Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels

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Local anaesthetics have been used clinically for well over a century, but the molecular mechanisms by which they alter specific functions of the peripheral nerve system remained unclear for a long time. Investigations during the last few decades presented evidence implicating the sodium (Na⁺) channel protein as a target for specific, clinically important, local anaesthetic effects on mammalian neurones. In this review I will present the state of knowledge of the action of local anaesthetics at the molecular level, with an emphasis on Na⁺ channels. After a brief survey of the history of concepts of local anaesthetic actions, the structure of the Na⁺ channel will be described with regard to its function in order to understand the recent findings that have followed the description of the amino acid sequence of the Na⁺ channel protein. At clinically relevant concentrations local anaesthetics can also affect potassium (K⁺) and calcium (Ca²⁺) channels, which might help explain some of their side-effects. General anaesthetics also interact with these targets (ion channels), but differences in selectivity compared with local anaesthetics have been reported. Current findings indicate that local anaesthetics also act on intracellular mechanisms, which raises the question of whether these might explain toxicity and other side-effects.

Historical view

Cocaine was first used as a local anaesthetic by Carl Koller and Sigmund Freud (the latter the founder of psycho-analysis). They noticed a numbing effect on the tongue after swallowing cocaine, and Koller, who was intent on finding a drug to anaesthetize the cornea, knew that Freud had relieved pain with cocaine. In fact they could demonstrate on themselves—using pins to touch their cornea in front of a mirror—that within minutes of applying cocaine they could no longer feel touch or pain. In 1884 they reported that they had enucleated painlessly a dog’s eye. Leonard Cornig, a neurologist in New York City, had tried in 1885 to inject cocaine solution (2%) between the spinous processes in a young dog, which resulted in insensibility within 5 min; this procedure was subsequently tried on patients, with the drug presumably acting in the epidural space. The lumbar puncture later introduced by Quincke produced spinal anaesthesia. Cocaine was widely used despite its disadvantages of high toxicity, short duration of anaesthesia, impossibility of sterilizing the solution and its cost (not to mention addiction). When in 1904 Alfred Einhorn, investigating degradation products of cocaine, synthesized procaine, he found that, “the anesthetic capability of cocaine is therefore a function of its acid group called by Paul Ehrlich the ‘anesthesiophoric’ group – the most potent being the benzoyl group”. Today we know that the majority of clinically used local anaesthetics consist of a benzene ring linked via an amide or ester to an amine group, and their names still end in ‘caine’.

Differential and use-dependent block by local anaesthetics

In those early days of anaesthesia a selective block of specific types of nerve fibre was noticed, termed ‘differential nerve block’, which was understood to be a sequential block of sensory information; a sequence of blockade of sharp pain, cold, warmth, touch, and finally conduction in motor fibres was considered most probable. A quantitative electrophysiological technique was employed by Gasser and Erlanger in 1929; they compared the different susceptibility of compound action potentials in nerves to pressure and cocaine-containing solutions in accordance with their own classification based on fibre size and conduction velocity (from Aδ – fastest to C-fibres – slowest). They suspected that diameter might be the main factor accounting for differential nerve block, based on the idea that the process responsible for impulse propagation was essentially similar in all fibres. With cocaine they observed that small fibres...
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Block mechanisms

QX 314 is a quarternary derivative of the local anaesthetic lidocaine that has a permanent positive charge. It is not in clinical use but has interesting features that have helped to elucidate the mechanism of blocking Na⁺ channels. This drug blocks the channels only when applied to their intracellular side.24 Most local anaesthetics, except benzocaine, are amine compounds, which are charged at a pH below 6. The uncharged form is lipid soluble.34 Biophysical calculations based on the electrical field across the cell membrane suggested that the binding site is at a distance from the external surface of the membrane of approximately 60% of the membrane diameter (an estimate that agrees fascinatingly well with what we now know from the molecular structure; see section below). This finding gave rise to the first ideas about the blocking mechanism: the ‘receptor’ is in the pore; the charged form acts on the ‘receptor’, and the drug molecules have to pass through the lipid membrane to act. Another blocking characteristic was observed at that time: nearly full sized Na⁺ currents could be elicited during the first depolarizing impulse in the presence of a local anaesthetic, but subsequent impulses elicited smaller and smaller peak currents.74 It was suggested that the drug binds cumulatively and that this block needs open channels. This accumulation of inhibition has been called use-dependent block or phasic block.20 79 Subsequently, the guarded receptor hypothesis was proposed,72 suggesting that the receptor is protected in the pore and that the channel needs to be open before it can be blocked. The impact of use-dependent block became manifest at higher firing frequencies of nerve fibres, where lower concentrations of local anaesthetics were needed to block compound action potentials (see Fig. 4).56

Structure of Na⁺ channels

Before we try to understand the mechanisms by which local anaesthetics block Na⁺ channels at the molecular level it is helpful to understand current thinking on the structure of the channels.

