#### Review

# Recent evidence for activity-dependent initiation of sympathetic sprouting and neuropathic pain

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**Abstract:** Traumatic injury or inflammatory irritation of the peripheral nervous system often leads to persistent pathophysiological pain states. It has been well-documented that, after peripheral nerve injury or inflammation, functional and anatomical alterations sweep over the entire peripheral nervous system including the peripheral nerve endings, the injured or inflamed afferent fibers, the dorsal root ganglion (DRG), and the central afferent terminals in the spinal cord. Among all the changes, ectopic discharge or spontaneous activity of primary sensory neurons is of great clinical interest, as such discharges doubtless contribute to the development of pathological pain states such as neuropathic pain. Two key sources of abnormal spontaneous activity have been identified following peripheral nerve injury: the injured afferent fibers (neuroma) leading to the DRG, and the DRG somata. The purpose of this review is to provide a global account of the abnormal spontaneous activity in various animal models of pain. Particular attention is focused on the consequence of peripheral nerve injury and localized inflammation. Further, mechanisms involved in the generation of spontaneous activity are also reviewed; evidence of spontaneous activity in contributing to abnormal sympathetic sprouting in the axotomized DRG and to the initiation of neuropathic pain based on new findings from our research group are discussed. An improved understanding of the causes of spontaneous activity and the origins of neuropathic pain should facilitate the development of novel strategies for effective treatment of pathological pain.

**Key words**: neuropathic pain; spared nerve injury; chronic constriction injury; ectopic activity; sympathetic sprouting; allodynia; hyperalgesia

### 1 Spontaneous activity in animal models of pathological pain

Pain resulting from either inflammation or direct physical damage (transection or compression) to peripheral nerve fibers is accompanied by a pathologically increased excitability of primary sensory neurons [e.g., dorsal root ganglion (DRG) neurons]. This abnormal excitability manifests in decreased spike generation threshold<sup>[1-3]</sup>, exaggerated after-discharge activity<sup>[3-6]</sup> and spontaneous spike generation by primary sensory neurons (Table 1).

Spontaneous activity originating from the DRG is rarely observed in the absence of injury<sup>[8]</sup> but is often seen after peripheral axotomy<sup>[3,11,14-20]</sup> or inflammation<sup>[13]</sup> and, therefore, may contribute to chronic pathologic pain. When spontaneous activity is present, impulse generation usually does not arise in the receptor endings but rather in the DRG<sup>[2,11,17,21]</sup> and the injury site of peripheral nerve (neuroma). Neuroma as a prolonged source of spontaneous activity was first reported by Wall, Gutnick, Waxman, and Basbaum in separate studies<sup>[8,22,23]</sup>, and was later confirmed by many other investigators<sup>[4,5,10]</sup>. Another site of spontaneous activity is at areas of demyelination along the peripheral nerve fibers<sup>[4,6]</sup>.

Table 1. Incidence of spontaneous activity in normal and pathological sensory afferents

	C-fibers		Aβ-fibers	
Animal model	Normal	Pathologic	Normal	Pathologic
CSNT <sup>[7]</sup>	-	-	1%	20%
CSNT <sup>[8]</sup>	4.5%	4.5%	5%	9%-14%
CSNT <sup>[9]</sup>	0%	0%	1.3%	8.6%
CSNT <sup>[10]</sup>	0%	3.4%	1%	22%
CCI <sup>[2]</sup>	0%	21%	0%-10%	9%-33%
SSI or SNL <sup>[1]</sup>	-	-	5%	10%-15%
CCD <sup>[11]</sup>	-	-	1%	8.6%
CCD <sup>[12]</sup>	-	-	2%	22%
CCD <sup>[3]</sup>	0%	8%	2.6%	4%-17%
LID <sup>[13]</sup>	0	11%	1.5%	13.2%

CSNT: complete sciatic nerve transection; CCI: chronic constrictive injury; SNL: spinal nerve ligation; CCD: chronic compression of the DRG; LID: localized inflammation of the DRG.

