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Pain behavior in *SCN9A* (Nav1.7) and *SCN10A* (Nav1.8) mutant rodent models

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Highlights

Rodent genetic models have highlighted the role of *SCN9A*- and *SCN10A*- encoded Nav1.7 and Nav1.8 voltage-gated sodium channels in pain control.

Global *Scn9a* knockout (KO) animals display pain insensitivity similarly to congenital insensitivity to pain in patients.

The conditional KO mouse lines allowed the assignment of *Scn9a* expressed in different neuronal populations in pain control.

Targeting Nav1.7 and Nav1.8 constitute potential therapies for pain.

Abstract

The two voltage gated sodium channels Nav1.7 and Nav1.8 are expressed in the peripheral nervous system and involved in various pain conditions including inflammatory and neuropathic pain. Rodent models bearing deletions or mutations of the corresponding genes, *Scn9a* and *Scn10a*, were created in order to understand the role of these channels in the pathophysiological mechanism underlying pain symptoms. This review summarizes the pain behavior profiles reported in *Scn9a* and *Scn10a* rodent models. The complete loss-of-function or knockout (KO) of *Scn9a* or *Scn10a* and the conditional KO (cKO) of *Scn9a* in specific cell populations were shown to decrease sensitivity to various pain stimuli. The Possum mutant mice bearing a dominant hypermorphic mutation in *Scn10a* revealed higher sensitivity to noxious stimuli. Several gain-of-function mutations were identified in patients with painful small fiber neuropathy. Future knowledge obtained from preclinical models bearing these mutations will allow understanding how these mutations affect pain. In addition, the review gives perspectives for creating models that better mimic patients' pain symptoms in view to developing novel analgesic strategies.

1. Introduction

Pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”, as re-defined recently by the International Association for the Study of Pain [1]. Pain is a leading cause of disability and disease burden [2]. As the treatment of pain is still often unsatisfactory, it is important to explore pain mechanisms for developing new therapeutic strategies [3, 4].

There are four major types of pain: nociceptive pain, inflammatory pain, neuropathic pain and dysfunctional pain [3]. Injured tissues or nerves release proinflammatory molecules and nerve growth factors which lead to peripheral sensitization. The pain message is transmitted to the spinal cord via the central terminal of primary afferents and then to the pain matrix in the brain that also exerts the descending pain control [5].

Small fiber neuropathies (SFNs) are disorders of A δ -fibers and C-fibers usually characterized by neuropathic pain symptoms and autonomic complaints [6]. Interestingly, in idiopathic SFNs, nearly 30% of patients have gain-of-function (GOF) mutations in the *SCN9A* gene encoding for the Nav1.7 channel protein [7]. These mutations produce impaired inactivation or an enhanced resurgent current of the Nav1.7 channel and induce increased excitability in the dorsal root ganglia (DRG) neurons [7]. Nav1.7 has been investigated as a target for analgesia but Nav1.7 inhibitors have not yet been developed as therapeutics [8, 9]. Additionally, *SCN9A* gene loss-of-function (LOF) results in congenital insensitivity to pain (CIP)[10]. Similar to *SCN9A* variants, several GOF mutations in the *SCN10A* gene encoding for the sodium channel Nav1.8 α -subunit have been reported in SFN patients, provoking neuronal hyperexcitability in the DRG neurons [11, 12].

Understanding the pathophysiological mechanisms underlying pain symptoms in painful SFN and other pain pathologies is important and requires preclinical models. In this review, we provide the profiles of nociceptive behaviors related to the Nav1.7 and Nav1.8 channels by evoking the different genetic models used in research until now.

2. The sodium voltage-gated channels Nav1.7 (SCN9A) and Nav1.8 (SCN10A)

Nav1.7 and Nav1.8 channels are voltage-gated sodium channels that play a critical role in the generation and conduction of action potentials and are important for the excitability of sensory neurons. They are composed of one α -subunit associated with one or more β -subunits. The α -subunit consists of four homologous domains (DI-DIV) consisting of six transmembrane segments [13, 14]. The tridimensional structure and biophysical properties of these channels have been reviewed recently [15].

