Neurosci Bull October 1, 2012, 28(5): 618–630. http://www.neurosci.cn
DOI: 10.1007/s12264-012-1276-9

·Review·

Dorsal root ganglion compression as an animal model of sciatica and low back pain

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Abstract: As sciatica and low back pain are among the most common medical complaints, many studies have duplicated these conditions in animals. Chronic compression of the dorsal root ganglion (CCD) is one of these models. The surgery is simple: after exposing the L4/L5 intervertebral foramina, stainless steel rods are implanted unilaterally, one rod for each vertebra, to chronically compress the lumbar dorsal root ganglion (DRG). Then, CCD can be used to simulate the clinical conditions caused by stenosis, such as a laterally herniated disc or foraminal stenosis. As the intraforaminal implantation of a rod results in neuronal somal hyperexcitability and spontaneous action potentials associated with hyperalgesia, spontaneous pain, and mechanical allodynia, CCD provides an animal model that mimics radicular pain in humans. This review concerns the mechanisms of neuronal hyperexcitability, focusing on various patterns of spontaneous discharge including one possible pain signal for mechanical allodynia – evoked bursting. Also, new data regarding its significant property of maintaining peripheral input are also discussed. Investigations using this animal model will enhance our understanding of the neural mechanisms for low back pain and sciatica. Furthermore, the peripheral location of the DRG facilitates its use as a locus for controlling pain with minimal central effects, in the hope of ultimately uncovering analgesics that block neuropathic pain without influencing physiological pain.

Keywords: animal model; sciatica; low back pain; dorsal root ganglion; excitability; cytokine; analgesia

1 Introduction

Animal models are widely used in the laboratory investigations of pain. Although there is considered to be a cleft between the pain symptoms in patients and those displayed in animals, so far, most of our understanding of neuropathic pain is based on experiments with animal models. Selection of a suitable model is important for elucidating certain pain symptoms. An ideal chronic pain model should meet the following standards: (1) the etiology of the symptoms should approximate the clinical situation; (2) related pain behavior should resemble specific chronic pain symptoms and be tractable to objective measurement; (3) the model should be conducive to the study of the underlying mechanisms; and (4) the preparation should be simple and repeatable with a high ratio of success. Dozens of models of neuropathic pain in rats and mice have been established over the past 20 years[1], each intended to cover a particular facet. Chronic compression of the dorsal root ganglion (CCD) is one such model which has been developed for the specific case of radicular pain induced by stenosis[2] (Fig. 1A).

In this review, we begin with a brief introduction to the anatomy of the intervertebral foramen and how the

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Article ID: 1673-7067(2012)05-0618-13
Received date: 2012-03-04; Accepted date: 2012-06-08

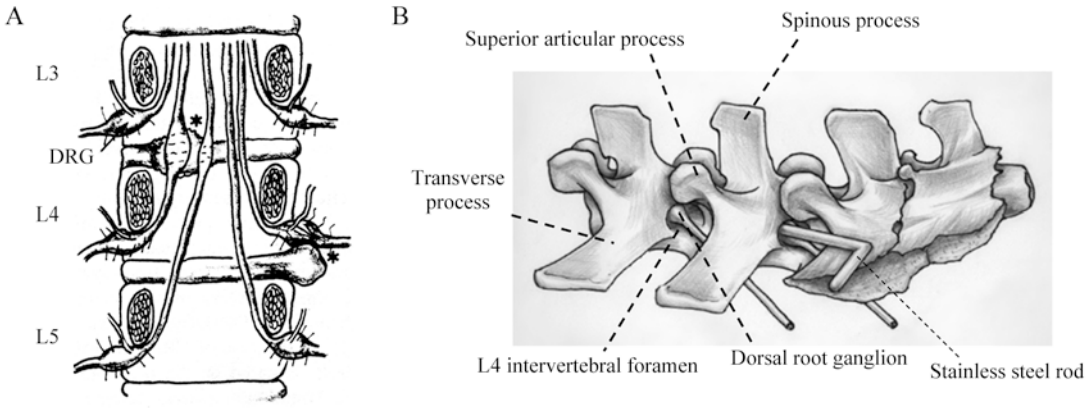

Fig. 1. A: Anatomical structure and pathological changes in the dorsal root ganglion (DRG) area in the coronal plane of the L3–L5 spinal column (modified from Fig. 2, P107, Pain 1996 - An Updated Review, editor: James N. Campbell). Herniation of the intervertebral disc can impact the DRG directly (asterisk, L4 right). It can also compress the dorsal root (asterisk, L3 left), damaging sensory axons directly and the DRG indirectly due to mechanical traction forces. B: The CCD model. The anatomy around the intervertebral foramen is displayed, and the DRG and spinal nerve pass through the intervertebral foramen where the L-shaped rod is inserted.

CCD model is established, then summarize the behavioral tests on this model, as well as the hyperexcitability developed, particularly the ectopic firing pattern produced after dorsal root ganglion (DRG) injury and its possible significance in neuropathic pain. After that, distinct properties of the CCD model in comparison with other models are discussed.

