rhythms/biological clock

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### ABSTRACT

Circadian rhythm describes the physical, psychological, and behavioural patterns of living organisms that respond to day and night light levels. The important bodily functions like hunger, sleep, gastrointestinal motility, mood, coordination, body temperature, gene transcription, sensory perceptions, sleep-wake cycles and hormone release etc are influenced by circadian rhythm. Abnormal circadian rhythm may result obesity, depression, diabetes, seasonal affective disorder, bipolar disorders and various sleep disorders. The neuromodulator dopamine, originate from small groups of neurons in the mesencephalon (the ventral tegmental area, the substantia nigra) and in the diencephalon. In the retina, olfactory bulb, striatum, midbrain, and hypothalamus, it has been shown to have that dopamine shows circadian like activities, where it regulates, clock genes in some of these areas. Thus, it is likely that dopamine is essential to mechanisms that maintain proper rhythmicity of these five brain areas. Dopamine receptors are located centrally and peripherally. Growing evidence that dopamine is involved in regulating circadian rhythms, either directly or indirectly, in the brain areas through various pathways and dopaminergic receptor groups centrally and peripherally, and plays vital role.

**Keywords:** Circadian rhythm, Biological clock, Dopamine

## INTRODUCTION

Circadian rhythm is a natural, biological process that displays an endogenous, entertainable oscillation of about 24 hours cycle in the physiological process of living beings. These rhythms are driven by a circadian clock that is present in all living beings, including plants, animals, fungi and cyanobacteria.<sup>1</sup> Word “circadian” comes from Latin, composing of “circa” and “dian”-circa, meaning “around” (or “approximately”), and dian or dies, meaning “day”-literally meaning of that is “about a day”. Circadian rhythms regulate many biological processes from gene transcription to behaviour, and disruption of these rhythms may lead to uncountable health risks.

The important bodily functions like hunger, sleep, coordination, mood, GI motility, gene transcription, sensory perceptions, body temperature, sleep-wake cycles,

and hormone release, etc. (Figure 1,2) can be influenced by circadian rhythm. Abnormal circadian rhythms associated with obesity, diabetes, depression, bipolar disorder, seasonal affective disorder and also linked to various sleep disorders, such as insomnia, metabolic disorders.<sup>2</sup> Circadian rhythms also determine human sleep patterns.

The circadian biological clock is controlled by a part of brain—the Suprachiasmatic nucleus (SCN), a group of cells in the hypothalamus – considered body’s “master clock”, it controls the production of melatonin (a hormone), that regulate sleep cycle. Since, SCN is located just above the optic nerves, which relay information from the eyes to the brain, it receives information about incoming light.<sup>3</sup> When there is less light-like at night-SCN conveys brain to make more melatonin and get drowsy (Figure 2).

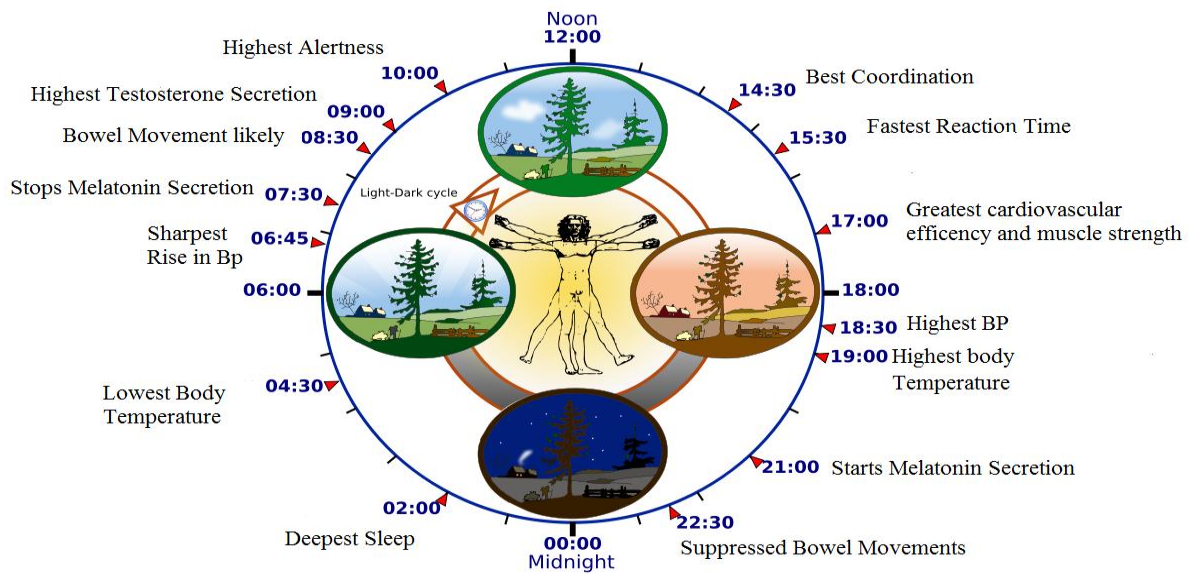


Figure 1: Features of the human circadian (24-hours) biological clock.<sup>7</sup>

