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UNDERSTANDING AND TREATING NEUROPATHIC PAIN

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Maladaptive neuropathic pain results from injury or disease of the nervous system. It is typically chronic and frequently intractable. Standard analgesics, such as opioids, are of little use, while the gabapentinoids, pregabalin and gabapentin, are not universally effective. In peripherally generated neuropathic pain, an initial inflammatory response releases a variety of mediators, including cytokines and prostaglandins that alter ion channel expression in primary afferent neurons. This initiates ectopic activity in sensory nerves and results in the release of ATP and a second group of mediators from primary afferent terminals. The level of spinal microglial activation is altered such that microglia releases a third set of mediators, notably brain-derived neurotrophic factor (BDNF), in the spinal dorsal horn. Through various mechanisms, BDNF increases excitatory synaptic transmission whilst decreasing inhibitory transmission. The resulting "central sensitization" contributes to the hyperalgesia, causalgia, and allodynia that are associated with neuropathic pain. It is suggested that targeting ion channels in the sensory nerves and excitatory transmission in the dorsal horn may lead to urgently needed new treatments for neuropathic pain. It is also suggested that the effectiveness of gabapentinoids may be increased by combining these agents with the TRPV1 agonist capsaicin.

Keywords: peripheral neuropathy, dorsal root ganglion, dorsal horn, cytokines, gabapentin.

INTRODUCTION

Pain is an unpleasant, yet vital, physiological process that signals on actual or potential tissue damage. By so doing, it ensures the survival of the species. In contrast, injury to the somatosensory system can produce "neuropathic" pain that lasts for months or years after any injury has healed [1, 2]. This maladaptive "disease of pain" has a 1.5-3% prevalence within the general population [3, 4] and imposes a significant financial burden on health-care systems. Neuropathic pain can be associated with diabetic, postherpetic, or HIV-related neuropathies, with fibromyalgia and osteoarthritis, and with traumatic nerve, spinal cord, or brain injuries (including stroke). It is characterized by allodynia (generation of a painful sensation in response to an innocuous stimulus), hyperalgesia (a heightened response to a noxious stimulus), and causalgia (an ongoing burning pain experienced by many neuropathic pain patients), as well as shooting or "electric shock-like" spontaneous pain. It is difficult to treat as it is characteristically resistant to the action of opioids and other "standard" analgesics. "Anti-allodynic" drugs, such as canabinoids, amitriptyline, gabapentinoids, and other anticonvulsants, are effective only in about 30% of patients [4-7]. There is a clear need therefore for improved understanding of the aberrations of sensory processing that underlie the emergence and persistence of neuropathic pain. This review will outline the current status of our understanding of the etiology of neuropathic pain, as might result from peripheral nerve trauma or disease-associated peripheral neuropathy. We will seek to identify aspects of the pathophysiological process that may represent targets for therapeutic intervention.

GENERAL MECHANISMS OF NEUROPATHIC PAIN: THE CCI MODEL

Peripheral nerve damage, such as that generated by chronic constriction injury (CCI) of the sciatic nerve, induces pain-related behaviors in rodents that are ethically and scientifically accepted as a model

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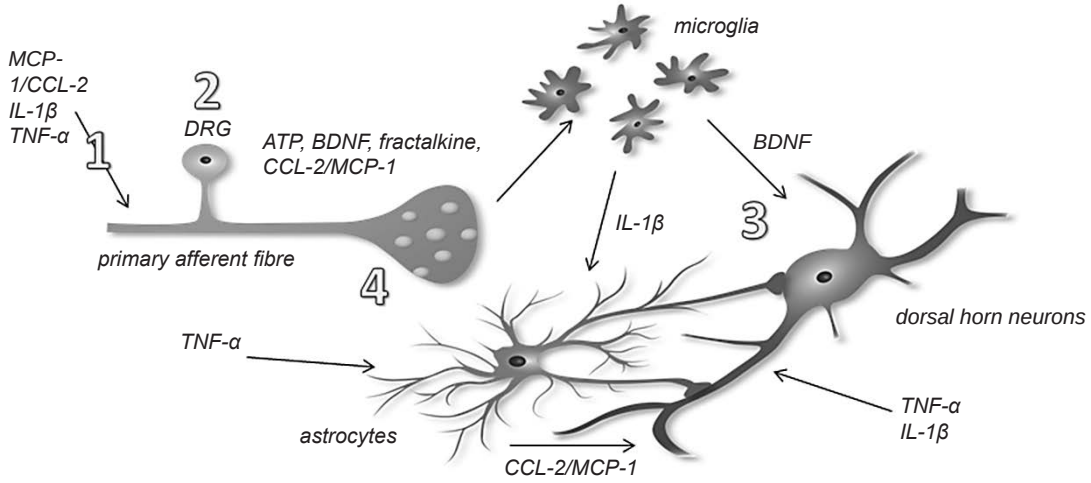
for many forms of human neuropathic pain. Seven- or more day-long CCI promotes release of pro-inflammatory cytokines, growth factors, and other mediators from damaged and inflamed tissue at the site of the injury [2, 7, 10, 11] (Fig. 1). These factors act directly on first-order primary afferent neurons to produce an enduring increase in their excitability [12-14]. This promotes release of a second set of mediators (cytokines, chemokines, neuropeptides, ATP, and growth factors) from glutamatergic primary afferent terminals in the spinal dorsal horn. These alter the state of activation of spinal microglial cells [15, 16], which, in turn, release yet another set of mediators, including brain-derived neurotrophic factor (BDNF). This set promotes a slowly developing increase in the excitability of second-order neurons in the dorsal horn of the spinal cord [16-19]. This change, which develops progressively during CCI, is known as central sensitization [20-24]. Whereas alterations in spinal microglial signaling trigger pain onset, enduring activation of astrocytes is thought to be responsible for the maintenance of central sensitization [7, 17, 25, 26]. The persistence of neuropathic pain also involves enduring changes in thalamic and cortical physiology [27, 28], changes in descending inhibition from the rostral ventromedial medulla [7, 29-33], and long-term sensitization of peripheral nociceptors [7, 33, 34]. Although neuropathic pain can result from a variety of insults to peripheral nerves, including diabetic or HIV-AIDS neuropathy [35, 36], axotomy [12, 13, 37], nerve crush [38], or compression injury [39], the appearance of ectopic action potentials and spontaneous activity in primary afferent fibres seems to be the initial trigger that initiates central sensitization in many, if not all, types of peripherally generated neuropathic pain [13, 24, 39-46], including that associated with *herpes zoster* [47] and HIV infection. More importantly, these changes in sensory nerve activity are maintained as long as the pain persists [13]. Persistent ectopic afferent activity is thought to provide increased excitatory drive to neurons in the already sensitized dorsal horn [48, 49].