2 The CCD model

2.1 Anatomy of the intervertebral foramina and establishment of the model As the spinal vertebrae are articulated with each other, their bodies form a strong pillar of support for the head and trunk, and the longitudinal vertebral foramen provides a canal that protects the spinal cord. Between each pair of cervical, thoracic, and lumbar vertebrae are bilateral apertures, the intervertebral foramina, which allow the passage of the spinal nerve root, dorsal root ganglion, spinal segmental artery, and transforaminal ligaments, as well as veins communicating between the internal and external plexuses. The size of the intervertebral foramen is variable due to spinal loading, posture, and pathology, and it can be occluded in degenerative arthritis and by space-occupying lesions such as tumors, metastases and disc herniations.

The CCD model is established at the lumbar 4/5 (L4/L5) intervertebral foramina (Fig. 1B), through which the spinal nerves are connected with the sciatic nerve. It is produced in the rat by implanting stainless steel rods unilaterally into the intervertebral foramina, one at L4 and the other at L5. Details of the procedure have been described previously[2]. In brief, under sodium pentobarbital anesthesia and sterile conditions, the intervertebral foramina at L4 and L5 on one side are exposed and L-shaped stainless steel rods are inserted to produce a steady compression against the L4/L5 DRGs. The procedure has two key aspects. One is the angle of rod insertion. An L-shaped needle is inserted into the intervertebral foramen at 30º with respect to the dorsal midline and 10º with respect to the vertebral horizontal line. When the needle tip reaches the DRG, the hind leg muscles of the operated side exhibit a slight, transient twitch. The needle is then withdrawn, and a fine, L-shaped stainless steel rod, 4 mm in length, is inserted along the path of the needle. Another key aspect is the diameter of the rods, selected with the intent of exerting high pressure on the DRG. The diameter (usually 0.5–0.8 mm) should be increased in relation to the animal's weight, but not so much as to destroy the capsule. Usually a diameter of 0.5–0.6 mm is selected for 200–250 g rats and diameters of 0.7 and 0.8 mm for 250–300 and 300–350 g, respectively.

2.2 Behavioral changes after establishment of the CCD model During 5–35 days post-surgery, the hindpaw ipsilateral to the injury shows a significant reduction in the latency of foot withdrawal to noxious heat and manifests persistent heat hyperalgesia[2]. Moreover, both the mean threshold force of punctate indentation and the mean threshold temperature of heating required to elicit a 50% incidence of foot withdrawal ipsilateral to the CCD are significantly lower than the preoperative values[3]. The number of foot withdrawals ipsilateral to the CCD during a 20-min contact with a temperature-controlled floor is significantly increased over preoperative values throughout 35 days of postoperative testing when the floor temperature is 4°C (hyperalgesia) and, to a lesser extent, when it is 30ºC (spontaneous pain)[3]. In contrast, sham operation and acute injury produce no changes in behavior other than slight mechanical hyperalgesia ipsilateral to the acute injury that lasts for 1 day[3].

Two kinds of mechano-allodynia have been noted in patients with neuropathic pain: static, assessed by the von Frey hair test, and dynamic, assessed by drawing a cotton bud cross the skin[4]. Dynamic mechano-allodynia is fairly common in patients, but has not been conclusively evidenced in any other animal model. In the CCD model, stroking the foot ipsilateral to the CCD with a cotton wisp during the first 2 postoperative weeks elicits a reflex withdrawal in most rats. However, to our knowledge, this kind of mechanical allodynia has not been reported in other animal models of neuropathic pain[5-7].

3 Development of DRG neuronal hyperexcitability after establishment of the CCD model

After CCD, injured DRG neurons exhibit the characteristics of hyperexcitability associated with the generation and maintenance of abnormal pain behavior. Such persistent somal hyperexcitability may amplify or distort the trains of action potentials generated from peripheral receptors or cause the generation of spontaneous ectopic discharges.

3.1 Hyperexcitability in DRG neurons The soma of the DRG neuron is normally excitable, and this excitability can increase and persist after injury of a peripheral nerve or the ganglion. Neuronal hyperexcitability has been reported in many studies of CCD. For instance, large DRG neurons from injured rats are more excitable than those from control groups, as indicated by their significantly decreased current threshold and action potential threshold and the increased number of discharges evoked by membrane depolarization[8,9]. In another study, an inflammatory soup consisting of bradykinin, serotonin, prostaglandin E2, and histamine remarkably increases the rates of spontaneous activity in CCD neurons, evokes more discharges in silent CCD neurons than in controls, and decreases the current and voltage thresholds for action potentials in both intact and dissociated preparations[10]. More specifically, studies have been designed to determine whether the increased excitability of DRG neurons produced by CCD persists after their dissociation and culture, i.e. whether the hyperexcitability is intrinsic to the soma. In this case, the hyperexcitability of the dissociated cells, especially the small cells, was shown to be produced by the dissociation process itself[11-13]. Hence the whole-ganglion preparation is better suited to the determination of neuronal properties related to injury. And some *in vivo* experiments or intact DRG intracellular recording results are more convincing.

