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Review Article

REVIEW ARTICLE

Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review

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Abstract

The focus of perioperative pain management should be to attempt to minimise the nociceptive input and reduce the risk of transition to central sensitisation. Gabapentinoids are being increasingly used as adjuncts for management of perioperative pain. Although gabapentinoids are classed as calcium channel blockers, their mechanisms of action are poorly understood. The analgesic effect in neuropathic pain is well evidenced but the role in postoperative pain is less certain. Medline and EMBASE database searches were conducted to identify studies relating to mechanisms of action and effects in experimental animal models of inflammatory and postoperative pain and human models of experimental pain. The effects of gabapentinoids may be attributed to depression of dorsal horn sensitivity through a multitude of mechanisms. They inhibit calcium mediated neurotransmitter release through effects on α2δ-1 subunits. They inhibit forward trafficking of α2δ-1 from the dorsal root ganglion, their recycling from endosomal compartments, thrombospondin mediated processes and stimulate glutamate uptake by excitatory amino acid transporters. Mechanisms not directly related to neurotransmitter release at dorsal horn include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions, and influence on the affective component of pain. Gabapentinoids are effective analgesics in most animal models of inflammation and postoperative pain but effects in human models are variable.

Keywords: alpha 2-delta subunit 1 protein; gamma-aminobutyric acid; pregabalin

The gabapentinoids, pregabalin and gabapentin, have been the cornerstone of pharmacological management of neuropathic pain.[1] Despite the widespread use in neuropathic pain, the precise mechanism of action is uncertain. The effect of gabapentinoids in pain are assumed to be because of direct inhibition of voltage gated Ca^{2+} channels by binding to its α2δ-1 subunit resulting in reduction of presynaptic Ca^{2+} influx and subsequent release of excitatory neurotransmitters such as glutamate. This assumption is not correct as calcium currents are not consistently reduced by acute application of gabapentinoids.[2] Despite this, most studies show that gabapentinoids inhibit release of neurotransmitters in neuronal tissues.[2] This review explores the possible mechanisms by which gabapentinoids inhibit neurotransmitter release despite the lack of acute effect on Ca^{2+} currents. This review has also sought to identify the analgesic mechanisms unrelated to the direct inhibition of neurotransmitter release at the dorsal horn.

Although there is good evidence for the effect on neuropathic pain, the role in postoperative pain is less certain. Gabapentinoids are being increasingly used in the perioperative period as part of multimodal analgesia.[3] However, the

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Editor's key points

- The analgesic actions of gabapentinoids can be attributed primarily to blockade of calcium channels, but have additionall targets as well.
- Gabapentinoids depress neuronal excitability through interactions with the α2δ-1 subunit, stimulate descending inhibition, inhibit descending serotonergic facilitation, inhibit inflammatory mediators, and influence the affective component of pain.
- They are effective in animal models of inflammation and postoperative pain, but effects in human models of inflammation are variable.

evidence to support its use in postoperative pain is limited because of the poor quality of evidence from clinical trials.[4] This review sought to determine the effects of gabapentinoids in animal models of postoperative and inflammatory pain and in human pain models. The implications for clinical practice are discussed.

Methods

Medline and EMBASE database searches were conducted to identify studies relating to mechanisms of action and effects in experimental pain models (Appendix A). The reference lists of selected articles were explored for additional studies. Only manuscripts published in English were included. The level of evidence could not be graded as most studies were exploratory in nature. Various themes relating to mechanisms were identified and selected studies described.