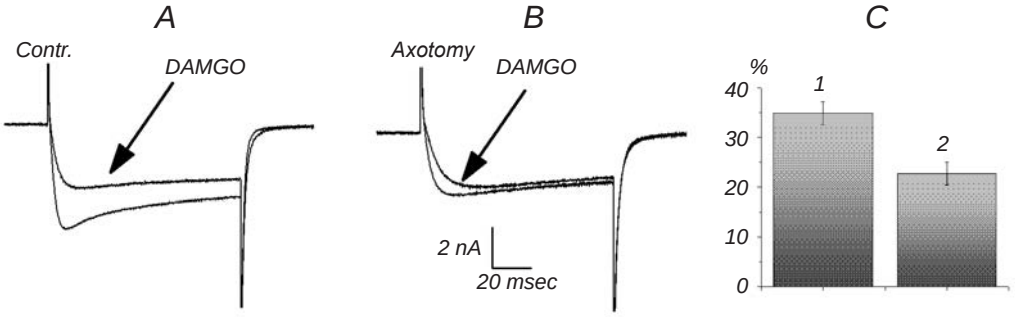
TARGETS FOR THERAPEUTIC INTERVENTION

As was mentioned above, neuropathic pain is relatively resistant to the action of opioids. This likely reflects down-regulation of μ-opioid receptors at a variety of points in nociceptive transmission pathways [50, 51]. Figure 2 illustrates high voltage-activated (HVA) Ca^{2+} channel currents (I_{Ca}) recorded from small neurons of the rat dorsal root ganglia (DRGs). In animals subjected to axotomy-induced nerve injury, the ability of the μ-opioid DAMGO to reduce N-type I_{Ca} is decreased [51]. In control animals, DAMGO reduced this current by 34.8 ± 2.3% (n = 15) compared to a



F i g. 1. Scheme to show interactions between primary afferents, dorsal horn neurons, microglia, and astrocytes in the context of chronic pain (modified from Biggs et al. [77] and reproduced here under a Creative Commons Attribution License; http://creativecommons.org/licenses/by/2.0).

Р и с. 1. Схема, яка ілюструє взаємодію первинних аферентів, нейронів дорсального рога, мікроглії та астроцитів у разі хронічного болю.



F i g. 2. Ten days of sciatic nerve injury (induced by axotomy) reduces μ-opioid effectiveness in small dorsal root ganglia (DRG) neurons. A and B) Examples of HVA Ca^{2+} channel currents recorded in response to voltage steps to –10 mV from –90 mV. Ba^{2+} was used as the charge carrier (for further details, see Abdulla and Smith [51]). The μ-opioid agonist DAMGO (1 mM) produces robust suppression of the current in a control DRG neuron (A), but a much weaker effect on a small DRG neuron derived from an animal 10 days after sciatic nerve section (axotomy, B). C) Summary of the effects of a μ-opioid on Ca^{2+} channel currents in small L4-L6 DRG neurons from control animals and those 10 days after sciatic nerve axotomy. Under control conditions (1), 1 mM DAMGO reduced the current by 34.8 ± 2.3% (n = 15) compared to 22.6 ± 2.3% (n = 12) depression in nerve-injured (axotomized, 2) animals (P < 0.03). Vertical scale) Suppression of HVA I_{Ca}, %.

Р и с. 2. Послаблення дії μ-опіоїду на дрібні нейрони гангліїв дорсальних корінців через 10 днів після ушкодження сідничного нерва (аксотомії).

22.6 ± 2.3% (n = 12) reduction in depression in nerve-injured (axotomized) animals (P < 0.03, Fig. 2C); an effect is likely attributable to decreased expression of functional opioid receptors.

