



Neurotransmitter Substances and Anatomical Localizations

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SUMMARY

Neurotransmitters are defined as chemical substances which are delivered to the synapse space of the presynaptic membrane and transmit a stimulus by binding to a receptor on the postsynaptic membrane to form a specific response. Neurotransmitters are found in a variety of biological fluids, including plasma, serum, cerebrospinal fluid, thrombocytes, saliva and urine. Neurotransmitters have an important role in brain neurological regulation and fulfillment of specific biological functions in the body. In this review, neurotransmitter substances will be mentioned in terms of the criteria used for their identification, mechanism of effect, classification, release, inactivation, detection methods, anatomical location and tasks.

Key Words: Anatomic localization, Neuroanatomy, Neurotransmitter substance

ÖZET

Nörotransmitter Maddeler ve Anatomik Lokalizasyonları

Nörotransmitterler, spesifik bir cevap oluşturmak için presinaptik membrandan sinaps aralığına saliverilen ve postsinaptik membrandaki bir reseptöre bağlanarak uyarıyı ileten kimyasal maddeler olarak tanımlanır. Nörotransmitterler, plazma, serum, cerebrospinal sıvı, trombositler, salya ve idrar da dahil olmak üzere çeşitli biyolojik sıvılarda bulunur. Beynin sinirsel regülasyonunda ve vücuttaki spesifik biyolojik fonksiyonların yerine getirilmesinde nörotransmitterlerin önemli bir rolü vardır. Bu derlemede, nörotransmitter maddelerin tanımlanmasında kullanılan kriterler, etki mekanizması, sınıflandırılması, salınımı, inaktivasyonu, tespit yöntemleri, anatomik olarak yerleşim yeri ve görevlerinden bahsedilecektir.

Anahtar Kelimeler: Anatomik lokalizasyon, Nöroanatomi, Nörotransmitter madde

INTRODUCTION

The nervous system is responsible for the uptake of various stimuli along with the endocrine, immunological system and sensory organs, and the coordination of the organism's reactions. The nervous system receives stimuli that affect the surface and/or inside of the body. These stimuli are recorded in the nervous system, transmitted, evaluated and form an active or passive response. This allows the nervous system to combine the reaction and adaptation in the body. In simple organisms, this function is entirely carried out by the sensory cells of the individual. These cells are stimulated by the environment. The resulting impulse is sent directly from a cell to a muscle or gland cell (König and Liebich, 2007).

The nervous system consists of nerve cells. Nerve cells are called neurons (Arıncı and Elhan 1997; Dursun, 2000). Neurons are connected by intercellular connections that allow the transmission of nerve impulses between muscle cells and gland cells. These gaps between the various cells involved in nerve signaling are called synapses and play an extremely important role in the transport of impulses. Impulses generated by the nervous system are transmitted in electrical or chemical form. An electrical signal is

produced by potentially reducing the membrane in the neurons (electrical synapse). A chemical signal is produced by the release of synaptic neurotransmitter substances. For example; acetylcholine, noradrenaline, dopamine, serotonin (König and Liebich, 2007). Chemical transmission is the most important mechanism of synaptic communication in the mammalian nervous system (Yetgin, 2014).

General Information

Neurotransmitter are described as a chemical substance synthesized from a neuron, released at a synapse following depolarization of the nerve terminal (generally dependent on inflow of calcium ions), which binds to the receptors on the presynaptic terminal and postsynaptic cells to form a specific response (Siegel and Sapru, 2006).

Neurotransmitters are found throughout the body and various biological fluids, including plasma, serum, cerebrospinal fluid, platelets, saliva and urine. Neurotransmitters fulfill specific biological functions in the body. Neurotransmitters also play an important role in the neurological regulation of the brain (Marc et al., 2011). There are over 60 different chemical substances used as neurotransmitters in the nervous system. Acetylcholine is

the first neurotransmitter to be discovered (Raven and Johnson, 1996).

Criteria used in defining neurotransmitters

For a chemical substance to be identified as a neurotransmitter, it must meet certain specific criteria. Some of these are:

1. The chemical substance that is likely to be a neurotransmitter has to be synthesized and stored in the neuron that uses it.
2. The chemical substance must be present in the presynaptic terminal and released in the amount that will produce a specific response to the postsynaptic target with neuron stimulation.
3. When the chemical substance is administered directly to postsynaptic neurons in biological quantities by spontaneous methods, it should produce the same effect as if released from the presynaptic neuron. The fulfillment of this criterion indicates the presence of receptors for that transmitter in the postsynaptic membrane.
4. There must be a mechanism to terminate the synaptic effect (Klein, 2008).

