
The nociceptive noxious heat-activated receptor - TRPV1, conducts calcium and sodium, thus producing a depolarizing receptor potential, leading to activation of nociceptive neurons. TRPV1-mediated calcium and sodium influx is negatively modulated by calcium, via calcium-dependent desensitization of TRPV1 channels. A mitochondrial Ca(2+) uniporter - MCU, controls mitochondrial Ca(2+) entry while a sodium/calcium transporter - NCLX shapes calcium and sodium transients by mediating sodium entry into and removing calcium from the mitochondria. The functional interplay between TRPV1, MCU and NCLX, in controlling the cytosolic and mitochondrial calcium and sodium transients and subsequently the nociceptive excitability, is poorly understood. Here, we used cytosolic and mitochondrial fluorescent calcium and sodium imaging together with electrophysiological recordings of TRPV1-induced currents in HEK293T cells and nociceptor-like dissociated rat dorsal root ganglion neurons, while modulating NCLX or MCU expression using specific small interfering RNA (siNCLX). We show that the propagation of the TRPV1-induced cytosolic calcium and sodium fluxes into mitochondria is dependent on coordinated activity of NCLX and MCU. Thus, knocking-down of NCLX triggers down regulation of MCU dependent mitochondrial Ca(2+) uptake. This in turn decreases rate and amplitude of TRPV1-mediated cytosolic calcium, which inhibits capsaicin-induced inward current and neuronal firing. TRPV1-mediated currents were fully rescued by intracellular inclusion of the fast calcium chelator BAPTA. Finally, NCLX controls capsaicin-induced cell death, by supporting massive mitochondrial Ca(2+) shuttling. Altogether, our results suggest that NCLX, by regulating cytosolic and mitochondrial ionic transients, modulates calcium-dependent desensitization of TRPV1 channels, thereby, controlling nociceptive signaling.


The relatively membrane-impermeable lidocaine derivative QX-314 has been reported to permeate the ion channels transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) to induce a selective inhibition of sensory neurons. This approach is effective in rodents, but it also seems to be associated with neurotoxicity. The authors examined whether the human isoforms of TRPV1 and TRPA1 allow intracellular entry of QX-314 to mediate sodium channel inhibition and cytotoxicity.
Acute brain insults and many chronic brain diseases manifest an innate inflammatory response. The hallmark of this response is glia activation, which promotes repair of damaged tissue, but also induces structural and functional changes that may lead to an increase in neuronal excitability. We have investigated the mechanisms involved in the modulation of neuronal activity by acute inflammation. Initiating inflammatory responses in hippocampal tissue rapidly led to neuronal depolarization and repetitive firing even in absence of active synaptic transmission. This action was mediated by a complex metabotropic purinergic and glutamatergic glia-to-neuron signalling cascade, leading to the blockade of neuronal KV 7/M channels by Ca(2+) released from internal stores. These channels generate the low voltage-activating, noninactivating M-type K(+) current (M-current) that controls intrinsic neuronal excitability, and its inhibition was the predominant cause of the inflammation-induced hyperexcitability. Our discovery that the ubiquitous KV 7/M channels are the downstream target of the inflammation-induced cascade, has far reaching implications for the understanding and treatment of many acute and chronic brain disorders. This article is protected by copyright. All rights reserved.

2015


We describe a method to map the location of axonal arbors of many individual neurons simultaneously via the spectral properties of retrogradely transported dye-labeled vesicles. We inject overlapping regions of an axon target area with three or more different colored retrograde tracers. On the basis of the combinations and intensities of the colors in the individual vesicles transported to neuronal somata, we calculate the projection sites of each neuron's axon. This neuronal positioning system (NPS) enables mapping of many axons in a simple automated way. In our experiments, NPS combined with spectral (Brainbow) labeling of the input to autonomic ganglion cells showed that the locations of ganglion cell projections to a mouse salivary gland related to the identities of their preganglionic axonal innervation. NPS could also delineate projections of many axons simultaneously in the mouse central nervous system.