Neurons in an injured DRG are characterized by the production of a subthreshold membrane potential oscillation (SMPO) and the resulting spontaneous firing. Studies have shown that these cells have a higher excitability than those without an SMPO, and that the SMPO underlies the pattern of spontaneous discharge (Fig. 2A–C), suggesting that it is the basic electrophysiological change in hyperexcitable DRG neurons[9,14,15]. The SMPO has properties similar to those demonstrated by the ligature model of neuropathic pain in which the L5 spinal nerve is tightly ligated proximal to its juncture with the L4 spinal nerve and distal to the L5 DRG[16]. In investigations using this model, the amplitude, frequency, and coherence of the SMPOs are voltage-sensitive, and give rise to action potentials upon reaching threshold. Their presence also proves to be a necessary condition for sustained spiking at both resting and depolarized membrane potentials, while neurons without

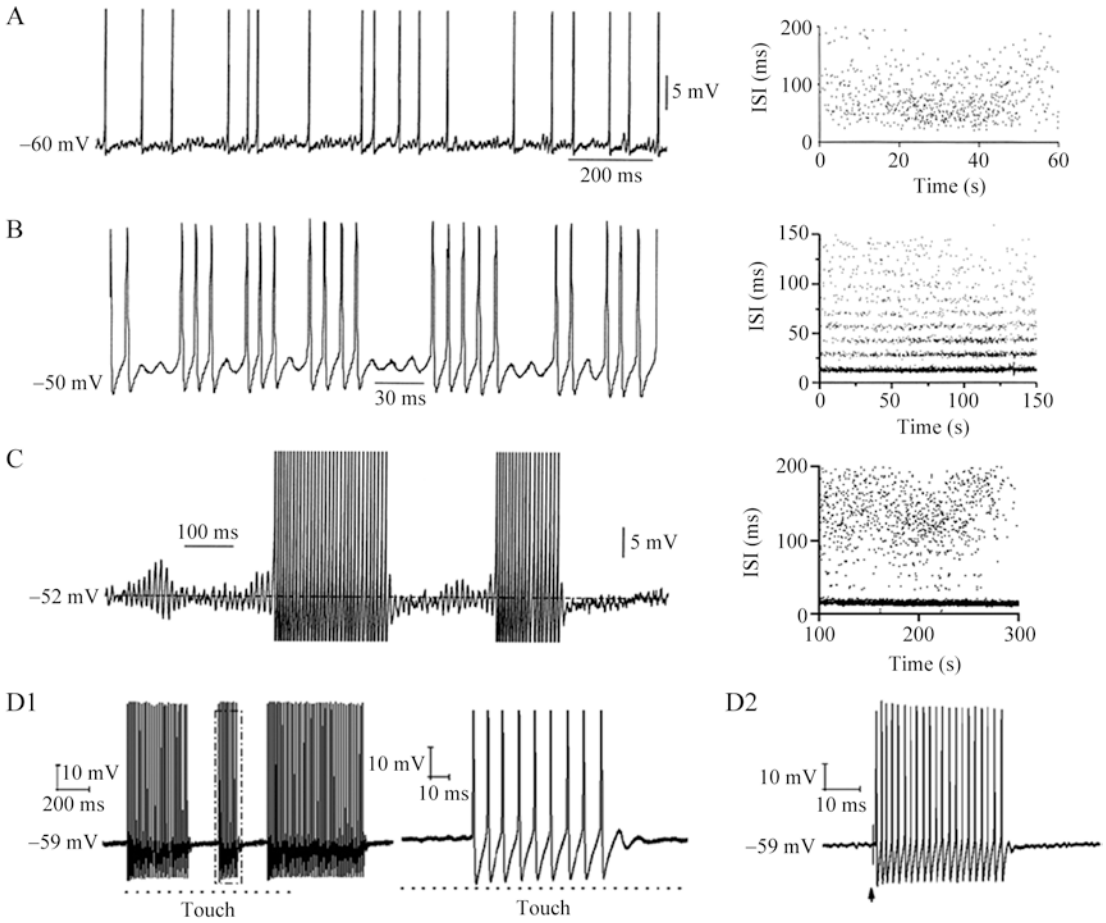

Fig. 2. Intracellular electrophysiological recordings in hyperexcitable neurons in the CCD model (cited from Xing *et al.*, Brain Res 2001[9]; Song *et al.*, Pain 2012[38]). A: Irregular spontaneous discharges and irregular subthreshold membrane potential oscillations (SMPOs) (left). Right panel: scatter-plot of interspike intervals (ISIs) of the same neuron. B: A portion of original recording of an integer multiple pattern of spontaneous discharge. Regular SMPOs can be seen when there are no spikes. The basic ISI and the bands can be clearly distinguished in the ISI scatter-plot (right), revealing an integer multiple pattern of spontaneous discharge. C: Bursting pattern of spontaneous discharges and spindle-like SMPOs. Right panel: ISI scatter-plot of the bursting pattern. D: Examples of evoked bursting (EB) induced in Aβ DRG neurons by touching the peripheral receptive field (D1) or stimulating the sciatic nerve (single pulse, arrow) (D2). The former evoked 3 EBs, which prolonged the response duration (D1, left). The right trace in D1 is an extension of the framed area in the left trace.

an SMPO are incapable of sustained electrical discharge, even when highly depolarized.