Nav1.7 is a tetrodotoxin-sensitive sodium channel which opens in response to small depolarizations [8]. Nav1.7 is preferentially expressed in the peripheral nervous system within sensory and sympathetic neurons [16, 17]. The Nav1.7 protein is detected in laminae I and II of the spinal cord dorsal horn at the primary afferent terminals of sensory neurons, as shown by investigations with epitope-tagged Nav1.7 mutant mice [18][17]. Nav1.8 produces a slow inactivating, tetrodotoxin-resistant current, and is known to recover rapidly from inactivation [8, 15]. Nav1.8 contributes to the rising phase of action potential [15]. Nav1.8 protein is expressed within the small-diameter sensory neurons of the trigeminal ganglion and DRG and in a part of medium- and large-diameter neurons as well as in lamina I and II of the spinal cord dorsal horn [8, 19-21][22].

The pain behavior analysis of genetic animal models for *Scn9a* and *Scn10a* showed that these sodium channels play important roles in acute pain sensation (nociception) and contribute to the sensitization of pain circuits, leading to hyperalgesia [23].

3. Role of *SCN9A* (Nav1.7) in pain behavior: lessons learnt from rodent models

3.1 Effect of channel absence as assessed in homozygote global KO mice and rats

Clinical genetic studies have reported that *SCN9A* LOF results in CIP. Genetic animal models were used to study CIP mechanisms. The impact of Nav1.7 protein absence has been assessed by the knockout (KO) *Scn9a* gene in mice (global KO) [24][25]. Also, partial KO rats were generated with Nav1.7 loss in DRGs, sciatic nerve, brainstem and gastrointestinal tissues but not in the olfactory tract [26]. These KO animals were profiled for pain behavior.

3.1.1 Effect on nociceptive behavior

Measurements of reflex behaviors to thermal and mechanical stimuli as well as more integrated or spontaneous pain tests were used to examine pain-like responses [27, 28]. Supraspinal responses to a noxious heat stimulus can be assessed by the hot plate test with paw reaction latency. Paw withdrawal latencies of wild-type (WT) and heterozygous WT/KO (HET) mice decreased with increasing temperature in the hot plate assay from 48 to 55°C while *Scn9a* KO mice were insensitive to heat [25] (Table 1). Sensitivity to mechanical stimuli was evaluated using Von Frey filaments for touch, tail clip, Randall-Selitto and a pressure analgesimeter to apply pressure application to paw and tail to assess allodynia and hyperalgesia [27, 28]. Global *Scn9a* KO mice were insensitive to pressure pain in the tail clip assay. However, in the Von Frey test, the KOs showed touch sensitivity similar to that of control mice [25]. The *Scn9a* LOF rats had no or faint responses to noxious chemical, thermal and prick stimuli [26, 29] (Table 1).

3.1.2 Effect on experimentally-induced pain

The formalin test is used for testing pain behaviors to formalin as a chemical irritant (phase I, 0-5 min) and subsequent acute inflammatory hyperalgesia (phase II, 10-40 min). The global *Scn9a* KO mice and LOF rats showed a strong reduction or no response in phases I and II in the formalin test [25, 26, 29]. The Complete Freund's adjuvant (CFA) model is aimed at studying chronic inflammatory hyperalgesia in rodents. WT and *Scn9a* KO HET control mice showed expected inflammatory hypersensitivity while whole KO mice displayed no pain-like behaviors [25] (Table 1). The *Scn9a* LOF rats did not experience hypersensitivity to experimentally-induced neuropathy [26]. In summary, *Scn9a* LOF induced insensitivity or strongly reduced sensitivity in rodents, a phenotype highly analogous to CIP patients.