2014


Tetrodotoxin (TTX)-resistant sodium channels are key players in determining the input-output properties of peripheral nociceptive neurons. Changes in gating kinetics or in expression of these channels by proinflammatory mediators are likely to cause the hyperexcitability of nociceptors and pain hypersensitivity observed during inflammation. Proinflammatory mediator, tumor necrosis factor ? (TNF?), is secreted during inflammation and is associated with the early onset, as well as long lasting, inflammation-
mediated increase in excitability of peripheral nociceptive neurons. Here we studied the underlying mechanisms of the rapid component of TNFα-mediated nociceptive hyperexcitability and acute pain hypersensitivity. We showed that TNFα leads to rapid onset, cyclooxygenase-independent pain hypersensitivity in adult rats. Furthermore, TNFα rapidly and substantially increases nociceptive excitability in-vitro, by decreasing action potential threshold, increasing neuronal gain and decreasing accommodation. We extended on previous studies entailing p38 MAPK-dependent, increase in TTX-resistant sodium currents by showing that TNFα via p38 MAPK, leads to increased availability of TTX-r sodium channels by partial relief of voltage dependence of their slow inactivation, thereby contributing to increase in neuronal gain. Moreover, we showed that TNFα also in a p38 MAPK-dependent manner, increases persistent TTX-r current by shifting the voltage dependence of activation to a hyperpolarized direction, thus producing an increase in inward current at functionally critical subthreshold voltages. Our results suggest that rapid modulation of the gating of TTX-r sodium channels plays a major role in TNFα-mediated nociceptive hyperexcitability during acute inflammation and may lead to development of effective treatments for inflammatory pain, without modulating the inflammation-induced healing processes.

2013


The peripheral terminals of primary sensory neurons detect histamine and non-histamine itch-provoking ligands through molecularly distinct transduction mechanisms. It remains unclear, however, whether these distinct pruritogens activate the same or different afferent fibers. Using a strategy of reversibly silencing specific subsets of murine pruritogen-sensitive sensory axons by targeted delivery of a charged sodium-channel blocker, we found that functional blockade of histamine itch did not affect the itch evoked by chloroquine or SLIGRL-NH2, and vice versa. Notably, blocking itch-generating fibers did not reduce pain-associated behavior. However, silencing TRPV1(+) or TRPA1(+) neurons allowed allyl isothiocyanate or capsaicin, respectively, to evoke itch, implying that certain peripheral afferents may normally indirectly inhibit algogens from eliciting itch. These findings support the presence of functionally distinct sets of itch-generating neurons and suggest that targeted silencing of activated sensory fibers may represent a clinically useful anti-pruritic therapeutic approach for histaminergic and non-histaminergic pruritus.


QX-314 (N-ethyl-lidocaine) is a cationic lidocaine derivative that blocks voltage-dependent sodium channels when applied internally to axons or neuronal cell bodies. Coapplication of external QX-314 with the transient receptor potential vanilloid 1 protein (TRPV1) agonist capsaicin produces long-lasting sodium channel inhibition in TRPV1-expressing neurons, suggestive of QX-314 entry into the neurons. We asked whether QX-314 entry occurs directly through TRPV1 channels or through a different pathway (e.g., pannexin channels) activated downstream of TRPV1 and whether QX-314 entry requires the phenomenon of "pore dilation" previously reported for TRPV1. With external solutions containing 10 or 20 mM QX-314 as the only cation, inward currents were activated by stimulation of both heterologously expressed and...
native TRPV1 channels in rat dorsal root ganglion neurons. QX-314-mediated inward current did not require pore dilation, as it activated within several seconds and in parallel with Cs-mediated outward current, with a reversal potential consistent with PQX-314/PCs = 0.12. QX-314-mediated current was no different when TRPV1 channels were expressed in C6 glioma cells, which lack expression of pannexin channels. Rapid addition of QX-314 to physiological external solutions produced instant partial inhibition of inward currents carried by sodium ions, suggesting that QX-314 is a permeant blocker. Maintained coapplication of QX-314 with capsaicin produced slowly developing reduction of outward currents carried by internal Cs, consistent with intracellular accumulation of QX-314 to concentrations of 50-100 ?M. We conclude that QX-314 is directly permeant in the "standard" pore formed by TRPV1 channels and does not require either pore dilation or activation of additional downstream channels for entry.

