Introduction

Since the largely serendipitous clinical discovery of the mood-elevating effects of certain monoamine oxidase inhibitors in the 1950s (in the treatment of tuberculosis) and of the phenothiazine analogues, imipramine and its congeners, in the late 1950s and early 1960s (in the process of developing new antihistaminic drugs), a half century passed. There are now almost two dozen antidepressant agents which work by nine distinct pharmacological mechanisms at the receptor level. However, opposite to the divergence in their pharmacological mechanisms at the receptor level, antidepressant drugs probably stimulate similar pathways in subcellular level. These subcellular events or so called beyond receptor effects are named neuroplasticity, and the mechanism may be called as adaptation. These after-receptor processes, through their effects on synaptic transmission, and gene expression are indeed capable of altering many molecular events in the brain. In this article, the mechanisms of actions of antidepressants at- and beyond- the receptors are discussed by documenting some of the evidence indicating such long-term alterations. Accordingly, the well-known effects of antidepressants on the receptor level are initiating events of antidepressant drug action, which enhance and prolong the actions of norepinephrine and/or serotonin and/or dopamine. Only if an adequate dose of an antidepressant is taken chronically, the increase in the synaptic norepinephrine and/or serotonin and/or dopamine stresses or perturbs the nervous system and the therapeutic response results from the adaptations that occur as a consequence of these chronic perturbations.

The Actions of Antidepressants at the Level of Cellular Receptors:

Classical Antidepressants

Monoamin oxidase inhibitors (MAOI) and Tricyclic antidepressants (TCA)

The mechanism of action of an MAOI is to increase the availability of the monoamine transmitters; norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT), by blocking their metabolism. The classical MAOIs (i.e. tranylcypromine) are nonselective and irreversible, but the newer MAOIs are selective for MAO-A or MAO-B as well as reversible for MAO-A. Several reversible inhibitors of MAO-A are currently in development, but only moclobemide is marketed in Turkey (2).

TCAs are actually five or more drugs included in one (1): a serotonin reuptake inhibitor activity, a norepinephrine reuptake inhibitor activity, an anticholinergic-antimuscarinic activity, an alfa1-adrenergic antagonist activity, and an antihistamine (H1) activity (3). They also inhibit sodium channels at overdose levels, causing potentially lethal cardiac arrhythmias and seizures. Therapeutic actions of the TCAs are due to serotonin reuptake inhibition as well as norepinephrine reuptake inhibition (3). The degree and selectivity of inhibition of the 5HT versus NE transporters differ across the family of TCAs with clomipramine being most potent at 5-HT reuptake pump, and desipramine and maprotiline being more potent at NE reuptake pump. Side effects of the TCAs can be explained by their effects on H1, M1, and alfa1 receptors.
Tablo 1. Antidepressants available in the market (worldwide).

1) Tricyclics and Tetracyclics (TCA)
   - Imipramine
   - Desipramine
   - Trimipramine
   - Clomipramine
   - Amitriptyline
   - Nortriptyline
   - Protriptyline
   - Doxepin
   - Amoxapine
   - Maprotiline

2) Monoamine Oxidase Inhibitors (MAOIs)
   - Tranylcypromine
   - Phenelzine
   - Moclobemide

3) Serotonin Selective Reuptake Inhibitors (SSRIs)
   - Fluoxetine
   - Sertraline
   - Paroxetine
   - Fluvoxamine
   - Citalopram

4) Dual Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)
   - Venlafaxine

5) Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)
   - Nefazodone
   - Trazodone

6) Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)
   - Buproprion

7) Noradrenergic and Specific Serotonergic Antidepressant (NaSSAs)
   - Mirtazapine

8) Noradrenaline Specific Reuptake Inhibitor (NRI)
   - Reboxetine

9) Serotonin Reuptake Enhancer
   - Tianeptine

**Selective Serotonin Reuptake Inhibitors (SSRI)**

As their name implies, SSRIs selectively inhibit serotonin transport. This action causes a sudden increase in serotonin predominantly in the somatodendritic area of serotonergic neurons. With chronic administration, the sustained increases of serotonin in the somatodendritic area of the serotonin neuron cause desensitization of the somatodendritic serotonin-1A autoreceptors (3,4,5).