The Na⁺-conducting part of the channel is called the α-subunit,45 46 a single polypeptide protein of relative molecular mass ~260 000.1 The functional amino acid sequence encoded by the corresponding cDNA results in a ~1950 amino acid chain which spans the cell membrane several times. The channel consists of four domains (DI–DIV; Fig. 1A),80 each containing six helices which span the membrane and are named the S1–S6 segments. The link between the S5 and S6 segments in each domain is of particular interest because these ‘pore loops’ form the outer pore and contain the amino acid sequence DEKA (in each domain). This structure represents the selectivity filter allowing primarily Na⁺ ions to pass through the pore (Fig. 1A). The region of the outer pore mouth is also involved in the binding of toxins such as TTX, batrachotoxin and conotoxins.58 78 85 Interestingly, the binding site for batrachotoxin, although localized at the outer pore mouth, seems to influence the binding potency of local anaesthetics at the inner pore regions.16 83 84 Two regions involved in gating were identified from early mutagenesis work with the Na⁺ channel. Firstly, as a voltage-dependent channel, it needs a voltage sensor, which would have to be a charged region. The most obvious charged regions are the S4 transmembrane helices, which each contain a number of positively charged lysine and arginine residues. Substituting uncharged amino acids at these points reduces the voltage sensitivity, suggesting that the S4 helices are the voltage sensors.75

An intracellular link between DIII and DIV is important for Na⁺ channel function: it underlies ‘fast’ inactivation and will be described in the next section (Fig. 1B). Another type
First, there is the closed state at potentials below ±70 mV. In addition to the pore-forming millisecond and allows Na\(^+\) ions to diffuse down their channel is initiated by depolarization of the transmembrane potential to the threshold potential (usually above ±40 mV). The pore in the channel is occluded so that Na\(^+\) ions cannot pass from one side to the other. Second, the open state of the outer pore mouth (for more details see section Structure of Na\(^+\) channel). Third, the inactivated state was shown to be a non-conducting mode of the channel, although gating currents were measured. Application of enzymes such as pronase, applied from the internal side in internally perfused squid giant axons, prevented this ‘fast’ inactivation process. It was therefore concluded that the inactivation gate is positioned on the inner side of the channel protein. A sequence of three amino acids is important for ‘fast’ inactivation, and is called the IFM particle; it is the cytoplasmic linker between domains III and IV (Fig. 1B). In ‘fast’ inactivation the IFM particle may function like a ‘lid’, plugging the pore (a ball on a chain is an alternative analogy) by binding to sites situated on or near the inner vestibule. The role of the IFM particle in binding of local anaesthetics is not fully understood but it seems that this ‘lid’ retains blockers inside the pore during use-dependent blockade. Therefore Na\(^+\) ions can no longer pass through the pore, even though the pore is open at the outer mouth. The fast inactivated state is of interest to anaesthesia for two reasons: this state seems to play an important role in high-affinity binding (discussed below), and the movement of the S4 segment in gating (important for activation and closing as described above) directly influences fast inactivation and vice versa.

