FORMS AND MECHANISMS OF HOMEOSTATIC SYNAPTIC PLASTICITY

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Long-term changes of neuronal network activity level result in the activity of excitatory and inhibitory synapses counteracting the change of the mean frequency of spike generation and contributing to network homeostasis maintenance. The review describes the manifestations of homeostatic synaptic plasticity *in vivo* and *in vitro*. The best investigated form of homeostatic synaptic plasticity, or "synaptic scaling" is the change of synapse intensity between excitatory neurons, multiple of initial synapse intensity and inversely proportional to the change of the frequency of spikes in postsynaptic neurons. However, the intensity of inhibitory synapses on excitatory neurons, as well as the intensity of excitatory synapses on inhibitory neurons, change directly proportionally to the change of spike frequency. There has been considered the central postsynaptic mechanism participating in the occurrence and further regulation of homeostatic plasticity of excitatory synapses — the alteration of the pool of α-amino-3-hydroxy-5-methyl-4-isoxasolpropionic acid receptors (AMPA-receptors). There have been characterized presynaptic molecular mechanisms and considered the role of concentration changes of intracellular calcium, molecules of cytoadherence, and the secretion of signal molecules in postsynaptic regulation of homeostatic plasticity.

Key words: synaptic plasticity; scaling; homeostasis; synapse.

The primary function of neuron is to receive, integrate and transmit information to other brain neurons. Neurons can alter their synaptic strength under different changes in environment. The most studied form of such adaptation of synaptic strength depending on activity level is Hebbian plasticity that includes long-term potentiation (LTP), and its counterpart, long-term depression (LTD).

The most of currently studied facts about the regulation of glutamatergic transmission depending on the activity level was discovered studying Hebbian plasticity, which is considered to be the base of memory and organization of neuronal networks during ontogenetic development. However, formation of functional networks require — in addition to LTP and LTD — the participation of some mechanisms for stabilization of total neuronal network activity, otherwise native mechanisms of positive feedback would destabilize network activity [1–4]. Chronic fluctuations of electrical activity of neuronal network cause compensatory alterations in synaptic strength of neurons which in turn affect the spike generation frequency, maintaining it within the optimal range. Such changes are called homeostatic plasticity or synaptic scaling [5]. Neuronal activity alterations should be rather long-term to induce homeostatic plasticity, i.e. it takes much longer time for induction of synaptic scaling than it is required for Hebbian plasticity, which can be initiated by synchronous activity of pre- and postsynaptic neurons within seconds [6].

There are various forms of homeostatic regulation of neuronal response, which vary depending on the increase of excitatory or inhibitory synapse strength [7–14], changes of internal excitability [15–19] or changes at the LTP and LTD induction mechanisms [2, 3, 17, 18]. All these forms of plasticity enable neurons to maintain homeostasis despite changes in the input signal and synaptic alterations. Recent studies [20–22] have shown synaptic scaling to co-exist simultaneously with other forms of synaptic plasticity.

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Moreover, it has been proved by computer modeling of neuronal networks that the co-action of synaptic scaling and feedforward inhibition creates optimal conditions for network training [23].

Mechanisms of homeostatic plasticity are believed to be of particularly importance during development, when there are many alterations of neuronal connections and synapses, which depend on the neuronal network activity level, and during the periods of increased plasticity, for example, during regeneration and recovery from injuries.

Experimental models used to study homeostatic synaptic plasticity

In most of the studies on the synaptic scaling, primary neuronal cultures are used as model systems. The advantage of such models *in vitro* is the ease of changing the total level of neuronal network activity with pharmacological manipulations, as well as the ease of measuring the synaptic strength using electrophysiological or immunocytochemical techniques [7, 8, 24].

In vivo models in their turn characterized by a more complex spatial organization and have more dense packing of neurons and synapses. Similar to pharmacological manipulation *in vitro*, application of tetrodotoxin (TTX) in the CA1 hippocampal area resulted in the increase of neuronal excitability that correlated with the increase of frequency or both frequency and amplitude (depending of the developmental stage) of miniature excitatory postsynaptic currents (mEPSC) mediated by receptors to α-amino-3-hydroxi-5-methyl-4-isoxazolepropionic acid (AMPA receptors, AMPARs) [25, 26].