Impact mechanisms of neurotransmitters

Neurotransmitters effect that either opening the ion gates directly (ionotropic action) or causing the formation of cAMP (metabotropic effect), which leads to the opening of ion gates in the postsynaptic cell and other effects. The exciter transmitter is called a transmitter, which allows the

wave of depolarization to occur by opening the Na channels. inhibitor transmitter that opens one or both of the K and Cl channels is called a transmitter. The excitation and inhibition of a transmitter depends not only on the nature of the transmitter but also on the structure of the receptor on the postsynaptic membrane. For example; 1- When a neuron is stimulated by acetylcholine, it is inhibited by glycine. There is an excitatory receptor for acetylcholine, and an inhibitor receptor for glycine. 2- Noradrenaline causes some synapses in the central nervous system (CNS), causing some inhibition. 3- Acetylcholine has a stimulatory effect on the neuromuscular junction, whereas it is inhibitory in the heart (Anonymous, 2017a).

In some transmitters made of monoamine or peptide, the "effect by state" may be relevant; That is, the transmitter may enhance or suppress a transmitter response of the classical exciter or inhibitor of the target neuron, but when applied alone does not alter membrane potential or ion conductivity or minimally affect. The effects according to this type of situation are defined as "modulator effect" (Burnstock, 1995; Aston-Jones et al., 2001).

Classification of neurotransmitters

Neurotransmitters are divided into three major classes: small molecule transmitters, neuroactive peptides and gas neurotransmitters. Classification of neurotransmitter substances in the nervous system is shown in Table 1 (Siegel and Sapru, 2006).

Table 1. Classification of neurotransmitters (Siegel and Sapru, 2006).

Small molecule Neurotransmitters	Neuroactive peptides	Gas Neurotransmitters
Acetylcholine	Opioid peptides	Nitric oxide
Excitatory amino acids	β -endorphin	
Glutamate	Methionine-Enkephalin	
Aspartate	Leucine-Enkephalin	
Inhibitor amino acids	Endomorphine	
GABA	Nociceptin	
Glycine	Substance- P	
Biogenic amines		
Catecholamines		
Dopamine		
Norepinephrine		
Epinephrine		
Indole amines		
Serotonin		
Imidazole amines		
Histamine		
Purines		
Adenosine Triphosphate		
Adenosine		

Colocalization of neurotransmitters in neurons

With the emergence of neuroanatomical and neurochemical techniques and the examination of numerous neuronal populations, it has been shown that the vast majority of neurons contain up to four neurotransmitter species, at least two in synaptic nodes. This is known as neurotransmitter colocalization. Large

molecule neurotransmitters are most likely to be colocalized with another large neurotransmitters. Small molecule neurotransmitters must be colocalized with each other, although this is rarely observed. When neurotransmitters are colocalized in a synaptic knot, they are often found in different storage vesicles. However, there are also cases where different large molecular

neurotransmitters are found in the same vesicle. Colocalization of neurotransmitters provides great flexibility in the functioning of a neuron. When large molecule neurotransmitters are colocalized with small molecule neurotransmitters, they may need a higher frequency of action potential discharge than large molecule neurotransmitters to release from the terminal. Thus, depending on the activity of the neuron, a neuron has neurotransmitter expression capacity in different modes. While low activity can only result in the release of small molecule neurotransmitters and produce a type of postsynaptic response, higher activity may result in the release of large molecule neurotransmitters, resulting in a different postsynaptic response (Klein, 2008).

The studies have focused on the colocalization of GABA and dopamin (Barreiro-Iglesias et al., 2009), GABA and glycine (Chen and Hillman, 1993), catecholamine and serotonin (Miceli et al., 1987), nitric oxide synthase (NOS) and GABA (Valtschanoff et al., 1992), cGMP and NOS (Mckee et al., 1994).