**Molecular determinants of local anaesthetic action on Na\(^+\) channels**

With the knowledge of the molecular structure of Na\(^+\) channels, especially the amino acid sequence of the pore-forming \(\alpha\)-subunit, it became possible to uncover the ‘receptor’ for local anaesthetics. Experiments on the rat brain Na\(^+\) channel IIa (Na\(_{\text{v}}\), 1.2) revealed that exchanging the amino acid phenylalanine (F) at position 1764 with alanine (A) made the channel (Fig. 1B) virtually insensitive to use-dependent block. Measurements of the IC\(_{50}\) for the inactivated wild-type Na\(^+\) channel with depolarizing pulses revealed a 1:1 binding relationship, with 300-fold smaller values compared with tonic blockade. In contrast, in the F1764A mutation the IC\(_{50}\) values for inactivated Na\(^+\) channels were only six times smaller than those for tonic blockade. Another mutant, Y1771A, exhibited less use-dependent block and reduced drug binding at depolarized potentials, but the effect was smaller than for F1764A. These results led to a model for the ‘receptor’ site of local action.
anaesthetics in the pore of the Na⁺ channel. The residues 1764 (F) and 1771 (Y) described above are hydrophobic aromatic residues separated by two turns on the same face of the protein helix of the pore-forming S6 segment (Fig. 1B). These amino acids are about 11 Å apart, and most effective local anaesthetics are 10–15 Å in length. The local anaesthetics have positively charged moieties at either end, which could interact through hydrophobic or π electrons with these kinds of amino acid residues. The substitution with alanine changed the size and the chemical properties in these mutants, with minimal effect on the protein secondary structure and demonstrated that these are probably the main determinants of drug binding for the opened channel. This idea is supported by experiments with the permanently charged local anaesthetic QX314 which after intra-oocyte injection displayed a use-dependent block of more than 50% in expressed wild-type Na⁺ channels but produced hardly any use-dependent block in the F1764A mutant. In these types of experiment the only possible access route to this site was via the open channel; recovery times comparable with those in the wild-type indicate that the escape pathway of the local anaesthetic is not altered.

Another mutation oriented towards the pore, I1760A (Fig. 1B), did not alter the local anaesthetic affinity of either the open or the inactivated state of the Na⁺ channel. Instead, the rate of drug dissociation from the mutant channel was found to be eight times faster than for wild-type channels. This might be explained by the fact that the I1760A mutation is closer to the extracellular side on the S6 segment at the channel outer mouth, and isoleucine is a bulky residue. It therefore seems likely that the drugs could escape more easily from the mutated channel. Confirmation came from experiments with externally applied QX314, normally ineffective, which rapidly blocked this mutant. Thus, the mutation created a pathway for the extracellular drug to enter, supporting the idea that faster recovery from drug-bound states with nearly unchanged use-dependent block properties is the result of easier escape of the drug from the channel.

An explanation emerges which identifies two binding sites in the pore of the brain Na⁺ channel (positions 1764 and 1771) whose hydrophobic parts interact with the corresponding regions of the local anaesthetic molecule. The residue oriented more towards the mouth of the pore (1760) guards the fast escape of the drug molecule to the extracellular side and protects the channel from extra-cellular drugs.

It should be noted that mutations in the S6 segment at positions other than those described above, I1761A, V1767A and N1769A, caused more pronounced blockade at holding potentials of −90 mV. The inactivation curve for these mutants was found to be shifted by 7–13 mV to more negative potentials, therefore the increased sensitivity might be caused by an increased proportion of inactivated Na⁺ channels. But even at more negative holding potentials where the inactivation was removed, it was found that...
mutations I1761A and V1766A were about three times more sensitive than wild-type Na⁺ channels under resting conditions. The mutation N1769A at holding potentials of -140 mV (where all fast inactivation was removed completely) was 15 times more sensitive than wild-type Na⁺ channels. The residues 1761 (I), 1766 (V) and 1769 (N) are oriented away from the inner pore towards the lipid phase of the membrane. It is therefore possible that mutations of these residues influence the increased sensitivity of the inner pore local anaesthetic receptor by an allosteric mechanism. It can also be imagined that these positions are responsible for the resting blockade, explaining the higher affinity of lipophilic drugs under resting conditions. In addition, one must consider the possibility that these mutations cause changes in the inactivation behaviour of the channels, perhaps by inducing the binding site in the pore in functionally inactivated binding confirmation.55

The same results have been obtained involving structurally similar locations in heart and muscle Na⁺ channels, explaining the absence of substantial differences in affinity of local anaesthetics for Na⁺ channel subtypes.5 Only the position numbers of the amino acids are different: for example 1579 and 1586 in rat skeletal muscle Na⁺ channels (Na, 1.4) correspond to positions 1764 and 1771, respectively, in rat brain Na⁺ channels (Na, 1.2).

DIII, the neighbour domain of D IV, also appears to be important for binding of local anaesthetics.84 90 Point mutations in the S6 segment of these domains resulted in a reduced affinity of local anaesthetics for neuronal and muscle Na⁺ channels. This indicates that at least some drug molecules are bound primarily at the S6 segment in DIV and DI but that the molecule also binds on the other side of the channel pore at the S6 segment of DIII.

