Sodium channel mutations in epilepsy and other neurological disorders

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Since the first mutations of the neuronal sodium channel SCN1A were identified 5 years ago, more than 150 mutations have been described in patients with epilepsy. Many are sporadic mutations and cause loss of function, which demonstrates haploinsufficiency of SCN1A. Mutations resulting in persistent sodium current are also common. Coding variants of SCN2A, SCN8A, and SCN9A have also been identified in patients with seizures, ataxia, and sensitivity to pain, respectively. The rapid pace of discoveries suggests that sodium channel mutations are significant factors in the etiology of neurological disease and may contribute to psychiatric disorders as well.

Introduction

Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in neurons. The sodium channel α subunits are large, transmembrane proteins with approximately 2,000 amino acid residues, composed of 4 homologous domains containing well-characterized voltage sensor and pore regions (Figure 1). The transmembrane segments are highly conserved through evolution. The 4 domains associate within the membrane to form a sodium-permeable pore, through which sodium ions flow down a concentration gradient during propagation of an action potential. The transmembrane sodium gradient is subsequently restored by the activity of the ATP-dependent sodium/potassium pump. The 3-dimensional structures of related bacterial potassium channels have recently been elucidated (1, 2).

Each sodium channel α subunit is associated with 1 or more β subunits, β1 to β4, that are transmembrane proteins with a single extracellular IgG loop and a short intracellular C terminus (Figure 1). Association with β subunits influences the level of cell surface expression, voltage dependence, and kinetics of the α subunit, as well as association with other signaling and cytoskeletal molecules (3, 4).

Duplication of the α subunit genes during evolution generated 9 mammalian genes encoding active channels that differ in tissue specificity and biophysical properties (Table 1) (5, 6). Many disease mutations have been characterized in the skeletal muscle and cardiac channels, but exploration of the role of the 7 neuronal sodium channels in disease is in an early stage.

β1 Subunit mutations and GEFS+

Generalized epilepsy with febrile seizures plus (GEFS+) (OMIM 604233) is a mild, dominantly inherited epilepsy characterized by febrile seizures in childhood progressing to generalized epilepsy in adults (7, 8). The first connection between sodium channels and epilepsy was the discovery of a β1 subunit mutation in a large Australian family with GEFS+ (9). Affected family members are heterozygous for the missense mutation C121W in the extracellular Ig domain of the β1 subunit. The mutant channel promotes cell surface expression of the α subunit but exhibits impaired modulation of sodium channel function and cell adhesion (10). A 5-amino acid deletion in the extracellular domain of β1 was subsequently found in a family with febrile seizures and early-onset absence epilepsy (11). Impaired inactivation of sodium channel α subunits is the likely mechanism relating β1 mutations to neuronal hyperexcitability in epilepsy.

Inherited and de novo mutations of SCN1A in GEFS+ severe myoclonic epilepsy of infancy

In 1999, linkage analysis in 2 large families localized a second GEFS+ locus to an interval of chromosome 2q24 that includes a sodium channel gene cluster (12, 13). Sequencing of SCN1A demonstrated that affected individuals are heterozygous for missense mutations in highly evolutionarily conserved amino acid residues, T875M in 1 family and R1648H in the other (14). Since the initial report, 11 additional SCN1A missense mutations have been reported in GEFS+ families (Figure 2A), approximately 10% of cases tested (14–25).

In 2001, Peter De Jonghe and colleagues discovered mutations of SCN1A in 7 patients with severe myoclonic epilepsy of infancy (SMEI) (26). This disorder is characterized by early onset, usually within the first 6 months of life, followed by progressive worsening of seizures often accompanied by mental deterioration (OMIM 182389). More than 150 mutations have been identified in children with this disorder (Table 2), approximately 50% of SMEI patients tested. As in GEFS+, the SMEI patients are heterozygous for the mutant alleles. Among 75 cases in which both parents have been tested, in 69 cases, or 90%, the mutations arose de novo in the affected children.