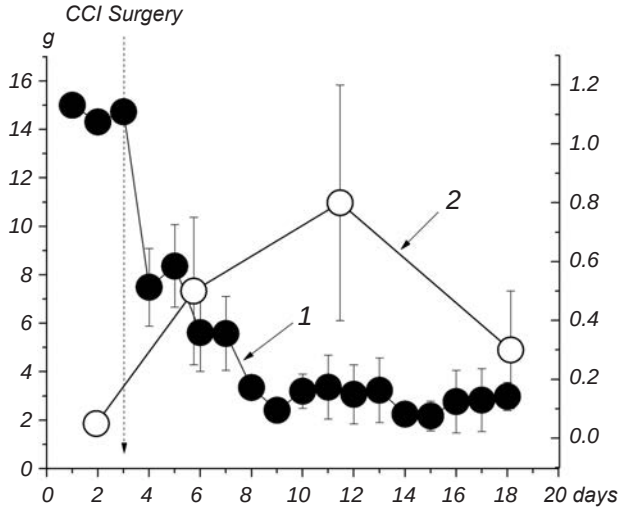
Non-opioid drugs with established clinical efficacy in neuropathic pain include cannabinoids, gabapentinoids (pregabalin and gabapentin), and noradrenaline/serotonin uptake blockers (amitriptyline and venlafaxine) [5]. The efficacy of drugs is related to etiology of the pain, with HIV-AIDS neuropathy being particularly resistant. As was mentioned, therapeutic management of all types of neuropathic pain combined is effective only in 30% of the patients. For this reason, new therapeutic approaches are urgently required. We will consider four possible points of intervention in the scheme shown in Fig. 1. These are: (i) blocking the action of inflammatory mediators at the site of injury, (ii) blocking consequences of mediator action at the site of injury, (iii) targeting synaptic transmission in the spinal dorsal horn, and (iv) augmenting the effectiveness of currently available therapies.

Blocking the Action of Inflammatory Mediators at the Site of Injury. Although it has been demonstrated repeatedly that interference with the actions of cytokines or growth factors can delay or prevent the *onset* of neuropathic pain in animal models [52-54], this may not be relevant to pain management in the clinical situation. Patients experiencing neuropathic pain are typically examined several months after an initial trauma. In the case of pain associated with disease-related neuropathies, it is impossible to determine when pathophysiological changes underlying the pain were actually initiated. Thus, therapies must be directed against chronic changes initiated by inflammatory mediators rather than toward blocking their action *per se*. This idea is underlined by data shown in Fig. 3. The latter illustrates the time course of changes in the withdrawal threshold for a pressure stimulus in rats subjected to CCI of the sciatic nerve. As the animals develop signs of allodynia and hyperalgesia, the withdrawal threshold drops from an initial value of about 15 g to 2.41 ± 0.49 g (n = 12) over a 6-day-long period but then remains practically constant for further 9 days (2.98 ± 0.58 g at day 15). Open circles on the graph are replotted values from the communication of Nadeau et al. [54] showing relative levels of IL-1β in the rat sciatic nerve after injury. The cytokine concentration peaks after about 7 days and then declines. At the 14th day, the cytokine concentration is starting to revert to control values, yet the reduced withdrawal threshold (indicative of allodynia) persists. Thus, blocking cytokine action (at least IL-1β action) is unlikely to be effective in the clinical situation. It is analogous to "closing the barn door after the horse has bolted." It is also possible that preventing all actions of cytokines may be deleterious, as this may compromise functional recovery of injured nerves [54].

Blocking Consequences of Mediator Action at the Site of Injury. Since, as was mentioned above,

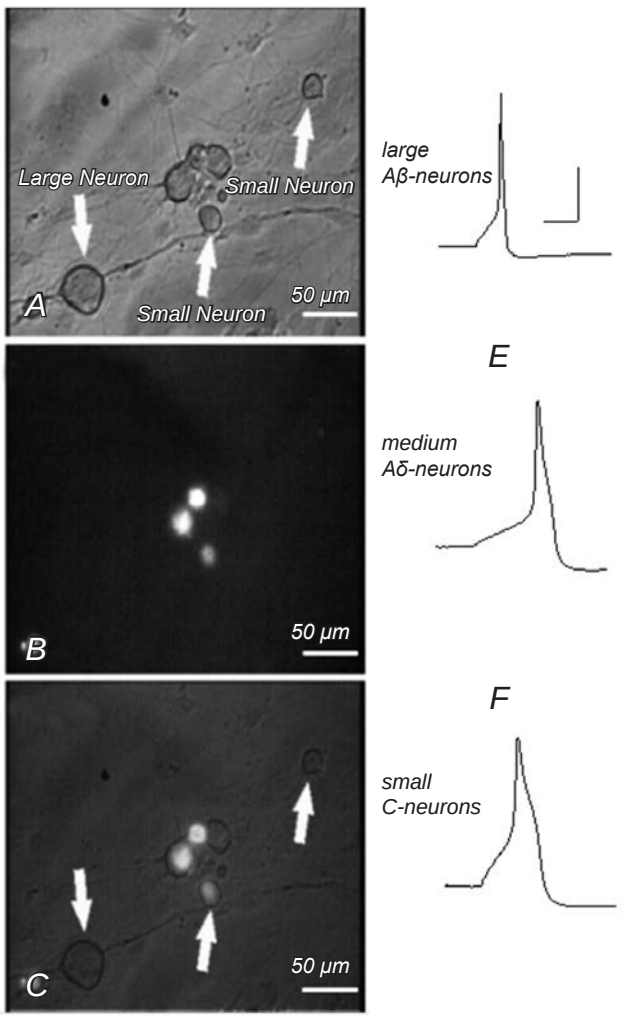
the appearance of ectopic action potentials and spontaneous spike activity in primary afferent fibres seems to be the initial trigger that initiates central sensitization in many, if not all, types of peripherally generated neuropathic pain [13, 24, 39-46]; ion channels in primary afferent neurons represent an attractive target for therapeutic intervention. It is relevant to mention in this context that several standard therapeutic approaches to treat neuropathic pain [5] are directly or indirectly targeted toward ion channels. For example, gabapentinoids affect Ca^{2+} channel expression [55-59], and some drugs, such as carbamazepine and ziconotide, target ion channels directly [60].