In one aspect benzocaine is different from the other local anaesthetic: it is the only clinically used local anaesthetic that is not charged (because of its low pKa). Yet it is still suggested that benzocaine shares the same binding site as other local anaesthetics,62 at least in the neuronal and muscle Na⁺ channels, and it could be speculated that it might be again in the inner pore. Admittedly, the low affinity of benzocaine compared with other local anaesthetics (IC₅₀ ~800 μM) and the missing use-dependent block62 82 do not suggest a very high affinity mechanism.

The small differences in potency and toxicity of enantiomers seems to have a counterpart on the molecular level. A stereoselectivity of around 1.5 was found for Na⁺ channels from skeletal muscle and human heart cells (Na, 1.5).44 Primarily in the human heart channel, it was demonstrated that the binding residues 1760 and 1765 (the corresponding positions in Na, 1.2 are 1764 and 1771) contribute to the weak stereoselectivity.

Tetrodotoxin-resistant Na⁺ channels
The description of the molecular mechanism presented above has been derived mainly from Na⁺ channels that are sensitive to TTX in the nanomolar range, as well as the cardiac channel, which is less sensitive but not insensitive to TTX. Typical TTX-resistant Na⁺ channels are found primarily in neurones of the dorsal root ganglia (DRG).2 They are termed SNS/PN3 and SNS2/NaN, in the new nomenclature Na⁺ 1.8 and Na⁺ 1.9, respectively.30 59 64 77 Apart from being some hundred times less sensitive to TTX, the current kinetics of these channels are slower than those of the ‘fast’ TTX-sensitive Na⁺ currents and their thresholds of activation and half-maximal inactivation are at more depolarized potentials (Fig. 2). Their distribution predominantly in small-to-medium sized DRG neurones connected to Aδ- and C-fibres immediately suggested a functional role in pain conduction. Beside their presence in the soma, there is electrophysiological and immunohistochemical evidence for the presence of TTX-resistant Na⁺ channels in peripheral nerve terminals23 38 53 and in nociceptor nerve terminals.13 73 Experiments13 73 on sensory nerve fibres innervating the dural membrane clearly showed that 50% of small Aδ-fibres and 85% of C-fibres were unaffected by 1 μM TTX! This indicates that TTX-resistant Na⁺ channels are important elements of signal transduction in the smallest nerve endings. Indeed, null mutant mice lacking the SNS/ PN3 Na⁺ channel show partial analgesia to painful stimuli.21

The question had already been raised in previous studies whether this TTX-resistant Na⁺ current is blocked by local anaesthetics. In fact, the blocking mechanisms were found to be very similar to those in TTX-sensitive Na⁺ currents, but the main difference was a 2–6 times lower affinity of TTX-resistant Na⁺ currents, depending on the type of local anaesthetic (Figs 3 and 4).10 58 66 One study demonstrated that TTX-resistant action potentials in small sensory neurones, which are involved in the generation and conduction of pain-related impulses, are suppressed by lidocaine and bupivacaine in a concentration-dependent manner at clinically relevant concentrations (Fig. 3).57 These concentrations were 3–4 times higher than those required to block TTX-sensitive Na⁺ currents in the same type of neurone. Furthermore, sensitivity to local anaesthetics was higher by a factor of 10–20 in firing frequency than in amplitude of the TTX-resistant action potentials (Fig. 4). This observation may be relevant for the analgesic properties of local anaesthetics, especially when considering that intensity of pain is encoded by the frequency of action potentials. In addition, it has been observed that the local anaesthetic concentration for half-maximal blockade of ion currents does not predict the relevant concentration required for a functional blockade of neuronal signal conduction.

Potassium channels
As with voltage-dependent Na⁺ channels, voltage-dependent and voltage-independent K⁺ channels are blocked by local anaesthetics. This is of interest because in the peripheral nervous system K⁺ channels contribute to the
falling phase of action potentials, determine the after-spike period and play a part in setting the resting potential. Voltage-gated K+ channels in particular have been investigated in dorsal horn neurones and DRG and partially in nerve fibres. The major difference between local anaesthetic action in voltage-gated K+ currents compared with Na+ currents is the lower affinity in the former. Depending on the type of voltage-dependent K+ current, the affinity for bupivacaine is 4- to 10-fold lower and for lidocaine it is 10- to 80-fold lower. This inhibition of K+ channels might be an additional explanation for broadening of the action potential in the presence of local anaesthetics, because the voltage-gated K+ currents contribute to the repolarization phase of action potentials.