3.2. Effect on *Scn9a* deletion in specific cell populations as assessed in conditional KO mice

To study the role of Nav1.7 in specific types of neurons, several mouse lines with conditional deletion of *Scn9a* have been generated using the Cre-Lox system. Mice with a floxed *Scn9a* gene (*Scn9a*^{lox/lox}) mice were created. This review will use the simplified name *Scn9a*^{fl/fl}. The *Scn9a*^{fl/fl} mice were crossed with different Cre mouse lines for *Scn9a* gene inactivation in different cell populations. The *Scn9a*^{fl/fl} mice were crossed with *Scn10a*^{cre/+} mice to obtain the *Scn9a* conditional KO (cKO) in primary nociceptive neurons [24, 30-35] (the simplified name in this review will be *Scn10a*^{Cre}-*Scn9a*^{fl/fl}). *Scn9a*^{fl/fl} mice were also crossed with *Avil*^{cre/+} mice to obtain *Scn9a* cKO in all sensory neurons [30, 32, 34, 36]. The name of this line in this review will be *Avil*^{Cre}-*Scn9a*^{fl/fl}. In addition, *Scn9a*^{fl/fl} mice were crossed with *Wnt1*^{cre/+} mice for *Scn9a* conditional gene inactivation in sensory and sympathetic neurons [30, 32, 34, 37]. In this review these cKO mice will be referred to as *Wnt1*^{Cre}-*Scn9a*^{fl/fl}. Moreover, *Scn9a* gene inactivation could be induced at the adult age. *Scn9a*^{fl/fl} mice were crossed with mice where the Cre-ERT transgene was driven by the CMV early enhancer/chicken beta-actin promoter, allowing Cre recombinase activation upon tamoxifen induction [38]. This cKO line will be named pCAGG^{CreERT}-*Scn9a*^{fl/fl}. Following tamoxifen induction, *Scn9a* expression was abolished in the DRG (mRNA, protein), trigeminal ganglia (mRNA) and sympathetic superior cervical ganglia (mRNA) in pCAGG^{CreERT}-*Scn9a*^{fl/fl} mice [38].

3.2.1. Effect on nociceptive behavior

Sensitivity to heat noxious stimuli was determined in the Hargreaves and hot plate tests. Altogether, the *Scn9a* cKO lines were less sensitive in the Hargreaves test. The *Scn10a*^{Cre}-*Scn9a*^{fl/fl} line showed decreased sensitivity with the slow ramp [24, 30, 32, 35] while the *Avil*^{Cre}-*Scn9a*^{fl/fl}, *Wnt1*^{Cre}-*Scn9a*^{fl/fl} and pCAGG^{CreERT}-*Scn9a*^{fl/fl} lines showed behavioral response deficits to both fast and slow heat ramps [30, 32, 37, 38], suggesting a differential contribution of Nav1.7 in the different neuron types for mediating the response to transduced heat [32]. Furthermore, in the more integrated hot plate test test, only the *Wnt1*^{Cre}-*Scn9a*^{fl/fl} and pCAGG^{CreERT}-*Scn9a*^{fl/fl} mice showed a pronounced response attenuation [30, 37, 38] (Table 1).

Response to cooling and extreme cold were measured by the acetone and cold plate tests [27]. The cKO lines displayed normal response on the cold plate in contrast to LOF rats that were less sensitive. In the acetone test, all the cKO lines showed deficits in cooling perception except the *Scn10a*^{Cre}-*Scn9a*^{fl/fl} line [30] (Table 1). This was corroborated by the attenuated response of *Avil*^{Cre}-*Scn9a*^{fl/fl} mice to cooling in the dynamic thermal place preference test [32] (Table 1). Altogether, these results on *Scn9a* cKO lines suggest that Nav1.7 expressed on Nav1.8 negative cells are implicated in cooling (acetone) response.

The cKO lines displayed pronounced analgesia to noxious pressure in the Randall-Selitto test (Table 1). The *Scn10a^{Cre}-Scn9a^{fl/fl}* mice showed normal response to touch in six articles from three laboratories [24, 30, 32, 34, 38, 39] except when they were tested with the Electronic von Frey Anesthesiometer [35]. This difference may have been due to the continuous force application and represent a pressure rather than a touch stimulus, thereby consolidating the data obtained with the Randall-Selitto test. Interestingly, both *Avil^{Cre}-Scn9a^{fl/fl}* and *Wnt1^{Cre}-Scn9a^{fl/fl}* mice but not *Scn10a^{Cre}-Scn9a^{fl/fl}* mice showed deficits in response to von Frey filaments applied to hairy skin [32] (Table 1), revealing mechanosensation by hair follicles dependent on Nav1.7 mainly in Nav1.8-negative neurons [32].

3.2.2. Effect on experimentally-induced pain

The role of Nav1.7 on Nav1.8-positive neurons in visceral pain was investigated with the *Scn10a^{Cre}-Scn9a^{fl/fl}* mice [31]. *Scn10a^{Cre}-Scn9a^{fl/fl}* animals had normal sensitivity, while *pCAGG^{CreERT}-Scn9a^{fl/fl}* mice displayed a decreased response in the acetic-acid-induced model [38]. Together, this suggests that that Nav1.7 in neurons other than Nav1.8 neurons contributed to visceral pain, while Nav1.8 was shown to contribute to visceral pain (see section 4.2.).