In the context of the scheme illustrated in Fig. 1, recent work in our laboratory was focused on studying the long-term actions of IL-1β on dissociated DRG-defined medium culture [14, 61, 62]. Since, as is illustrated in Fig. 3, nerve injury causes a peak increase in the IL-1β concentrations after 7-day-long CCI, and this is returning to control values after 14 days [54], we exposed DRG neurons to IL-1β (100 pM) for periods of 5 to 6 days. Recordings were made from large neurons defined by brief sharp action potentials, from medium-sized neurons with somewhat broader spikes, which are believed to be the cell bodies of nociceptive Aδ fibers, and from two categories of small cells with broad spikes (Fig. 4). The latter represent cell bodies of C-fibers, but those binding the plant lectin IB4 are thought to be non-peptidergic, whereas those failing to bind the lectin may be peptidergic and are more likely to be nociceptive. The effects of IL-1β were cell type-specific. Whereas the excitability of medium



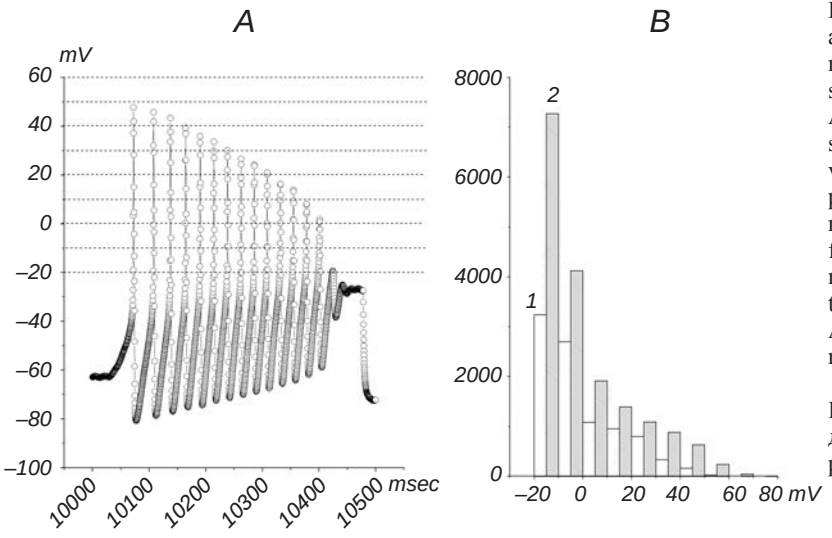
F i g. 3. Comparison of changes in the withdrawal threshold (1, g) and relative levels of IL-1β (2) in the sciatic nerve following chronic constriction injury (CCI) of the rat sciatic nerve. Open circles represent the time course of the effects of relative concentrations of IL-1β replotted from the published data of Nadeau et al. [54]. Filled circles represent the withdrawal thresholds of the operated limb determined with Von Frey filaments (s.e.m. are also shown for results on 12 animals).

Р и с. 3. Порівняння змін порога відсмикування кінцівки (*1*, ліва шкала, г) і відносного рівня IL-1β (*2*, права шкала, ум. од.) у сідничному нерві після хронічного передавлювання (*CCI*, позначено пунктирною лінією) цього нерва.



F i g. 4. Illustration of neuron types in the rat dorsal root ganglion (DRG). A) Phase-contrast photomicrograph of cultured DRG neurons to show that large and small neurons can be readily distinguished in such cultures. B and C) After incubation of neurons with fluorescently labeled IB4; some small cells exhibit IB4 binding, whereas others do not (marked with open arrows). D-F) Action potentials recorded from large, medium, and small DRG neurons, respectively.

Р и с. 4. Типи нейронів у дорсальнокорінцевому ганглії щура.