A voltage-independent K+ channel was also found to be blocked by local anaesthetics in sensory neurones. This ‘flicker’ K+ channel (so termed because of its flickering kinetics in high K+ solutions) is found mainly in thin myelinated fibres of frog sciatic nerves and was highly sensitive to local anaesthetics, requiring only 0.21 μM bupivacaine for half-maximal blockade. This is the most sensitive ion channel in this preparation. Up to now this ‘flicker’ channel has not been detected in mammalian fibres.

In addition to these K+ channels, the ATP-sensitive K+ channel in heart muscle cells has been found to be sensitive to lidocaine and bupivacaine. This blockade of K+ channels may explain side-effects and toxic effects of local anaesthetics in organs other than the peripheral nervous system, especially if the many subtypes of K+ channel have different sensitivities. Another mechanism was described for the Ca2+-activated large conductance K+ channel.
Calcium channels

Because the structure of voltage-dependent Ca\textsuperscript{2+} channels closely resembles that of Na\textsuperscript{+} channels, it is not surprising that Ca\textsuperscript{2+} currents, especially in DRG, were found to be blocked by local anaesthetics.\textsuperscript{65,66,79} A concentration–response curve for tetracaine in high-voltage-activated Ca\textsuperscript{2+} currents (L-, N-, Q- and P-types) revealed an apparent dissociation constant of 80 μM. When specific blockers were used for L- and N-type Ca\textsuperscript{2+} channels, it was found that the L-type was more sensitive than either the N-type Ca\textsuperscript{2+} channel or the remaining low-voltage-activated Ca\textsuperscript{2+} current (T-type). Local anaesthetics other than tetracaine also depressed high-voltage-activated Ca\textsuperscript{2+} currents but were of different potency; the rank sequence was dibucaine > tetracaine > bupivacaine >> procaine = lidocaine. How could this finding be interpreted? Ca\textsuperscript{2+} channels are extremely important in synaptic transmission and in muscle cells, where they are involved in the coupling of electrical excitability with mechanical contraction. In human peripheral nerves, not only the central ends of the fibres in the dorsal horn but also some thin (mainly C) fibres contain Ca\textsuperscript{2+} channels.\textsuperscript{53} The functional consequences are suggested by a recent study in which tail-flick latencies to radiant heat nociception were measured in the tails of mice to test the effect of subcutaneous infiltration of bupivacaine and Ca\textsuperscript{2+}-modulating drugs.\textsuperscript{70} It was found that an L-type Ca\textsuperscript{2+} channel agonist reduced the duration of action and potency of bupivacaine anaesthesia. Nifedipine and nicardipine, antagonists of L-type Ca\textsuperscript{2+} channels, increased the effects of bupivacaine. Other Ca\textsuperscript{2+} channel subtype blockers were also investigated but did not modify bupivacaine anaesthesia. Since there is no musculature in the tail, the results suggest that in some axons Ca\textsuperscript{2+} channels, at least in heat nociceptors in the skin, are sufficient to support propagation of action potentials.

Although the half-maximal blockade of Ca\textsuperscript{2+} channels occurred at higher concentrations compared with Na\textsuperscript{+} channels (~5–15 times), their blockade might contribute to interrupting the transmission at concentrations required for spinal anaesthesia. What this means for the synaptic transmission in the dorsal horn, which is triggered by Ca\textsuperscript{2+} channel opening, requires further investigation. This again raises the question of whether Ca\textsuperscript{2+} channels as targets of local anaesthetics underlie side-effects or toxic effects in other organs. Besides these unwanted effects, there are some similarities between local anaesthetics and Ca\textsuperscript{2+} channel blockers (e.g. verapamil which showed a use dependence similar to local anaesthetics).\textsuperscript{71} This might be an interesting alternative target of the well-known pro-arrhythmic activity of some local anaesthetics on Na\textsuperscript{+} channels in heart muscle cells.