The *Scn9a* cKO lines were assessed for inflammatory pain. Both *Scn10a^{Cre}-Scn9a^{fl/fl}* and *Avil^{Cre}-Scn9a^{fl/fl}* lines displayed reduced response in the two formalin test phases [24, 30], while *pCAGG^{CreERT}-Scn9a^{fl/fl}* mice had an attenuated response in phase I only [38]. In the carrageenan inflammatory model, thermal hyperalgesia was absent in *Scn10a^{Cre}-Scn9a^{fl/fl}* mice [24] (Table 1). In the CFA model, heat hypersensitivity was abolished in both *Scn10a^{Cre}-Scn9a^{fl/fl}* and *pCAGG^{CreERT}-Scn9a^{fl/fl}* animals while mechanical allodynia was reduced only in the latter mice [38]. Altogether, these results highlighted the contribution of Nav1.7 in peripheral neurons in inflammatory hyperalgesia.

Neuropathic pain is caused by neuronal injury in the peripheral or central nervous system, and preclinical models have been developed [27]. Chronic constriction injury (CCI), spinal nerve transection (SNT), partial sciatic nerve ligation (pSNL) and spared-nerve injury (SNI) were utilized as nerve injury models in the *Scn9a* cKO mouse lines [30, 32, 38, 40]. The *Scn10a^{Cre}-Scn9a^{fl/fl}* mice developed mechanical but attenuated cold allodynia following CCI or pSNL, while they showed normal allodynia after SNT (Table 1). The *Avil^{Cre}-Scn9a^{fl/fl}* mice showed cold and mechanical allodynia during SNT but attenuated allodynia following CCI (Table 1). Deleting *Scn9a* in both sensory and sympathetic neurons (*Wnt1^{Cre}-Scn9a^{fl/fl}*) abolished allodynia upon SNT or CCI (Table 1). In *pCAGG^{CreERT}-Scn9a^{fl/fl}* mice, SNI induced weak cold allodynia but normal mechanical hypersensitivity [38]. In *Avil^{Cre}-Scn9a^{fl/fl}* and *Wnt1^{Cre}-Scn9a^{fl/fl}* mice, oxaliplatin-induced neuropathic pain and cancer-induced pain developed as in control littermates (Table 1). Furthermore, in a burn injury model, Nav1.7 in Nav1.8-positive neurons contributed to heat but not mechanical hyperalgesia [33] (Table 1).

Altogether, the behavioral analyses of KO and cKO animals showed that Nav1.7 is a major contributor to both acute nociception and experimentally-induced chronic hyperalgesia and revealed the role of Nav1.7 in specific neuronal populations in the different pain models.

3.3. Nav1.7 and the opioid pathway

LOF mutations in humans or global *Scn9a* KO in mice or rats lead to insensitivity to pain. The *Preproenkephalin* (*Penk*) gene encodes for the endogenous opioid peptide enkephalin, an endogenous pain-controller. Interestingly, *Penk* mRNA was found to be elevated in *Avil^{Cre}-Scn9a^{fl/fl}* DRGs. The opioid antagonist naloxone reversed hyposensitivity in a *SCN9A*-null CIP patient and in *Avil^{Cre}-Scn9a^{fl/fl}* mice [36]. *Penk* expression was also increased in *Wnt1^{Cre}-Scn9a^{fl/fl}* animals. *Wnt1^{Cre}-Scn9a^{fl/fl}* mice were crossed mu (MOR) or delta (DOR) opioid receptor KO mice, and *Scn9a* KO-driven analgesia was abolished in triple *Wnt1^{Cre}-Scn9a^{fl/fl}/MOR/DOR* KO mice [37]. Altogether, this suggested that endogenous opioids contribute to analgesia driven by *Scn9a* gene inactivation. However, naloxone did not reverse analgesia in *Scn9a* LOF rats [29] and PENK was not expressed or up-regulated in sensory neurons differentiated from a patient with CIP [10]. Hence, the link between loss of Nav1.7 and the opioid system in CIP is still a matter of debate.

4. Role of Nav1.8 in pain behavior: lessons learnt from mouse models

4.1. Pain behavior in the *Scn10a^{T790A}* possum mice.

The mouse mutant termed Possum which carries a T790A hypermorphic mutation of the *Scn10a* gene was identified following N-ethyl-N-nitrosourea mutagenesis. These mutants have posture abnormalities and deficits [41]. They had normal responses to Von Frey filaments but an increased response to a needle prick on the hindpaw [41, 42][42]. They displayed increased sensitivity on the cold plate at -1°C but normal sensitivity on the hot plate [41]. Following mustard oil application to the hindpaw, Possum mice remained motionless [42], the relationship of this behavior to pain remaining unknown. In the CFA inflammatory model, Possum mice showed normal mechanical allodynia [41] (Table 2). In summary, the Possum mice had hyperactive Nav1.8 channels and showed increased sensitivity to extreme noxious mechanical and cold stimuli but not to the other pain challenges.

