

2012

A review into the role of voltage gated sodium channels 1.8 and 1.9 in pain states: and medical uses of this knowledge

Morfey, M.

Morfey, M. (2012) 'A review into the role of voltage gated sodium channels 1.8 and 1.9 in pain states; and medical uses of this knowledge', *The Plymouth Student Scientist*, 5(1), p. 294-303.
<http://hdl.handle.net/10026.1/13976>

The Plymouth Student Scientist
University of Plymouth

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

A review into the role of voltage gated sodium channels 1.8 and 1.9 in pain states; and medical uses of this knowledge

Matt Morfey

Project Advisor: [Stephen Thompson](#), School of Biomedical & Biological Sciences, Plymouth University, Drake Circus, Plymouth, PL4 8AA

Abstract

This review is aimed at discussing the role of voltage gated sodium channels (VGSC) Nav 1.8 and 1.9 in pain states. This involves establishing their role in pain states such as neuropathic and inflammatory pain, and which of these pain states the individual channels impact on and to what effect. Establishing this will involve an exploration of which neurones these channels are located around the body, sensory or nociceptive, as well how their activity impacts on their function. Also discussed will be how the routes of activation of these VGSC impacts on their role in pain sensation and detection within the neurones in which they are found. This will be achieved by the analysis of studies and investigations collected spanning a 30-year period. These experiments use many different techniques that can be compared to draw a strong conclusion on the role of Nav 1.8 and 1.9. This will be used to indicate possible uses of this knowledge in the medical fields such as anaesthesia, suggesting useful implications of the research.

What are voltage gated sodium channels?

Voltage gated sodium channels are complex transmembrane proteins that allow the rapid flow of sodium ions across the membrane creating a current that is involved in the depolarising upstroke of an action potential generated in an excitable sensory neurone (Cummins et al, 2007).

The basic structure of the VGSC are a large α subunit which carries the functional capacity, accompanied by one or two smaller ancillary β subunits which have chaperone characteristics in that they stabilise the α subunit (Okuse et al 2002). The α subunit is comprised of four domains all of which are themselves made up of six segments, which all interact to provide function to the channel. Conformational changes in the S4 segment on all four domains of the α subunit alter the state of the channel between inactive, closed and open states and thus controlling the flow of the sodium current (Amir et al 2006).

Tetrodotoxin (TTX) is a substance from the liver of puffer fish (Cummins et al 2007; Amaya et al 2000), which is used to categorise two groups within the isoforms of VGSC. An isoform is defined as sensitive to TTX (TTX-s) if its current is inhibited at a concentration of less than $1\mu\text{Mol}$, and resistant (TTX-r) if it takes a higher concentration for inhibition (Elliott and Elliott 1993; Kostyuk et al 1981). Although both these papers are dated the work they detail is of huge importance and the correlation between the findings reinforces the conclusion of each in providing a base for further development. TTX-s VGSC are the channels: 1.1-1.4 and 1.6, 1.7; channels 1.5 and 1.8, 1.9 are all the TTX-r channels (Amir et al 2006). The ability to divide between the nine sodium channel isoforms currently known about has been vital to understanding the role of each of the channels in the body. This breakdown into individual channels was possible due to characterisation of each channels electrophysiological characteristic, for example matching up sodium current with the channel responsible for generation of that current (Golden, 2001; Goldin et al, 2000). This research development shows the advances of further work carried out on the original findings of Elliott and Elliot 1993; Kostyuk et al 1981, as without these classifications and categories of the sodium channels it would not be possible to identify individual channels and their roles in the body.

Where are they located?

This work is focused on the role of VGSC 1.8 and 1.9, formally known as SNS and SNS2 respectively, which are TTX-r. TTX-r sodium currents were found originally primarily in the subpopulation of small diameter sensory neurons though to be involved in nociception (Caffery et al, 1992; Roy and Narahashi, 1992; Elliott and Elliott, 1993). This work was further advanced and reinforced when the TTX-r current was found to dominate the A δ and C fibres (Gold et al 2003; Amaya et al 2000; Padilla et al 2007), shown to be thermo receptors and nociceptors (Amaya et al 2000). This is key as six independent studies have all concluded the presence of TTX-r current in neurones confirmed as nociceptive, This has strong implications that TTX-r VGSC 1.8 and 1.9 do have a role in the sensation and detection of noxious stimuli, and the initiation of nociceptor activity in pain states; or they would be