While studying homeostatic synaptic plasticity in vivo, the deafferentation of sensory inputs is often used for the blockade of neuronal network activity in order to induce homeostatic changes in neurons [27, 28]. For example, the elimination of visual stimuli results in positive scaling of synapses of excitatory neurons of visual cortex [15, 29–34]. Moreover, in certain conditions of sensory deprivation homeostatic regulation of the total number of synaptic AMPARs is accompanied by the change of the number of synaptic calcium-permeable AMPARs [30, 31, 35].

Organotypic cultures combine the advantages of both *in vitro* and *in vivo* models. The advantages are the ease of activity manipulation using pharmacological agents and the preservation of the major aspects of native structural organization. Pozo and Goda recently reviewed in detail the pros and contras of all the mentioned experimental models [36].

Homeostatic plasticity in synapses between excitatory neurons

According to the principle of synaptic scaling, the activity of postsynaptic neuron changes homeostatically through the modifications of synaptic inputs [5, 7, 37]. Synaptic scaling of the excitatory transmission was first discovered using cortical and spinal cord neural cultures that were chronically treated pharmacologically [21, 38]. The main finding was the increase of AMPAR-mediated synaptic strength after reduction or total suppression of neuronal activity. The fundamental feature of synaptic scaling is its contribution to the maintenance of average activity level within the dynamic range optimal for effective transmission of information between neurons [1, 21]. The changes in synaptic input can have an effect on integrative characteristics of synapses and potentially modulate the threshold of LTP and LTD induction.

One of changes in postsynaptic neurons caused by synaptic scaling is the alteration of AMPAR-mediated transmission and in particular the alteration of the amplitude of AMPAR-mediated mEPSC [7]. These alterations are often accompanied by the regulation in the composition of synaptic AMPARs [24, 38–40]. Incubation of neuronal cultures with TTX or antagonists of AMPARs (in order to block electrical activity of neurons) for the period from several hours to several days causes accumulation of AMPARs in synapse and correlates with the increase of amplitude of AMPAR-mediated mEPSC. On the other hand, incubation of neurons with antagonists of A-type gamma-aminobutyric acid ($GABA_A$) receptors results in the reduction of synaptic pool of AMPARs and the decrease of the amplitude of AMPAR-mediated mEPSC. In addition, mEPSC frequency alterations [39, 41] can be limited in some synapses [41] and depend on the developmental stage [42]. Alterations of the frequency of AMPAR-mediated mEPSC can be explained by variation in the number of functional synapses, or changes in functional state of presynaptic neuron, or postsynaptic silencing/recovery of synaptic activity. Regardless of whether there are alterations in frequency or amplitude of AMPAR-mediated mEPSC during synaptic scaling, synaptic scaling is accompanied by the change in the number of calcium-permeable AMPARs [1, 39, 43–47].

Homeostatic plasticity of excitatory synapses on inhibitory neurons and inhibitory synapses on excitatory neurons

Currently, a great number of studies concerned with homeostatic plasticity is carried out on excitatory neurons. However, in a normally functioning brain the regulation of synaptic strength of inhibitory neurons plays a key role, especially during the so-called critical period of development [48, 49] and during synchronization of neuronal activity [50–52], as well as in the process of memory training and formation [53, 54]. The plasticity of inhibitory system is also involved in pathological processes, such as epileptogenesis and appearance of drug addiction [55, 56].

The maintenance of an average level of activity becomes possible if an increase of activity causes the strengthening of glutamatergic inputs on GABAergic interneurons, and their inhibition is induced during the total activity blockade. In studies on hippocampal cultures the increase of mEPSC amplitude in parvalbumin-expressing inhibitory neurons after long-term increase of activity level was discovered, as well as the decrease of mEPSC amplitude after activity blockade [9]. Alterations of mEPSC amplitude were caused by changes in expression of GluR4-subunits of AMPARs following their coaggregation with secreted neuronal activity-regulated pentraxin (NARP or NP2).