4.2. Effect of Nav1.8 channel absence as assessed in global KO mice

4.2.1. Effect on nociceptive behavior and spontaneous pain

The studies on *Scn10a* KO mice revealed deficits in both mechanical and thermal perception (Table 2). *Scn10a* KO mice showed analgesia to noxious mechanical pressure [32, 40, 43], but no change in reaction to touch in the Von Frey test [33, 34, 40, 43-45]. Concerning responses to thermal stimuli, *Scn10a* KO animals showed increased withdrawal latency to slow but not to fast heat ramps in the Hargreaves test [32]. The same analgesia was found in *Scn10a* KO mice when using the slow heating condition in the paw flick and tail flick tests [43] but not in other studies with fast heating [40, 44, 45]. Accordingly, a slow temperature ramp allowed detecting analgesia in *Scn10a* KO mice. *Scn10a* KO mice were less sensitive in the tail-flick test [43] but normally sensitive in the hot plate test integrated in all the temperatures tested [40, 43, 45]. *Scn10a* deficient mice also revealed a reduced response to extreme but not to mild cold [46, 47] (Table 2) and were less sensitive in visceral pain models [48].

4.2.2. Effect on experimentally-induced pain

The *Scn10a* KO animals were tested in both inflammatory and neuropathic models. The response of mutant mice to formalin was similar to that of control mice. Following carrageenan inflammation, hyperalgesia onset was slightly delayed in *Scn10a* KO mice [43]. In the CFA model, mutant mice displayed both thermal and mechanical hyperalgesia, with faster recovery from heat pain [45]. These results suggest a role of Nav1.8 in the kinetics of inflammatory pain but not in lowering nociceptive thresholds. The null mutants developed heat and mechanical hypersensitivity following burn injury [33] and SNT [32]. *Scn10a* KO mice showed attenuated cold allodynia in the SNI model [45] and reduced cold allodynia to CCI injury in one out of two reports [32, 45] (Table 2). Taken globally, the Nav1.8 channel contributes to cold allodynia in neuropathic pain models.

4.3. Effect on the channel as assessed in Nav1.8-Cre mice

Knock-in mouse lines that express Cre-recombinase driven by the *Scn10a* locus were generated [19, 20, 24] to develop conditional KO mice with nociceptive neurons, *Scn10a*^{Cre/+}. These mice had normal behavior in the mechanical and heat pain tests [19, 20, 24](Table 2). Inflammatory and SNL-induced neuropathic pain developed normally in *Scn10a*^{Cre/+} mice [24]. [20] (Table 2). Therefore, as the *Scn10a*^{Cre/+} mice behaved as WT mice in the pain models, they were used to conditionally inactivate their genes of interest in nociceptive neurons.

5. Perspectives

The genetic rodent models described here, together with pharmacological approaches that are beyond the scope of this short review, showed that Nav1.7 and Nav1.8 play important roles in nociception and chronic hyperalgesia. Two teams have developed sensory neurons differentiated from patient-derived Induced

Pluripotent Stem Cells that model inherited erythromelalgia [49-51]. This novel preclinical model provides a platform which enables the assessment of the sodium channel function in vitro in cells from patients.

GOF mutants of *SCN9A* and *SCN10A* have been reported in SFN patients with chronic pain while LOF mutants of *SCN9A* lead to a loss of pain perception in CIP patients. These data suggest that *SCN9A* is mandatory for pain in humans, and that elucidating the role of *SCN10A* requires more investigation. Novel rodent genetic models for the GOF mutations found in SFN patients could be generated by homologous recombination or CRISPR-Cas9 techniques. Also, the other sodium channels including the Nav1.9 channel playing important roles in pain and mutations in these channels have been identified [4, 8, 13, 15]. Genetic models for mutations in these other genes will allow improving understanding of their roles in chronic pain.