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Importantly, not only injured neurons but also adjacent intact neurons in neuropathic rats may become spontaneously active and hyper-excitable<sup>[10,24,25]</sup>. In part, axonal or neuronal cross-excitation may be responsible for this hyperexcitability<sup>[26,27]</sup>. Recent studies demonstrate that spontaneous activity not only develops in DRGs after peripheral injury and inflammation, but also occurs in DRG following direct mechanical compression<sup>[3,11]</sup> or even inflammatory irritation without any traumatic injury<sup>[13]</sup>. Ectopic spontaneous discharges generated within the chronically compressed ganglia were recorded from neurons with intact, conducting, myelinated or unmyelinated peripheral nerve fibers. The incidence of spontaneously active myelinated fibers was 8.61% for CCD rats *versus* 0.96% for previously nonsurgical rats<sup>[11]</sup>.

Recently, it was discovered that localized unilateral inflammatory irritation of an L5 DRG by depositing a drop of immune activator, zymosan, on top of the ganglion produced behavioral evidence of chronic bilateral cutaneous hyperalgesia and allodynia<sup>[13]</sup>. Extracellular electrophysiological recordings from teased dorsal root fibers from the chronically inflamed DRG (LID), revealed the presence of abnormal ectopic discharges in subpopulations of neurons with myelinated or unmyelinated axons. The discharge originated within the DRG and persisted over 21 days after a single zymosan application. The patterns of ectopic discharge were similar to those recorded from primary sensory neurons with transected peripheral axons (e.g.<sup>[14,16,17,23,28]</sup>) and to those recorded from compressed DRG neurons<sup>[11]</sup> except that higher percentage (e.g. 32%) of the inflamed, spontaneously active DRG neurons had a bursting pattern (Fig. 1). The presence of ectopic discharges originating from the inflamed ganglion suggests that the DRG somata have become hyper-excitable despite having intact, functioning axonal processes and having no physical injury.

### 2 Ionic and cellular mechanisms of spontaneous activity

The increased excitability of sensory neurons that occurs in various chronic pain models seems to reflect changes in a number of different ion channels, according to electrophysiological, immunohistochemical, and gene expression studies<sup>[29-38]</sup>.

Altered expression of ion channels such as upregulation of sodium channels and downregulation of potassium channels contributes, at least partially, to the enhancement of neuronal excitability and to the generation of spontaneous activity<sup>[39-41]</sup>. Both tetrodotoxin (TTX)-sensitive and Acta Physiologica Sinica, October 25, 2008, 60 (5): 617-627



Fig. 1. Inflamed A $\beta$  neurons exhibited spontaneous activity with bursting patterns. Three typical bursting patterns recorded extracellularly from dorsal root fibers of inflamed ganglia on postoperative day 7. Reproduced from Xie *et al.*, Neuroscience, 2006<sup>[13]</sup>.

-resistant sodium currents are sensitive to a variety of local anesthetics<sup>[42-48]</sup>. In neuropathic animal models, administering lidocaine or TTX systemically suppressed the ectopic discharges recorded extracellularly in the neuroma, DRG, or spinal horn neurons in a dose-dependent manner<sup>[49-54]</sup>. Systemic lidocaine treatment also prevented thermal hyperalgesia and cutaneous thermal abnormalities in rats after peripheral nerve inflamation (PNI)<sup>[55]</sup>, whereas local infusion of lidocaine into the compressed DRG reduced development of tactile allodynia<sup>[56]</sup>.

Excitability of neurons is determined mostly by resting membrane potential (V<sub>m</sub>) and action potential (AP) threshold level. Neuronal ability to repeatedly fire and parameters of this repetitive firing (spontaneous or bursting) depend on the rate of AP decay and events following a single spike or series of spikes such as afterhyperpolarization or post-tetanic hyperpolarization. Recent discoveries have shown that spontaneous fluctuations of V<sub>m</sub> may trigger spontaneous AP in DRG neurons<sup>[2,3,41,57]</sup>. Neuropathy does not appear to affect resting V<sub>m</sub> of primary afferent neurons in most neuropathic animal models<sup>[2,3,41,57]</sup>. However, neuropathy increases the incidence of subthreshold membrane oscillations of resting  $V_m^{[1,9,58]}$  and decreases AP threshold<sup>[1-3]</sup>. As proposed by Amir et al.<sup>[58]</sup>, subthreshold V<sub>m</sub> oscillations are likely caused by reciprocal activity of a phasically activating voltagedependent, tetrodotoxin-sensitive Na<sup>+</sup> conductance and a passive, voltage-independent K<sup>+</sup> leak. Under normal conditions and during neuropathy, neurons that are capable of spontaneous activity or repetitive firing during slight depolarization have a shorter afterhyperpolarization<sup>[1,59]</sup>.