Once the somatodendritic autoreceptors desensitize, neuronal impulse flow is no longer as readily inhibited by serotonin. Thus, neuronal impulse flow is turned on(6). This causes increased release of serotonin from axon terminals, which causes desensitization of postsynaptic serotonin receptors as a final step. Desensitization of these receptors may contribute to the therapeutic actions of SSRIs or it could account for the development of tolerance to acute side effects of SSRIs. The pharmacological profile of an SSRI is to cause powerful but delayed disinhibition of 5-HT neurotransmission, presumably from every 5-HT pathway in the central nervous system (CNS). The disinhibition of serotonergic neurotransmission in the pathway from midbrain raphe to prefrontal cortex is presumed to mediate the antidepressant effect of SSRIs (7,8).

The SSRIs can also have side effects that are bothersome, such as anxiety, sleep disturbances, sexual dysfunction, and gastrointestinal disturbances (1). For these side effects, 5-HT2 and 5-HT3 receptors of certain serotonergic pathways are blamed. For instance, for the development of sexual dysfunction in the form of decreased libido, reduced pleasurable and reduction in arousal- the reciprocal relationship between serotonin and dopamine (with serotonin tending to inhibit sexual functioning and dopamine tending to enhance sexual functioning)- is presumed to play a role. It is presumed that the SSRIs, by disinhibiting serotonergic pathways that innervate mesolimbic dopamine systems may cause sexual dysfunction. This may also explain why agents that promote dopamine- such as buproprion or stimulants- can often reverse SSRI-induced loss of libido. On the other hand, for the sexual dysfunction in the form of ejaculation and orgasm problems, the serotonin pathway descending from brain stem down the spinal cord to spinal neurons that mediate various spinal reflexes is thought to be the cause. Increased serotonergic flow through this pathway inhibits sexual functioning. Evidence that serotonin mediates its negative effects on sexual functioning via 5-HT2 receptors comes from observations that 5-HT2 antagonists can occasionally reverse SSRI-induced sexual dysfunction and the antidepressants that possess 5-HT2 antagonistic effects don’t seem to induce sexual dysfunction (9,10).

SSRI-induced akathisia and agitation are hypothetically mediated by stimulating 5-HT2 receptors in the serotonin pathway that projects to the basal ganglia (11). This may be due to in part to the fact that serotonin inhibits dopamine release there. Thus, increasing serotonin may produce a mild pseudo-dopamine deficiency state and concomitant symptoms of akathisia and agitation.

SSRI-induced anxiety and even occasional panic attacks are hypothetically mediated by stimulating 5-HT2 receptors in the serotonin pathway that projects to the hippocampus and limbic cortex (12). SSRI-induced insomnia is hypothetically mediated by stimulating 5-HT2 receptors in brain stem sleep centers, particularly the serotonergic pathway that projects to the cholinergic neurons in the lateral tegumentum. Stimulation of the 5-HT3 receptors both in CNS pathways such as the brain stem vomiting center and the pathway to hypothalamus, and the gut itself appears to be responsible for various gastrointestinal side effects of the SSRIs (13). Disinhibition of the serotonin pathway from brain stem to hypothalamus, which mediates aspects of appetite and eating behaviors, may be responsible for the reduced appetite, nausea, and even weight loss associated with SSRIs.

**Serotonin / Norepinephrine / Dopamine Reuptake Inhibition (SNRI) (Venlafaxine)**

The pharmacologic effect of venlafaxine is dose dependent (1). At low doses, it is essentially an SSRI, at medium to high doses, additional NE reuptake inhibition occurs, and at high to very high doses DA reuptake inhibition also occurs (14).