The presence of an SMPO also suggests a property, membrane resonance, characterized by the selective response of a neuron to inputs at preferred frequencies[17]. Our previous research on injured DRG neurons found that noise enhances the SMPOs in a subset of neurons that have a high-frequency (20–100 Hz) intrinsic resonance[18]. This finding suggests a future direction for exploring modulating factors in the generation of chronic pain signals. Meanwhile, work by LaMotte's group using the CCD model has revealed another type of spontaneous discharge, which occurs in the absence of SMPOs[19]. They also confirmed that its origin was most likely the axon, which can also be injured during DRG compression[19]. Such spontaneous discharges are consistent with invasion of the soma by retrograde spikes[20]. Their properties also resemble those of evoked bursts (Fig. 2D1, D2), which are discussed in Sections 4.1 and 4.2.

3.2 Potential mechanisms of hyperexcitability In the

CCD model, the primary sensory neurons may be affected directly by compression injury or indirectly by the activation of satellite glial cells and their adjacent immune cells. These cells release a variety of inflammatory mediators and neurotransmitters which can change the microenvironment of the neurons, resulting in somal hyperexcitability and the associated behavioral changes.

3.2.1 Signaling pathways for DRG neuronal hyperexcitability Numerous signaling pathways in DRG sensory neurons are implicated in the induction of hyperexcitability associated with pain. Using specific agonists and inhibitors of protein kinase A (PKA), Hu and co-workers determined that PKA modulates spontaneous activity in injured DRG neurons with myelinated axons[21]. By investigating norepinephrine (NE) sensitivity in the CCD model, we further determined that PKA-mediated triggering and enhancement of SMPOs may be responsible for the excitatory effects of NE on sensory neurons in neuropathic rats[15]. More recently, Song *et al.* found that *in vivo* application of PKA and protein kinase G (PKG) antagonists transiently depresses the behavioral hyperalgesia induced by CCD[22]. In contrast, application of these agents to the ganglia of naive, uninjured animals hardly affected the electrophysiological properties of DRG neurons and foot withdrawal, suggesting that sensitizing actions of the PKA/PKG pathways in the DRG are enabled by prior injury or stress[22].

Other signaling pathways modulating the hyperexcitability of injured DRG neurons have also been identified. Extracellular signal-regulated protein kinase, whose activation is a marker for the sensitization of dorsal horn neurons in persistent pain[23], is activated in DRG neurons following CCD, and may contribute to their hyperexcitability through down-regulating a fast-inactivating K^+ current[24]. Using the behavioral tests discussed in Section 2.2, Ding and co-workers have demonstrated a possible involvement of the TRPV4–NO–cGMP–PKG signaling cascade in CCD-induced thermal hyperalgesia[25].

3.2.2 Cytokines and chemokines Cytokines are small proteins constitutively expressed on the external membrane surface in precursor form and can diffuse over short distances to act on nearby cells. Inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) induce a further cascade of cytokine production which may increase the excitability of sensory neurons in normal rats and contribute to spinal synaptic plasticity in inflammatory pain[26]. The CCD injury has been shown to increase neuronal responses to inflammatory cytokines[27]. Exogenous TNF-α causes pain and mechanical allodynia when applied to the normal DRG, and further enhances ongoing allodynia when administered to the compressed DRG. Endogenous TNF-α contributes to the early development of mechanical allodynia in rats with chronic DRG compression[28].

Chemokines are chemotactic cytokines that induce leukocyte migration and recruitment to sites of nerve injury; they are known to contribute directly to nociception by exciting DRG neurons[29]. Using the CCD model, White *et al.* demonstrated increased expression of monocyte chemoattractant protein-1 (MCP-1) and its cognate receptor, β chemokine receptor-2, in the compressed DRG. Application of MCP-1 to an intact preparation of compressed DRG *in vitro* has potent excitatory effects on DRG neurons, and this does not occur in control ganglia[30]. Furthermore, the injury-induced effects of MCP-1 depend on the site of injury, with greater effects after ganglion injury than after injury of spinal or peripheral nerve[31]. An effect of MCP-1 has also been found in spinal astrocytes through the MCP-1–NMDA receptor signaling pathway[32], further confirming the common effects of MCP-1 in chronic pain. Nerve injury sometimes leads to chronic neuropathic pain associated with neuroimmune activation and neuroinflammation in both the peripheral and central nervous systems. Such pain may now be considered a neuroimmune disorder[33]. Future studies may highlight the role of the immune system in modulating chronic pain in the CCD model and possible therapeutics against the development and maintenance of neuropathic pain.

3.2.3 Glial cells The cell bodies of sensory neurons in the DRG are enveloped by satellite glial cells (SGCs); the latter can also be affected by axonal damage that contributes to neuropathic pain. Since SGCs express receptors for numerous neuroactive agents, they receive signals from other cells and respond to environmental changes.

As activation of SGCs may in turn influence neighboring neurons, they are likely to affect signal transmission in sensory ganglia[34]. SGCs in lumbar DRGs respond within 12 h after the onset of CCD, as indicated by their increased expression of glial fibrillary acidic protein (GFAP), and within one week[35], their intercellular coupling through gap junctions is significantly enhanced. With respect to controls, SGCs in the compressed DRG also exhibit a significantly reduced inwardly rectifying potassium (Kir) current, increased input resistance and a depolarized resting membrane potential. The Kir current in SGCs surrounding spontaneously active neurons is significantly reduced 1 day after compression but recovers within 7 days. These results show that in the compressed DRG of the CCD model, reduced Kir current and enhanced GFAP expression in SGCs are correlated with the development of neuronal hyperexcitability, although details of the sensory neuron–glial cell interactions remain unclear[35].