Postsynaptic mechanisms of homeostatic synaptic plasticity

Dynamic regulation of postsynaptic AMPARs is a critical mechanism underlying different forms of synaptic plasticity in many cerebral areas. AMPARs are the main excitatory postsynaptic glutamate receptors in central nervous system. It is formed by four various subunits (currently, GluR1–GluR4 are the most commonly used abbreviations of these subunits, however in the most recent nomenclature GluA1–GluA4 are used), which assemble a tetrameric functional ligand-dependent ion channels [57]. The assembly of AMPARs occurs through dimerization in such a manner that in most brain areas prevail heterotetrameric AMPARs consisting of GluR1- and GluR2-dimers, i.e. GluR1/GluR2-heteromers [57]. The most of mammalian AMPARs contain GluR2-subunits, which undergo the replacement of glutamine 607 in a pore loop with arginine at RNA level [58, 59]. Structural features of GluR2-containing receptors (e.g., positive charge in physiological pH) cause their properties such as impermeability for Ca^{2+}, sensitivity to polyamines and internal current rectification [60–62]. Although originally AMPARs without GluR2-subunits were found in interneurons only [63–67], recent studies [68, 69] have shown that under specific conditions they are present also in synapses of pyramidal neurons. Postsynaptic calcium-permeable AMPARs were found to be strongly regulated and depend on the neuronal activity level [68, 69].

One of the basic postsynaptic mechanisms participating in synaptic scaling is the regulation of AMPAR pool on postsynaptic membrane. Deprivation of activity or reduced sensory excitation of neurons for a long time (from several hours up to several days) results in accumulation of AMPARs subunits [31, 39, 40, 42, 43, 46]. The majority of researchers agree that there is the accumulation of GluR1-subunits, but there are also data that there is an accumulation of GluR2-subunits. The increase in the number of GluR1-subunits requires translation of GluR1 mRNA in dendrites [19, 43, 44] and is regulated by retinoic acid [19, 44, 46].

There is evidence indicating that the blockade of neuronal activity in dissociated hippocampal cultures with pharmacological agents results in the increase of the content of both GluR1-, and GluR2-subunits in a synapse [24, 40, 70] due to GluR2-regulatory mechanism [70, 71]. It has been suggested that the neuronal activity blockade can trigger global synaptic scaling, which regulates the content of both GluR1- and GluR2-subunits, while the blockade of N-methyl-D-aspartate receptors (NMDARs) simultaneously with the activity blockade can have specific effect on individual synapses and increase the number of calcium-permeable receptors [5]. In the studies showing simultaneous regulation of GluR1 and GluR2, there was used either TTX, or CNQX — specific antagonist of AMPARs for activity blockade [24, 40, 70, 71]. When NMDARs antagonist (2R)-amino-5-phosphonovaleric acid (APV) was also applied, TTX caused regulation of GluR1 and has no effect on synaptic level of GluR2 [19, 43, 44, 46].

Recently the homeostatic regulation of metabotropic glutamate receptors of astrocytes has been reported [72]. Physiological significance of this plasticity form still remains unclear.

Presynaptic mechanisms of homeostatic synaptic plasticity

Chronic activity blockade results in activation of presynaptic neuron functions as evidenced by the increase of volume of presynaptic neurons, the increase in the frequency of quantal release, the increase of synaptic vesicles recycling, as well as the rising neurotransmitter release probability, which is associated with the increase of quantal volume of neurotransmitter [73–76]. Although homeostatic changes of quantal volume of neurotransmitter are attributed mainly to postsynaptic component, there has been also described an additional presynaptic component which relates to activity-dependent modulation of vesicular glutamate transporter expression [76]. In fact, the presynaptic mechanism underlying the homeostatic change of neurotransmitter release probability is not well studied. Regarding the dependence of neurotransmitter release on Ca^{2+} concentration, it can be expected that some of Ca^{2+}-dependent signaling pathways are involved in this process. This hypothesis is supported by the studies on neuromuscular junctions of a fruit fly: the changes in calcium influx through calcium channels of P/Q-type result, at least partially, in activity-dependent compensatory changes of presynaptic strength [77–79]. It seems that in synapses in the central nervous system of vertebrata, homeostatic processes in presynaptic neurons result from the change of calcium influx in response to action potential (AP) [80]. The latest studies have shown that calcium sensor synaptotagmin as well as synaptic vesicle protein 2 (SV2B) participate in the increase of neurotransmitter release probability [81], moreover, P/Q-type calcium channels become enriched by pore-forming $Ca_v2.1$-subunit due to neuron activity blockade [82]. These findings enable to suppose that neurotransmitter release probability is regulated homeostatically through the control of voltage-gated calcium channels, which cause calcium influx in presynaptic terminals.