G-proteins and G-protein-regulated channels

Although local anaesthetics are primarily considered to be blockers of ion channels, recent studies suggest a common intracellular site of action on different G-protein-coupled receptors.\textsuperscript{36} They showed that recombinant M1 muscarinic receptors expressed in oocytes were inhibited by local anaesthetics in a stereoselective and non-competitive manner, suggesting a protein interaction. G-protein α-subunits involved in mediation of lysophosphatidic acid, M1, trypsin, and angiotensin AT\textsubscript{1A} receptor signalling were characterized. Lidocaine and its analogue QX314 were applied into oocytes expressing these receptors. Since the AT\textsubscript{1A} receptor, previously shown to be unaffected by local anaesthetics, was found not to signal via Go\textsubscript{q}, but via Go\textsubscript{q}, and Go\textsubscript{αi, q}, the intracellular effect of local anaesthetics is most likely to be on the Go\textsubscript{q} subunit. Blockade of the muscarinic M3 receptor was described by the same group, even though the M3 receptor lacks the extracellular terminus that explained the binding of local anaesthetics to M1 receptors.\textsuperscript{35}

There is evidence that G-protein-gated inwardly rectifying K\textsuperscript{+} channels are blocked by local anaesthetics.\textsuperscript{69} In addition, it has been shown that bupivacaine mobilizes intracellular calcium ions via the inositol trisphosphate signalling cascade in sensory neurones.\textsuperscript{41} Taken together, these pathways might also explain why local anaesthetics exhibit side-effects in other organs, and justify future work to elucidate whether they act in the same way in brain and heart.

General anaesthetics and ion channels

Clearly, the clinical effects of general and local anaesthetics are different. However, axonal ion conductance has been investigated as a possible mechanism of action of general anaesthetics.\textsuperscript{6,15,16} A partial blockade of mainly Na\textsuperscript{+} currents was found but this was not sufficient to suggest peripheral conduction blockade as a major mechanism. Compared with results with ligand-gated ion channels in the central nervous system (described in more detail in other articles in this issue) the general anaesthetics are less potent at voltage-gated ion channels. However, subsequent research has found that, depending on the species from which the channel originated, voltage-gated currents can be affected at clinically relevant concentrations of potent inhalation anaesthetics.\textsuperscript{25,27,64} For example, in Na\textsuperscript{+} channels the half-maximal values of inactivation were shifted to more hyperpolarized values, resulting in fewer Na\textsuperscript{+} channels being available to be opened.

Besides voltage-gated K\textsuperscript{+} channels, a class of leak or background K\textsuperscript{+}-selective channels is known. These
channels are formed by two transmembrane segments with the conserved motif called the P domain and therefore named 2P domain K⁺ channels. Members of this class of 2P domain K⁺ channels, such as TREK-1, TREK-2, TASK-1 and TASK-2, have been reported to be activated by volatile anaesthetics. TASK-1, in contrast to the other types, is also blocked by the local anaesthetic bupivacaine. The 2P domain K⁺ channels are not uniformly affected by volatile anaesthetics: TASK-2 but not TASK-1 is stimulated by chloroform, while TASK-1 is partially inhibited by diethyl ether. Even though the stimulation of channel activity by halothane is specific, other 2P domain K⁺ channels—TWIK-2, THIK-1, TALK-1 and TALK-2—are inhibited. For channels sensitive to anaesthetics it was demonstrated that the C terminus but not the N terminus was crucial.

Perspectives for local anaesthetics

Early hypotheses based on non-specific interactions of lipid-soluble anaesthetics with membrane bilayers have largely given way to the current idea that membrane-associated proteins, particularly ion channels, are specifically modulated by local anaesthetics. Indeed, Na⁺ channels have been identified as a major target, with two different blocking mechanisms, tonic and phasic. The use-dependent (phasic) block by local anaesthetics seems to be the mechanism that underlies the very high sensitivity of Na⁺ channels which is based on the binding of local anaesthetic molecules in the channel pore to few specific amino acids. A recent investigation tested a benzomorphan derivative, crobenetine (BIII 890 CL), which produces a very pronounced use-dependent block of Na⁺ and K⁺ channels in peripheral nerve. This agent was designed to protect the brain after permanent focal cerebral ischaemia, its highly use-dependent Na⁺ channel block makes it a possible candidate as a local anaesthetic and for treatment of neuropathic pain.

Another specific suppression of pain might be expected from a drug that targets TTX-resistant Na⁺ channels (e.g. Naα, 1.8 and Naβ, 1.9), whose expression is confined to Aδ and C pain-mediating fibres. However, the development of drugs that exhibit selective blockade of neuronal TTX-resistant Na⁺ channels while leaving TTX-sensitive channels unblocked is still to be accomplished.

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