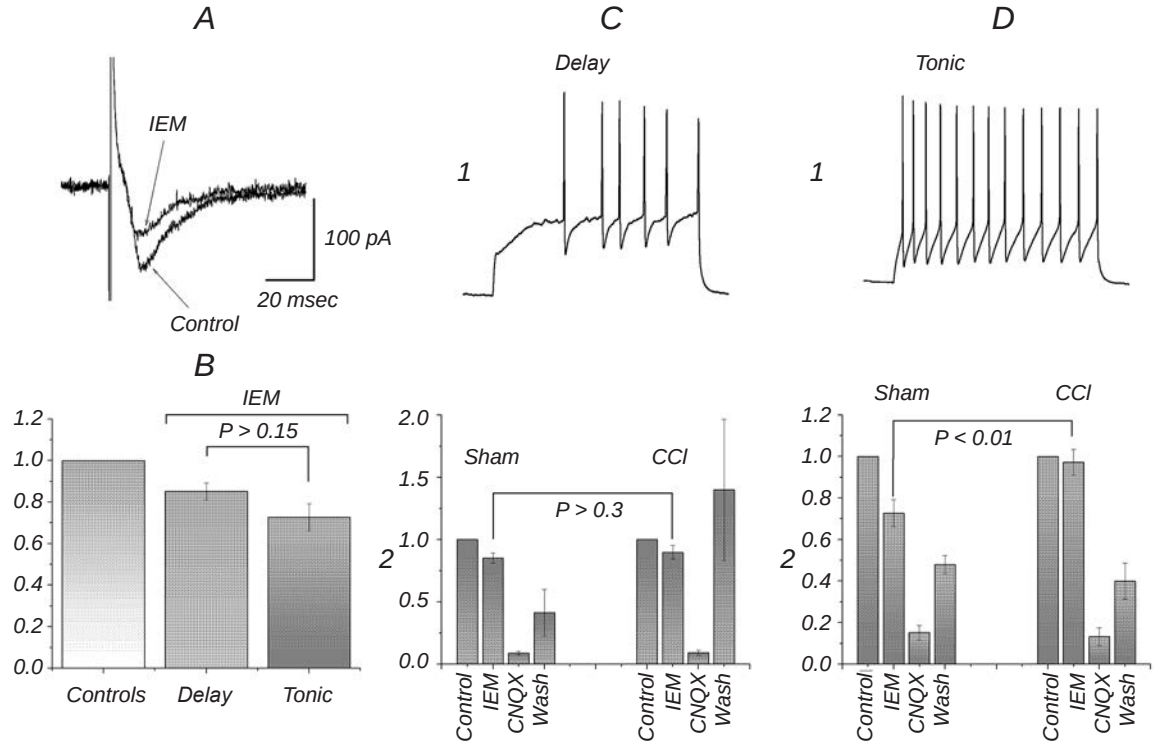
F i g. 5. Use of all-point histograms to illustrate an IL-1β-induced increase in the excitability of medium DRG neurons. A) Action potentials (APs) evoked using a standard current-clamp command (0 to 2 nA in 500 msec). Resting potential was standardized to –60 mV by steady-state current injection. Digital points describing AP trajectories have been assigned to 10 mV bins starting from –20 mV. Abscissa) Time, msec; ordinate) voltage, mV. B) Resultant histograms using all digital points collected from 22 control neurons (1) and 23 neurons maintained in the presence of 100 pM IL-1β (2) for 5-6 days. Note increased points per bin for neurons maintained in the presence of the cytokine, indicating that more AP were generated in this population. Abscissa) Voltage, mV (voltage bins 10 mV); ordinate) number of digital points.

Р и с. 5. Використання "всеточкових" гістограм для ілюстрації підвищення збудливості середніх за розмірами нейронів дорсальнокорінцевих гангліїв.

units and small IB4+ cells was increased, that of small IB4– neurons was unchanged, and that of large neurons was decreased. Data demonstrating increased excitability of medium cells from our original work [61] has been transformed as an "all-point histogram" in Fig. 5. The original digital points used to describe action potential discharges in response to a standard depolarizing current ramp were assigned to 10 mV bins starting at –20 mV (A). Data points were collected from 19 control medium neurons and 25 medium neurons exposed to IL-1β. The presence of more points in all 10 mV bins positive with respect to –20 mV is indicative of increased action potential discharges in the continued presence of the cytokine. Although excitability of both medium and small IB4+ neurons was increased, dissimilar underlying ion mechanisms operated in the two cell types [62]. Thus, IL-1β significantly increased rates of hyperpolarization-activated cyclic nucleotide-gated current (I_H) activation in medium neurons and produced a leftward shift in the voltage dependence of activation of tetrodotoxin-sensitive sodium current (TTX-S I_{Na}). There were also reductions in the densities of various potassium currents (I_K), such as Ca^{2+}-dependent ($I_{K,Ca}$) and A-type components. In small IB_4+ DRG neurons, IL-1β significantly slowed the rate of TTX-S I_{Na} inactivation and reduced the $I_{K,Ca}$ density without affecting A-type components of I_K.

The general implication from these findings is that reduction of voltage-gated sodium channel currents, enhancing of increasing K^+ currents, or reduction of I_H may represent prospective therapeutic approaches to neuropathic pain. Decreases in K^+ channel currents can be attenuated by the use of K^+ channel activators [63]. These include retigabine [64, 65] for Kv7.2 and 7.3 channels and SKA-31, DCEBIO, and CyPPA for intermediate- and small-conductance $I_{K,Ca}$ channels [66-68] . A wide variety of Na^+ channel blockers are available; some local anesthetics, newer compounds, such as ranolazine [69], the tarantula venom peptide ProTx-II [70], and certain sea anemone toxins [71], target Na_V 1.7, a channel subtype strongly implicated in neuropathic pain [72, 73]. Recently, the I_H channel blocker ivabradine was approved for the management of certain cardiac dysrhythmias and angina, but its ability to block I_H in DRG neurons remains to be demonstrated with respect to its ability to attenuate signs of neuropathic pain.