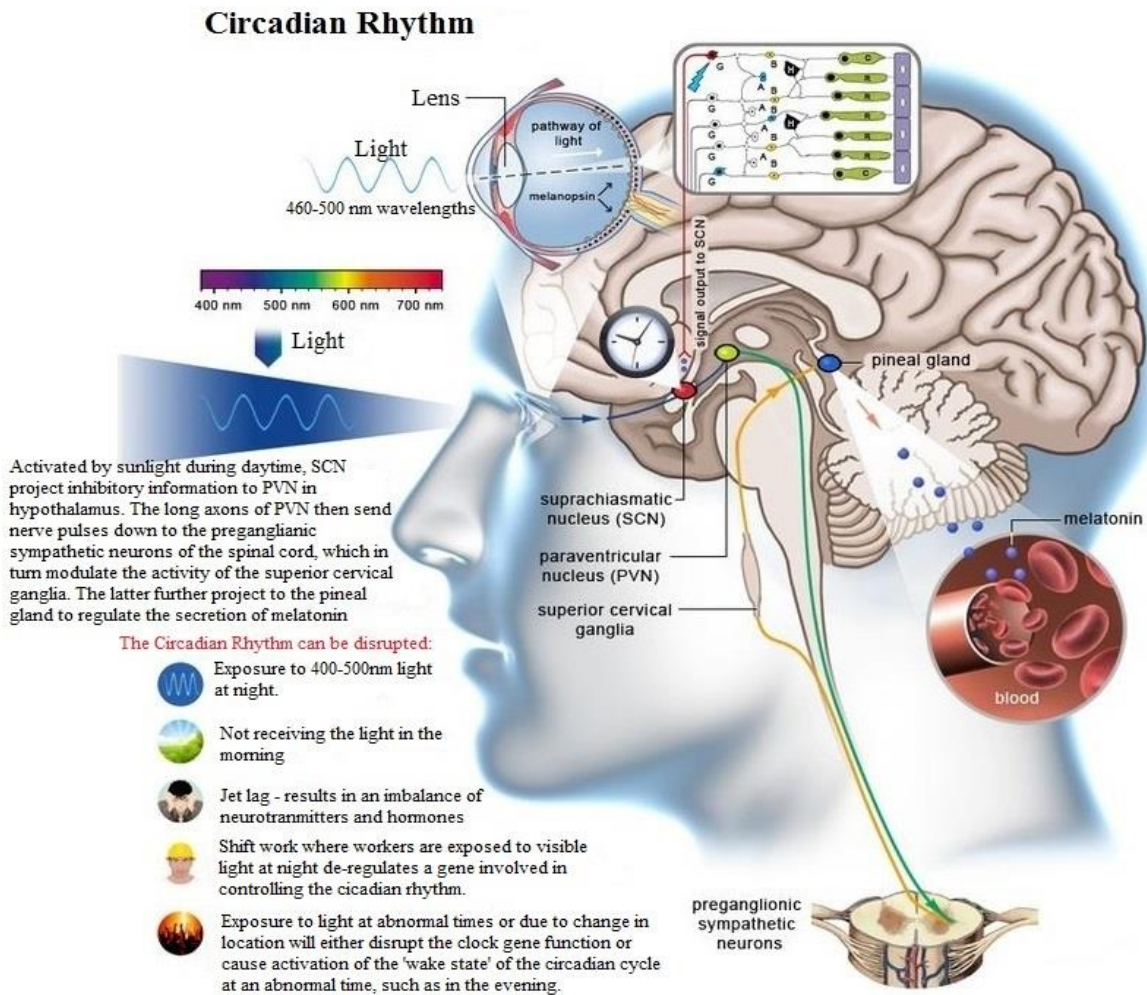


Figure 2: Circadian rhythm.<sup>8</sup>

Disruption to rhythms can occur in many conditions like exposure to 400-500 nm light at night, not receiving light in the morning, Jet lag, shift workers, and exposure to light at abnormal times, and it usually has a negative effect in short term e.g. jet lag occurs when travellers suffer from disrupted circadian rhythms that is due to travel to different

time zones and they experience the symptoms of fatigue, disorientation and insomnia (Figure 2).<sup>4</sup>

### SYNTHESIS AND SECRETION OF DOPAMINE

Pathways for synthesis of dopamine (Figure 3).