The hyperpolarization-activated cyclic nucleotide gated current ( $I_{\rm H}$ ) plays a key role in the regulation of neuronal excitability, and increases in this current can confer the types of changes seen in sensory neuron properties in the

LID, CCD, and other chronic pain models - spontaneous activity, repetitive firing in response to depolarizing stimuli, and membrane oscillations<sup>[60-63]</sup>.

Electrophysiological studies of adult rat DRG neurons indicate that  $I_{\rm H}$  is found in virtually all large neurons, many medium sized neurons, and a small subset of small neurons<sup>[59,62,64-66]</sup> (for example, see Fig. 2). Hence this current is present in the subset of cells most commonly found to demonstrate bursting or high frequency spontaneous activity in various pain models.  $I_{\rm H}$  current density has been



Fig. 2. Recording of  $I_{\rm H}$  from intact DRG using discontinuous single electrode voltage clamp (dSEVC). *A*: Example of  $I_{\rm H}$  current elicited by a step from -60 to -120 mV with single electrode voltage clamp.  $I_{\rm H}$  is measured as the slowly developing inward current.  $I_{\rm H}$ , but not the instantaneous current, was blocked by 10 µmol/L ZD7288 (bottom trace; *B*, *C*).

shown to increase in the CCD model<sup>[67]</sup>. Ectopic activity in the spinal nerve ligation model is also sensitive to blockers of  $I_{\rm H}^{[68,69]}$ , suggesting that this current plays a role in several different pain models. The importance of changes in  $I_{\rm H}$  for pain behaviors is suggested by *in vivo* studies showing that systemic injection of  $I_{\rm H}$  blockers markedly reduces pain behaviors. This has been found for the spinal nerve ligation model<sup>[68,70]</sup>; these authors also showed that effective plasma concentrations of the  $I_{\rm H}$  blocker used were low enough to be specific for  $I_{\rm H}$ , and that the site of action was not the spinal cord and was likely to be in the DRG.

## **3** Spontaneous activity-mediated sympathetic sprouting

In humans, traumatic injury to soft-tissue, bone, and/or nerve often leads to a chronic pain state, known as complex regional pain syndrome (CRPS, previously described as reflex sympathetic dystrophy and causalgia) that is characterized by ongoing pain with associated allodynia and hyperalgesia<sup>[71]</sup>. Intriguingly, in some patients the pain and hyperalgesia are maintained by efferent noradrenergic sympathetic activity and circulating catecholamines (sympathetically maintained pain, SMP)<sup>[72]</sup>, and may be partly responsive to sympathetic blockade, while in others the pain is sympathetically independent (SIP)<sup>[73]</sup>. Patients with SMP or SIP often present with similar signs and symptoms<sup>[71,74]</sup>. Clinically, SMP is the component of many various painful conditions such as CRPS, phantom pain, neuralgias, and herpes zoster. The lack of understanding of the neurophysiological mechanisms by which the sympathetic system invades the peripheral sensory system has hindered progress in the treatment of these painful conditions.

Recent studies indicate that spontaneous activity of the primary sensory neurons may play a critical role in the development of SMP. The main discharge patterns for spontaneously active large DRG neurons<sup>[8,14,15,28]</sup> include bursting discharge, regular high-frequency (tonic) (up to 100 Hz) and irregular low-frequency discharge (less than 15 Hz), whereas most small neurons fire with an irregular, low frequency discharge pattern<sup>[19,28]</sup>. Both incidence and discharge rate of spontaneous activity are much higher in myelinated large and medium DRG neurons than unmyelinated small DRG neurons as demonstrated in virtually all neuropathic animal models (Table 1).