2012


Increased expression of the transient receptor potential vanilloid 1 (TRPV1) channels, following nerve injury, may facilitate the entry of QX-314 into nociceptive neurons in order to achieve effective and selective pain relief. In this study we hypothesized that the level of (QX-314/capsaicin) (QX-CAP)?induced blockade of nocifensive behavior could be used as an indirect in-vivo measurement of functional expression of TRPV1 channels. We used the QX-CAP combination to monitor the functional expression of TRPV1 in regenerated neurons after inferior alveolar nerve (IAN) transection in rats. We evaluated the effect of this combination on pain threshold at different time points after IAN transection by analyzing the escape thresholds to mechanical stimulation of lateral mental skin. At 2 weeks after IAN transection, there was no QX-CAP mediated block of mechanical hyperalgesia, implying that there was no functional expression of TRPV1 channels. These results were confirmed immunohistochemically by staining of regenerated trigeminal ganglion (TG) neurons. This suggests that TRPV1 channel expression is an essential necessity for the QX-CAP mediated blockade. Furthermore, we show that 3 and 4 weeks after IAN transection, application of QX-CAP produced a gradual increase in escape threshold, which paralleled the increased levels of TRPV1 channels that were detected in regenerated TG neurons. Immunohistochemical analysis also revealed that non-myelinated neurons regenerated slowly compared to myelinated neurons following IAN transection. We also show that TRPV1 expression shifted towards myelinated neurons. Our findings suggest that nerve injury modulates the TRPV1 expression pattern in regenerated neurons and that the effectiveness of QX-CAP induced blockade depends on the availability of functional TRPV1 receptors in regenerated neurons. The results of this study also suggest that the QX-CAP based approach can be used as a new behavioral tool to detect dynamic changes in TRPV1 expression, in various pathological conditions.

2011

Binshtok, AM. 2011 Mechanisms of nociceptive transduction and transmission: a machinery for pain sensation and tools for selective analgesia [58].
Many surgical and dental procedures depend on use of local anesthetics to reversibly eliminate pain. By the blockade of voltage-gated sodium channels, local anesthetics prevent the transmission of nociceptive information. However, since all local anesthetics act non-selectively on all types of axons they also cause a loss of innocuous sensation, motor paralysis and autonomic block. Thus, approaches that produce only a selective blockade of pain fibers are of great potential clinical importance. In this chapter we will review the recent findings describing mechanisms of pain transduction and transmission and introduce novel therapeutic approaches to produce pain-selective analgesia.


{BACKGROUND} AND {PURPOSE} We have developed a strategy to target the permanently charged lidocaine derivative lidocaine N-ethyl bromide (QX-314) selectively into nociceptive sensory neurons through the large-pore transient receptor potential cation channel subfamily V (TRPV1) noxious heat detector channel. This involves co-administration of QX-314 and a TRPV1 agonist to produce a long-lasting local analgesia. For potential clinical use we propose using lidocaine as the TRPV1 agonist, because it activates TRPV1 at clinical doses. {EXPERIMENTAL} {APPROACH} We conducted experiments in rats to determine optimal concentrations and ratios of lidocaine and QX-314 that produce the greatest degree and duration of pain-selective block when administered nearby the sciatic nerve: reduction in the response to noxious mechanical (pinch) and to radiant heat stimuli, with minimal disruption in motor function (grip strength). {KEY} {RESULTS} A combination of 0.5% QX-314 and 2% lidocaine produced 1 h of non-selective sensory and motor block followed by ≥9 h of pain-selective block, where grip strength was unimpaired. QX-314 at this concentration had no effect by itself, while 2% lidocaine by itself produced 1 h of non-selective block. The combination of 0.5% QX-314 and 2% lidocaine was the best of the many tested, in terms of the duration and selectivity of local analgesia. {CONCLUSIONS} AND {IMPLICATIONS} Targeting charged sodium channel blockers into specific sets of axons via activation of differentially expressed large-pore channels provides an opportunity to produce prolonged local analgesia, and represents an example of how exploiting ion channels as a drug delivery port can be used to increase the specificity and efficacy of therapeutics.