4 Ectopic discharges generated by CCD: properties, functions and mechanisms

4.1 Ectopic firing patterns recorded from the CCD model DRG neurons injured by chronic compression generate a high incidence of spontaneous activity in a variety of temporal patterns, such as periodic firing, irregular firing, and bursting[2] (Fig. 2).

Integer multiples firing (IMF) is one such special firing pattern characterized by interspike intervals that are integer multiples of one basic duration. These are recorded from injured DRG A-neurons, in which underlying SMPOs of relatively stable amplitude and frequency are also found. IMF can be induced in other periodically-firing DRG neurons by local application of the Na^+ channel blocker tetrodotoxin (TTX), through decreasing the SMPO amplitude or elevating the action potential threshold[14].

Bursting consists of periods of rapid spiking followed by quiescent periods and occurs widely in the nervous system. Spontaneous bursting (SB) has been shown to occur in injured DRG neurons, where its dynamic mechanism has also been investigated[9,36]. The complex irregular pattern of SB in these neurons was found to be deterministic, based on an analysis of a recorded series of interburst intervals and the dynamical systems theory of elliptic bursting (the subHopf/fold cycle type burster) developed by Eugene M. Izhikevich[36,37].

Another important form of bursting firing observed in the CCD model is evoked bursting (EB), a peripheral input spike followed by somatic burst-firing. EBs can be evoked by innocuous touch in the neuron's receptive field or by electrical stimulation exciting only Aβ fibers of the sciatic nerve (Fig. 2D). In a recent study, we demonstrated that the incidence of EB significantly increased after CCD (43.3% *vs* 13.3% in control). EB is maintained by an SMPO, and its duration increases when the membrane is depolarized[38]. In injured DRG neurons, SB sometimes coexists with EB. The voltage-sensitivity of burst duration and the discharge generation dependence on SMPOs have also been reported in SB neurons. However, EB can be distinguished from SB in at least two ways: one is the much faster upstroke of the first spike, the other is the membrane potential level at which the bursting starts[38]. These features indicate that EB and SB are distinct firing patterns. In the next section we discuss the significance of the identification of EB.

4.2 Ectopic discharges of different types may be pain signals for different symptoms It is now extensively accepted that the level of ectopic discharges is well correlated with that of pain behaviors in neuropathic rats[39], since blocking spontaneous discharges attenuates pain behaviors in both neuropathic animals and clinical cases[40-43]. Similarly, the spontaneous discharges in the injured DRG neurons of the CCD model play a critical role in both the initiation and maintenance of the neuropathic pain state. In light of the many different types of firing patterns recorded from these neurons, it seems reasonable to ask if any are associated with specific types of pain.

Tactile allodynia, the nociceptive response provoked by innocuous mechanical stimuli[44], is a common feature of neuropathic pain. There is clear evidence that myelinated Aβ fibers contribute to tactile allodynia in animals, as well as in humans with peripheral neuropathy[44,45]. EB, as noted above, was identified from the CCD model with obvious tactile allodynia behavior at a much higher incidence than

in normal rats. The fact that EB depends on peripheral input from Aβ afferents accords with the conditions required for the production of tactile allodynia. Other investigations[46] have demonstrated that the pressure-evoked afterdischarge of wide dynamic range (WDR) neurons in the dorsal horn is a cellular correlate of tactile allodynia. Our work has confirmed this correlation in the CCD model. We have also found that blockade of EB at the DRG level suppresses the afterdischarge of WDR neurons, suggesting that EB contributes to tactile allodynia and may be a candidate for its pain signal[38].

These results suggest that injured DRG neurons have abundant patterns of abnormal spontaneous electrical activity that may prove useful in decoding the relationships between these patterns and the afferent signals they carry.