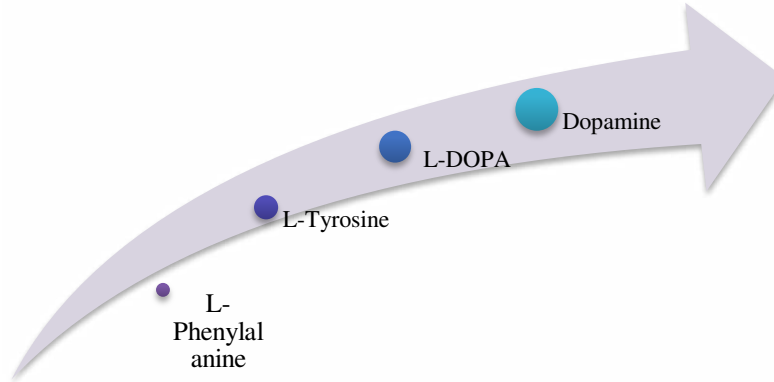


Figure 3: (A) primary pathway of dopamine synthesis

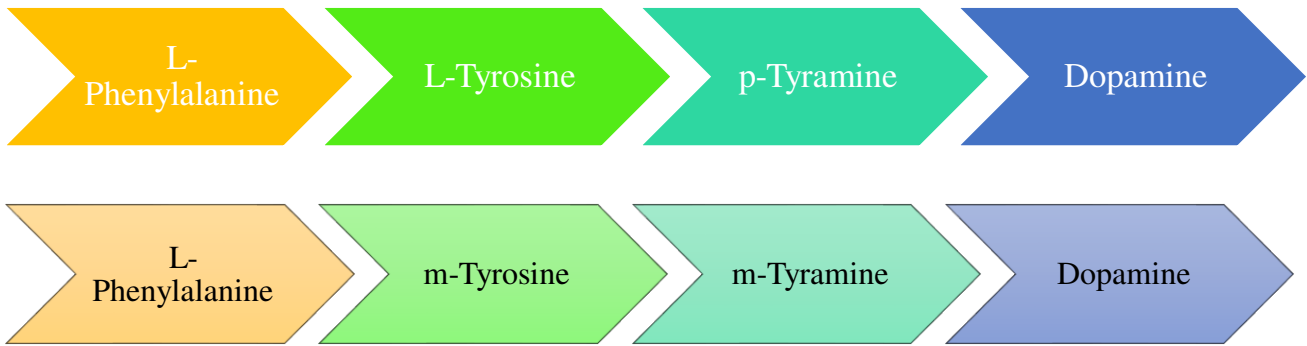


Figure 3: (B) minor pathways of dopamine synthesis

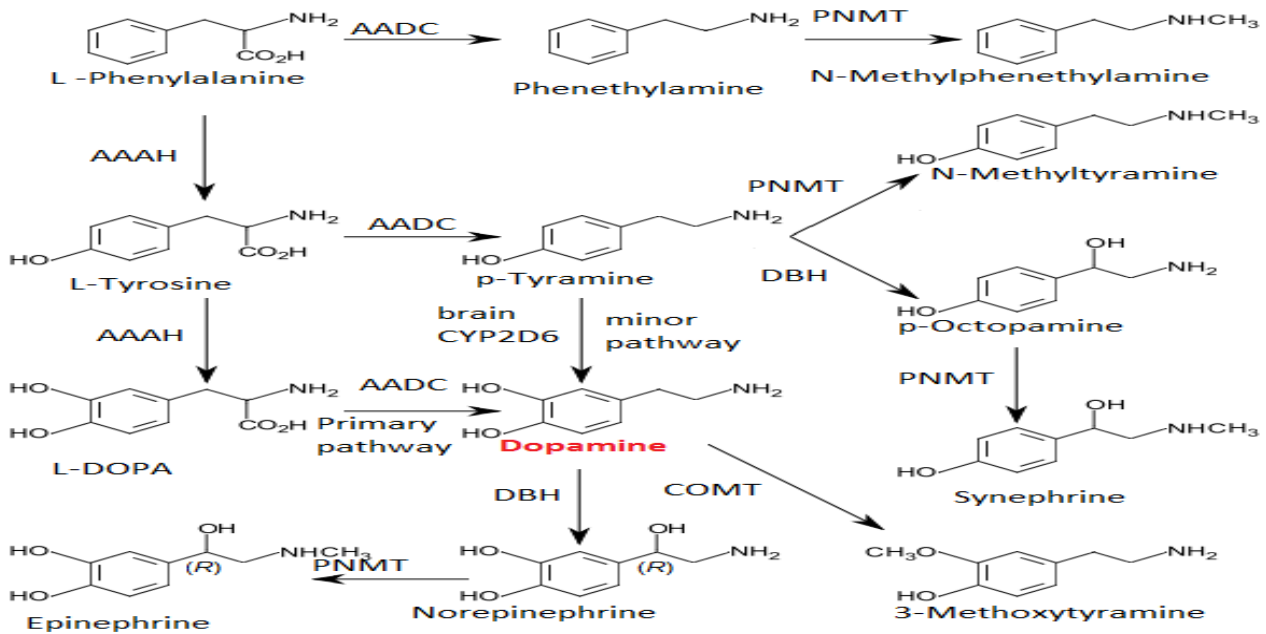


Figure 3: (C) Synthesis of dopamine.<sup>9</sup>



In humans, the amino acid phenylalanine derives catecholamine and phenethylaminergic amines. Dopamine is produced from L-tyrosine via L-DOPA; the recent

evidence has shown that CYP2D6 is expressed in the human brain and catalyses the biosynthesis of dopamine from L-tyrosine via p-tyramine.