Release steps of neurotransmitters

Release of small molecule neurotransmitters

The steps involved in the synthesis, transport and release of small molecule neurotransmitters are shown below:

- 1- The enzymes required for the synthesis of small molecule transmitters are synthesized from within the neuronal cell body of the granular endoplasmic reticulum.
- 2- They are transported to the Golgi apparatus.
- 3- Within the Golgi apparatus, they are modified (e.g., sulfation, glycosylation)
- 4- Analyzable enzymes (e.g., acetylcholinesterase, tyrosine hydroxylase) are transported along the axon to the nerve end by slow anterograde axonal transport (0.5-5 mm / day) through microtubules. The remaining enzymes are transported by rapid anterograde axonal transport.
- 5- The precursors necessary for the synthesis of small molecule neurotransmitters are introduced through the transport proteins located within the plasma membrane of the nerve ending and the neurotransmitters are synthesized within the presynaptic nerve terminal from the precursors. The enzymes necessary for neurotransmitter synthesis are synthesized in the neuronal cell body and transported to the nerve terminal.
- 6- The synthesized neurotransmitter pool in the cytoplasm is taken up into small vesicles by vesicular membrane transport proteins. Small-molecule transmitters generally contain open-core vesicles. The norepinephrine and serotonin include dense-core vesicles.
- 7- Neurotransmitters are released via exocytosis as a result of appropriate stimulation (Siegel and Sapru, 2006).

Release of neuropeptide neurotransmitters

These neurotransmitters usually mediate the slowing of brain function. The steps involved in the synthesis, transport and release of neuropeptide neurotransmitters are shown below:

- 1- Polypeptides much bigger than the last peptide transmitter (also referred to as the pre-propeptide) are synthesized in the granular endoplasmic reticulum, where it is turned into a propeptide. The enzymes necessary for the division of the polypeptides are also synthesized in the granular endoplasmic reticulum.
- 2- Propeptide and enzymes are transported to the Golgi apparatus where the vesicles are packaged.

3- Propeptide and enzyme-filled vesicles are transported to the nerve endings along the axon by rapid axonal transport (400 mm/day) via microtubules. Adenosine triphosphate, which requires "motor" protein such as kinesin, is required for this transport.

4- Protopropeptide cleavage enzymes to produce smaller peptide neurotransmitters remain within large dense nucleated vesicles.

5- Peptide neurotransmitters are then released into the synaptic cleft via exocytosis.

6- Subsequently, the peptide transmitters will diffuse away and be reduced by proteolytic enzymes. Once reduced, the peptide transmitters are not transferred to the nerve terminal in the same situation as the small molecule neurotransmitter (Siegel and Sapru, 2006).

Inactivation of neurotransmitters

The activities of neurotransmitters can be stopped with four different mechanisms:

- 1- Diffusion: Neurotransmitters move away from the synaptic cleft, where it no longer acts as a receptor.
- 2- Deactivation (enzymatic degradation): A specific enzyme changes the structure of the neurotransmitter. Therefore, the neurotransmitter is not recognized by a receptor. For instance, the acetylcholinesterase enzyme acetylcholine separates choline and acetates.
- 3- Glial cells: Astrocytes remove neurotransmitter substances from the synaptic cleft.
- 4- Reuptake: All neurotransmitter molecules are taken back into the released axon terminal. Norepinephrine is a common pathway to stopping the action of dopamine and serotonin. These neurotransmitters are removed from the synaptic cleavage as they can not bind to receptors (Anonymous, 2017b).

Detection methods of neuroactive substances

The methods used to analyze the effects and the natural structure of neuroactive substances are quite broad. Some of the basic methods commonly used in neuroscience to investigate the functions of neuroactive substances, behavioral and modelial formulas are: Bio and radioisotope assays, microdialysis and electrochemical discoveries, autoradiography, chromatography, Immunohistochemical methods, In situ hybridization (ISH), dyeing and monitoring of neuroanatomical pathways, electrophysiology, behavioral tests (Halbach and Dermietzel, 2002b).