4.3 Transmembrane currents associated with ectopic discharge Ectopic discharges that may contribute to the neuropathic pain occurring after CCD are determined by changes in the currents flowing through the DRG neuron plasma membrane. Hence the regulation of these currents has attracted a great deal of attention, most of which has focused on the hyperpolarization-activated current (I_h), the TTX-sensitive and -insensitive Na^+ currents (TTX-S I_{Na} and TTX-R I_{Na}), the fast-inactivating and sustained K^+ currents (I_{KA} and I_{Kdr}), and the persistent Na^+ current (I_{NaP}). In comparison with controls, CCD significantly increases the current density and activation rate of I_h, and since I_h activation provides a depolarizing current to the neuron, an increase of I_h enhances neuronal excitability[47]. To study the effects of CCD on spiking and its associated voltage-gated Na^+ and K^+ currents, cutaneous afferent neurons of medium size (35–45 μm) from the hindpaw of a rat CCD model were identified by fluorogold labeling and selected for whole-cell patch-clamp recording. The reduction in I_{KA}, a hyperpolarizing shift in TTX-S I_{Na} activation, and an increase in TTX-R I_{Na} relative to recordings from control neurons may all contribute to the enhanced excitability of the injured neurons and thus to the pain and hyperalgesia associated with CCD[48]. Similar results, i.e. increased TTX-R and TTX-S I_{Na} but decreased density of the delayed rectifier voltage-dependent K^+ current, have been extended to medium-sized DRG neurons, which mediate both nociceptive and non-nociceptive sensory modalities[49]. In the CCD model, persistent and transient Na^+ currents (I_{NaP} and I_{NaT}) were investigated using recordings made under voltage clamp from injured DRG neurons. Since the presence of low concentrations of lidocaine (10 μmol/L) suppresses SMPOs in these neurons by selectively inhibiting I_{NaP} but not I_{NaT}, the persistent Na^+ current is likely to mediate the generation of SMPOs[50]. This conclusion was confirmed by the work of Yang *et al.*, who also showed that I_{NaP} contributes to the shaping of the neuron's repetitive firing. Addition of the anticonvulsant drug gabapentin, which is used in the treatment of chronic pain, to injured A-type DRG neurons abolishes the SMPOs and decreases the amplitude of the associated membrane resonance through the inhibition of I_{NaP}, thereby inhibiting SMPO-dependent repetitive spiking and burst firing[51].

CCD neurons with EB exhibit an increased current density of I_{NaP} and I_h in addition to reduction of an α-dendrotoxin (α-DTX)-sensitive current (I_{DTX}). The increased I_h activated by afterhyperpolarization of peripheral afferent action potentials is necessary for EB generation and a balance between I_{DTX} and I_{NaP} might be necessary for EB maintenance[38].

Taken together, these changes in transmembrane currents may contribute to the decreased excitation threshold and/or accommodation that occur after CCD. It is worth noting that most of the investigations discussed above were carried out in medium-to-large DRG neurons, so those channels expressed predominantly on small DRG neurons, such as the transient receptor potential channels, have received little attention.

5 Properties distinguishing CCD from other models

Neuropathic pain is induced by many factors through diverse mechanisms. Unraveling these mechanisms requires laboratory animal models that replicate as far as possible the pathophysiological states present in patients. Table 1 briefly compares six peripheral neuropathic pain models[2,3,5,6,52-56]. In this section, we also discuss the dis-

Table 1. Comparison of different neuropathic pain models

Model	Establishment	Aim	Features	Disadvantages	References
CCD	Insert L-shaped fine stainless-steel rods into the L5/L4 intervertebral foramina to compress the DRG.	To mimic the low back pain and sciatica caused by foraminal stenosis or disc herniation	Maintainance of peripheral input, absence of motor disorders, recordings of abundant patterns of ectopic discharge	The rod used for compression may induce a response different from the biological staffs like those of herniated intervetebral disc.	[2][3]
Axotomy	Ligate and transect the sciatic nerve.	To develop experimental anesthesia dolorosa induced by damage of sciatic and saphenous nerves	Entire denervation of the distal hindlimb, thereby blocking all sensory input from the denervated zone	Autotomy and/or self-mutilation	[52][53]
CCI	Place four loosely constrictive ligatures around the sciatic nerve.	Peripheral mononeuropathy resembling causalgia by the injury of common sciatic nerve	Most of the A fibers have Wallerian degeneration, while ~50% of the C fibers are preserved.	Difficulty in controlling the number and type of injured nerves; damage to the motor function controlling the hind foot	[6]
SNL	Ligate either the L5 or both L5 and L6 spinal nerves on one side.	To develop sympathetic-dependent neuropathic pain	The levels of injured and intact spinal segments are completely separated, allowing for their independent experimental manipulations.	Clinical cases are rare.	[5]
SNI	Transect the tibial and common peroneal nerves in the popliteal fossa, leaving the remaining sural nerve intact.	Partial denervation in which the lesioned territories acquire a *de novo* innervation by the spared nerves	Permit behavioral testing of regions of non-injured skin adjacent to the denervated areas.	Mechanisms underlying the generation of pain signals are difficult to determine.	[54]
PSNL	Tightly ligate the dorsal 1/3–1/2 of the thickness of the sciatic nerve.	To mimic the causalgiform pain disorders in humans	The maintenance and production of the sensory disorders depend on sympathetic nervous outflow.	Difficult to study the mechanism underlying the injury site	[55][56]

CCD, chronic compression of the DRG; CCI, chronic constriction injury; PSNL, partial sciatic nerve ligation; SNL, spinal nerve ligation; SNI, spared nerve injury.

tinctive features of the CCD model in depth.

5.1 Maintenance of peripheral input Various models are used to mimic the neuropathic pain arising from lesions or diseases affecting the somatosensory system. The axotomy model, which involves complete nerve transection in an intact limb and results in self-mutilation of the digits, mimics to some extent the spontaneous "phantom pain" experienced by patients with amputation. In any case, the human syndrome modeled by this assay, phantom limb pain, in which the primary sensory neurons are completely dissected from peripheral input, is rare[52]. The chronic constriction injury (CCI) or Bennet-Xie model constricts the sciatic nerve without complete axotomy. In this model, behavioral signs of spontaneous pain, hyperalgesia, and

mechanical/thermal allodynia, along with rare cases of autotomy behavior, have been observed[6]. Also, Wallerian degeneration occurs in most of the fibers, especially in those of the A type, thereby blocking peripheral input from the corresponding neurons' receptive fields.