The mutation spectrum in SMEI differs from that in GEFS+. Approximately half of the SMEI mutations are nonsense or frame-shift mutations that result in protein truncation (Figure 2B). The truncation mutations are randomly distributed across the SCN1A protein, including the N-terminal domain, transmembrane segments, cytoplasmic loops, and C terminus. The remaining SMEI mutations are missense mutations that, as in GEFS+, are concentrated within the transmembrane segments of the protein (Figure 2C). Within the large cytoplasmic loops of the α subunits, the only missense mutations are those located very close to the adjacent transmembrane segments.

Nonstandard abbreviations used: GEFS+, generalized epilepsy with febrile seizures plus; SMEI, severe myoclonic epilepsy of infancy.

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Recurrent mutations in SCN1A

Approximately 25% of reported mutations in SCN1A have occurred independently more than once (27, 28). Examination of the altered nucleotides at the sites of recurrent mutation revealed 2 frequent mechanisms. Fifteen mutations resulted from deamination of mCpG dinucleotides, including 5 CpGs located in an arginine codon of the CGA class. Deamination converts this codon to UGA, a nonsense codon, resulting in an R-to-X mutation at the amino acid level. Two tetranucleotide direct repeats in SCN1A have been the sites of frameshift mutations due to deletion of 1 copy of the repeat. The likely mechanism is slipped-strand mispairing. The frameshift mutations are at amino acid residues K1846 and L1670.

Rare mutations of SCN2A

Although SCN1A and SCN2A are closely related genes, similar in size and exon organization, only a few epilepsy mutations have been detected in SCN2A (Figure 2D) (29–32). The difference may be partly accounted for by the likelihood that many more patients have been screened for SCN1A mutations. Most missense mutations of SCN2A were found in patients with benign familial neonatal-infantile seizures (OMIM 607745), mild syndromes that present within the first year of life but do not progress to adult epilepsy (Table 2). One truncation mutation of SCN2A has been identified in a patient with intractable epilepsy resembling SMEI (30).

Haploinsufficiency of SCN1A

A small proportion of human genes exhibit haploinsufficiency, meaning that abnormal function results from quantitative reduction of gene expression to 50% of normal levels. Among the epilepsy mutations, the most severe phenotypes are found in individuals who are heterozygous for loss-of-function mutations of SCN1A. This is indicated by the high proportion of truncation mutations among SMEI patients, and the lack of truncation mutations in patients with GEFS+, which is milder (Figure 2, A and B). In SMEI, the clinical features of early onset, seizure severity, and progressive mental deterioration do not differ between patients with truncations located near the N terminus or the C terminus, which indicates that loss of function is the common cause. Rhodes et al. examined the functional effect of 5 missense mutations from patients with severe SMEI and found that 2 of those also result in complete loss of channel activity (33).

Unlike SCN1A, SCN2A appears not to exhibit haploinsufficiency. In contrast to the many null mutations of SCN1A, only a single truncation mutation has been identified in SCN2A, in a patient with a severe form of epilepsy resembling SMEI (30) (Figure 2D). In this case the truncated protein was reported to have a dominant-negative effect, rather than loss of function (30).

Analysis of mice with knockout alleles supports the conclusion that SCN1A exhibits haploinsufficiency while SCN2A does not. Heterozygotes for the SCN1A knockout allele exhibit spontaneous seizures and reduced lifespan (34), while heterozygotes for the SCN2A-null allele are viable without visible abnormalities (35). SCN8A-heterozygous-null mice lack visible abnormalities, but

Table 1

Mammalian voltage-gated sodium channel genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Human chromosome</th>
<th>Major expression</th>
<th>Minor expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1A</td>
<td>Na,1.1</td>
<td>2q24</td>
<td>CNS, PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Na,1.2</td>
<td>2q24</td>
<td>CNS, PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN3A</td>
<td>Na,1.3</td>
<td>2q24</td>
<td>CNS, PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN4A</td>
<td>Na,1.4</td>
<td>17q23</td>
<td>Skeletal muscle</td>
<td>Skeletal muscle, brain</td>
</tr>
<tr>
<td>SCN5A</td>
<td>Na,1.5</td>
<td>3p21</td>
<td>Cardiac muscle</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Na,1.6</td>
<td>12q13</td>
<td>CNS, PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Na,1.7</td>
<td>2q24</td>
<td>PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN10A</td>
<td>Na,1.8</td>
<td>3p21</td>
<td>PNS</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>SCN11A</td>
<td>Na,1.9</td>
<td>3p21</td>
<td>PNS</td>
<td>Cardiac muscle</td>
</tr>
</tbody>
</table>