Small molecule neurotransmitters

1. Acetylcholine

Acetylcholine is a neurotransmitter found at the neuromuscular junction, at the post-synaptic and presynaptic terminals of the parasympathetic nervous system, at the presynaptic terminal of the sympathetic nervous system and at the same time in various regions of the CNS. Acetylcholine, a neurotransmitter localized to both the peripheral and central nervous system, is synthesized by choline acetyltransferase, the synthesis of its rate-limiting enzyme, from the presynaptic terminal of choline and acetylcoenzyme (CoA). Acetylcholine, like many other neurotransmitters, has the ability to bind to both ionotropic and metabotropic receptors. Ligand-capped sodium (nicotinic receptor) in skeletal muscles is also an excitatory neurotransmitter that can bind directly to ion channels and cause them to open. An inhibitor neurotransmitter that binds to G-protein bound receptors that allows the opening of potassium ion channels in the heart. Acetylcholine is found in the autonomic nervous

system, specific sympathetic and parasympathetic preganglion. At the same time, it has also localized to areas of the CNS such as the striatum interneurons, forebrain neuron projection, brain stem and motor neurons of spinal cord. Acetylcholinesterase enzyme is located within the synaptic cleft of the postsynaptic membrane. This enzyme separates acetylcholine to choline and acetyl CoA (Patestas and Gartner, 2006).

In some degenerative brain diseases such as Alzheimer's disease, dysfunction occurs in the cholinergic system (Halbach and Dermietzel, 2002a). Acetylcholine is one of the important neurotransmitters in the brain. It is important for attention, cortical activation, reward and pain senses, memory and learning. Acetylcholine has played a major role in stabilizing motor toning against the possible effects of movement and dopamine (Johnston and Silverstein, 1998; Cooper et al., 2003; Herlenius and Lagercrantz, 2004).

2. Excitatory amino acids

2.1 Glutamate-Aspartate

L-glutamate and L-aspartate amino acids are the most abundant excitatory neurotransmitters in the CNS. The excitatory effect of both amino acids has been confirmed by several studies and it has been confirmed that they play a key role as excitatory amino acids in brain tissues (Halbach and Dermietzel, 2002a). Glutamate is the main excitatory neurotransmitter in mammalian CNS. At the end of 1970s it was fully accepted that glutamate was found the first amino acid neurotransmitter (Zeyden et al., 2008).

Glutamate is found in almost every region of the brain, as well as the presynaptic terminals of the dorsal root ganglia of the spinal canal. Glutamate, probably the most common excitatory neurotransmitter, is synthesized from glutamine in the presynaptic terminal catalyzed by the glutaminase enzyme. When the glutamate is released into the synaptic cleft in the CNS, it must be removed rapidly. Otherwise glutamate will cause postsynaptic neurons to change the repetitive stimulus resulting in neuronal degeneration and gradual death. This stage is known as excitotoxicity. Free glutamate in the cleft of synapse is endocytosed by the presynaptic terminal to prevent toxicity. The glutamate, which is endocytosed by the presynaptic terminal, is converted by glutamine synthetase enzyme to glutamine, which is then converted to glutamate form. The same reaction occurs in glial cells. All this sequence is known as the glutamine-glutamate cycle (Patestas and Gartner, 2006). Glutamate is involved in many metabolic pathways and is found throughout the mammalian brain (Platt, 2007). Glutamate may be a potent neurotoxin. Long-term stimulation of neurons by the excitatory amino acids can cause neuronal deaths or injuries (Siegel and Sapru, 2006). It has been reported that the glutamate concentration decreases in the hippocampus and anterior frontal cortex of schizophrenic patients (Shah et al., 2002).

3. Inhibitor amino acids

3.1. GABA

GABA is an important inhibitor neurotransmitter of mammalian CNS. GABA was accepted as a neurotransmitter at the end of the 1960s and at the beginning of the 1970s (Bowery and Smart, 2006). Gamma aminobutyric acid (GABA) is an inhibitor neurotransmitter used in approximately 30% of the CNS neurons. GABA is produced from glucose by way of glutamate, whose conversion to GABA is catalyzed by the enzyme glutamic acid decarboxylase. When GABA is released in the

presynaptic terminal where free neurotransmitter molecules are present, they are rapidly absorbed again by presynaptic terminals and neuroglia using GABA - specific membrane associated transport proteins. GABA is found in Purkinje cells of the cerebellum and in the local peripheral interneurons (Patestas and Gartner, 2006). Decreased neuronal inhibition effect of GABA in neurons causes epileptic discharges resulting in seizure development (Eroğlu, 2012).