Targeting Synaptic Transmission in the Spinal Dorsal Horn. We have shown that CCI increases excitatory synaptic drive to putative excitatory neurons in the rat *substantia gelatinosa* whilst decreasing excitatory synaptic drive to putative inhibitory neurons [74, 75]. Both effects are mediated, at least in part, by the release of BDNF from microglia [19, 76, 77]. Although the use of various types of glutamate antagonists has been suggested for use in neuropathic pain, results have been quite disappointing. This was perhaps because consideration was not given to the possibility that different glutamate (AMPA) receptor subtypes may exist on excitatory and inhibitory spinal cord neurons. In order to alleviate pain, it would seem desirable to selectively target AMPA receptors (AMPARs) on excitatory neurons. We, therefore,



F i g. 6. Actions of IEM 1460 on excitatory synaptic transmission in *substantia gelatinosa* neurons. A) Superimposed recordings of evoked field EPSCs from the dorsal root entry zone before and after application of 50 mM IEM 1460 (IEM). B) Diagram illustrating nearly similar effectiveness of IEM 1460 on tonic ($n = 14$) and delay ($n = 18$) neurons ($P > 0.15$). In C, 1) Characteristic firing pattern of a delay neuron to a depolarizing current command; 2) lack of the effect of CCI on the pharmacological properties of delay neurons. IEM 1460 (50 mM) produces nearly similar amounts of depression of evoked EPSCs in neurons ($n = 14$) from sham-operated (control) animals and in those from animals subjected to CCI ($n = 10$; $P > 0.3$). In D, 1) Characteristic firing pattern of a tonic neuron in response to a depolarizing current stimulus; 2) CCI alters the pharmacological properties of tonic neurons. IEM 1460 (50 mM) produces noticeable depression of evoked EPSCs in neurons from sham-operated animals ($n = 18$) but not in neurons from animals subjected to CCI ($n = 14$; $P < 0.01$). Vertical scales in C2 and D2) Normalized amplitudes of field eEPSCs; control values are taken as 1.0.

Р и с. 6. Впливи IEM 1460 на збуджуючу синаптичну передачу в нейронах желатинозної субстанції.

used the selective polyamine blocker IEM1460 [78] to examine the distribution of Ca^{2+}-permeable AMPA receptors (CP-AMPARs) on tonic-firing (putative inhibitory) and delay-firing (putative excitatory) neurons in the rat *substantia gelatinosa* [79]. Figure 6A illustrates superimposed evoked EPSCs (eEPSCs) in a *substantia gelatinosa* neuron by stimulation of the dorsal root entry zone. IEM 1460 (50 μM) reduced the amplitude of the response by 35%, and the response was almost completely eliminated by the subsequent addition of 5 μM CNQX (data not shown). IEM reduced the eEPSC amplitude in delay neurons by 14.9 ± ± 0.04% ($n = 14$) and that in tonic neurons by 16.8 ± ± 0.65% ($n = 18$). Because the intensity of suppression in the two cell types is not significantly dissimilar ($P >$ > 0.15; B), primary afferent synapses activate at least nearly similar populations of AMPARs on tonic and delay neurons. It has been suggested, however, that Ca^{2+}-permeable AMPARs that lack GluA2 subunits play a major role in the etiology of inflammatory pain [80]. If a similar situation is true for neuropathic pain, this would suggest that drugs, such as IEM1460, would exert therapeutic benefit. In putative excitatory delay neurons, IEM reduces the eEPSC amplitude to a comparable extent in neurons from sham-operated and CCI animals. There is no obvious increase in IEM sensitivity (C). In contrast, there is a loss of IEM sensitivity in tonic neurons (D). It could be argued, therefore, that IEM1460 would continue to impede excitatory drive to excitatory neurons without that in CCI animals, while affecting that to inhibitory neurons. To the best of our knowledge, however, IEM has not yet been tested *in vivo* in chronic pain models. One issue that may impair the effectiveness of IEM is the