found at a higher proportion in non nociceptive sensory neurones. The VGSC 1.8 and 1.9 are found in the peripheral nerve endings of neurones as well as the dorsal root and trigeminal ganglions (Padilla et al 2007); this implies they could influence peripheral and central sensitisation of C and A δ nociceptors (Woolf 2004). This is supported by findings that many C fibres expressing 1.8 or 1.9 co-express TRPV1, the capsaicin receptor formally known as VR1 (Tominaga et al 1998; Caterina et al 1997). TRPV1 is the receptor for noxious thermal stimuli, and thus is strong support that VGSC 1.8 and 1.9 are involved in nociceptive processing's, due to the co- localisation.

However this support is countered by findings that only forty percent of 1.9 expressing trigeminal nociceptors co- express TRPV1 (Padilla et al 2007), a finding supported by Amaya et al 2000, who showed the presence of small TRPV1 expressing neurones which expressed neither 1.8 or 1.9 VGSC. This would suggest that 1.8 and 1.9 are not fundamental to sensitising thermal hypersensitivity, which would see a one hundred percent co- localisation thus limiting any contribution they would make to a pain state.

On the other hand co- expression to a level of forty percent does suggest a certain level of involvement in thermal nociceptor activity. This is supported by findings that all 1.8 expressing neurones are trkA positive, many of which also express TRPV1 along with 1.9 (Amaya et al 2000).

This is also substantial support for the role of 1.8 VGSC in pain states as trkA is involved in peptidergic nociceptors expressing CGRP, and are intimately linked with inflammatory pain (Woolf et al 1994).

Despite not showing a one hundred percent co-expression of 1.9 with trkA, Amaya et al 2000 did show no co-localisation of the 1.9 VGSC with NF200, found in non- nociceptive sensory neurones, again supporting the role of 1.9 in nociception. These findings went on to show that 1.8 could co-localise with NF200, suggesting a possible role in conditions such as allodynia, when considered with co- localisation of trkA. Allodynia occurs when a stimulus, which is not normally detected as noxious, is able to initiate a nociceptive response, for example touching sunburn.

How are they activated?

Activation of VGSC is as the name suggests due to transmembrane potentials. Lysine and threonine, which are positively charged amino acids, are in large number in the S4 'sensory' regions of all four domains in the α chain of the sodium channel. These S4 regions are influenced by changes in the transmembrane electric field surrounding the channel and thereby induce their purpose as the voltage sensory region, conferring open, closed or inactive states (Priest and Hunter 2006; Amir et al 2006).

Due to the individual electrophysiological properties of the channels, the voltage required to open each channel is different. VGSC 1.9 for example is active at resting membrane potential of around -60 and -70 mV meaning it cannot individually provoke an action potential, but plays a role in contributing to sub threshold electro-genesis in the neurone (Cummins et al 1999; Herzog

et al 2001). This means although VGSC 1.9 does not initiate a depolarising upswing of an action potential it does play a role in raising the resting membrane excitability and thus reducing the activation threshold of the nociceptors, which they have been shown to localise. This again suggests a role of Nav 1.9 in sensitisation of the nociceptor.

In response to tissue or nerve injury the body releases inflammatory mediators such as TNF α , PGE2 and bradykinin, as part of a normal immune response. These inflammatory mediators are known to interact with and sensitise nociceptors in the periphery and can lead to peripheral and central sensitisation (Oprea and Kress 2000). This is done by PGE2 by binding to trkA expressed on the nociceptor activating cAMP, and up regulating PKA and PKC. PKA and PKC cause phosphorylation of the proteins lysine and threonine, causing post translational modification and a resultant change in activity of receptors and ion channels in the neurone they localise, such as TRPV1 and VGSC 1.9 in nociceptors. Clinical evidence of this is PKA phosphorylation causes a reduction in the activation threshold of the TTXr sodium voltage gated channels, thus increasing their activity; which are involved in nociception (England et al 1996). This shows that inflammatory mediators lead to the phosphorylation of sensory receptors and ion channels and thus increase neuronal excitability; this could initiate an action potential assisted by the increased activity of 1.8 and 1.9 (Amaya et al 2006; Gold et al 1996; 1998; 2002). This reinforces the role of Nav 1.8 and 1.9 in inflammatory pain, as they are both present in nociceptors and activated by the inflammatory mediators that sensitise them.

