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ANALGESIA

Picking out the pieces of GABA receptors

Inflammatory diseases and neuropathic insults are often accompanied by severe chronic pain that can be unresponsive to conventional analgesic treatments. Although inhibitory GABAergic neurons control the relay of nociceptive signals from the periphery to higher areas of the CNS, systemic $GABA_A$ receptor-enhancing drugs such as benzodiazepines — used clinically for their sedative, anxiolytic and anticonvulsant effects — largely lack clinical efficacy for pain. Now, Knabl and colleagues, writing in *Nature*, show that analgesia can be achieved by targeting specific $GABA_A$ receptor subtypes.

First, the authors demonstrated that intrathecal injections of the classic benzodiazepine diazepam exerted dose-dependent antinociceptive effects at the level of the spinal cord. To identify the $GABA_A$ receptor isoforms responsible for the antinociceptive activity, four types of $GABA_A$ receptor point-mutated knock-in mice were studied. These mutant mice had benzodiazepine-sensitive $GABA_A$ receptor subunits — either α1, α2, α3 or α5 — that were selectively rendered insensitive to diazepam. All four types of diazepam-insensitive mice developed nearly identical pain sensitization as wild-type mice after induction of inflammation or peripheral nerve injury. When the antinociceptive activity of diazepam was assessed, similar anti-hyperalgesic effects were seen in mice carrying diazepam-insensitive α1 subunits compared with wild-type. By contrast, diazepam-induced anti-hyperalgesia was reduced in α2-mutant mice in the two pain models that were tested — inflammation-induced heat hyperalgesia, and cold allodynia and mechanical allodynia evoked by peripheral nerve injury. Mice with α3 or α5 mutations showed smaller reductions, and only in a subset of pain models.

To investigate the benzodiazepine-sensitive $GABA_A$ receptor isoforms expressed at sites where the anti-hyperalgesic effects of diazepam might originate, the authors used electrophysiological recordings from superficial dorsal horn neurons of the spinal cord and dorsal root ganglion (DRG) nociceptive neurons, and confocal immunofluorescence microscopy of dorsal horn $GABA_A$ receptor α-subunits. Both series of experiments indicated that intrinsic dorsal horn neurons express mainly $GABA_A$ receptor isoforms containing α2 and α3 subunits, whereas α2 is the dominant diazepam-sensitive $GABA_A$ receptor α-subunit in DRG neurons.

As results indicated that the spinal antinociceptive effect of diazepam is mediated predominately by $GABA_A$ receptor isoforms containing the α2 and α3 subunits, the authors next tested whether analgesia could be achieved after treatment with a subtype-selective benzodiazepine-site agonist, L-838,417.

L-838,417 is a partial agonist at α2, α3 and α5 subunits and an antagonist at α1 subunits. In rats, this compound produced anti-hyperalgesia in inflammatory and neuropathic pain models. L-838,417 did not impair motor coordination, and although its maximum analgesic effect was comparable with morphine, unlike this opioid, L-838,417 did not lose efficacy in a chronic dose regime.

Although yet to be tested in clinical studies, this study identifies $GABA_A$ receptors containing α2 and α3 subunits as crucial components of spinal pain control, and provides a rationale for the development of subtype-selective $GABA_A$ receptor modulators as a potential new class of drugs for chronic pain.

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ORIGINAL RESEARCH PAPERS Knabl, J. *et al.* Reversal of pathological pain through specific spinal $GABA_A$ receptor subtypes. *Nature* **451**, 330–334 (2008)