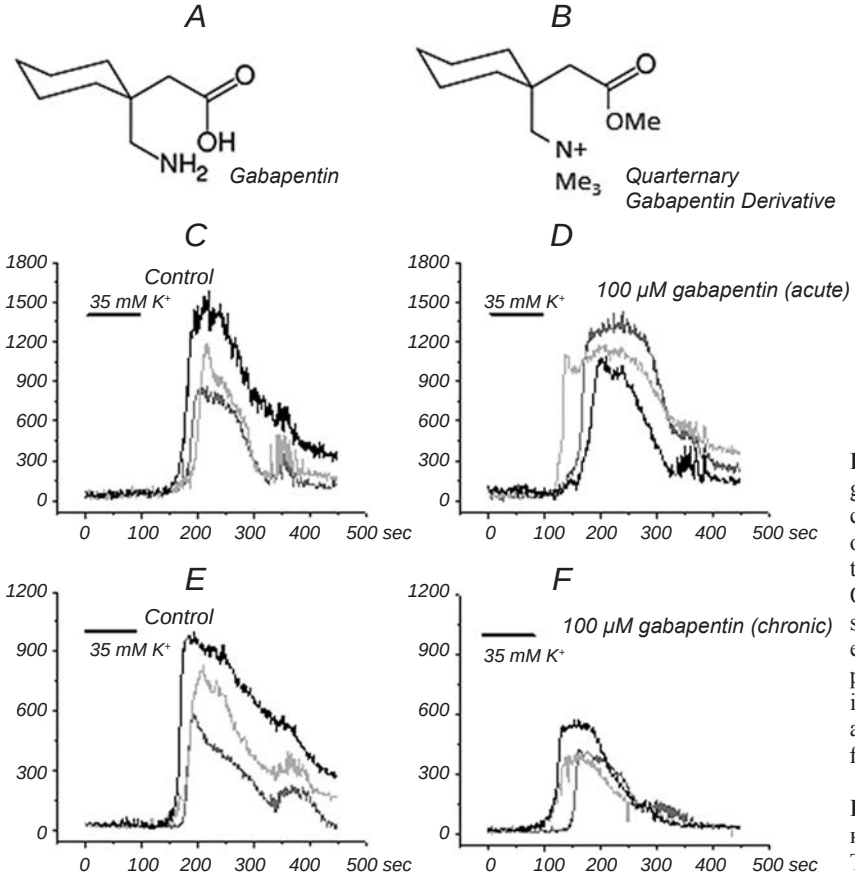
possibility that not all tonic neurons are inhibitory [81].

Augmenting the Effectiveness of Currently Available Therapies. As was mentioned above, the gabapentinoid drugs gabapentin and pregabalin are first-line treatments for various forms of neuropathic pain in Western Europe and North America [4-7]. The effectiveness of these drugs is ascribed to the appearance of dose-dependant side effects, which preclude the use of higher and, potentially, more effective doses. It may be suggested that targeting gabapentinoids to nociceptive neurons and increasing their antiallodynic effectiveness might lessen the dizziness, drowiness, fatigue, and peripheral edema seen with these substances.

Gabapentinoids are transported into neurons via the L-neutral amino acid transporter system [82, 83]. Once inside, they bind with the β2δ accessory subunit of voltage-gated Ca^{2+} channels [55-57, 84]. Since this subunit is involved in trafficking and insertion of Ca^{2+} channels into the cell membrane [85], prolonged exposure to gabapentinoids reduces the surface expression of Ca^{2+} channels. This is thought to impair voltage-gated Ca^{2+} influx into nerve terminals and to reduce neurotransmitter release. Such an action at primary afferent terminals is assumed to attenuate transfer of nociceptive information [55].

We suggest that TRPV1 channels may be used to load neurons with gabapentinoids. This idea was developed from observations with local anesthetics. Because local anesthetics must reach an intracellular site of action to exert their effect [86], quaternary (permanently positively charged) local anesthetics, such as $QX\ 314^+$, are ineffective when applied extracellularly, as they fail to cross the plasma membrane. Yet when TRPV1 channels are opened by capsaicin, a potent anesthetic effect of $QX\ 314^+$ is observed both *in vitro* and *in vivo* [87, 88]. This effect is ascribed to the permeation of open TRPV1 channels by $QX\ 314^+$.

We have preliminary data to show that gabapentinoids can also enter neurons through open pores of the TRPV1 channels [89]. We synthesized a positively charged quaternary analog of gabapentin (Fig. 7A and B) [90] and used it to replace all cations in the extracellular fluid (Na^+, K^+, and Ca^{2+}). Whole-cell recordings



F i g. 7. Augmentation of the effectiveness of gabapentinoid by their permeation through TRPV1 channels. A) Structure of gabapentin. B) Structure of its quaternary analog [90]. C-F) Monitoring of the dorsal horn excitability by means of confocal Ca^{2+} imaging. Sample 35 mM K^+-induced Ca^{2+} signals. While signals are unaffected by acute exposure to 100 mM gabapentin (C and D), a pronounced attenuation of Ca^{2+} signals is seen in a culture exposed to gabapentin for 5 days (E and F). Abscissa) Time, sec; ordinate) arbitrary fluorescence units.

Р и с. 7. Підвищення ефективності габапентиноїдів внаслідок їх проникнення через канали TRPV1.

were made from small DRG neurons that express TRPV1 channels [91, 92]. When TRPV1 channels were opened by capsaicin, an inward current carried exclusively by the quarternary analog of gabapentin was noted. Since it was attached to the only available charge carrier, gabapentin must have entered neurons through TRPV1 channels. We then used organotypic cultures of the rat spinal cord and monitored their excitability by exposing them to high-potassium (35 mM) challenge and recording changes in intracellular calcium by means of confocal imaging and fluo-4 AM [93]. After 5-day-long exposure to 100 μM gabapentin, Ca^{2+} responses were significantly reduced, whereas acutely applied gabapentin was ineffective (C-F) [89]. Chronic exposure to gabapentin at a lower dose (10 μM) failed to reduce the dorsal horn excitability when applied alone. However, when the cultures were transiently exposed to capsaicin (three 1-h-long applications) in the continued presence of this low (subeffective) concentration of gabapentin (10 μM), a clear suppression of excitability, as monitored by evoked Ca^{2+} response, was seen (data not shown) [89]. Thus, capsaicin augments gabapentinoid effectiveness *in vitro*, but we have yet to demonstrate whether this combination is superior to gabapentinoids alone in relief of allodynia *in vivo*.