2010


We tested whether it is possible to selectively block pain signals in the orofacial area by delivering the permanently charged lidocaine derivative QX-314 into nociceptors via TRPV1 channels. We examined the effects of co-applied QX-314 and capsaicin on nociceptive, proprioceptive, and motor function in the rat trigeminal system. QX-314 alone failed to block voltage-gated sodium channel currents (I(Na)) and action potentials (APs) in trigeminal ganglion (TG) neurons. However, co-application of QX-314 and capsaicin blocked I(Na) and APs in TRPV1-positive TG and dental nociceptive neurons, but not in TRPV1-negative TG neurons or in small neurons from TRPV1 knock-out mice. Immunohistochemistry revealed that TRPV1 is not expressed by trigeminal motor and trigeminal mesencephalic neurons.
Capsaicin had no effect on rat trigeminal motor and proprioceptive mesencephalic neurons and therefore should not allow (QX-314) to enter these cells. Co-application of (QX-314) and capsaicin inhibited the jaw-opening reflex evoked by noxious electrical stimulation of the tooth pulp when applied to a sensory but not a motor nerve, and produced long-lasting analgesia in the orofacial area. These data show that selective block of pain signals can be achieved by co-application of (QX-314) with (TRPV1) agonists. This approach has potential utility in the trigeminal system for treating dental and facial pain.


{BACKGROUND} Nociceptive-selective local anesthesia is produced by entry of the permanently charged lidocaine-derivative (QX-314) into nociceptors when coadministered with capsaicin, a transient receptor potential vanilloid 1 ([TRPV1]) channel agonist. However, the pain evoked by capsaicin before establishment of the (QX-314-mediated) block would limit clinical utility. Because (TRPV1) channels are also activated by lidocaine, the authors tested whether lidocaine can substitute for capsaicin to introduce (QX-314) into nociceptors through (TRPV1) channels and produce selective analgesia. {METHODS} Lidocaine (0.5% [17.5 {mM}], 1% [35 {mM}], and 2% [70 {mM}]) alone, (QX-314) (0.2% [5.8 {mM}]) alone, and a combination of the two were injected subcutaneously and adjacent to the sciatic nerve in rats and mice. Mechanical and thermal responsiveness were measured, as was motor block. {RESULTS} Coapplication of 0.2% (QX-314) with lidocaine prolonged the nociceptive block relative to lidocaine alone, an effect attenuated in (TRPV1) knockout mice. The 0.2% (QX-314) alone had no effect when injected intraplantary or perineurally, and it produced only weak short-lasting inhibition of the cutaneous trunci muscle reflex. Perisciatric nerve injection of lidocaine with (QX-314) produced a differential nociceptive block much longer than the transient motor block, lasting 2 h (for 1% lidocaine) to 9 h (2% lidocaine). Triple application of lidocaine, (QX-314), and capsaicin further increased the duration of the differential block. {CONCLUSIONS} Coapplication of lidocaine and its quaternary derivative (QX-314) produces a long-lasting, predominantly nociceptor-selective block, likely by facilitating (QX-314) entry through (TRPV1) channels. Delivery of (QX-314) into nociceptors by using lidocaine instead of capsaicin produces sustained regional analgesia without nocifensive behavior.


Pain is a major unmet medical need which has been causally linked to changes in sodium channel expression, modulation, or mutations that alter channel gating properties or current density in nociceptor neurons. Voltage-gated sodium channels activate (open) then rapidly inactivate in response to a depolarization of the plasma membrane of excitable cells allowing the transient flow of sodium ions thus generating an inward current which underlies the generation and conduction of action potentials (AP) in these cells. Activation and inactivation, as well as other gating properties, of sodium channel isoforms have different kinetics and voltage-dependent properties, so that the ensemble of channels that are present determine the electrogenic properties of specific neurons. Biophysical and pharmacological studies have
identified the peripheral-specific sodium channels Na(v)1.7, Na(v)1.8 and Na(v)1.9 as particularly important in the pathophysiology of different pain syndromes, and isoform-specific blockers of these channels or targeting their modulators hold the promise of a future effective therapy for treatment of pain.