PNS, peripheral nervous system.
subtle deficiencies have been detected in tests of learning and anxiety (36). The β1 and β2 genes do not exhibit haploinsufficiency in mice heterozygous for targeted knockout alleles (37, 38).

Functional effects of SCN1A missense mutations
Twenty SCN1A missense mutations have been evaluated in functional assays (23, 24, 33, 39–46). Functional analysis is complicated by the difficulty of cloning neuronal sodium channel cDNAs, which are uniquely unstable during propagation in bacterial cultures (unlike the muscle sodium channel cDNAs or the calcium and potassium channel cDNAs). Functional studies in the Xenopus oocyte system and in transfected mammalian cells do not always agree, and there is little experimental basis for extrapolation to in vivo effects. Nonetheless, some interesting patterns have emerged relating altered channel function to the neuronal hyperexcitability that is thought to underlie seizure disorders.

One common functional abnormality is impaired channel inactivation leading to increased persistent current. Normally, the voltage-gated sodium channels open rapidly in response to altered membrane potential and inactivate rapidly, declining to 1% of maximal current within a few milliseconds (Figure 3A). In 3 different GEFS+ mutations (14, 19), persistent current was increased to 2–5% of peak current (39) (Figure 3A). In the context of the neuron, this persistent current is thought to reduce the depolarization threshold required for firing, resulting directly in hyperexcitability.

Another common mechanism is demonstrated by the GEFS+ mutation D188V, which spends less time in the inactivated state than the wild-type channel (Figure 3B). The result is greater availability of channels for opening in response to depolarization, another route to hyperexcitability. The altered biophysical properties of representative mutant channels are summarized in Table 3.

A unique biochemical mechanism was observed for the missense mutation D1866Y, located in the C-terminal domain of SCN1A, in a family with GEFS+ (23). In the Xenopus oocyte system, the mutant channel exhibited a depolarized shift in voltage dependence of fast inactivation; the effect was tenfold greater in the presence of the β1 subunit (Figure 3C). Modeling with the program NEURON (http://www.neuron.yale.edu/neuron/) indicated that this shift is sufficient to produce neuronal hyperexcitability. Because the difference between the wild-type and mutant channels was increased by the presence of the β1 subunit, the effect of the mutation on subunit interaction was tested. Yeast 2-hybrid screen and co-immunoprecipitation demonstrated direct interaction between the C-terminal cytoplasmic domains of the α and β subunits, which was impaired by the D1866Y mutation (23). The D1866Y mutation thus defines an intracellular interaction domain that appears to be required, in combination with the extracellular interaction domain (23), to form the stable α/β complex. Since mutations in either SCN1A or β1 can result in GEFS+, it is not surprising that impaired interaction between the 2 subunits could also cause the disease.

The GEFS+ mutation R1648H has been examined in 3 expression systems with different outcomes. When the mutation was introduced into the rat SCN1A cDNA and examined in the Xenopus

**Table 2**

| Sodium channel mutations in patients with various types of epilepsy |
|------------------------|-----------------|-----------------|
| SCN1A Na,1.1            | SCN2A Na,1.2    | SCN1B β1        |
| (at least 90% sporadic) | 150             | 1               |
| GEFS+                   | 13              | 2               |
| ICEGTC                  | 7               | -               |
| Infantile spasms        | 1               | -               |
| Benign familial neonatal-infantile | - | - |