DISCUSSION

We have considered four possible targets for therapeutic intervention in neuropathic pain. These were blocking the action of inflammatory mediators at the site of injury, blocking consequences of mediator action at the site of injury, targeting synaptic transmission in the spinal dorsal horn, and augmenting the effectiveness of currently available therapies.

As was discussed above, it is unlikely that blocking the actions of peripheral inflammatory mediators will be effective, as the persistence of neuropathic pain results from chronic changes initiated by initial exposure to cytokines, such as IL-1β. It is likely that these chronic downstream changes are already well-established in most clinical presentations of neuropathic pain.

Targeting ion channels in DRG neurons is, however, a more attractive influence. We were among the first laboratories to characterize the changes in ion channels and excitability of DRG neurons that were induced by peripheral nerve injury [12, 94-96]. We demonstrated up-regulation of TTX-sensitive and TTX-resistant Na^+ channels [96] and down-regulation of Ca^{2+} channels and various types of K^+ channels [95]; these findings have been replicated, refined, and greatly extended over the last 13 years [97-104]. Increases in the hyperpolarization-activated cation current (I_H) [105, 106], as well as increased expression of $Na_v1.7$ sodium channels and $Ca_v3.2$ T-type calcium channels have also been observed during various pain states [35, 107-109]. Although all such changes are capable of increasing the neuronal excitability, it is likely that dissimilar ion channels are affected in different types of neuropathic pain. For example, axotomy, chronic DRG compression, and chronic exposure to the pro-inflammatory cytokine IL-1β all increase the DRG neuron excitability [12, 14, 37, 40, 42, 43, 61,110]. Axotomy affects Ca^{2+}-, K^+-,and TTX-sensitive and resistant Na^+ channels [95, 96], whereas long-term IL-1β application and DRG compression affects H-currents (carried by HCN channels; Fig. 5) [14, 61, 110, 111]. The T-type Ca^{2+} channel currents are increased by CCI and in diabetic neuropathy [35, 107] but not by axotomy [95].

This raises an important point. Because increases in the DRG excitability are brought about by different ion channel mechanisms in different nerve injury situations and/or disease states, it is likely that drugs that target injury-specific or disease-specific changes in ion channels will be effective in specific clinical situations. This may be the key to developing therapeutic approaches to some of the most intractable forms of neuropathic pain, such as that associated with HIV-AIDS neuropathy. The appropriate ion channels have to be identified.

We have also considered interfering with synaptic transmission in the dorsal horn, and our *in vitro* results suggest that blockers of CP-AMPARs may be effective, but this has yet to be demonstrated in animal models of neuropathic pain *in vivo*.

Lastly, we considered the possibility of improving the gabapentinoid effectiveness by combining of these drugs with capsaicin. Since TRPV1 channels are often associated with nociceptive fibers and are up-regulated in certain pain states, TRPV1-facilitated entry of gabapentinoids will preferentially target pain transmission. Since topical capsaicin is already in use in pain management [112-116], its use in the combination may permit the use of lower doses of gabapentinoids, thereby reducing their tendency to promote drowsiness, peripheral edema, and dizziness. The combination may also allow one to use lower doses of capsaicin, which is currently applied topically

in quite high concentrations [114-116]. Although this causes acute pain, which can last for days, it can relieve chronic pain for a month or more. The acute allogenic actions of capsaicin do, nevertheless, decrease the patient compliance. Thus, the possibility of using lower doses of topical capsaicin to augment the gabapentinoid effectiveness would also have potential therapeutic advantages.

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РОЗУМІННЯ МЕХАНІЗМІВ І ЛІКУВАННЯ НЕЙРОПАТИЧНОГО БОЛЮ

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Р е з ю м е

Нейропатичний біль, який майже не підлягає адаптації до якого є відсутньою, виникає внаслідок ушкоджень або захворювань нервової системи. Він, як правило, має хронічний характер і часто є неусувним. Звичайні аналгетики, такі як опіоїди, в цих ситуаціях є малопридатними, а габапентиноїди (прегабалін і габапентин) ефективні не в усіх випадках. При нейропатичному болю, що виникає в периферичних структурах, початкова запальна відповідь викликає вивільнення різноманітних медіаторів, включно з цитокінами та простагландинами, які змінюють експресію іонних каналів у первинних аферентних нейронах. Це призводить до ініціації ектотопічної активності в сенсорних нервах і вивільнення АТФ і другої групи медіаторів із терміналей первинних аферентів. Рівень активації спінальної мікроглії змінюється таким чином, що остання вивільнює третій набір медіаторів, зокрема мозковий нейротрофічний фактор (BDNF), у дорсальний ріг спинного мозку. Через низку механізмів BDNF посилює збуджуючу синаптичну передачу та послаблює гальмівну. „Центральна сенситизація", що розвивається в результаті, зумовлює гіпералгезію, каузалгію та алодинію – феномени, асоційовані з нейропатичним болем. Наявність змін в іонних каналах сенсорних нервових структур і модуляції збуджуючої передачі в дорсальному розі визначає високу необхідність вишукувань нових підходів у лікуванні нейропатичного болю. Робиться припущення, що ефективність габапентиноїдів може бути збільшена за рахунок сполучення цих агентів з агоністом рецепторів TRPV1 капсаїцином.

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