Inhibition of astrocyte activation is involved in the prevention of postoperative latent pain sensitization by ketamine and gabapentin in mice

Sir,
The pharmacologic management of postoperative pain has currently a double purpose: On one hand to reduce the intensity of the acute pain after surgery, and, on the other hand, to prevent the development of chronic postsurgical pain. Previous studies have shown that an inhibition of the glial activation is involved in the prevention of postoperative hyperalgesia (POH) by ketamine (KET) and gabapentin (GBP). However, only a few data exist on the involvement of the glial activation in the prevention of the postoperative latent pain sensitization (PS) mediated by KET or GBP.

Because of this, the antihyperalgesic effects of KET and GBP were evaluated in a plantar incision pain model (previously validated in our laboratory in mice, which mimics the characteristics of the postoperative pain in humans. The work was in agreement with both the European Directive 2010/63/EU and the Ethical Guidelines-International Association for the Study of Pain. The protocol was approved by the institutional review board (CEEA-PRBB, Spain). We assessed POH and PS, the later substantiated by naloxone (1 mg/kg) administration. Surgery (incision plus saline, INC + SS group) induced a significant POH in mice at 4h and 1 day. On days 20–21, naloxone, but not saline, administration induced hyperalgesia of a similar magnitude to day 1 [Figure 1]. KET (INC + KET) and GBP (INC + GBP) partially prevented POH at 4h and 1 day (P < 0.001), and PS at 21 day after naloxone (P < 0.001) [Figure 1]. No hyperalgesia was observed in sham-operated animals at any time point (control group, data not shown). Glial immunoreactivity was assessed at day 1, concurring with the period of maximal hyperalgesia, and also on day 21 after saline or naloxone administration. On day 1, the increase in microglia immunoreactivity was prevented by KET and GBP (P < 0.001); neither saline nor naloxone administration on day 21 induced microglia re-activation [Figure 2]. Immunoreactive astrocyte activation on day 1 promoted by surgery was partially prevented by KET and GBP (P < 0.001). The administration of naloxone (but not saline) on day 21, induced astrocyte re-activation, which was partially prevented by both KET and GBP (P < 0.001) [Figure 2] scale bars: panels A and B, 50 μm.

Our findings indicate that the antihyperalgesic effects of KET and GBP, two of the most important adjuvants currently employed in clinical practice to prevent chronic pain after surgery, could be partially mediated by an inhibition of microglia and astrocyte activation. It is known that N-methyl-D-aspartate -nitric oxide (NMDA-NO) pathways are involved in the development of hypersensitivity, and NO promotes glial fibrillary acidic protein expression in surgery. Surgery (incision plus saline, INC + SS group) induced a significant POH in mice at 4h and 1 day. On days 20–21, naloxone, but not saline, administration induced hyperalgesia of a similar magnitude to day 1 [Figure 1]. KET (INC + KET) and GBP (INC + GBP) partially prevented POH at 4h and 1 day (P < 0.001), and PS at 21 day after naloxone (P < 0.001) [Figure 1]. No hyperalgesia was observed in sham-operated animals at any time point (control group, data not shown). Glial immunoreactivity was assessed at day 1, concurring with the period of maximal hyperalgesia, and also on day 21 after saline or naloxone administration. On day 1, the increase in microglia immunoreactivity was prevented by KET and GBP (P < 0.001); neither saline nor naloxone administration on day 21 induced microglia re-activation [Figure 2]. Immunoreactive astrocyte activation on day 1 promoted by surgery was partially prevented by KET and GBP (P < 0.001). The administration of naloxone (but not saline) on day 21, induced astrocyte re-activation, which was partially prevented by both KET and GBP (P < 0.001) [Figure 2] scale bars: panels A and B, 50 μm.

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Figure 1: Effects of ketamine (50 mg/kg) and gabapentin (100 mg/kg) in a murine model of incisional pain. Data expressed as mean ± standard error mean.*P < 0.001 versus baseline; **P < 0.001 versus INC + SS
Thus, the blockade of NMDA by KET could suppress NO liberation by NMDA neuronal receptors through the reduction of astrocyte immunoreactivity. The decrease of spinal glial activation by GBP could be due to an indirect modulation of the neuronal voltage-gated calcium channels α2/δ-1 subunits, concurrent with Ca2+-dependent glutamate release from astrocytes.

To the best of our knowledge, this is the first time that a delayed astrocytic activation, concomitant with a PS partial inhibition, has been shown to be partially prevented by KET and GBP in a model of post incisional pain. Further studies are warranted.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
Research Letter

Romero-Alejo E, Puig MM, Romero A. Inhibition of CGS 8216, a benzodiazepine receptor antagonist, led to subsequent identification of possible endogenous effectors (benzodiazepine endocoids or endozepines) for benzodiazepines. The discovery of specific benzodiazepine site is different from GABA binding site and is specific for modulatory site of GABA receptor.

Benzodiazepines are the drugs that selectively bind to target for the treatment of AD has not been explored in details. The role of other neurological mechanisms, for example, cholinergic, glutamatergic, and cytokine systems (e.g., memantine), has been reiterated the need to find new molecular targets.

In AD, incidence of AD was found to be 11.67% in 55 years of age and above age group and 15.54% in 65 years and above age group. In a study conducted in Southern India, incidence of AD was found to be 11.67% in 55 years of age and above age group and 15.54% in 65 years and above age group.

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Research Letter

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Flumazenil is a benzodiazepine receptor antagonist. It is used to reverse the adverse psychomotor, amnestic, and sedative effects of benzodiazepine receptor agonists.

Previously, effects of flumazenil in memory loss have been studied, but its effect on memory acquisition have been studied, and above age group and 15.54% in 65 years and above age group.

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