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Pain free and awake to enjoy it!

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Benzodiazepines (BZ) are best known for their sedative and anxiolytic properties when given systemically. Not surprisingly, therefore, few clinicians would consider BZ as a first choice analgesic even though patients have reported that BZ can produce analgesia [5]. BZ are also administered intrathecally for analgesia and to relieve spasticity but the complexity of this route precludes routine use. As the analgesic, sedative and anxiolytic effects of BZ are all mediated by GABAA receptors, there are questions as to whether these effects can be separated pharmacologically.

GABAA receptors are pentamers formed by the combination of at least 12 different subunits (6 alpha, 3 beta, 3 gamma, 1 delta, 1 epsilon, 1 Pi) with the most common types consisting of two alpha, two beta and one gamma subunit. Each GABAA receptor subtype has a unique distribution in the CNS as well as specific pharmacological activity. BZ bind to, and modulate, the activity of a subgroup of GABAA receptors known, appropriately enough, as the BZ receptors. The binding site of BZ receptors is between an alpha subunit with a histidine residue ($\alpha 1$, 2, 3 or 5) and a gamma subunit. The subunit variation among the different BZ-binding receptors underlies the different clinical effects. For example, receptors with the $\alpha 1$ subunit mediate the sedative effects of BZ while GABAA receptors with $\alpha 2$ or $\alpha 3$ subunits are responsible for the anxiolytic actions.

There is already evidence from preclinical studies that intrathecal injection of BZ is antinociceptive [1;9] and studies with “anxiolytic” agonists indicate that the analgesic effect is independent of the GABAA $\alpha 1$ subunit [8]. When administered systemically rather than intrathecally, however, analgesic effects can be masked or complicated by the sedative and anxiolytic manifestations, which has obviously reduced the use of BZ for pain. Now, Knabl and colleagues in this issue of *Pain* [7] present innovative data addressing the issue of analgesic versus other effects of BZ using several lines of mice with genetically altered GABAA receptors.

Knabl *et al.* used mice with point mutations of selected alpha subunits of the GABAA receptor and tested the effect of the deletions on formalin induced pain behavior. First, they showed that in wild type mice systemically administered diazepam (the prototypical BZ) produced both analgesia and sedation, but in mice with point mutations of the $\alpha 1$ subunit the sedative effects were abolished, but the antinociception remained. Next, they showed that in mice with point mutations of the $\alpha 1$, together with a point mutation of the $\alpha 2$ or $\alpha 3$ subunits, both the sedative and the antinociceptive effects of systemically administered diazepam were abolished. Point

mutations of the $\alpha 1$ together with $\alpha 5$ subunits did not abolish the antinociceptive effect of diazepam. These results suggest that the $\alpha 2$ and $\alpha 3$ subunits are responsible for the analgesic properties of the BZ. Finally, Knabl and colleagues showed that diazepam lost its antinociceptive effects in the $\alpha 2$ and $\alpha 3$ point mutation mice, whether the diazepam was administered systemically or intrathecally. Based on these results, the authors concluded that systemically administered diazepam works via spinal GABAA receptors.

These results are exciting because they provide the strongest evidence yet that analgesic and sedative effects of BZ are mediated by different receptors. What is not yet fully established, however, is what precisely underlies the analgesia. It is well known that BZ have strong anxiolytic properties that are mediated by the $\alpha 2$ and $\alpha 3$ GABAA subunits. It is also clear, though not generally appreciated, that reducing anxiety, whether behaviorally [4;10] or pharmacologically [3;6;11] is antinociceptive. One could argue that the antinociceptive effects seen following intrathecal injections could result from anxiolysis (i.e. a spillover supraspinal effect). The weight one puts on the results of the intrathecal injection experiments rests in large part on how sure one can be that there is no leakage of spinal CSF to supraspinal sites.

One of the authors of this commentary (L.J.) has personal experience, from humans implanted with intrathecal pumps, that BZ do indeed leak to the supraspinal compartment, causing sedation and anxiolysis. To further resolve this question, it would be reassuring to see electrophysiological studies on spinal cord nociceptive neurons showing changes commensurate with the interruption of nociceptive pathways following intrathecal benzodiazepine application. Previous studies have not been able to document such changes [2]. Future studies that include anxiety measures are also important, as if there were no change in anxiety following intrathecal diazepam in the mice with point mutations of the $\alpha 1$ subunit, then the pure analgesic properties of BZ would be more firmly established.

Despite the caveats above, the possibility of dissociating the antinociceptive effects from other properties of BZ is significant. The results of this study should stimulate a reexamination of the BZ as analgesics and open the field to the development of new classes of drugs targeted to the GABAergic system.

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Figure 1.

Diagram representing the findings of Knabl and colleagues (this issue of Pain) in the mouse and the implications for human pain management. Knabl *et al.* presents evidence that systemic and intrathecal administered BZ act at the spinal level to produce analgesia through the $\alpha 2$ and $\alpha 3$ subunits of the BZ receptor (a subgroup of the GABAA receptors). At the supraspinal level, BZ produce sedation through the $\alpha 1$ subunit and anxiolysis through the $\alpha 2$ and $\alpha 3$ subunits of the receptor. It is not known whether the $\alpha 2$ and $\alpha 3$ subunits of the BZ receptor also have analgesic action at the supraspinal level.