3.2. Glycine

Glycine, one of the most common inhibitor neurotransmitters of the spinal canal, is synthesized by the serine hydroxymethyltransferase enzyme (Patestas and Gartner, 2006). Glycine is found in body fluids and tissue proteins in significant quantities. It is not an essential amino acid, but is found as an intermediate product in protein metabolism, peptides and bile salts. Glycine was implicated as an inhibitor neurotransmitter to the spinal cord, lower brainstem and retina (Siegel and Sapru, 2006).

4. Biogenic amines

4.1. Catecholamines

Three important catecholamines with similar properties are dopamine, norepinephrine and epinephrine (Patestas and Gartner, 2006). Catecholamines are synthesized from tyrosine amino acid. Thanks to the tyrosine hydroxylase enzyme, tyrosine is converted to DOPA (dihydroxyphenylalanine). DOPA is converted to dopamine (dihydroxy phenylethylamine) with DOPA-decarboxylase. Dopamine is turned into noradrenaline with the enzyme dopamine- β -hydroxylase. Noradrenaline is converted to adrenaline by the help of phenylethanolamine-N-methyl transferase (Ganong, 2005).

4.1.1. Dopamine: Dopamine neurons are found mainly in the ventral tegmental area, the substantia nigra and the arcuate nucleus of the hypothalamus. Axons emerging from the substantia nigra reach the striatum. Axons from the ventral tegmental area reach the nucleus accumbens, the limbic system and the prefrontal cortex. Axons from the arcuate nucleus reach the pituitary gland (Girault and Greengard, 2004).

Dopaminergic activity is associated with motivational behavior (Svensson and Mathe', 2002). It has been reported that changes in dopaminergic activity in the striatum and prefrontal cortex are associated with memory (Myhrer, 2003). Dopamine plays a role in transmitting information between nuclei in the basal ganglia in the brain and controls voluntary movements (Sherwood, 2007). Dopamine also leads to changes in learning and memory by different mechanisms (Breitenstein et al., 2006). Regularly cellular and molecular signaling of dopamine and glutamate is known to function in learning method, adaptation, language translation functions, synaptic plasticity and long-term memory consolidation (Berke and Hyman, 2000). At the same time, Dopamine has been reported to play an important role in the pleasure mechanism and may be associated with drug dependence, coercive behavior, loss of attentiveness and schizophrenia (Robert and Benoit, 2008).

4.1.2. Noradrenaline (Norepinephrine): Noradrenalin (NA) is secreted from the axonal ends of a large number of neurons located in the brain stem and hypothalamus of cell bodies. NA is also secreted from most postganglionic neurons of the sympathetic nervous system (Kandel et al., 2000). It plays a very important role in the fulfillment of the functions of the locus ceruleus, cortex, hippocampus, amygdala, thalamus, hypothalamus and behavioral responses such as awakening, stimulation, discrimination

of fear stimuli, eating behavior and learning (Aston-Jones et al., 1994, Ressler and Nemeroff, 2000). Increased levels of noradrenalin cause symptoms such as stress, fear, tachycardia, involuntary tremor, mouth instability, increase in blood pressure and sweating (Ninan, 1999).

4.1.3. Adrenaline (Epinephrine): Epinephrine is an excitatory neurotransmitter derived from norepinephrine. Epinephrine is very rarely used as a neurotransmitter in CNS neurons and is limited to the front of the medulla oblongata (Patestas and Gartner, 2006).

5. Indole amine

5.1 Serotonin: Serotonin is derived from tryptophan, an amino acid which is converted into 5-hydroxytryptophan by the rate-limiting enzyme tryptophan-5-hydroxylase. Serotonin is an excitatory neurotransmitter (Patestas and Gartner, 2006).

Serotonin and serotonergic neurons have localized into the pons, midbrain, medulla, epiphyseal gland, hypothalamus, substantia nigra and raphe nuclei in the brainstem. (Herlenius and Lagercrantz, 2004; Patestas and Gartner, 2006; Siegel and Sapru, 2006). These neurons have some cognitive functions as well as functions that include stimulation and sleep modulation. In addition, these neurons may have regulatory effects on catecholamine levels (Patestas and Gartner, 2006).