The evaluation of reflexive pain behavior has been applied in preclinical pain research for decades. Present and future genetic models could be tested in more clinically relevant approaches of spontaneous pain behavior, the attenuation of pathological pain, and restoring functions that are decreased in pain patients [27, 28]. In addition, exploring the roles of *Scn* genes in pain behavior would necessitate the study of mutations in different genetic backgrounds and in both sexes [52]. More globally, the combination of genetic models and other approaches including genetic screening will allow identifying additional components of chronic pain [4].

6. Summary

This review summarized the literature published on pain behavior in *Scn9a* and *Scn10a* genetic rodent models. Deleting *Scn9a* and *Scn10a* either in the whole body or in specific neuron populations attenuates pain responses, mirroring the clinical features of CIP patients. The analysis of genetic animal models for the mutations found in SFN patients would reveal how these mutations mediate SFN-related pathology including pain.

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Table 1. Pain Behaviors in *Scn9a*(Nav1.7)-related genetic models

	<i>Scn9a</i> LOF rats; <i>Scn9a</i> Global KO [25, 26, 29]	<i>Scn10a</i> ^{Cre} - <i>Scn9a</i> ^{fl/fl} ; <i>Advill</i> ^{Cre} - <i>Scn9a</i> ^{fl/fl} [24, 30-35, 39]	<i>Wnt1</i> ^{Cre} - <i>Scn9a</i> ^{fl/fl} ; pCAGG ^{CreERT} - <i>Scn9a</i> ^{fl/fl} [30, 32, 34, 37-38]
Basal nociception			
Mechanical			
Von Frey	↘; =	=; ↘	= ↘; =
Randall-Selitto or tail clip	na; ↘	↘	↘
Pin-prink	↘; na	na	na
Heat			
Hargreaves	↘; na	↘; =; ↘	↘
Hot Plate or tail immersion	↘	=	↘
Cold			
Acetone	↘	=; ↘	↘; na
Cold Plate or Dry ice	↘	=	=; na
Dynamic thermal place preference, cooling	=	na; ↘	na; ↘
Inflammatory pain			
Formalin Phase I	↘	=	ND; ↘
Formalin Phase II	↘	↘	ND; =
CFA or Carrageenan			
Hargreaves	na; ↘	↘; na	na; ↘
Von Frey	na	↘; na	na; =
Neuropathic pain			
SNT			
Acetone	na	=	↘; na
Von Frey	na	=	↘; na
CCI			
Acetone	na	↘	↘; na
Von Frey	na	=; ↘	↘; na
pSNL, SNL or SNI			
Acetone	na	↘; na	na; ↘
Von Frey	↘; na	=; na	na; =
Oxaliplatin			
Acetone	na	=	=; na
Von Frey	na	=	=; na
Other pain models			
Cancer-induced pain	na	na; =	=; na
Burn injury			
Hargreaves	na	↘; na	na
Von Frey	na	=; na	na

CCI: Chronic Constriction Injury; CFA: Complete Freund's Adjuvant; KO, knockout; LOF: Loss-of-function; na: not available; SNI: Spared Nerve Injury; pSNL: partial sciatic Nerve Ligation; SNL: Spinal Nerve Ligation; SNT: Spinal Nerve Transection;
=: no change; ▼ : less sensitive compared to control

Table 2. Pain Behaviors in *Scn10a* (Nav1.8)-related genetic models

	<i>Scn10a</i> Global KO [32-34, 40, 43, 44-48]	<i>Scn10a</i> ^{Cre/+} [19-20, 24]
Basal nociception		
Mechanical		
Von Frey	=	=
Randall-Selitto	↘	=
Heat		
Hargreaves	= ↘	=
Tail Flick or immersion	= ↘	na
Hot Plate	=	=
Cold		
Acetone	=	na
Cold plantar	=	na
Cold plate	= ↘	na
Inflammatory pain		
Formalin	=	=
Carrageenan	=, delayed	=
CFA		
Von Frey	=	=
Hargreaves	=, recover faster	=
Neuropathic pain		
SNT/SNL		
Acetone	=	na
Von Frey	=	=
Hargreaves	=	=
CCI & SNI		
Acetone	= ↘	na
Von Frey	=	na
Oxaliplatin		
Von Frey	=	na
Other pain model		
Burn injury	=	na

CCI: Chronic Constriction Injury; CFA: Complete Freund's Adjuvant; KO: knockout; na: not available; SNI: Spared Nerve Injury; SNL: Spinal Nerve Ligation; SNT: Spinal Nerve Transection
 =: no change; ↘ less sensitive compared to control.