**Serotonin-2 Receptor Antagonism with Serotonin Reuptake Blockade (Nefazodone, Trazodone)**

The only difference between SSRIs and nefazodone (and trazodone) is 5-HT2 receptors are blocked by nefazodone and trazodone, whereas stimulated by the SSRIs (1). Owing to this difference, nefazodone and trazodone don’t cause some of the side effects that SSRIs may cause such as the short-term increase in anxiety or insomnia, akathisia, and sexual dysfunction.
Norepinephrine and Dopamine Reuptake Inhibition (Bupropion)

The only antidepressant that ignores the serotonin system and acts selectively on the norepinephrergic and dopaminergic systems is bupropion (15). The pharmacologic effect of bupropion suggests clinical actions in areas where boosting norepinephrine and dopamine would be especially desired. There are some data suggesting that symptoms of dopamine deficiency could include psychomotor retardation, anhedonia, hypersonmia, cognitive slowing, inattention, pseudodementia, and craving (16). Such symptoms may be preferably targeted by bupropion. Moreover, because of its dopaminergic and noradrennergic activity it may have some benefical effects in attention deficit disorder (17) and in the treatment of smoking cessation (18). On the other hand, the pro-adrennergic activity of bupropion can also go too far, with overstimulation, agitation, insomnia or nausea as possible adverse effects (1,19). With controlled-release formulations, its effect of increasing seizure frequency is not different from the other antidepressants (20).

Alpha-2 Antagonism plus Serotonin-2 and Serotonin-3 Antagonism (Mirtazapine)

Mirtazapine is also called as NaSSA, noradrenergic and specific serotonergic antidepressant (21). By this, it is implied that mirtazapine has both pro-adrenergic and pro-serotonergic actions and its serotonergic actions are selectively directed away from the 5-HT2 and 5-HT3 receptors to the 5-HT1A receptor. The pro-adrenergic and pro-serotonergic actions are due to its alpha2-antagonist properties. alpha2-antagonist disinhibits both serotonin and norepinephrine neurotransmission. Like nefazodone, mirtazapine does not cause the side effects of SSRIs due to 5-HT2 stimulation. Since it is also a serotonin-3 antagonist, it doesn’t share the actions of SSRIs that lead to 5-HT3 stimulation, such as gastrointestinal disturbances. On the other hand, due to its strong antihistamine properties, mirtazapine has the side effects of weight gain and sedation (1.21).

Noradrenalin Specific Reuptake Inhibitor (NRI) (Reboxetine)

Reboxetine is the first truly selective noradrenaline (norepinephrine) reuptake inhibitor. Pharmacologically and chemically unrelated to TCA or SSRIs, reboxetine has significant affinity for the noradrenaline transporter, and little affinity for other neurotransmitters including serotonin, dopamine, histamine, muscarinic and alpha adrenergic sites. NE depletion studies suggest that while NE reuptake inhibition may improve all core symptoms of depression, NE regulation may be most closely correlated with patient’s improvements in energy, interest, concentration, agitation, helplessness, and hopelessness. Reboxetine, therefore, through its mechanism of action may be useful for those depressed patients with either anergic symptoms or for those patients with comorbid anxiety. The selectivity of reboxetine for NE and benign side effect profile which are less likely observed than other drugs and placebo (i.e. dry mouth, constipation, and sexual dysfunction) lead the drug to be well tolerated (22).

Serotonin Reuptake Enhancer (Tianeptine)

Tianeptine is a tricyclic compound of dibenzothiazepine type which is the only representative of this subgroup. Tianeptine increases the presynaptic uptake of serotonin after single as well as repeated administration, but this action is not linked to any effects on the 5-HT post-synaptic systems (23). Tianeptine has no affinity for afa1 adrenergic and H1 antihistaminic receptors. This affinity is responsible in a large part for the sedative anxiolytic properties of antidepressants. Tianeptine has no affinity for the muscarinic receptors (23,24). In clinical trials, the double-blind trials confirm the antidepressant efficacy in essentially neurotic depressive syndromes, similar to that of imipramine and amitriptyline. They do not show a shorter onset of time for antidepressant activity. The therapeutic profile appears to be neither stimulating nor sedative. Some arguments are in favor of an anxiolytic activity (24). Others favor a more psychotonic profile. Tianeptine can be classified among the mid-position antidepressants. With respect to clinical acceptability, tianeptine has no anticholinergic effect and no cardiovascular effect. As with any active pharmaceutical products, this medicine may cause somewhat unpleasant side effects in certain patients. Although such effects are rare, usually mild and temporary, they include gastralgia, abdominal pain, dry mouth, anorexia, nausea, vomiting, flatulence, insomnia, drowsiness, nightmares, asthenia, and tachycardia (23,24).