6. Imidazole amine

6.1 Histamine: Histamine is a pharmacologic agent that is released by mast cells and basophils. Histamine capillaries are responsible for the leakage from the veins and also for the contraction of the bronchial smooth muscles. In the nervous system, the hypothalamus is localized to the median eminence and mostly into the pituitary gland. Histamine has been shown to be able to influence sensory, memory and learning through H1 receptors (Patestas and Gartner, 2006). Histidine is decarboxylated by the histidine decarboxylase enzyme to form histamine. Histamine is metabolized by two enzymes: histamine methyltransferase and diamine oxidase (Siegel and Sapru, 2006).

7. Purines

Recently, ATP (adenosine triphosphate) has been implicated as a neurotransmitter. Purinergic transmission was seen in the bladder, intestinal, smooth muscle and vas deferens. ATP is also responsible for the pain mechanisms. Adenosine is accepted purinergic neurotransmitter. However, it is not a classical neurotransmitter because it is not stored in presynaptic vesicles and is not released in a calcium dependent manner. Adenosine is obtained by the degradation of ATP by extracellular enzymes (Siegel and Sapru, 2006).

Neuropeptides

1.Somatostatin: Somatostatin, released by one of the diffuse neuroendocrine system cells (DNES) and produced by one of the paracrine hormones, was first observed in the digestive tract. Somatostatin is an inhibitor of neurotransmitter in CNS and localized to hypothalamus, amygdala and small spinal ganglion cells (Patestas and Gartner, 2006).

2. Substance - P: Substance-P was first discovered in the digestive tract. Later, unipolar neurons of trigeminal and dorsal root ganglia were observed along with spinal cord, hippocampus and neo-cortex. Substance - P, one of the most important neurotransmitters of nociception, is an excitatory neuropeptide (Patestas and Gartner, 2006).

3. Opioid Peptides: Opioid neuropeptides constitute an important subgroup of neuropeptides, formed by the combination of at least 20 neurotransmitter substances. Although three categories (enkephalin, endorphin,

dynorphin) are examined, three important features are common: 1 - they are mostly inhibitors. 2- They bind to opium receptors in post synaptic membrane. 3- They serve as an agonist of substance-p, containing pain (Patestas and Gartner, 2006).

Enkephalin is a neurotransmitter used by many interneurons as well as synapses in the dorsal horn of the spinal cord. Enkephalin is also used as a neurotransmitter in the limbic system, the cerebral cortex, the striatum, and the raphe nuclei of the brainstem. Endorphin is mostly localized to the hypothalamus. Dynorphine is localized in amygdala, limbic system and hypothalamus (Patestas and Gartner, 2006).

Nitric oxide (NO)

Nitric oxide is a gas derived from the amino acid of L-arginine by the action of nitric oxidase enzyme (Bredt and Snyder, 1992; Meller and Gebhart, 1993). NO is a very reactive molecule and therefore has a very short half-life (Yilmaz and Yur, 2010). It is not only a gas but also an inhibitor neurotransmitter (Patestas and Gartner, 2006). There are three forms of nitric oxide, neuronal (nOS), endothelial (eNOS) and inducible (iNOS) nitric oxide (Macnaughton, 1998; Li and Billiar, 1999; Malinski, 2007). In general, iNOS is a form distributed throughout the body after appropriate induction or stimulation; eNOS is located in the endothelial cells (Alexander, 1998), found in the vascular endothelium (Burette et al., 2002); and nNOS is found in dorsal root ganglia (Zhang et al., 1993; Ruda et al., 1994; Wu et al., 1998), in the spinal cord in neurons in the superficial layer of the dorsal horn, as well as in the intermediolateral cell column, around the central canal (Valtschanoff et al., 1992; Herdegen et al., 1994; Traub et al., 1994), in some motor neurons of the ventral horn (Dun et al., 1993; Terenghi et al., 1993; Wu et al., 1998) and in ependymal cells (Soyguder et al., 2004). Nitric oxide is an important determinant of pain in the body. It may also function in memory formation as it is located in the hippocampal formation. In addition, NO is also found in the olfactory system, the cerebellum, the striatum, the cerebral cortex and the hypothalamus (Arıcıoğlu, 2005; Patestas and Gartner, 2006). The role of NO as a transmitter in the CNS is still under investigation (Siegel and Sapru, 2006).

As a result, It is hoped that this study will be useful for research on neurotransmitter substances.

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