The second important question is how homeostatic regulation of the circulation of synaptic vesicles occurs when neurotransmitter release is increased. The investigation of M. Müller et al. [83] on neuromuscular junctions of a fruit fly identified the participation of protein Rab3-GAP (Rab3-GTP-activating protein) in homeostatic signaling system that is associated with Rab3-GAP participation in neurotransmitter release from presynaptic neurons. Dickman and colleagues using the genetic screening method on neuromuscular junctions of a fruit fly showed the gene snapin interacting with dysbindin and SNAP25 — a component of SNARE complex — to be involved in presynaptic mechanisms of homeostatic plasticity [84]. Researchers proved the silencing of gene snapin to block homeostatic modulation of neurotransmitter release from presynaptic neuron, which was induced by inhibition of postsynaptic glutamate receptors.

Another evidence of alterations of presynaptic functions during homeostatic changes was obtained by Wang and co-workers [85] in the model of experimental autoimmune autonomous gangliopathy (AAG). Antibodies to acetylcholine

receptors from AAG patients were administered to mice, and quick recovery of synaptic transmission was observed. Significant increase of spontaneous mEPSC frequency can be the result of increased neurotransmitter release after every AP. The same reasons seem to explain the cases of partial AAG remission in patients with high level of antibodies to acetylcholine receptors in clinic.

The role of signaling molecules in homeostatic plasticity

Calcium. Recent studies have proved that one of the signals initiating homeostatic synaptic plasticity is calcium, the concentration of which is strictly regulated in neurons. It plays a key role in many cellular processes. The study of Ibata and colleagues [6] showed the blockade of somatic calcium transport to have the same effect on synaptic strength as impulse activity. Moreover, they found that activity deprivation cause decrease of the expression of nuclear Ca^{2+}-calmodulin-dependent kinase (CaMKIV) that is likely to happen through alterations in gene transcription. It can indicate that a neuron somehow perceives fluctuations in intracellular calcium level as an activity marker, and thus it regulates gene expression in soma that reflects on synapse. In addition, the researchers found the activity decrease for a long time period to result in the increase of calcium influx to presynaptic neuron after AP generation that has an effect on the probability of neurotransmitter release from presynaptic neuron, which is proportional to the amount of presynaptic calcium influx raised to the power of three [86].

TNFα. The findings obtained by Stellwagen and Malenka [87] appeared to be unexpected when they demonstrated that secreted soluble tumor necrosis factor alpha (TNFα) participates in positive synaptic scaling during activity blockade. Interestingly, TNFα is secreted mainly by glial cells rather than neurons. On the other hand, the finding makes sense: glial cells are widespread in central nervous system, and are closely related to neurons and able to estimate the level of their activity [88]. Glial origin of TNFα controlling synaptic scaling was supported by the following observations. First, the neurons of wild type mice were incapable of synaptic scaling when cultivated together with glial cells from TNFα-knockout mice. Secondly, while the neurons from TNFα-knockout mice did not show the ability for synaptic scaling when cultivated with glia from the same mice, the cultivation with glia from wild type mice was enough to recover synaptic scaling in TNFα-knockout neurons [36].

It seems that positive scaling caused by TNFα can be explained by its participation in transport of GluR1 subunits of AMPARs to membrane surface. Injection of TNFα to operated rats resulted in the increase of recovery period and in the development of toxicity because of the expression of calcium-permeable AMPARs [89].

Steinmetz and Turrigano [90] in their study found the effect caused by TNFα to depend on culture state: in control synapses it caused the increase of quantal amplitude of AMPARs, in synapses, which had undergone scaling, quantal amplitude decreased after TNFα treatment.

Stück et al. made another interesting discovery *in vivo*. The effect of TNFα depends on its concentration in a particular experiment. So, when mean concentration of TNFα (0.1 mmol) was used, its effects were opposite to those demonstrated in experiments with maximum and minimum concentrations [91].