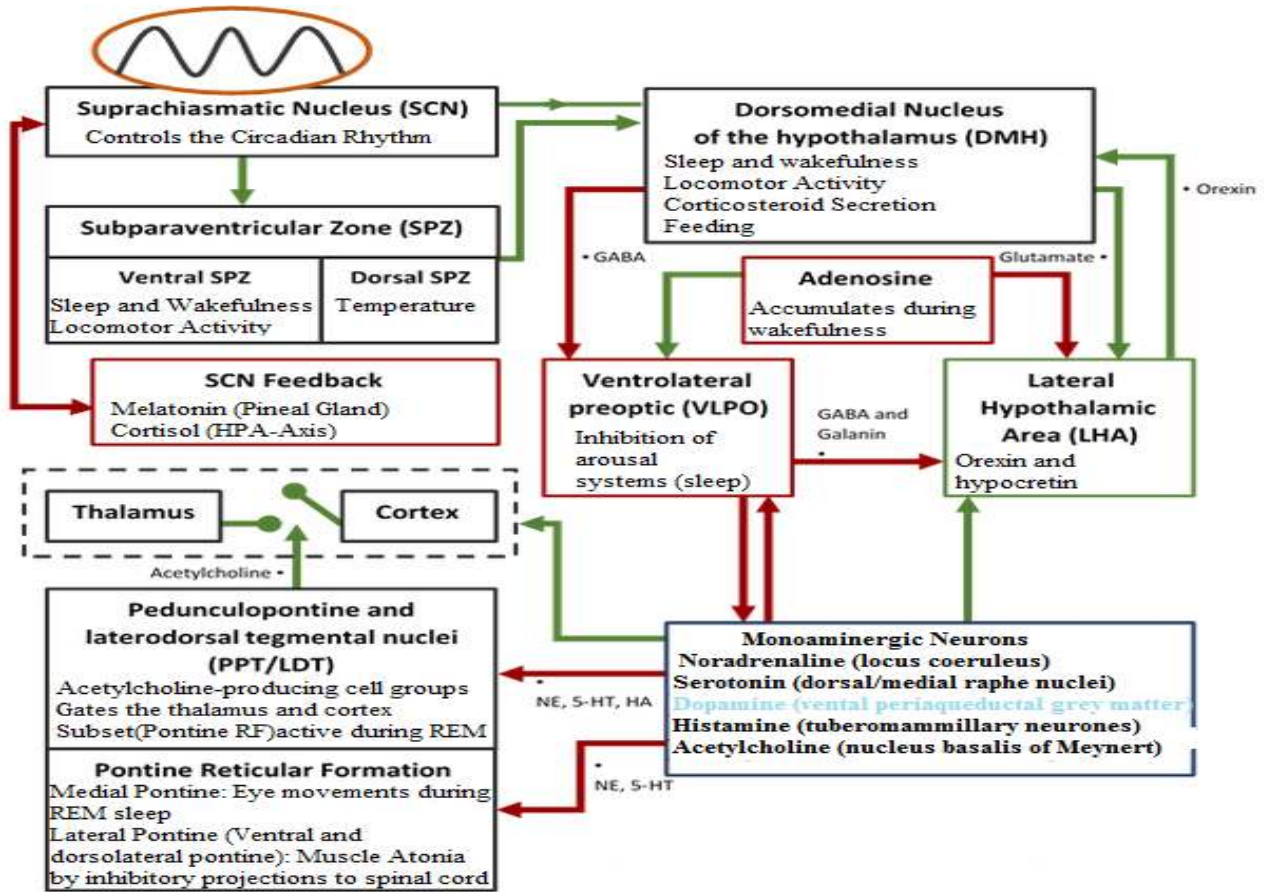


Figure 4: Representation of sleep/wake mechanism and interplay of different brain structures and contribution of dopamine.

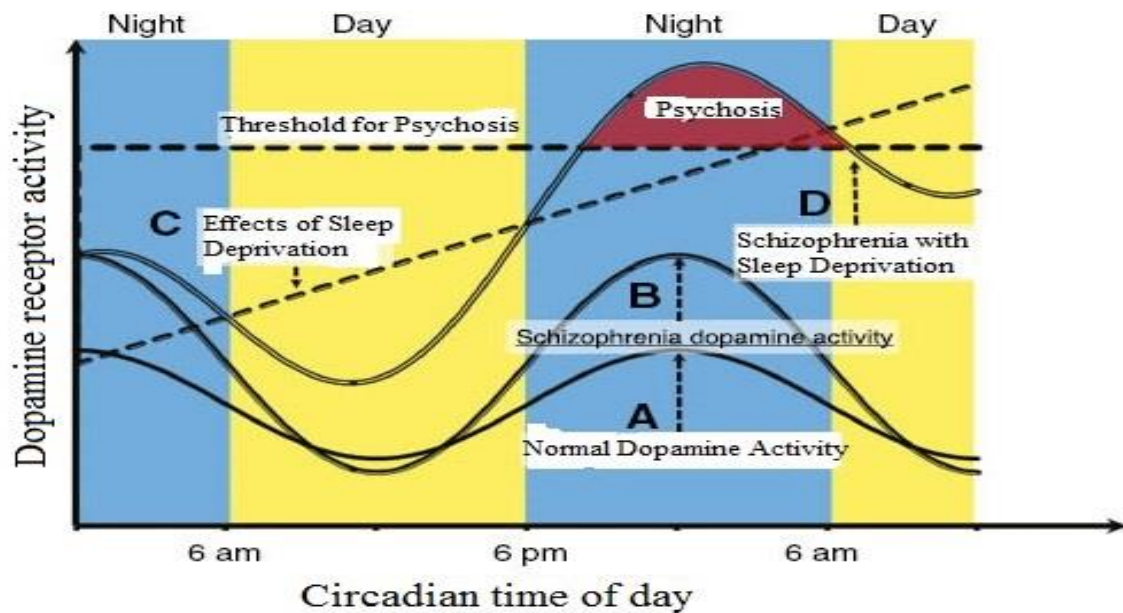


Figure 5: The role of sleep and circadian rhythms in regulating dopamine activity and psychosis & schizophrenia.<sup>10</sup>

## DOPAMINE AS A MODULATOR OF CIRCADIAN RHYTHM

The neuromodulator dopamine, originate from small groups of neurons in the mesencephalon (the ventral tegmental area, the substantia nigra) and in the diencephalon. Generally, dopaminergic projections are very diffuse and reach large portions of the brain. The dopamine actions are diverse in time scale from few hundreds of milliseconds to several hours.