A distinctive property of the CCD model is that most of the peripheral inputs are preserved, including those hyperexcitable neurons that also retain functional connectivity with their peripheral targets. We have been able to record afferent signals originating in the skin and muscle spindles from most dorsal root fibers (unpublished results). This means that in the CCD model, discharges from receptive fields can still be transmitted centrally. Somatic primary sensory neurons are designed to "speak only when spoken to", and to respond specifically to peripheral stimulation. But injured sensory neurons may develop "opinions of their own" when a portion of their axon or soma becomes sufficiently hyperexcited to generate ectopic action potentials[3,6,57-59]. As the somata of injured DRG neurons may themselves be the origin of these spontaneous discharges, the question arises as to how the ectopic activity interacts with peripheral signals at the membrane level. We have begun to address this issue in our recent investigations of EB[38].

5.2 Inflammation and compression injury in the CCD model mimics radicular pain in humans Although low back pain is among the most common of medical complaints[60], its pathophysiology is poorly understood. Among the many attempts to duplicate this condition in experimental animals, the CCD model is one of the most direct for inducing the prevalent clinical pain syndromes caused by stenosis[1], e.g. from a laterally-herniated disc or foraminal stenosis. Intervertebral disc herniation is considered to produce pain primarily by mechanical compression[61,62], while the syndrome's reversibility has been demonstrated by Song and co-workers. In their study, removal of the rods producing the disc compression after the second week prompted recovery at both the behavioral and electrophysiological levels[63]. In addition to the direct compression established in the CCD model, other investigators have found that inflammatory responses play a key role in the development of radicular pain. Gu *et al.* demonstrated that the level of an inflammatory marker, inhibitory factor kappabeta-alpha, is up-regulated in both the compressed DRG and the adjacent spinal cord[64]. Consistently, Homma *et al.* have reported that mechanical allodynia induced in the DRG can be partially blocked by a concurrent local administration of a mixture of soluble TNF receptors, suggesting that TNF-α contributes to the early development of mechanical allodynia[28].

With the spinal compression characteristic of the CCD model localized to the DRG, both sensory neurons and spinal nerves are injured, thereby mimicking the effects of protrusion of an intervertebral disc seen clinically. Moreover, the rods used in the establishment of CCD are attacked by the immune system, incurring sterile inflammation. Insertion of these rods can also damage spinal segmental vessels passing through the intervertebral foramina, which would tend to strengthen the inflammatory response. (Although the clinical situation may differ, the condition has symptoms similar to those of herniation of the nucleus pulposus.) Hence both the spinal compression and its attendant inflammation may be involved in the behavioral and physiological consequences of CCD, making the effects of the model all the more similar to the complexities of the clinical situation. Therefore, CCD is an animal model mimicking radicular pain in humans[65]. Consistent with this correspondence, recent therapies have focused attention on the relief of symptoms due to spinal compression by the reconstruction of holes within the blocked lamina of the vertebra[66].

Many similar models have been developed based on the CCD paradigm[64,67]. One such modified version was created by compressing the DRG with SURGIFLO™ (Johnson & Johnson, Somerville, NJ)[64], a hemostatic gelatin matrix that hardens within minutes after injection and is extensively used in surgery. Rats subjected to DRG compression with SURGIFLO™ develop thermal hyperalgesia and mechanical allodynia that last more than 30 days. The benefit of using this biologically degradable material compared to a metal rod is that its texture is similar to that of a herniated disc, thereby more closely duplicating some

clinical conditions[64]. The data suggest that this modified rat model for chronic compression of the lumbar DRG may be a useful tool for exploring the mechanisms of radicular pain, as well as for the development of new therapeutic options for its treatment.

6 Conclusion

A schematic drawing of the proposed mechanisms underlying the hyperexcitability of DRG neurons in the CCD model is given in Fig. 3. In brief, compression of the nerve root and the DRG as well as accompanying inflammatory factors contribute to the consequences of establishing the model, which mimics the clinical radicular pain of patients experiencing spontaneous pain, hyperalgesia and allodynia. The increased excitability of DRG cells is considered to be associated with the generation and maintenance of the neuropathic pain state. The wide range of firing patterns recorded from injured DRG neurons suggests the usefulness of their varied spontaneous discharges in decoding peripheral sensory signals. Therefore, use of this animal model is likely to increase our understanding of the neural mechanisms for low back pain and sciatica.