2008


BACKGROUND Transient receptor potential vanilloid 1 channels integrate nociceptive stimuli and are predominantly expressed by unmyelinated C-fiber nociceptors, but not low-threshold mechanoreceptive sensory or motor fibers. A recent report showed that the transient receptor potential vanilloid 1 channel agonist capsaicin allows a hydrophilic quaternary ammonium derivative of lidocaine, {QX-314}, to selectively block C fibers without motor block. The authors tested whether a similar differential block would be produced using amphipathic N-methyl amitriptyline, amitriptyline, bupivacaine, or lidocaine, either alone or together with 0.05% capsaicin, in a rat sciatic nerve block model. {METHODS} Rats (n = 8/group) were anesthetized with sevoflurane, and 0.2 ml of drug was injected either alone or with capsaicin (simultaneously or 10 min later) next to the sciatic nerve in the sciatic notch. Motor function was assessed by the extensor postural thrust. Nociception was evaluated by the nocifensive withdrawal reflex and vocalization evoked by pinch of a skin fold over the lateral metatarsus (cutaneous pain) with a serrated forceps. {RESULTS} N-Methyl amitriptyline, amitriptyline, bupivacaine, or lidocaine, followed by injection of capsaicin 10 min later, each elicited a predominantly nociceptive-specific blockade. In comparison, simultaneous application of each local anesthetic with capsaicin did not elicit a clinically significant differential block, with the exception of N-methyl amitriptyline. {CONCLUSIONS} Both tertiary amine local anesthetics and their quaternary ammonium derivatives can elicit a predominantly sensory/nociceptor selective block when followed by injection of capsaicin. The combined application of transient receptor potential vanilloid 1 channel agonists and various local anesthetics or their quaternary ammonium derivatives is an appealing strategy to achieve a long-lasting differential block in regional analgesia.


A cardinal feature of inflammation is heightened pain sensitivity at the site of the inflamed tissue. This results from the local release by immune and injured cells of nociceptor sensitizers, including prostaglandin E(2), bradykinin, and nerve growth factor, that reduce the threshold and increase the excitability of the peripheral terminals of nociceptors so that they now respond to innocuous stimuli: the phenomenon of peripheral sensitization. We show here that the proinflammatory cytokine interleukin-1beta ([IL-1beta]), in addition to producing inflammation and inducing synthesis of several nociceptor sensitizers, also rapidly and directly activates nociceptors to generate action potentials and induce pain hypersensitivity. [IL-1beta] acts in a p38 mitogen-activated protein kinase (p38 [MAP] kinase)-dependent manner, to increase the excitability of nociceptors by relieving resting slow inactivation of tetrodotoxin-resistant voltage-gated sodium channels and also enhances persistent (TTX-resistant) current near threshold. By acting as an [IL-1beta] sensor, nociceptors can directly signal the presence of ongoing tissue inflammation.
2007


(BACE1) activity is significantly increased in the brains of Alzheimer's disease patients, potentially contributing to neurodegeneration. The voltage-gated sodium channel (Na(v)1) beta2-subunit (beta2), a type I membrane protein that covalently binds to Na(v)1 alpha-subunits, is a substrate for {BACE1} and gamma-secretase. Here, we find that {BACE1-gamma-secretase} cleavages release the intracellular domain of beta2, which increases {mRNA} and protein levels of the pore-forming Na(v)1.1 alpha-subunit in neuroblastoma cells. Similarly, endogenous beta2 processing and Na(v)1.1 protein levels are elevated in brains of {BACE1-transgenic} mice and Alzheimer's disease patients with high {BACE1} levels. However, Na(v)1.1 is retained inside the cells and cell surface expression of the Na(v)1 alpha-subunits and sodium current densities are markedly reduced in both neuroblastoma cells and adult hippocampal neurons from {BACE1-transgenic} mice. {BACE1}, by cleaving beta2, thus regulates Na(v)1 alpha-subunit levels and controls cell-surface sodium current densities. {BACE1} inhibitors may normalize membrane excitability in Alzheimer's disease patients with elevated {BACE1} activity.