In the retina, olfactory bulb, striatum, midbrain, and hypothalamus dopamine has been shown to have circadian like activities, where it regulates, and is regulated by, clock genes in some of these areas. Thus, it is likely that dopamine is essential to mechanisms that maintain proper rhythmicity of these five brain areas (Figure 4, 5).

The disruption in the circadian rhythm i.e. sleep/wake mechanism (can occur in many conditions like exposure to 400-500nm light at night, not receiving light in the morning, jet lag, shift workers, and exposure to light at

abnormal times), that is regulated by different brain structures, and neurotransmitters especially dopamine leads to many health issues, e.g. psychosis, schizophrenia, bipolar disorder and some sleep disorders such as delayed sleep phase disorder (DSPD) (Figure 5).<sup>5</sup>

The recent identification of 5 dopamine receptors subtypes provides a basic for understanding dopamine’s central and peripheral actions which plays an important role both centrally and peripherally (Figure 6-9).

## CELLULAR EFFECT

In humans, dopamine has a high binding affinity at dopamine receptors and at hTAAR1 (human trace amine-associated receptor 1); by binding to and activating cell surface receptors dopamine exerts its effects. In mammals, 5 subtypes of dopamine receptors have been identified, which labelled from D1 to D5, which function as metabotropic, G protein-coupled receptors, that exert their effects via a complex second messenger system.

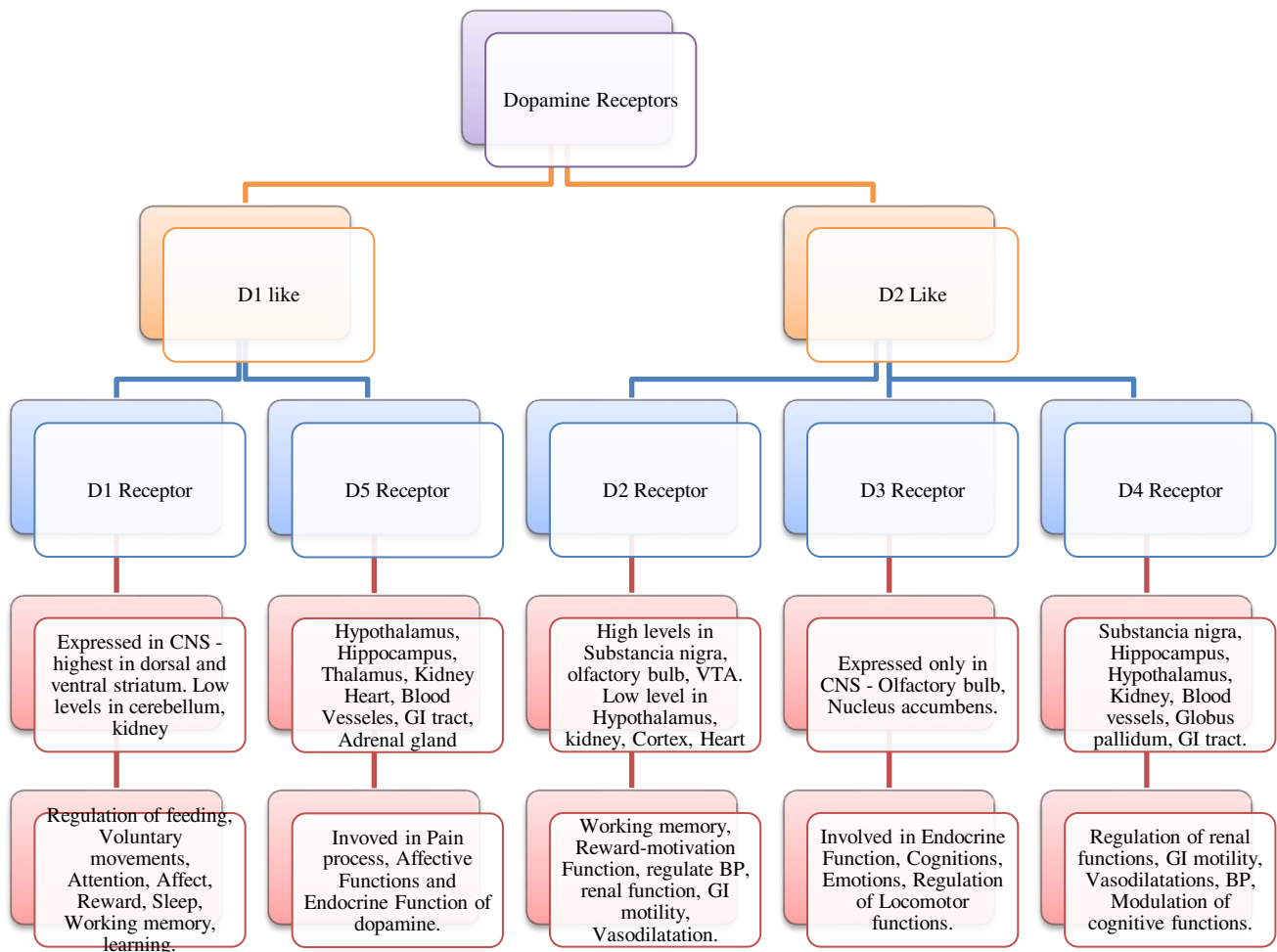
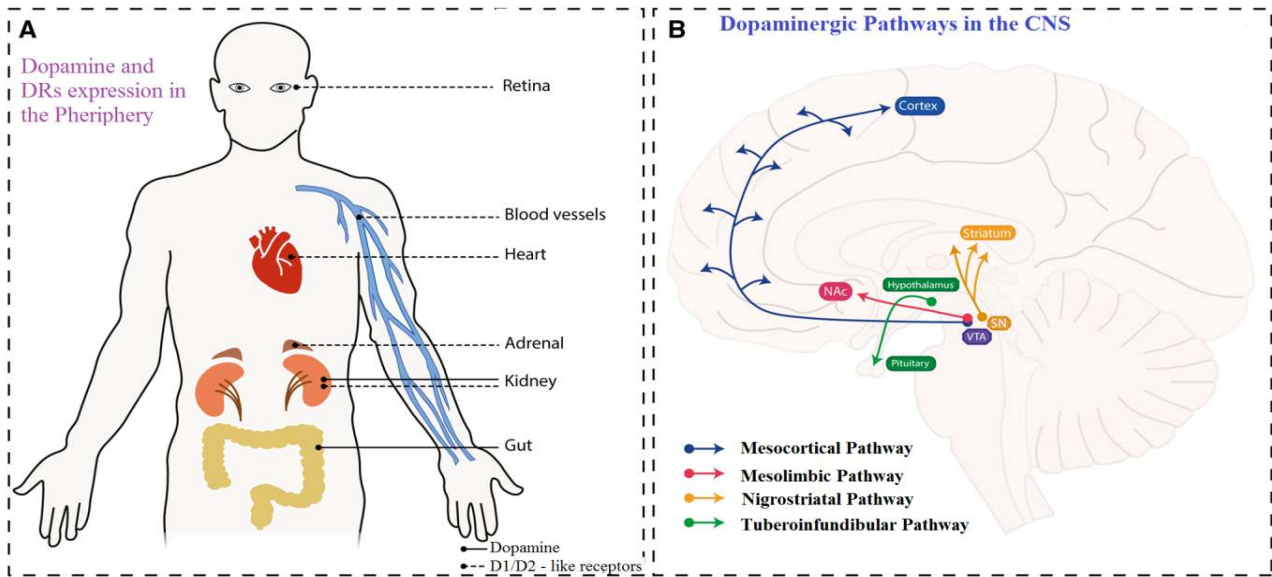