These large and medium-sized DRG neurons are also much more likely to be sites of sympathetic sprouting. Moreover, since the number of spontaneously active DRG neurons (e.g., 17% of 8 000-10 000 neurons)<sup>[8,28,75]</sup> in a single ganglion is much greater than that of basket cells (neurons surrounded by a ring of sympathetic fibers)<sup>[76]</sup>, the reasonable assumption is that only DRG cells with a certain discharge pattern (e.g., bursting discharge) or with a greater discharge rate (e.g., >15 Hz)<sup>[14]</sup> may trigger sympathetic sprouting. This is supported by the findings that higher percentage of spontaneously active neurons in the axotomized DRG are co-localized with sympathetic fibers<sup>[77]</sup> and that nerve injury-induced sympathetic sprouting is decreased by local or systemic administration of lidocaine[77-79] (Fig. 3, 4). It was found that systemic lidocaine beginning at the time of surgery via repeated i.p. injections or an implanted osmotic pump remarkably reduced sympathetic sprouting (e.g., the density of sympathetic fiber and the number of DRG neurons surrounded by sympathetic fibers) in nerve-injured DRGs. The effects of systemic lidocaine lasted more than 7 d after the termination of lidocaine administration. Similar results were obtained after topical application of lidocaine or TTX to the nerve trunk to block abnormal discharges originating in the neuroma. Results strongly suggest that sympathetic sprouting in pathologic DRG is associated with abnormal spontaneous activity originating in the DRG or the injured axons (e.g., neuroma). It is not clear why nerve blockade reduced sympathetic

sprouting in the axotomized DRG, however, recent studies from our laboratory revealed that nerve blockade beginning at the time of nerve injury prevented DRG cells from generating spontaneous activity at later time<sup>[77]</sup>. This finding provides new insight into the mechanisms underlying sympathetic sprouting and increases our current understanding of the prolonged therapeutic effects of lidocaine on neuropathic pain syndromes.

The facts that sympathetic sprouting has been observed in intact ganglia ipsilateral or contralateral to the injury in rats with peripheral nerve injury<sup>[80]</sup>, and has been found in compressed DRGs<sup>[81]</sup> without axotomy suggest that nerve injury may not be the only factor that triggers or mediates sympathetic sprouting. This is confirmed by recent findings that localized inflammatory irritation of the DRG in-



Fig. 3. Schematic drawing of the sciatic nerve blockade using implanted osmotic minipump filled with TTX or lidocaine.



Fig. 4. Effects of local nerve block on complete sciatic nerve transcetion (CSNT)-induced sympathetic sprouting. A: Color inverted image showing TH-immunoreactive fibers sprouting from perivascular plexuses in a DRG section of CSNT rats on POD 14. B: Image is generated after tracing all the TH-immunoreactive fibers in A. C: Microscopic photographs of basket-like structures (arrows). D: Nerve block decreased sympathetic fiber density measured on POD 14. Scale bar, 50 µm. \*\*P<0.01, Student's t-test. Reproduced from Zhang et al., Pain, 2004[78].

duces sympathetic sprouting<sup>[13]</sup> and systemic administration of steroid decreases the density of sympathetic fibers and the number of basket structures<sup>[82]</sup>. It suggests that inflammatory responses in the axotomized DRG may be another attributing factor in the abnormal sympathetic sprouting.

### 4 Activity-dependent expression and/or release of neurotrophins

Both NGF and its homologue (NT-3) are neurotrophic factors that are essential for development of sympathetic neurons<sup>[83-86]</sup>. After nerve transection, NGF protein levels and NGF-immunoreactivity (IR) in the DRG are dramatically increased as early as 2 d after surgery<sup>[87]</sup> which is parallel to the occurrence of sympathetic sprouting in the same animal model. A recent study using in situ hybridization and immunohistochemical techniques found that NGF and NT-3 synthesis was up-regulated in glial cells surrounding neurons in axotomized DRG after nerve injury<sup>[88]</sup>. Sympathetic sprouting around the axotomized neurons was associated with IR for the p75 NGF receptor in glial cells. In another study, using a line of transgenic mice overexpressing NGF in glial cells, trigeminal ganglia from adult transgenic mice possessed significantly higher levels of NGF protein in comparison to age-matched, wild-type mice<sup>[89]</sup>. The sympathetic axons extended into the trigeminal ganglia of transgenic but not wild-type mice and formed perineuronal plexuses surrounding only those neurons immunostained for NGF. In addition, such plexuses were accompanied by glial processes from nonmyelinating Schwann cells<sup>[89]</sup>. These results implicate glial-cell-derived neurotrophins in the induction of sympathetic sprouting following nerve injury.