ICEGTC, intractable childhood epilepsy with generalized tonic-clonic seizures.
The effects of GEFS+ mutations on SCN1A channel properties have been studied in the *Xenopus* oocyte system and in transfected mammalian cells. (A) Whole-cell recordings from HEK tsA201 cells transfected with the indicated mutant SCN1A cDNAs demonstrate increased persistent current from the mutant channels (39). (B) Mean normalized amplitudes of sodium currents elicited by 80-Hz pulse trains in HEK cells expressing SCN2A cDNA containing the GEFS+ mutation D188V demonstrate reduced cumulative inactivation of the mutant channel during high-frequency trains of channel activation (40). (C) Voltage-dependent gating of SCN1A cDNA constructs in *Xenopus* oocytes expressed in the absence (left) or presence (right) of the β1 cDNA (85). See text for discussion.

We investigated the in vivo effect of an SCN2A mutation with impaired inactivation in the Q54 transgenic mouse (48). Analysis of the mutation SCN2A*Δ1866Y* in the *Xenopus* oocyte system revealed an increase in persistent current and in the percentage of current that inactivated with a slow time constant (Figure 4, B and C) (49). When the mutant cDNA was expressed in transgenic mice under the control of the neuron-specific enolase promoter, the mice exhibited progressive seizures of hippocampal origin accompanied by loss of neurons called hippocampal sclerosis (Figure 4, A and E). Persistent sodium current was detected in recordings from CA1 neurons of the transgenic mice (Figure 4D), demonstrating agreement between the *Xenopus* assay and the in vivo effect. The phenotype of the Q54 mice most closely resembles human mesial temporal lobe epilepsy.

**Toward mutation-specific therapy**

Selecting the appropriate antiepileptic drug for newly diagnosed epilepsy patients is a difficult process, and many drugs have adverse side effects. An important goal of mutation characterization is the development of individualized treatments tailored to each patient mutation. It is already clear that sodium channel blockers are con-

Table 3

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Major biophysical abnormalities observed in indicated experimental system</th>
</tr>
</thead>
<tbody>
<tr>
<td>D188V</td>
<td>Decreased entry into and increased rate of recovery from slow inactivated state (m) (40)</td>
</tr>
<tr>
<td>T875M</td>
<td>Enhanced entry into slow inactivated state (X) (45); enhanced entry and hyperpolarizing shift into steady-state slow inactivation (m) (39, 42)</td>
</tr>
<tr>
<td>W1204R</td>
<td>Hyperpolarized shift in voltage dependence of activation (m) (46); increased persistent current (m) (39)</td>
</tr>
<tr>
<td>R1648H</td>
<td>Increased rate of recovery from fast inactivation (X) (45); increased persistent current (m) (39); slowed inactivation and increased recovery from inactivation (m) (41)</td>
</tr>
<tr>
<td>R1648C</td>
<td>Increased persistent current (m) (33)</td>
</tr>
<tr>
<td>I1656M</td>
<td>Depolarized shift in voltage dependence of activation (m) (43)</td>
</tr>
<tr>
<td>G1674R</td>
<td>No measurable sodium current (m) (33)</td>
</tr>
<tr>
<td>D1866Y</td>
<td>Depolarized shift in voltage dependence of fast inactivation (X) due to reduced association with β1 subunit (m) (23)</td>
</tr>
</tbody>
</table>

The most prominent effects observed in each study are indicated; most mutations altered several biophysical properties of the channel. m, transfected mammalian cells; X, *Xenopus* oocyte system.
Figure 4

An SCN2A mutation with persistent current causes seizures in the Q54 transgenic mouse. (A) Focal motor seizure in a Q54 mouse. (B) The GAL879–881QQQ mutation is located in the D2S4–S5 linker. (C) The mutant channel generates persistent current in Xenopus oocytes. (D) Whole-cell sodium currents recorded from CA1 hippocampal neurons from presymptomatic Q54 mice demonstrate increased persistent current. (E) Nissl-stained sections of hippocampus area CA3 reveal extensive neuronal cell loss in a Q54 mouse compared with a wild-type littermate. Adapted with permission from Neuroscience (48).