Figure 6: Role of dopamine receptors at different sites.<sup>11</sup>

## Role of Dopamine : Central And Peripheral



**Figure 7: In central and peripheral systems - distribution of dopamine, dopamine receptors, and dopaminergic pathways.**

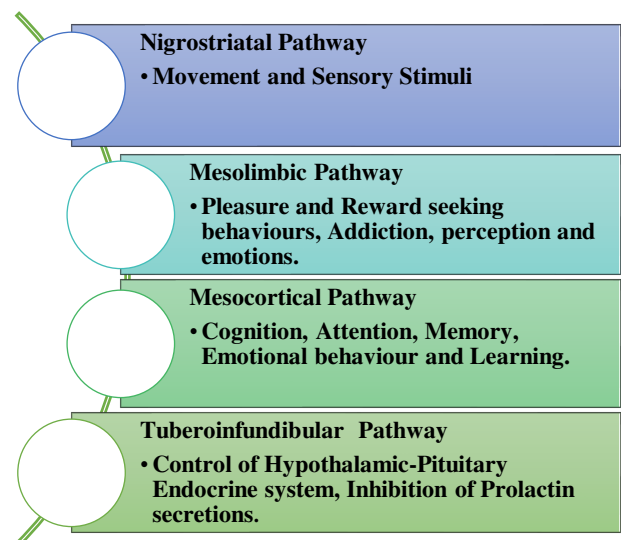
These receptors divided into two families - known as D1-like & D2-like receptors.<sup>6</sup> For receptors located on neurons in the nervous system, the ultimate effect of D1-like receptors activation (D1 and D5) can be - excitation (via opening of sodium channels) or inhibition (via opening of potassium channels); And the ultimate effect of D2-like receptors activation (D2, D3, and D4) is usually inhibition of the target neuron (Figure 6-9). Consequently, describing dopamine itself as either excitatory or inhibitory is incorrect: its effect on a target neuron depends on the types of receptors present on the membrane of that neuron and on the second messenger i.e. cAMP internal responses on that neuron. D1 receptors are the most numerous dopamine receptors in the human nervous system; D2 receptors are next; while D3, D4, and D5 receptors are present at significantly lower levels

A-expression of dopamine and dopamine receptors (D1/D2-like receptors) in the periphery. dopamine (continuous black arrow) is produced in kidney and gut while dopamine receptors (dashed black arrow) are located mainly in retina, blood vessels, heart, adrenal, and kidney. B - Distribution of the four main dopaminergic pathways in the central nervous system. VTA is the source of mesocorticolimbic system: dopaminergic neurons project to cortex via mesocortical pathway (blue) and, to nucleus accumbens via mesolimbic pathway (red). Dopamine neurons in the substantia nigra project to the striatum and form the nigrostriatal pathway (yellow). The tuber indubular pathway (green) is formed by dopaminergic neurons that project from hypothalamic nuclei (arcuate nucleus and periventricular nucleus) to the pituitary. DRs—dopamine receptors; CNS—central nervous system; VTA –

ventral tegmental area; SN—substantia nigra; NAc—nucleus accumbens.