Adaptive Ability of Brain (synaptic plasticity):

Even though the inhibitory actions of antidepressants on reuptake or monoamine oxidase are immediate, their clinical efficacy requires weeks of treatment (25). This time delay on the onset of treatment response has resulted in the view that it is chronic adaptations in brain function, rather than increases in synaptic norepinephrine serotonin per se, that underlie the therapeutic effects of antidepressant drugs. Thus, the focus of research on antidepressant mechanisms has shifted increasingly from the immediate effects of antidepressants to effects which develop more slowly. The anatomic focus of research on antidepressants also has shifted. While monoamine synapses are still considered the immediate target of antidepressant drugs, more attention is now focused on target neurons, in which chronic alterations in signal transduction systems and gene expression arise.

The so called synaptic plasticity or neuroplasticity is the adaptive ability of the human brain. If the right neurons are stimulated with adequate intensity within certain time constraints, a long-term change occurs, such as alternations in dendritic function, synaptic remodeling, long-term potentiation, axonal sprouting, neurite extention, synaptogenesis, and even neurogenesis (25-27). This stimulation may result from environmental events or psychotropic drugs including the antidepressants. For a long period of time, much of the biological investigation in psychiatry has focused on synaptic pharmacology, especially on neurotransmitter turnover and neurotransmitter receptors, disregarding this brain-adaptive ability (26,27).

Recently, Hyman and Nestler proposed a framework for understanding psychotropic drug action “initiation and adaptation”. This framework capitalizes on recent advances in molecular neurobiology and places acute and chronic
drug effects in a functional context (26). Immediate dosing of antidepressants produces little in the way of subjective or behavioral effects (other than side effects). Substantial improvement in depressive symptoms occurs only if the drugs are taken at adequate dosage and with adequate frequency and permanence. However, it may not be necessary to maintain constant therapeutic serum levels for efficacy (25,26). Therefore, based on the framework developed by Hyman and Nestler, antidepressant-induced increases in synaptic serotonin or norepinephrine or dopamine, can be conceptualized as initiating events for long-term changes in neural function (26). It is the adaptive response of the nervous system to adequate repeated perturbations mediated through these initial targets that produces the therapeutic responses to antidepressants. These adaptations are rooted in homeostatic mechanisms that exist, presumably, to permit cells to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu. Chronic administrations of antidepressant drugs create perturbations in neurotransmitter function that likely exceed the strength and time course of almost any natural stimuli. The result of these types of repeated perturbations or initiating events is to seize normal homeostatic mechanisms within neurons, thereby producing adaptations that lead to substantial and long-lasting alterations in neural function. These adaptations may be both quantitative, which involve simple up- or down-regulation of signaling through a given pathway in response to a certain stimulus, and also qualitative, like adaptations leading to remodeling of synapses or altering brain’s response not only to initiating stimulus but to other stimuli as well. Such qualitative changes may be involved in long-term actions of antidepressant drugs (26).

The Molecular Basis of Signal Transduction:

Once a neurotransmitter binds to its receptor, the receptor must pass the signal encoded by the neurotransmitter to the interior of the receiving cell. On the basis of the ways in which different neurotransmitter receptors transmit signals to the cell interior, these receptors have been divided into two classes:

1. The receptors that act as ligand-gated channels; these receptors contain an intrinsic pole or channel through which ions can pass in response to the binding with neurotransmitter (ligand) (e.g., Glutamate and d-Aminobutyric acid) (GABA) receptors.

2. G-Protein-linked receptors; In this case, the conformational change caused by neurotransmitters binding to cell surface receptors activate intracellular proteins called G-proteins (28).

All of the noradrenergic receptors and 16 of the 17 known serotonin receptors (the one exception is the 5-HT3 receptor which contains a cation selective channel intrinsic to the macromolecule), all five of the known dopamine receptors, all five of the known muscarinic receptors, and all of the known neuropeptide receptors are G-protein linked receptors. In addition to their receptors that have ligand-gated channels, a subset of glutamate and GABA receptors are G-protein linked (29). G-proteins that have been activated by neurotransmitter receptors exert two major types of effects within neurons; they can act in the membrane to directly regulate the behavior of ion channels, and they can regulate second messenger systems (25,26).