And the combined effect of multiple susceptibility factors may result in greater clinical severity in some individuals. The influence of modifier genes is amenable to analysis using genetic differences between inbred strains of mice as models. Modifier genes that influence susceptibility to spontaneous seizures (56), kainate-induced seizures (57), electroconvulsive shock (58), and pentylenetetrazol-induced seizures (59) have been mapped to specific mouse chromosomes. Recently, we mapped 2 modifier loci, Moe1 (modifier of epilepsy) and Moe2, that influence clinical severity of epilepsy due to a sodium channel mutation in Scn2aQ54 mice (60). With current genomic technology, it is feasible to clone modifier genes and evaluate their role in human disease. For example, a gene that modifies the severity of an SCN8A-induced movement disorder was recently cloned and identified as a putative RNA splicing factor (61).

SCN8A and movement disorders

Mutations of Scn8a in the mouse result in movement disorders such as ataxia, dystonia, and tremor (62). Conditional inactivation of Scn8a in cerebellar neurons results in a milder ataxia (63, 64). Screening of 150 patients with sporadic or inherited ataxia identified 1 protein truncation mutation that is likely to cause loss of function of SCN8A (36). Further screening will be worthwhile to determine the prevalence of SCN8A mutations in patients with inherited and sporadic movement disorders.

SCN9A and inherited pain

SCN9A encodes the sodium channel Na\textsubscript{v1.7}, which is expressed in peripheral sensory and sympathetic neurons and is localized in the nerve terminals of sensory neurons (65). The missense mutation L858H, in a transmembrane segment, was identified in a Chinese kindred with autosomal dominantly inherited primary erythermalgia (OMIM 113020), a disorder characterized by intermittent pain, redness, heat, and swelling in the extremities (66). A second mutation

For example, a gene that modifies the severity of an SCN8A-induced movement disorder was recently cloned and identified as a putative RNA splicing factor (61).
in a nearby residue, I848T, was found in a sporadic case of erythromelalgia. Functional analysis detected a hyperpolarizing shift in activation and slowed deactivation in both mutants, as well as increased current amplitude in response to slow, small depolarizations, consistent with predicted hyperactivity at the cellular level (67). A third mutation, F1449V, close to D3S6, lowers the current threshold required for predicted hyperactivity at the cellular level (67). A third mutation, F1449V, close to D3S6, lowers the current threshold required for predicted hyperactivity at the cellular level (67).

Thus far, the evolutionary conservation of the mammalian sodium channel would be valuable for the treatment of chronic pain. Thus far, the evolutionary conservation of the mammalian sodium channel would be valuable for the treatment of chronic pain.

Table 4
Mouse models of neurological disorders with sodium channel mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Channel</th>
<th>Mutation</th>
<th>Disorder</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1A</td>
<td>Na,1.1</td>
<td>Targeted null</td>
<td>Seizures in heterozygote; homozygous lethal at P16</td>
<td>(34)</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Na,1.2</td>
<td>Targeted null</td>
<td>No abnormalities in heterozygote; homozygous lethal at P1</td>
<td>(35)</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Na,1.6</td>
<td>Spontaneous null</td>
<td>Paralysis, lethal</td>
<td>(62)</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Na,1.7</td>
<td>Targeted null</td>
<td>Lethal</td>
<td>(70)</td>
</tr>
<tr>
<td>SCN10A</td>
<td>Na,1.8</td>
<td>Targeted null</td>
<td>Pain resistant</td>
<td>(70)</td>
</tr>
<tr>
<td>SCN1B</td>
<td>β1</td>
<td>Targeted null</td>
<td>Seizures in heterozygote; lethal seizures in homozygote</td>
<td>(38)</td>
</tr>
<tr>
<td>SCN2B</td>
<td>β2</td>
<td>Targeted null</td>
<td>Heterozygote normal; homozygote susceptible to seizures</td>
<td>(37)</td>
</tr>
</tbody>
</table>