BDNF. Brain-derived neurotrophic factor (BDNF) is one of the first molecules, which role in the induction of homeostatic synaptic plasticity was discovered. Participation of BDNF in signaling pathways of homeostatic plasticity was revealed in both GABAergic and glutamatergic systems [92]. The precursor of brain-derived neurotrophic factor, pro-BDNF, is synthesized by excitatory and inhibitory neurons, processed and accumulated in neurons as BDNF [93], or turns into BDNF outside the cell with the help of plasmin [94]. In hippocampal neurons BDNF is released through Ca^{2+}-mediated mechanism, and its effectiveness increases after burst electric stimulation [95], and is regulated by synaptogamin IV [96]. Once released, BDNF binds to TrkB-receptors and initiates signal cascades essential for synaptic plasticity regulation [97, 98].

In TTX-treated cortex cultures injection of BDNF influence the amplitude of excitable synapses in a different ways in pyramidal neurons and interneurons: synaptic scaling of AMPA currents induced by TTX was prevented in synapses between two pyramidal neurons, but was observed in synapses between pyramidal neurons and interneurons [12]. Moreover, BDNF application resulted in an increase of AP number in interneurons, though had no effect on pyramidal neurons, while simultaneous application of BDNF and TTX attenuated the rise in AP number which was observed after TTX administration in both pyramidal cells and interneurons [12, 99]. In addition, in GABAergic synapses of cultured hippocampal neurons, simultaneous application of BDNF and TTX blocked the decrease of mIPSC amplitude observed after TTX application [100].

These findings make it plausible to suggest that BDNF can reduce the excitability of dendrites by selective support of inhibitory synaptic activity. Moreover, BDNF can also have an effect on synaptic strength changes by the regulation of protein synthesis in dendrites, and BDNF itself can be locally synthesized according to the activity level [95, 101, 102]. Further studies should help to understand a great variety of BDNF effects in homeostatic synaptic plasticity, in particular, spatio-temporal regulation of its synthesis and expression [97] and the mechanism which helps BDNF-TrkB signaling to have a specific effect on the synaptic strength changes depending on a cell type.

Retinoic acid. Retinoic acid (RA), or vitamin A, has recently been added to the list of diffusible molecules involved in homeostatic synaptic plasticity. In addition, RA, primarily known because of its participation in the regulation of gene expression during development, plays a key role in adult brain, in particular, in the processes of LTP and LTD [103].

Recent studies on dissociated and organotypic hippocampal cultures [46] have shown that synaptic scaling caused by activity blockade by simultaneous but not separate application of TTX and APV is accompanied by the increase of RA concentration [46]. Note that application of RA itself results in rapid increase of AMPARs that prevents synaptic scaling caused by TTX and APV. This form of synaptic scaling stimulates local synthesis of GluR1 through

signaling by RA receptors RARα located in dendrites [19, 46]. The requirement of simultaneous blockade of NMDA-receptors during TTX application for the increase of GluR1 expression corresponds to a previously predicted role of basal synaptic NMDA-receptor-mediated activity in depression of local translation of GluR1 [44]. Moreover, this discovery demonstrates the role of RA signaling in the regulation of GluR1 local synthesis.

RA signaling pathways are involved in various forms of synaptic plasticity, and thus, various members of the families of RA receptors can have an effect on particular forms of synaptic plasticity, i.e. RARα participating in synaptic scaling [19, 46] and RXRγ — in long-term depression [95]. Moreover, regulation of the variety of neuronal genes by RA signaling pathways is expected to be able to have an effect on synaptic plasticity in a number of ways [103].

Cell adhesion molecules. These molecules stabilize synapses and regulate cell to cell and cell to extracellular matrix adhesion. In addition to their structural function, which is of special importance in synapse formation, recent studies have shown the essential role of cell adhesion molecules in the modulation of synaptic efficacy, including homeostatic adaptations. Integrins can "sense" alterations in extracellular matrix caused by activity-induced secretion of signal proteins, and trigger intracellular signaling pathways and alterations of actin cytoskeleton in dendritic spines, which in their turn determine the change of synaptic strength. Homophilic and heterophilic adhesion proteins, which cross-link pre- and postsynaptic neurons, can coordinate the alterations of neurotransmitter release and the amount of postsynaptic receptors during homeostatic adaptations. In contrast to secreted molecules, which diffuse in extracellular space, synaptic adhesion proteins are more anchored in the membrane to regulate local alterations in a particular synapse. However, it should be noted, that regulated adhesion protein transport, e.g. activity-dependent endocytosis of N-cadherin [105, 106], can also change the sensitivity of a particular synapse to adaptive response, which depends on the synaptic adhesion protein level.