This is supported by work which shows that inflammatory mediators sensitise the peripheral terminals of nociceptors by reducing the transducer channel threshold needed for an action potential, being the increase in VGSC activity (Julius and Basbaum 2001; England et al 1996). This supports the role of VGSC 1.8 and 1.9, as other findings suggested that only 1.8 VGSC could actually assist the generation of action potential, and that 1.9 contributed little to propagation of an action potential spike (Amir et al 2006).

However when inflammatory mediators cause the phosphorylation and therefore change in VGSC activity, this contributes to a decreased activation threshold by raising the baseline membrane excitability level involving Nav 1.9 (Amir et al 2006). This idea fits with studies that show Nav 1.9 to have slow activation and inactivation kinetics (Priest et al 2005), suggesting a role in sensitisation, as the activation threshold of the nociceptor has been lowered, and can remain after the immediate inflammatory response.

Nav 1.8 however has properties suggesting a possible role in the sustained neuronal firing during neuropathic conditions, again due to slow activation inactivation kinetics; Nav 1.8 is able to assist with the spike initiation of an action potential (Rush et al 1998; Amir et al 2006).

Further evidence in activation kinetics for the role of 1.9 in nociception is that nerve growth factor (NGF) is shown to increase both the activity of Nav 1.9, by phosphorylation, but also by increasing the number of the channels

expressed in the neurone (Gold et al 1996). This increase in channel expression was demonstrated by the discovery of C fibres that are normally 'silent'. These fibres become activated by the inflammatory soup released in response to injury, and behave just as all other C fibre nociceptors, except they have a ninety percent expression of Nav 1.9 (Amir et al 2006).

All these studies demonstrate the role of inflammatory mediators in increasing the TTX-r current form VGSC 1.8 and 1.9 providing strong evidence of their involvement peripheral terminal hypersensitivity, and a role in inflammatory pain states (Gold 1999).

These studies, through the involvement of inflammatory mediators, all suggest that Nav 1.8 and 1.9 are involved in inflammatory pain but do not supply much evidence of neuropathic pain. This idea that Nav 1.8 and 1.9 are only involved in inflammatory pain fits with the work described above which suggest a critical role of inflammatory mediators in the mediation and control of the activity of the Nav 1.8 and 1.9. This is supported by work which finds that Nav 1.8 is not involved in neuropathic pain, which is pain incurred when no noxious external stimuli is present, (Kerr et al 2001; Nassar et al 2005). However, other works show that 1.8 anti- sense oligonucleotides have an anti hypersensitivity role following nerve injury (Lai et al 2002). This does suggest a role of Nav 1.8 and possibly 1.9 in neuropathic pain. This may be explained by the slow activation and inactivation kinetics of the channels as described by Priest et al 2005. This may be because the activity of the Nav 1.8 and 1.9 is maintained long after the inflammatory mediators that cause the modulation of their activity; and are therefore still sensitising the nociceptor, thus providing hypersensitivity in neuropathic conditions, then they are active.

What are the uses of this work?

One use of this data in medical terms is that blockage of the channels Nav 1.8 decreases the nociceptive behavioural response to noxious stimuli both thermal and mechanical (Akopian et al 1999). This is also shown with Nav 1.9 were null mice were shown to display around a fifty percent drop in response to inflammatory pain (Priest et al 2005). This reinforces the earlier statement that Nav 1.8 and 1.9 are involved in pain states with direct effects.

Several studies also suggest that blocking Nav 1.8 and 1.9 may have longer-term effects on nociception, by reducing sensitisation. As has been discussed, persistent hyperalgesia caused by this shows a clear role of Nav 1.9 in thermal nociception. This is supported by Leo et al 2009, who show Nav 1.8 and 1.9 could play a role in thermal allodynia in neuropathic states. The role of Nav 1.8 in mechanical pain, such as contact with a hard surface, is demonstrated by anti- sense oligonucleotides that, as discussed reduce 1.8 expression, and could reverse mechanical allodynia

Inflammatory induced hypersensitivity reduction by inhibiting or blocking VGSC is also shown by Amaya et al 2006; who showed a reduced hypersensitivity induced by inflammatory mediator bradykinin, and from capsaicin, the activator of thermal receptors. In both tests wild type mice

showed a much greater hypersensitivity reaction to the stimuli than the Nav 1.9 null mice being tested on.