Mice with neuronal sodium channel mutations

The development of mouse models is keeping pace with the identification of human mutations, and several lines are available for analysis of disease mechanisms. The features and availability are summarized in Table 4. Four lines with various types of seizures are already available, the Q54 transgenic line with a missense mutation of SCN2A and the knockout lines for SCN1A, SCN1B, and SCN2B. Generation of tissue-specific and inducible knock-in mice carrying specific epilepsy-related sodium channel mutations is in progress in several laboratories. Electrophysiological recordings of neurons from knock-in mice are likely to provide the most reliable information for understanding the relationship between specific mutations and the severity of disease. Because of the effort involved in generating these models, only a small number of selected mutations can be analyzed in vivo. Recordings from mice with SCN8A mutations have revealed different effects on sodium currents in different types of neurons (75–77). In Purkinje cells, for example, SCN8A deficiency reduces bursting activity and resurgent current (77), while in cortical pyramidal neurons the major effect is reduced persistent sodium current (76). Analysis of SCN1A-null homozygotes revealed reduced current density in interneurons but not in excitatory neurons of the hippocampus (34). In addition to elucidating the pathophysiology of epileptogenesis, mouse models will permit evaluation of therapies directed toward specific classes of sodium channel mutations.

Persistent issues: sodium channels and disease

The identification of nearly 200 sodium channel mutations in patients with epilepsy raises several issues for future research. The relatively subtle functional effects of some of the epilepsy mutations considered candidates for a causal role in autism. The missense mutation R1902C, located within a calmodulin-binding domain of SCN2A, was subsequently found to confer a calcium-dependent conformational change on the complex of calmodulin with the C terminus of Na,1.2 (72). In this context it is interesting that mutations of the voltage-gated calcium channel C4a,1.2 were recently identified in families with Timothy syndrome, a multiorgan disorder with autism as a feature (73).

Preliminary indication that sodium channel variants may influence cognitive function comes from heterozygotes for a null allele of SCN8A, who exhibit a variety of cognitive defects (36). Impaired learning was also observed in heterozygous-null mice (36). An influence of SCN8A on attempted suicide was indicated by preferential transmission of 1 allele of a single-nucleotide polymorphism.
suggest that the nervous system is intolerant of even minor variation in the properties of these channel proteins, which have a direct role in neuronal firing. The large number of de novo mutations in the sporadic disorder SMEI suggests that mutation should be considered as a possible cause of neurological disease even in the absence of family history. A de novo mutation of SCN9A was identified in a sporadic case of erythro-
glia. Development of genotyping technology has made it easier to screen for mutations, and a commercial sequencing test for SCN1A mutations was recently introduced. However, the cost of several thousand dollars per test, as well as ethical and practical concerns about the implications of mutation detection, may slow the application of genetic testing for neurological disease.

Evaluation of coding variants detected in genetic screens poses significant challenges. Which missense mutations cause disease and which are neutral? Large numbers of unaffected controls (approximately 1,000) must be tested to provide statistically significant evidence that a variant discovered in a patient is not also found in unaffected individuals. Functional assays can be helpful in recognizing disease mutations, but the difficulty of generating expression constructs and interpreting assays in exogenous expression systems makes these tests problematic for clinical applications.

Does quantitative variation in sodium channel abundance due to mutation in noncoding regulatory sequences contribute to neurological disease? The haploinsufficiency of SCN1A revealed by the loss-of-function coding mutations suggests that reduced expression itself may be sufficient to cause disease. Screening for variation in expression requires access to neuronal RNA samples. Recent studies using cDNA microarray hybridization or allele-spe-
cific primer extension reactions suggest that as many as 20% of human genes may vary in expression levels among individuals (78). This interesting area remains essentially unexplored.

If we could identify variants in modifier genes underlying the variable expressivity of sodium channel mutations, perhaps using animal models carrying human mutations, new targets for treatment intervention might result. The growing role of sodium channel mutations in neurological disease provides increased incentive for developing new and more specific sodium channel inhibitors. We anticipate that large-scale sequencing of ion channel genes from patients with epilepsy and other neurological disorders will be carried out within the next few years, with major impact on our understanding of the issues discussed here.

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