Most local anaesthetics used clinically are relatively hydrophobic molecules that gain access to their blocking site on the sodium channel by diffusing into or through the cell membrane. These anaesthetics block sodium channels and thereby the excitability of all neurons, not just sensory neurons. We tested the possibility of selectively blocking the excitability of primary sensory nociceptor (pain-sensing) neurons by introducing the charged, membrane-impermeant lidocaine derivative (QX-314) through the pore of the noxious-heat-sensitive (TRPV1) channel. Here we show that charged sodium-channel blockers can be targeted into nociceptors by the application of {TRPV1} agonists to produce a pain-specific local anaesthesia. (QX-314) applied externally had no effect on the activity of sodium channels in small sensory neurons when applied alone, but when applied in the presence of the {TRPV1} agonist capsaicin, (QX-314) blocked sodium channels and inhibited excitability. Inhibition by co-applied (QX-314) and capsaicin was restricted to neurons expressing (TRPV1.) Injection of (QX-314) together with capsaicin into rat hindpaws produced a long-lasting (more than 2 h) increase in mechanical and thermal nociceptive thresholds. Long-lasting decreases in pain sensitivity were also seen with regional injection of (QX-314) and capsaicin near the sciatic nerve; however, in contrast to the effect of lidocaine, the application of (QX-314) and capsaicin together was not accompanied by motor or tactile deficits.

2006


We report that {GTP} cyclohydrolase ({GCH1}), the rate-limiting enzyme for tetrahydrobiopterin ({BH4}) synthesis, is a key modulator of peripheral neuropathic and inflammatory pain. {BH4} is an essential cofactor for catecholamine, serotonin and nitric oxide production. After axonal injury, concentrations of
{BH4} rose in primary sensory neurons, owing to upregulation of {GCH1}. After peripheral inflammation, {BH4} also increased in dorsal root ganglia ({DRGs}), owing to enhanced {GCH1} enzyme activity. Inhibiting this de novo {BH4} synthesis in rats attenuated neuropathic and inflammatory pain and prevented nerve injury-evoked excess nitric oxide production in the {DRG}, whereas administering {BH4} intrathecally exacerbated pain. In humans, a haplotype of the {GCH1} gene (population frequency 15.4%) was significantly associated with less pain following diskectomy for persistent radicular low back pain. Healthy individuals homozygous for this haplotype exhibited reduced experimental pain sensitivity, and forskolin-stimulated immortalized leukocytes from haplotype carriers upregulated {GCH1} less than did controls. {BH4} is therefore an intrinsic regulator of pain sensitivity and chronicity, and the {GTP} cyclohydrolase haplotype is a marker for these traits.


In layer 4 of the somatosensory cortex, the glutamatergic synapses that interconnect spiny stellate ({SpS}) neurons, which are the major targets of thalamocortical input, differ from most other neocortical excitatory synapses in that they have an extremely large {NMDA} receptor ({NMDAR}-mediated) component that is relatively insensitive to voltage-dependent Mg2+ blockade. We now report that this unique feature of the {NMDA} response reflects the distinctive subunit composition of the underlying receptors. We studied {NMDAR-mediated} miniature {EPSCs} ({mEPSCs}) and {NMDA} channel currents in tangential brain slices of mouse barrel cortex, which exclusively contain layer 4. {NMDAR-mediated} {mEPSCs} in {SpS} neurons were prominent at negative membrane potentials, and {NMDA} channels in outside-out patches excised from the somata of the same neurons had relatively low conductance and reduced susceptibility to Mg2+ block. These are characteristic features of heteromeric {NMDAR} assemblies that contain the {NR2C} subunit. Some patches also contained {NMDA} channels with higher conductance and a greater sensitivity to Mg2+. In the neocortex of transgenic mice in which a beta-galactosidase (lacZ) indicator gene was controlled by the {NR2C} promoter, the lacZ indicator was densely expressed in layer 4. In current-clamp recordings, blockade of {NMDARs} caused hyperpolarization and an increase in apparent input resistance. Our data demonstrate that the {SpS} neurons of layer 4 functionally express {NR2C} subunits; this is the likely explanation for their ability to generate large {NMDAR-mediated} {EPSPs} that are effective at resting potential, without previous depolarization.
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