This is clear support for the role of Nav 1.9 in hypersensitivity as well as a clear indication of a treatment perspective of inhibiting the action of VGSC.

These findings support the work of Lai et al 2002, who showed the role of Nav 1.8 in hypersensitivity, using antisense oligonucleotides; a technique of blocking the function of a strand of mRNA. This is a technique also used by Gold et al 2003 who also showed a loss of Nav 1.8 leads to a reduction in allodynia and hyperalgesia.

The role of Nav 1.8 and 1.9 appears to span across multiple pain categories, such as thermal and mechanical. PGE₂, able to produce thermal hyperalgesia in wild type mice is not able to induce the same effects to a significant level in Nav 1.9 null mice (Priest et al 2005)

This is supported by Coggeshall et al 2004 and Khasar et al 1998, who proposed and demonstrated that 1.8 and 1.9 mediating sensory neurones might be an underlying factor in inflammatory hyperalgesia. This is shown by anti-sense KO of Nav 1.8 resulting in an increase in the base threshold to nociceptive stimuli, therefore reducing hyperalgesia as the membrane excitability drops. This is demonstrated by studies that show use of anti-sense KO 1.8 blocks the development of hyperalgesia from PGE₂. PGE₂ release is also accompanied by an up regulation of Nav 1.8 in the DRG reinforcing a role in sensitisation, as PGE₂ is aimed at sensitising the target neurone and allowing for an action potential, which appears to involve VGSC's. This is demonstrated by studies that show use of anti-sense KO 1.8 blocks the development of hyperalgesia from PGE₂ (Amir et al 2006). This is supported by Coggeshall et al 2004 and Khasar et al 1998, who proposed and demonstrated that 1.8 and 1.9 mediating sensory neurones might be an underlying factor in inflammatory hyperalgesia. This is shown by anti-sense KO of Nav 1.8 resulting in an increase in the base threshold to nociceptive stimuli, therefore reducing hyperalgesia as the membrane excitability drops (Coggeshall et al 2004).

Inflammatory induced hypersensitivity reduction by inhibiting or blocking VGSC is also shown by Amaya et al 2006; who showed a reduced hypersensitivity induced by inflammatory mediator bradykinin, and from capsaicin, the activator of thermal receptors. In both tests wild type mice showed a much greater hypersensitivity reaction to the stimuli than the Nav 1.9 null mice being tested on.

This is clear support for the role of Nav 1.9 in hypersensitivity as well as a clear indication of a treatment perspective of inhibiting the action of VGSC.

These findings support the work of Lai et al 2002, who showed the role of Nav 1.8 in hypersensitivity, using antisense oligonucleotides; a technique of blocking the function of a strand of mRNA. This is a technique also used by

Gold et al 2003 who also showed a loss of Nav 1.8 leads to a reduction in allodynia and hyperalgesia.

The role of Nav 1.8 and 1.9 appears to span across multiple pain categories, such as thermal and mechanical. PGE₂, able to produce thermal hyperalgesia in wild type mice is not able to induce the same effects to a significant level in Nav 1.9 null mice (Priest et al 2005). This shows a clear role of Nav 1.9 in thermal nociception. This is supported by Leo et al 2009, who show Nav 1.8 and 1.9 could play a role in thermal allodynia in neuropathic states. The role of Nav 1.8 in mechanical pain, such as contact with a hard surface, is demonstrated by anti-sense oligonucleotides that, as discussed reduce 1.8 expression, and could reverse mechanical allodynia (Dong et al 2007).