The effects of G-proteins on ion channels are generally more subtle than those produced by ligand-gated channels. Most often, G-proteins don’t cause ion fluxes that directly cause action potentials. Rather, they effect the behavior of ion channels, such as potassium or calcium channels that can alter the intrinsic excitability of neurons or affect the ability of neurons to release neurotransmitters. As a result, the most significant effect of G-protein regulation of ion channels is often an alteration in the responses of neurons to subsequent stimulation by excitatory or inhibitory inputs subserved by glutamate or GABA receptors. The other major effect of G-proteins within neurons is to regulate enzymes that produce second messengers (26).

Neurotransmitters are first messengers, carrying information between neurons (30). Many second messengers (e.g. cyclic adenosine monophosphate-CAMP, inositol three-phosphate, and calcium ions) are small water-soluble molecules that diffuse throughout the cytoplasm to activate their targets. Other second messengers, such as diacylglycerol, remain associated with the membrane (26). With a few exceptions, second messengers exert their effects by regulating enzymes called protein kinases and protein phosphatases (30,31). While protein kinases act by transferring a phosphate group to specific protein substrates within cells, protein phosphatases do the opposite and remove phosphate groups from proteins. Since phosphorylation changes the conformation of the protein, it produces significant changes in how protein works. Virtually, every type of protein can be regulated by phosphorylation, meaning that all biological processes that occur within neurons are subject to dynamic regulation by neurotransmitters and second messenger systems (31).

In addition to neurotransmitters, there are other types of chemical messengers utilized by the nervous systems, trophic factors or growth factors (30-32). The best known of the trophic factors is the nerve growth factor which operates at least in part through protein kinases (26,30-32). But, these protein kinases phosphorylate proteins on different amino acid residues than the second-messenger regulated protein kinases. There are some data suggesting the existence of a cross-talk between neurotransmitter-activated intracellular signaling pathways and trophic factor pathways (26). The ability of protein kinases to phosphorylate proteins in the cell is not limited to the cytoplasm. In addition to their ability to phosphorylate a wide array of substrate proteins, including ion channels, neurotransmitter receptors, cytoskeletal structures, enzymes that synthesize neurotransmitters, ribosomal proteins, they can also phosphorylate certain proteins in the nucleus so called transcription factors (32).

Transcription factors (or trans-acting factors) are specialized proteins that control gene expression by binding to certain short sequences of deoxyribonucleic acid-DNA called cis-regulatory elements so that environmental signals can be converted into activation or repression of the expression of the gene to which the related transcription factor binds. Among hundreds of transcription factors cAMP response element binding protein (CREB) and Fos are the two well-known ones (26,30-32). It has been shown that, CREB regulates genes for neurotransmitter synthetic enzymes (e.g., tyrosine hydroxylase), proteins involved in programmed cell death/neurogenesis (e.g., B-cell lymphoma protein-2; bcl-2), and for numerous neuropeptides (e.g., endogenous opioid peptides) (25,26,28-32).
Neuroplasticity and Adaptive Responses of Brain as Mechanisms Underlying Antidepressant Actions:

Recent studies demonstrate that structural alterations occur in response to stress in primates and also in patients with mood disorders. Moreover, studies demonstrate that these structural alterations are reversible upon administration of antidepressants (31-33). Studies in rodents and nonhuman primates demonstrate that exposure to stress can cause alteration in the processes and number of neurons. Repeated stress is reported to cause atrophy of CA3 pyramidal neurons in the hippocampus, including a decrease in the number and length of apical dendrites (31,32). In addition, exposure to stress has been shown to decrease the proliferation of cells in the dentate gyrus of the hippocampus (34).

Brain imaging studies demonstrate that the volume of the hippocampus is decreased in patients with depression (35). There is evidence indicating volumetric and cellular loss in the subgenual frontal cortex of patients with major depression (36,37). Furthermore, it has been reported that chronic administration of antidepressants can prevent this atrophy either by blocking or opposing the stress-induced cell death (29-32,38).

