EDITORIAL

N-type Calcium Channel Blocker for Pain Treatment

Chronic pain, including cancer-related pain and neuropathic pain, remains difficult to treat despite many years of extensive preclinical research. Currently, there is a rather short list of medications that can be effectively used to treat chronic pain. One of the clinical issues related to drug therapy is that side effects often develop at or below a drug’s therapeutic level. For example, the n-type calcium channel blocker ziconotide was approved for the treatment of severe pain, but its side effects such as autonomic dysfunction severely limit its clinical utility. Moreover, ziconotide was approved for the intrathecal administration, which also significantly minimizes its clinical availability.

In this issue, Kolosov et al. [1] report that a novel n-type calcium channel blocker leconotide, an agent from the category of \(\omega\)-conotoxin, may have the antihyperalgesic effect as well. They compared the effect of leconotide and ziconotide in a rat model of painful diabetic neuropathy. Three outcomes from this study are of particular interest. First, while leconotide and ziconotide produced a comparable antihyperalgesic effect, the side effect profile of leconotide (locomotor activity and vascular responses) was clearly better than that of ziconotide. Second, leconotide was effective when administered intravenously suggesting an effective alternative delivery method for n-type calcium channel blockers other than intrathecal administration. Third, the effect of leconotide was enhanced by the potassium channel modulator flupirtine at the dose ineffective by itself. This study suggests that leconotide, as a novel n-type calcium channel blocker, may be potentially useful due to its improved side effect profile and new route of drug delivery.

Despite several advantages of leconotide as demonstrated in this study, its potential for clinical use remains to be determined. For example, the agent was tested for a single pain condition using a preclinical model. The leconotide dose that showed no side effects produced slightly better than 50% reduction of hyperalgesia, suggesting that the potential therapeutic window may be limited as well. Moreover, the bioavailability issue was not specifically examined in this study. A potential approach to expanding the therapeutic window of n-type calcium channel blockers may be achieved by the combination of leconotide with a potassium channel blocker (e.g., flupirtine), each at a much lower dose. Nonetheless, this preclinical study raises the possibility that the therapeutic effect of n-type calcium channel blockers may be improved by choosing agents with a more favorable side effect profile and clinically convenient delivery route.

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