Conclusion

In conclusion the work described here shows a clear involvement on both Nav 1.8 and 1.9 in pain states. This is shown by the numerous studies showing their localisation in nociceptive fibres both C and A δ (Gold et al 2003; Amaya et al 2000). These channels were also shown to co-localise with trkA and TRPV1 both of which are shown to be involved in nociception (Tominaga et al 1998; Amaya et al 2000), thus supporting a role of Nav 1.8 and 1.9 in this area. This work then went on to show that the involvement of inflammatory mediators such as bradykinin and PGE₂ are strong implications of involvement in inflammatory pain. This was shown by an up regulation of the channels Nav 1.8 and 1.9 when in the presence of the mediators, both in number of channels expressed and excitability of those channels. The role that the channels play is also indicated by the action of the inflammatory mediators, as they cause phosphorylation of the α subunit. This phosphorylation is the same form of action they make on other parts of a sensory neurone when inducing sensitisation via changes in structure of receptors. This leads to implications of the role of Nav 1.9 especially as well as 1.8 in sensitisation of the nociceptive sensory neurones, something supported by the slow activation and inactivation kinetics of the channels (Priest et al 2005). These slow activation and inactivation kinetics play a role in sensitisation, and leads to a possible role in neuropathic pain, as the action of the channel may out last the duration of the inflammatory mediators. Therefore the VGSC may still be sensitising the nociceptor after the inflammatory response has run its course, thus contributing to neuropathic pain.

This leads to possible medical advances due to this knowledge, as blocking of the Nav channels using anti-sense knockdowns leads to reduced hypersensitivity which could have uses in anaesthetics used in hospitals. This could be useful in reducing possible allodynia following surgery or a serious wound. Another area of use for this knowledge is in drug treatments for inflammatory and potentially neuropathic pain states and conditions, for example rheumatoid arthritis. Here the treatment could potentially be used to alleviate symptoms of allodynia resulting from progressive joint destruction.

However the work analysed here is not strong enough to conclude a clear use of Nav 1.8 and 1.9 inhibition in neuropathic pain, suggesting further work is

needed to reinforce this conclusion, before being put into practical use. This is due to the disagreement between sources such as Kerr et al 2001 and Dong et al 2007 who contradict each other on the involvement of Nav 1.8 and 1.9 in neuropathic pain conditions. This level of controversy is not present in the involvement of Nav 1.8 and 1.9 in inflammatory pain, which all sources investigated seem to support allowing for a strong conclusion to be drawn, reinforces potential uses such as in drug treatments.

References

- Akopian; Souslova et al. 1999. *A tetrodotoxin- resistant sodium channel expressed by sensory neurones*. *Nature*. 379: 257- 262.
- Amaya; Decostered et al. 2000. *Diversity of expression of the sensory neurone specific TTX-r voltage gated sodium channels SNS and SNS2*. *Molecular and Cellular Neuroscience*. 15: 331- 342.
- Amaya; Wang et al. 2006. *The voltage gated sodium channel Nav1.9 is an effector of peripheral inflammatory pain hypersensitivity*. *Journal of Neuroscience*. 26 (50): 12852- 12860.
- Amir; Argoff et al. 2006. *The role of sodium channels in chronic inflammatory and neuropathic pain*. *The Journal of Pain*. 7 (5): 1- 29.
- Caterina; Schumacher et al. 1997. *The capsaicin receptor. A heat- activated ion channel in the pain pathway*. *Nature*. 389: 816- 824.
- Coggeshall; Tate; Carlton. 2004. *Differential expression of TTX-r sodium channel 1.8 and 1.9 in normal and inflamed rats*. *Neuroscience Letters*. 355: 45- 48.
- Cummins; Dib- Hajj et al. 1999. *A novel persistent tetrodotoxin resistant sodium current in SNS - null and wild type small primary sensory neurones*. *Journal of Neuroscience*. 19 (24): RC43
- Cummins; Sheets; Waxman. 2007. *The role of sodium channels in nociception: implications for mechanisms of pain*. *The Journal of Pain*. 131 (3): 243- 257.
- Dong; Goregoaker et al. 2007. *Small interfering RNA- mediated selective knockdown of Na(V) 1.8 tetrodotoxin- resistant sodium channel reduces mechanical allodynia in neuropathic rats*. *Neuroscience*. 146: 812- 821.
- Elliot and Elliott. 1993. *Characterisation of TTX- sensitive and TTX-resistant in small cells from adult rat dorsal root ganglion*. *Journal of Physiology*. 463: 39- 56.
- Gold. 1999. *Tetrodotoxin- resistant Na⁺ currents and inflammatory hyperalgesia*. *Proceeding of the National Academy of Science*. 96: 7645- 7649.