N-cadherin is Ca^{2+}-dependent homophilic cell adhesion protein with an established role in the regulation of synapse formation and morphology of spines [107, 108]. It binds to actin of cytoskeleton through α- and β-catenins, also can bind to synaptic skeleton proteins through PDZ-binding domain of β-catenins to modulate pre- and postsynaptic functions [109–113]. N-cadherin also can interact with AMPARs subunits directly through their extracellular domains [114, 115] to modify synaptic activity. Recent studies suggest that N-cadherin/β-catenin complex plays a role in bidirectional regulation of synaptic AMPARs during homeostatic synaptic scaling [112]. In hippocampal neuronal cultures suppression of β-catenin expression after synaptogenesis prevented both the increase and decrease of mEPSC amplitude caused by continuous administration of TTX and bicuculline, respectively. The mechanism of N-cadherin/β-catenin complex regulation of synaptic scaling has not been studied yet.

Integrins are heteromeric transmembrane receptors to extracellular matrix and contra-receptors to adjacent cells, which regulate various signaling pathways [116]. Their role in homeostatic synaptic plasticity has been recently revealed (it is described in detail in the review of McGeachie et al. [117]). Several subtypes of integrins are expressed in the nervous system, where they regulate synapse maturation and its functioning [118–120].

A recent studie of hippocampal neurons have shown the necessity for the presence of β3-integrins to increase the concentration of synaptic AMPARs after activity blockade [121, 122]. Under basal conditions β3-integrins stabilize synaptic AMPARs by inhibiting the mechanisms initiating internalization of their GluA2-subunits. It is important that the inhibition of β3-integrin expression specifically prevents homeostatic increase of mEPSC in TTX treated neurons.

But how can β3-integrins detect the changes in network activity in order to regulate synaptic AMPARs? As mentioned above, the suppression of presynaptic activity by TTX results in the increase of TNFα release by astrocytes. It causes the enhancement of β3-integrins expression in postsynaptic neurons that enhances the suppression of internalization of GluA2-subunits and causes their accumulation in synapses [122].

Conclusion. Homeostatic plasticity has several forms which serve to the maintenance of neuronal network stability and mean level of its activity. Postsynaptic mechanisms are associated with the regulation of expression and composition of AMPARs. Presynaptic mechanisms involve the alterations in the organization of active zones. The phenomenon of homeostatic plasticity has been proved both *in vitro* and *in vivo*. The list of molecules, ions and substances involved in mechanisms of homeostatic plasticity formation and regulation is extremely large. Among them there are factors of gene expression, secretory molecules, cell adhesion molecules, etc. The mechanisms involved in the formation of this complex phenomenon are not yet fully elucidated.

Recently there has been discovered a variety of previously unknown characteristics of synaptic scaling, and there has been revealed a growing number of pathways and cascades participating in its formation. Homeostatic plasticity has lately been supposed to have an effect not only on synaptic strength but also to determine the pattern of connections between the components of neuronal network [123]. There has been demonstrated the ability to maintain optimal neuronal activity level through the change of dendrite length [124]. Jakawich et al. [125] revealed the role of ubiquitinated proteasomal system in the alteration of synaptic strength due to chronic changes of activity level. The change of local protein synthesis level [126] and so-called sumoylation (SUMOylation, from protein name — Small Ubiquitin-like MOdifier protein [127]) play a key role in the induction of homeostatic plasticity. The strength of synapses and the number of dendritic spines were proved to be controlled according to the principle of homeostatic synaptic plasticity also at genetic level [128].

With the development of computer technology, studies of homeostatic plasticity by means of computer modeling became more widespread [21, 27, 34, 37, 129, 130].

Violations in synaptic scaling can result in some pathological states. For instance, the abnormalities in regulation of GABAergic have been revealed in patients with drug addiction, and there is information that homeostatic

plasticity mechanisms are involved during the action of ischemia factors, as well as in developmental diseases [131–135]. Therefore, the studying of homeostatic plasticity is one of the most urgent problems of modern neurobiology.

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