A wealth of evidence has been accumulated during the last few decades demonstrating that the production and/or release of the growth factors are normally controlled by axonal and/or neuronal electrical activity<sup>[90-101]</sup>. Some recent evidence from electrical activity recordings of single glial cells and neurons suggest that neuronal activity is more intricately linked with that of glial cells than previously thought<sup>[102-104]</sup>. For example, depolarization and hyperpolarization of glial membranes has been measured in response to similar electrical activity in adjacent neurons<sup>[105]</sup>. Conversely, glial cells may affect neuronal activity through a similar mechanism<sup>[106,107]</sup>. These glial membrane responses may be accompanied by changes in the concentration of ions within the glial cells. Some glial cells respond to the presence of glutamate or electrical stimulation with slow alternating flows

of calcium ions into and out of the cells. These so-called calcium waves are passed to adjacent glial cells<sup>[108,109]</sup>. This phenomenon appears to be yet another method whereby glial cells communicate with surrounding neurons. Recently, it has been shown that glial cells are activated by fractalkine, which is tethered to the neuronal membrane by a mucin stalk. When the neuron is sufficiently activated, the stalk breaks, releasing fractalkine into the extracellular fluid<sup>[110-113]</sup>. Based on the above evidence, spontaneous activity of the DRG neurons may regulate the synthesis/release of neurotrophins from neighboring glial cells by electrical signaling.

### 5 Early spontaneous activity is the trigger for persistent neuropathic pain

After peripheral nerve injury, modifications are observed at several anatomical locations, including: 1) a large increase in spontaneous (ectopic) impulse discharge in the injured afferent fibers leading to the DRG, and in DRG cell bodies<sup>[114]</sup>; 2) abnormal contacts between sympathetic and sensory nervous systems<sup>[76]</sup>; and 3) changes in the spinal cord and brain. Although much is known about what molecular and cellular changes occur at these sites in neuropathic pain, including changes in gene expression<sup>[38,115,116]</sup>, it is not clear what event(s) and which anatomical site(s) are critical in initially triggering the development of neuropathic pain.

In commonly used animal models of neuropathic pain, pain behaviors appear within the first 12 h-2 d post injury<sup>[117-119]</sup>. Spontaneous activity appears this rapidly also. Most other pathological changes, such as spinal cord sensitization and altered gene expression, begin later than this. Spontaneous afferent activity is therefore a likely candidate for initiating chronic pain. A key observation is that temporarily blocking spontaneous activity reduces or eliminates spontaneous pain, hyperalgesia, and allodynia in a variety of pain models. This has been demonstrated in several different models and using methods to suppress spontaneous activity that vary widely in their specific targets<sup>[25,70,120-123]</sup>.

In recent studies using rat models of neuropathic pain, it was shown that local, short-term nerve blockade of this afferent activity permanently inhibits the subsequent development of both thermal hyperalgesia and mechanical allodynia (Fig. 5). Timing is critical — the nerve blockade must last at least 3-5 d and is effective if started immediately after nerve injury, but not if started at 10 d after injury when neuropathic pain is already established<sup>[124]</sup> (Fig. 6). The results validate the principle of pre-emptive analgesia.

Bupivacaine TTX В Thermal pain score (As) CCI CCI + saline Δ CCI + Bupivacaine 10 CCI + TTX ▲ CCI 70 70 10 20 60 50 60 10 Aechanical pain score (Ag) D С 5 5 10 60 70 20 30 40 50 ſ 70 5 5 10 Days post operation