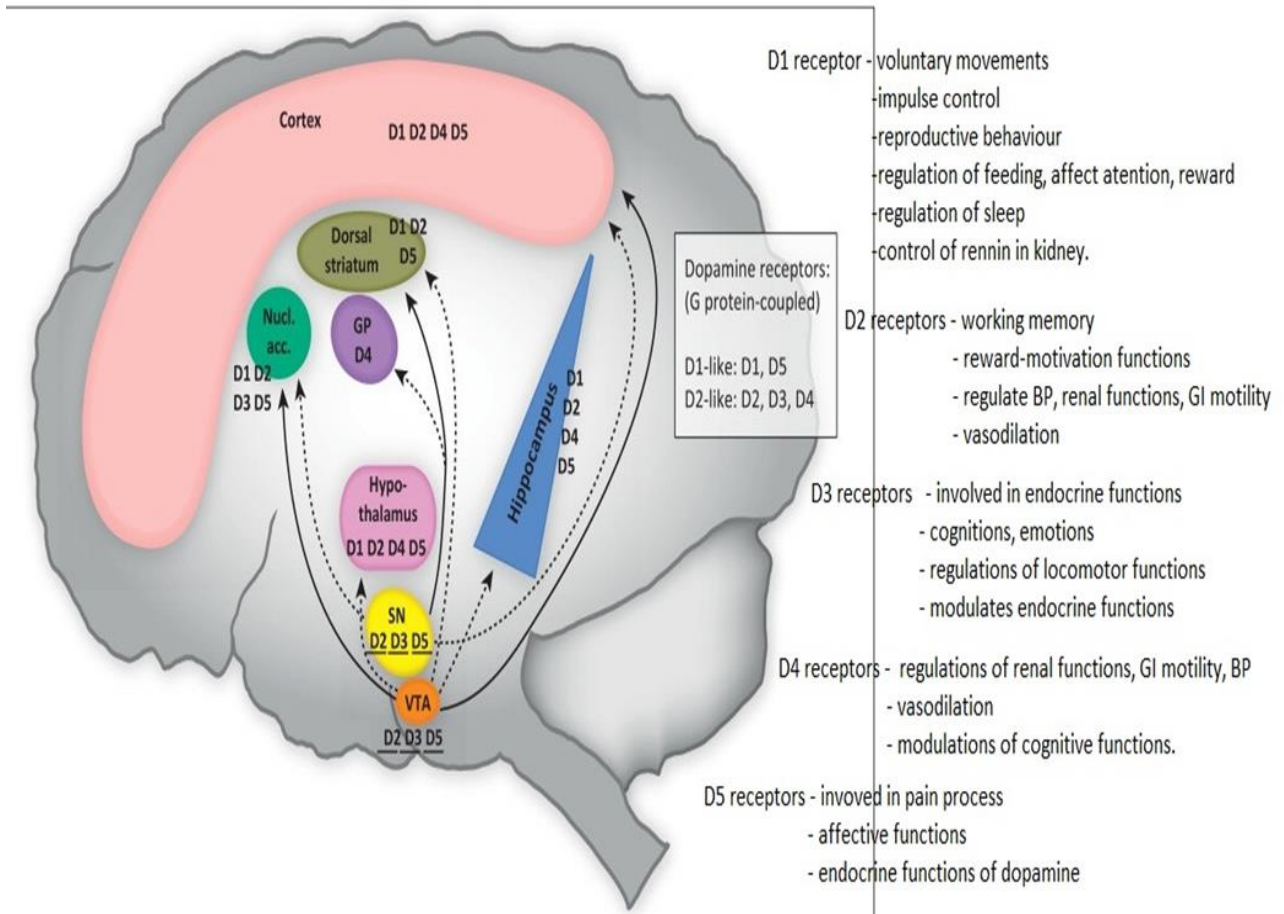
### NERVOUS/CENTRAL EFFECT

Dopamine plays an important role in executive functions, motivation-reward, arousal, reinforcement, motor control, as well as lower-level functions like lactation, sexual gratification, and nausea in the CNS. The pathways and dopaminergic cell groups make up the dopamine system as a neuromodulator. Dopamine central/nervous functions can be divided on the basis of pathways (Figure 7-9).



**Figure 8: Dopamine pathways and their major functions.**





**Figure 9: Distribution of dopamine receptors in brain and their function and pathways.**

## Nigrostriatal pathway & EPS

**Anatomy**

- Projections from substantia nigra (pars compacta) to striatum (caudate and putamen).

**Physiology**

- Stimulation of purposeful movement.

Parkinson's disease: loss of dopaminergic neurons in the pars compacta of the substantia nigra.