Neurotrophic factors, including brain derived neurotrophic factor-BDNF, nerve growth factor, and neurotrophic factor-3 were originally characterized by their action during development and maturation of neurons. However, these neurotrophic factors are also expressed in the adult brain and are known to influence the survival and function of mature neurons. In this context, recently, it has been shown that neurogenesis can take place in the adult brain as well (29-32). The expression of BDNF in the hippocampus is downregulated by exposure to stress. It is possible that the downregulation of BDNF may contribute to the atrophy of neurons and reduced neurogenesis in the hippocampus and subgenual frontal cortex of the depressed patients. Chronic antidepressant administration increases the expression of BDNF in the hippocampus and frontal cortex, and hence promotes neurogenesis. Induction of BDNF in the hippocampus is observed with different antidepressants, but not with nonantidepressant psychotropic drugs. Besides, chronic administration of antidepressant drugs has been shown to avoid the stress-induced decrease in the expression of BDNF (31,32). The possibility that up regulation of BDNF contributes to the therapeutic actions of antidepressants is further supported by the behavioral studies. Chronic infusion of BDNF into the midbrain produces antidepressant effect in the Porsolt forced swim test and Seligman’s learned helplessness model (39).

More specific data indicating the adaptive response of brain in response to chronic use of antidepressant drugs comes from the antidepressant-induced changes in various neurotransmitter receptors and enzymes involved in neurotransmitter synthesis. Among these is the down regulation of postsynaptic b-adrenergic receptors in response to chronic antidepressant treatment in the rat cerebral cortex (40,41). This effect is produced by all of the cyclic antidepressants and even by chronic electroconvulsive seizures. Moreover, it has been shown that chronic administration of the tricyclic antidepressant imipramine regulates tyrosine hydroxylase activity in dopaminergic brain regions, including the cell body and terminal field regions of the mesolimbic and nigrostriatal pathways of the rat brain (42). Imipramine makes this effect via phosphorylation-dependent regulation of enzyme affinity for its pterin cofactor. Of note, imipramine’s regulatory effect of tyrosine hydroxylase activity in ventral tegmental area was found to be dependent on the strain of the rat; with chronic exposure decreasing the enzyme activity (tyrosine hydroxylase) in the Sprague-Dawley rats, but slightly increasing the enzyme activity in the Wistar rats. These observations- that large individual differences exist in biochemical response to antidepressant treatments are consistent with the clinical observations of individual differences in the therapeutic responsiveness of depressed patients to antidepressant drugs. Another finding indicating the adaptive response of brain to antidepressants is the desensitization of 5-HT 1A autoreceptors present on the serotonergic neuronal cell bodies with the chronic administration of these drugs (1,6). Compatible with the theory of adaptation, a recent meta-analysis has shown that antidepressant efficacy does not change accordingly to the pharmacokinetic half life of the antidepressant drug (43,44). Yildiz and Sachs demonstrated that there is no difference in the extent of clinical improvement between single versus multiple daily dosing for short, intermediate, and long half life antidepressant agents (43). As originally assumed by Hyman and Nestler, sustained therapeutic serum levels of antidepressant drugs are not necessary for achievement of therapeutic activity. Thus, it can be concluded that it is the adaptive response of the human brain to adequate repeated perturbations mediated through the initial targets that produces the therapeutic responses to antidepressants, providing further support for the adaptation theory.

Conclusions:

According to the so called “initiation and adaptation” framework, the well-known effects of antidepressants on receptor level are the initiating events of antidepressant drug action, which enhance and prolong the actions norepinephrine and/or serotonin and/or dopamine. Only if an adequate dose of an antidepressant is taken chronically, the increase in the synaptic norepinephrine and/or serotonin and/or dopamine stresses or perturbs the nervous system and the therapeutic response results from the adaptations that occurs as a consequence of these chronic perturbations (25-32).

We still lack an understanding of the precise adaptations which occur in response to antidepressants that lead to the relief of symptoms. However, recent advances in molecular and cellular biology indicates that mood disorders are related with an impairment of neuroplasticity and cellular resilience, and antidepressants or other mood regulating drugs exerts their effects through the enhancement of brain’s adaptive ability or in other words neuroplasticity and cellular resilience. Continued progress in understanding the neurobiology of antidepressant drugs will lead to further identification of this phenomenon and development of more effective and faster acting therapeutic agents. Additional basic research studies are required to determine the functional relevance of these effects at the neurochemical, morphological, and behavioral levels. Moreover, additional imaging studies are required to determine the relevance of these adaptations to the etiology and treatment of mood disorders.
References:


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