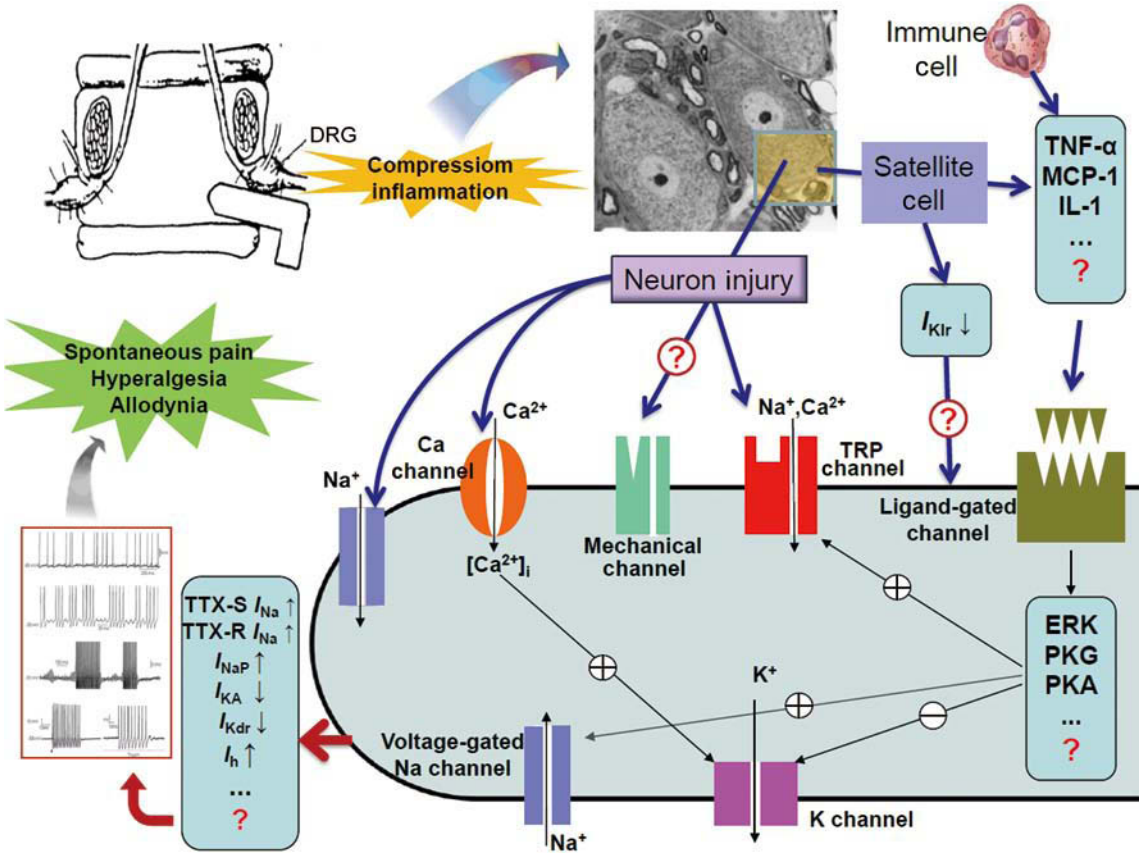

Fig. 3. Schema of the proposed mechanisms underlying the hyperexcitability of DRG neurons in the CCD model. The L5 intervertebral foramen and the inserted "L" shaped rod are displayed in the left upper panel; under these conditions both compression and inflammation contribute to the consequences of CCD. A simplified scheme illustrating some of the molecular events in the hyperexcitable neurons is shown at the bottom right. These events might develop in the enlarged area of the yellow square showing a neuron and satellite (middle upper panel). The effects of chemokines from either satellite cells or immune cells are proposed. Colored symbols represent ion channels on the neuron membrane. DRG, dorsal root ganglion; ERK, extracellular signal-regulated protein kinase; I_{KA}, fast-inactivating K^+ current; I_{Kdr}, sustained K^+ current; I_{Kir}, inward-rectifier K^+ current; I_h, hyperpolarization-activated current; I_{NaP}, persistent Na^+ current; IL-1, interleukin 1; MCP-1, monocyte chemoattractant protein-1; PKG, protein kinase G; PKA, protein kinase A; TNF-α, tumor necrosis factor alpha; TTX-R I_{Na}, TTX-insensitive Na^+ currents; TTX-S I_{Na}, TTX-sensitive Na^+ current.

One possible target for future research is clarifying the relationship between peripherally-induced firing patterns at the DRG level and pain symptoms at the behavioral level. It is presently unclear how these firing patterns differ during the processing of sensory signals, either as a direct effect of the injury or in an indirect way, such as through central sensitization. Apart from our preliminary results on EB, still less is known about the correlation of ectopic discharge patterns to different pain symptoms. In this respect, various types of DRG neurons may play different roles corresponding to hypothetical preferred firing patterns. Furthermore, the mechanism for the hyperexcitability of injured DRG neurons is not as highly developed as that of other neuropathic pain models. Some mechanically-sensitive channels may play a key role in low back pain, as therapeutic stretch alleviates the pain sensations in some cases. Determining the relevant subtypes of such channels by PCR methods may prove useful in the development of appropriate clinical therapies.

Current analgesic therapy has side-effects, especially drugs that penetrate the blood-brain barrier. Alternative painkiller development focused on the periphery should take advantage of the CCD model, although this approach is still in its infancy. The development of an analgesic using spontaneous discharge as the target to specifically quench the ectopic pain signal would then perfectly satisfy the ideal standard advocated by the International Association for the Study of Pain: to block neuropathic pain without influencing physiological pain.

Acknowledgements: This review was supported by the National Natural Science Foundation of China (30870829). We are grateful to Dr. Victor Z. Han and Dr. Gerhard Magnus for English editing and to Jie Men and Lun Yan for helping to design the cover image.

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