Gold; Levine; Correa. 1998. *Modulation of TTX-r INa by PKC and PKA and their role in PGE2- induced sensitisation in rat sensory neurones in vitro*. *Journal of Neuroscience*. 18: 10345- 10355.

Gold; Reichling et al. 1996. *Hyperalgesic agents increase a tetrodotoxin resistant Na⁺ current in nociceptors*. *Proceeding of the National Academy of Science*. 93:1108-1112.

Gold; Weinreich et al. 2003. *Redistribution of Nav 1.8 in uninjured axons enables neuropathic pain*. *Journal of Neuroscience*. 23:158- 166.

Gold; Zhang et al. 2002. *Prostaglandin E(2) modulates TTX-R I(Na) in rat colonic sensory neurones*. *Journal of Neurophysiology*. 88: 1512- 1522.

Goldin; Barchi et al. 2000. *Nomenclature of voltage gated sodium channels*. *Neuron*. 28: 365- 368

Goldin. 2001. *Resurgence of sodium channel research*. *Annual Review of Physiology*. 63: 871- 894.

Herzog; Cummins; Waxman. 2001. *Persistent TTX- resistant current affects resting potential and response to depolarisation in simulated spinal sensory neurones*. *Journal of Neurophysiology*. 86: 1351- 1364.

Joshi; Mikusa et al. 2006. *Involvement of the TTX-r sodium channel 1.8 in inflammatory and neuropathic, but not post- operative, pain states*. *Journal of Pain*. 123 (1-2): 75- 82.

Julius; Basbaum. 2001. *Molecular mechanisms of nociception*. *Nature*. 413: 203- 210.

Kerr; Souslova et al. 2001. *A role for TTX- resistant sodium channel Nav 1.8 in NGF induced hyperalgesia, but not in neuropathic pain*. *Neuroreport*. 12: 3077- 3080.

Khasar; Gold; Levine. 1998. *A tetrodotoxin- resistant current mediates inflammatory pain in the rat*. *Neuroscience Letters*. 256: 17- 20.

Kostyuk; Veselovsky; Tsyndrenko. 1981. *Ionic currents in somatic membrane of rat dorsal root ganglion neurones- I sodium currents*. *Neuroscience* 6: 2423- 2430.

Lai; Gold et al. 2002. *Inhibition of neuropathic pain by decreased expression of tetrodotoxin resistant sodium channel Nav 1.8*. *Journal of Pain*. 95: 143- 152.

Nassar; Levato et al. 2005. *Neuropathic pain develops normally in mice lacking both Nav 1.7 and 1.8*. *Molecular Pain*. 1: 24.

Okuse; Malik- Hall et al. 2002. *Amexin II light chain regulates sensory neurone specific sodium channel expression*. *Nature*. 417: 653- 656.

Oprea and Kress. 2000. *Involvement of the proinflammatory cytokines tumour necrosis factor- α , IL-1 β and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin*. *Journal of Neuroscience*. 20: 6289-6293.

Padilla; Couble et al. 2007. *Expression and localisation of Nav 1.9 sodium channel in enteric neurones and in trigeminal sensory endings: implications for intestinal reflex function and orofacial pain*. *Molecular and Cellular Neuroscience*. 35: 138- 152.

Priest; Hunter. 2006. *Voltage gated sodium channels as molecular targets for neuropathic pain*. *Drug Development Research*. 67: 360- 375.

Priest; Murphy et al. 2005. *Contribution of TTX-r voltage gated sodium channel 1.9 to sensory transmission and nociceptive behaviour*. *Proceeding of the National Academy of Science*. 102 (26): 9382- 9387.

Rush; Brau et al. 1998. *Electrophysiological properties of sodium current subtypes in small cells in adult rat dorsal root ganglions*. *Journal of Physiology*. 511: 771- 789.

Tominaga; Caterina et al. 1998. *The cloned capsaicin receptor indicates multiple pain-producing stimuli*. *Neuron*. 21: 531- 543.

Woolf. 2004. *Pain: moving from symptom control to mechanism- specific pharmacologic management*. *Annals of Internal Medicine*. 140: 441- 451

Woolf; Safieh- Garabedian et al. 1994. *Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity*. *Neuroscience*. 62: 327- 331.