Nociceptive pathways, voltage-gated calcium channels, and the α2δ subunit

Nociceptors are pseudo-unipolar: the cell bodies are located in the dorsal root ganglion (DRG), a single process bifurcates into a central axon that project to second-order neurons and local interneurons in the dorsal horn of the spinal cord, and a peripheral axon travels through the spinal nerve to the periphery.[5] After nerve injury or inflammation, the stimulation threshold of nociceptors is reduced. The sensitised nociceptors are activated by minimal stimuli—a process known as peripheral sensitisation that causes primary hyperalgesia. The action potentials that are transmitted to the nociceptors are relayed to the spinal dorsal horn through the central axon and to the periphery through the peripheral axon. This causes membrane depolarisation, activation of voltage-gated calcium channels (VGCCs) and calcium influx, triggering release of glutamate as a major neurotransmitter along with neuromodulators such as substance P, calcitonin gene-related peptide, and brain-derived neurotrophic factor. These are released both peripherally at the site of inflammation and in the dorsal horn, to produce an excitatory signal at the post synaptic targets.[5] The effects on the dorsal horn neurons of the spinal cord are mediated by the postsynaptic glutamate receptors—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate, *N*-methyl-D-aspartate and kainite.[6] Many neurons also regulate neurotransmitter release through expressing presynaptic glutamate receptors.[7] The excitatory interneurons in the dorsal horn are also glutamatergic. The enhanced release of glutamate in the dorsal horn of the spinal cord causes increased activation of postsynaptic nociceptive neurons resulting in central sensitisation and secondary hyperalgesia. The spinal cord is clearly an important site for modulation of central sensitisation, as it receives multiple inputs from peripheral neurons, interneurons, astrocytes, microglia, and descending modulatory controls.[8]

Generally, this process of sensitisation reverts back to normal after pain resolves with normal wound healing. However, persistent transmission of nociceptive signals leads to persistent central sensitisation through neuroplastic changes in the dorsal horn and higher centres, such as degeneration of inhibitory interneurons and remodelling of neuronal synapses by glial cells.[8]

Voltage-gated calcium channels

Voltage-gated and ligand-gated channels that are permeable to inorganic ions such as sodium, potassium, chloride, and calcium are essential for electrical activity of excitable cells such as neurons.[9] Calcium differs from the other ions as it also serves as an important signalling entity. Influx of calcium ions through high-voltage activated (HVA) calcium channels trigger a wide range of responses including gene transcription, neurotransmitter release, neurite outgrowth and activation of calcium dependent enzymes.[9]

VGCCs are comprised of multiple subunits: α_1, β, γ, and $\alpha_2\delta$ (Fig 1).[10] The α1subunit allows entry of calcium ions. It comprises four homologous domains (I–IV), each of which contain six transmembrane helices (S1–S6). The extracellular α_2 subunit is attached to the δ subunit via a disulfide linkage. The β subunit is entirely intracellular. VGCCs are classified into HVA (L-, P/Q-, N-, R-) and low-voltage activated (LVA; T-type) VGCCs.[11] Dorsal root ganglion cell bodies and presynaptic terminals that form synapses with dorsal horn neurons express increased density of N-type VGCCs.[10] The L-type channels are extensively found in both excitable and non-excitable tissues. Although less extensively studied, other subtypes may be involved in the pain pathway.[10]

α2δ subunit and pain

The auxiliary $\alpha_2\delta$ and β subunits have four isoforms and enhance the plasma membrane expression and function of HVA calcium channels but not LVA channels.[12] The α2δ-1 isoform that mediates the effects of gabapentinoids is present in the brain, skeletal, cardiac, and smooth muscle. α2δ-2 and α2δ-3 subunits are present in non-neuronal tissues in addition, whereas α2δ-4 is expressed in retinal neurons and other non-neuronal tissues.[12]

The α2δ-1 unit has widespread distribution in the mouse brain, especially in the cerebral cortex, hippocampus, and cerebellum.[12] Elevated concentration of α2δ-1 subunit is clearly associated with augmented pain processing. DRG neurons show increased expression after peripheral nerve damage in animal models of neuropathic pain.[13–16] The peak expression of $\alpha_2\delta$-1 occurs 7 days after injury and takes several months to decline, with a temporal relationship with the onset and resolution of evoked behaviours.[15] Deletion of α2δ-1 gene in mice models of neuropathic pain is associated with marked behavioural deficit in mechanical and cold sensitivity.[17] Intrathecal antisense oligonucleotides (synthetic polymers that can alter synthesis of specific proteins) complementary to a region in the α2δ-1 gene can reverse mechanical hypersensitivity in nerve ligation models.[14] The concentrations are elevated in the dorsal horn and mimic that of the DRG with decrease in concentrations and reversal of allodynia after