Fig. 5. Local application of nerve blockers during the initial stage of neuropathic pain is sufficient to inhibit the subsequent development of neuropathic pain. Rats with chronic constriction injury (CCI) of the sciatic nerve were tested for thermal pain (A, B) and mechanical pain (C, D). Thermal hyperalgesia lasted over 30 d, and mechanical allodynia lasted over 60 d. Nerve blockade applied at the initial stage of neuropathic pain (shaded areas) by 200 mg bupivacaine (A, C) or by TTX (7-day) (B, D) prevented the development of neuropathic pain. Duration of blocker activity (shaded areas) was estimated in previous experiments. Mechanical pain threshold was defined as the lowest applied force that caused at least three withdrawals out of the five consecutive applications, with a cutoff value of 18 g. Cutaneous sensitivity to mechanical and thermal stimuli was expressed as difference scores, with negative values corresponding to increased pain sensitivity. For all data shown, the groups with nerve blockade (n = 6-7) differed significantly from the group with CCI only (n = 6; one-way ANOVA with Dunnett's post test, P<0.01). The CCI plus saline pump group (n = 6) did not differ significantly from CCI only. Reproduced from Xie *et al.*, Pain, 2005<sup>[124]</sup>.



Fig. 6. Once the neuropathic pain is established, bupivacaine or TTX nerve blockade is no longer effective in preventing subsequent pain behaviors. Rats with CCI were tested for thermal pain (A, B) and mechanical pain (C, D). Difference scores are presented for each experiment, using the same format as in Fig. 5. Contrary to the results in Fig. 5, application of TTX or bupivacaine starting 10 d after onset of neuropathic pain (shaded areas) was not effective in preventing subsequent thermal hyperalgesia or mechanical allodynia. Omitting data from the blockade period (days 10-17), there were no significant differences between drug-treated and untreated groups in either of the CCI experiments shown (One-way ANOVA with Dunnett's post test or Mann-Whitney test). Reproduced from Xie *et al.*, Pain, 2005<sup>[124]</sup>.

Jun-Ming ZHANG *et al*: Recent Evidence for Activity-Dependent Initiation of Sympathetic Sprouting and Neuropathic Pain 623



Fig. 7. Proposed mechanism for activity-dependent sympathetic sprouting following peripheral nerve injury.

Furthermore, these findings demonstrate that the critical time window is immediately post-operative and may need to be 4-5 d long, and that such analgesia may need to act at the level of the DRG rather than in the spinal cord or higher centers.

Effective nerve blockade also prevents subsequent development of spontaneous afferent activity from the injured or axotomized DRG neurons measured electrophysiologically<sup>[77,124]</sup>. Similar results were obtained in different pain models (e.g., CCI, SNI and CSNT) and with two blockade methods (200 mg of a depot form bupivacaine at the injury site, or perfusion of the injured nerve just proximal to the injury site with TTX). These results indicate that early spontaneous afferent fiber activity is the key trigger for the development of pain behaviors, and suggest that spontaneous activity from the injury site may be required for many of the later changes in the sensory neurons, spinal cord, and brain observed in neuropathic pain models. Many preclinical and clinical studies of pre-emptive analgesia have used much shorter duration of blockade, or

have not started immediately after the injury, or have used agents active in the spinal cord that may not have reduced ectopic activity in the DRG. Results suggest that effective pre-emptive analgesia can be achieved only when nerve block is administered early after injury and lasts several days. In addition, results suggest that applying local blockers of spontaneous activity to a limited area of peripheral nerve might have a dramatic impact on the development of neuropathic pain while avoiding the toxicity that occurs with systemic drugs.

#### 6 Summary

Abnormal sympathetic sprouting has been observed in a variety of animal models of pathological pain with or without damage to the peripheral axons. Sprouted fibers are found preferentially surrounding large- and medium-sized sensory neurons with spontaneous activity. Both of the fiber density and the number of basket are decreased by local nerve blockade or by systemic administration of antiinflammatory corticosteroid. Similar results are found for nerve injury-induced pain behaviors. As illustrated in Fig. 7, these findings support an inflammation-driven and activitymediated mechanism for nerve injury-induced sympathetic sprouting and neuropathic pain.

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Acta Physiologica Sinica, October 25, 2008, 60 (5): 617-627

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### 624

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Acta Physiologica Sinica, October 25, 2008, 60 (5): 617-627

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#### 626

Jun-Ming ZHANG *et al*: Recent Evidence for Activity-Dependent Initiation of Sympathetic Sprouting and Neuropathic Pain 627

123.

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