**Figure 10: Nigrostriatal pathway and EPS.**

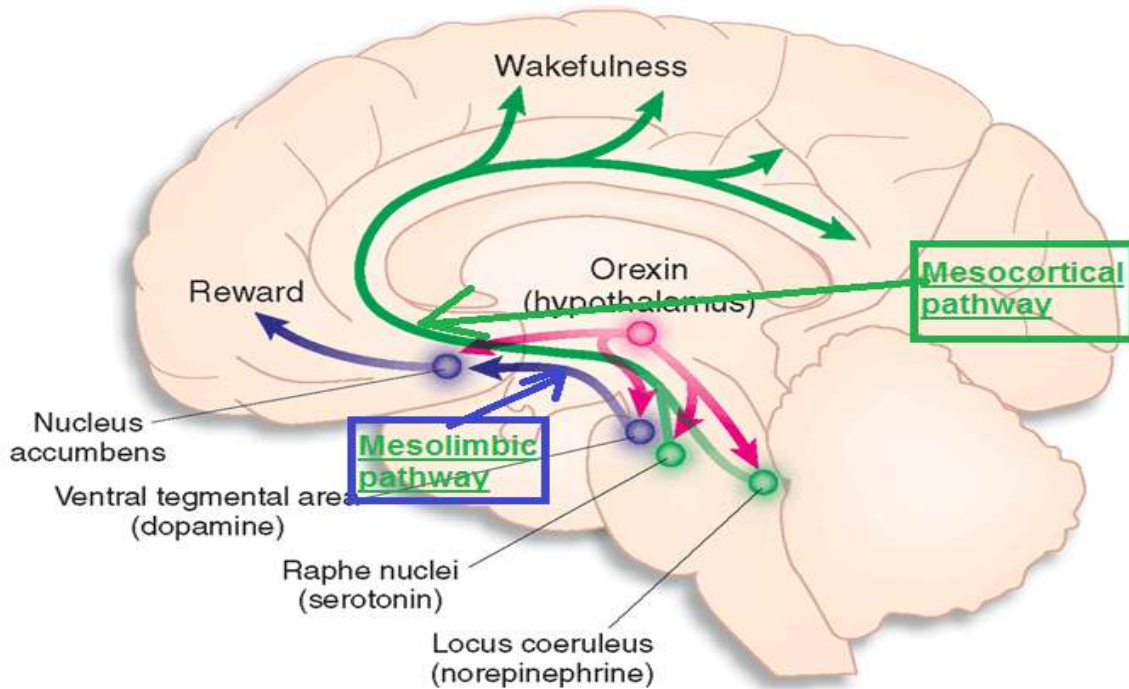


Figure 11: The mesolimbic and mesocortical pathways.

## Tuberoinfundibular Pathway and Release Of Prolactin

### Anatomy

- Hypothalamus (arcuate and periventricular nuclei) to infundibular region (median eminence).

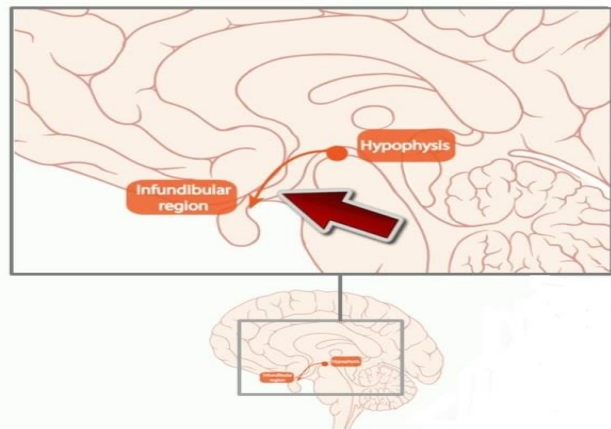


Figure 12: Tuberoinfundibular pathway.

## NIGROSTRIATAL PATHWAY

The substantia nigra is a small area in midbrain that forms a component of the basal ganglia. It has two parts - an input area called the pars compacta and an output area called the pars reticulata. The dopaminergic neurons are mainly found in pars compacta (A8 cell group) and nearby (A9 cell group). In humans, the projection of dopaminergic neurons from the substantia nigra to pars compacta to the dorsal striatum, and formed the nigrostriatal pathway, that plays a very significant role in the control of motor function and in learning of new motor skills (Figure 10) These neurons are especially vulnerable to damage, and

when a large number of them die the result parkinsonian syndrome.

## THE MESOLIMBIC AND MESOCORTICAL PATHWAY

The ventral tegmental area (VTA) is another area of midbrain. The VTA dopaminergic neurons projects to the prefrontal cortex via the mesocortical pathway most prominently and remaining projects to the nucleus accumbens via the mesolimbic pathway. These two pathways together collectively termed the mesocorticolimbic projection. The VTA also sends



dopaminergic projections to the amygdala, cingulate gyrus, hippocampus, and olfactory bulb. Mesocorticolimbic neuron pathway involve in reward and other aspects of motivation (Figure 11).

### TUBEROINFUNDIBULAR PATHWAY

In the tuberoinfundibular pathway, dopaminergic projections influence prolactin release. The pathway consists of dopaminergic projections from the hypothalamus (more specifically the arcuate and periventricular nuclei or median eminence) to the infundibular region. Dopamine released into the portal circulation, which connecting the anterior pituitary gland with the median eminence and it is very important because the role of dopamine release in the tuberoinfundibular pathway is to tonically inhibit prolactin release (Figure 12).

### CONCLUSION

Dopamine is involved in regulating circadian rhythms, either directly or indirectly, in the brain areas through various pathways and dopaminergic receptor groups centrally and peripherally and thus plays vital role in circadian rhythm.

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