male rats, but deteriorated withdrawal in females. Neither sex steroid hormones, nor phytoestrogens changed metamizol analgesic action. Mosaic immunohistochemical effects were revealed.
Conclusion: Increasing pain sensitivity estradiol and phytoestrogens did not decrease metamizol and morphine analgesia. Data show that fluctuations in sex hormone levels should be considered for individualization of analgesic therapy.

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SYNERGISTIC ANALGESIC INTERACTION BETWEEN MORPHINE AND BIM-46187

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BIM-46187 is a new anticancer agent that acts as a modulator of the heterotrimeric G protein complex. Considering that opioids are second and third-line of choice for the pain management of tumor patients and that opioid receptors belong to the large superfamily of G protein-coupled receptors, the possible interaction of BIM-46187 on the analgesic effects of morphine has been studied in experimental models of pain. The interaction between BIM-46187 (i.v.) and morphine (i.p.) was evaluated by isobolographic analysis of analgesia in the carrageenan-induced hyperalgesia (ED50 = 0.42 and 0.61 mg/kg for BIM-46187 and morphine, respectively) and the chronic constriction injury (ED50 = 2.5 and 1.4 mg/kg for BIM-46187 and morphine, respectively) models in rats. In both models the co treatment with the compounds (ratio 1/1) resulted in a synergistic analgesic effect and resulted in a reduction by at least 20 fold in the dose of morphine. In contrast, the co treatment of BIM-46187 and morphine up to 3 mg/kg of each compound did not increase side effect assessed in the rotarod test in rats. A positive interaction on the analgesic effects was also observed in the model of carrageenan induced hyperalgesia when BIM-46187 was associated with fentanyl, another opioid agonist structurally unrelated to morphine. In conclusion, the opioid sparing effect resulting from the synergy observed with the co treatment of BIM-46187 may be clinically relevant during the management of cancer.

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THE NEW ANTICANCER AGENT BIM-46187 ELICITS ANALGESIC PROPERTIES

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BIM-46187 is a new modulator of the heterotrimeric G protein complex, a potential new target in cancer therapy. Cancer is associated to pain syndromes resulting from direct tumour involvement or from cancer-directed therapy. Considering that many mediators of pain act through G protein coupled receptors, the effects of intravenous administration of BIM-46187 were evaluated on different experimental models of pain.
BIM-46187 elicited a dose dependent analgesic effect in the models of carrageenan-induced hyperalgesia (ED50 = 0.42 mg/kg) and of chronic constriction injury (ED50 = 2.5 mg/kg) in rats. Moreover, BIM-46187 (3 mg/kg; i.v.) was also effective in the model of neuropathy induced by taxol in rats. BIM-46187 up to 10 mg/kg modified neither the paw oedema induced by carrageenan nor the motor performance assessed by the rotarod test in rats. In mice, BIM-46187 up to 10 mg/kg was ineffective in the hot plate test suggesting a lack of effect on acute nociception. These results indicate that, unlike other anticancer agents, BIM-46187 possesses analgesic properties and suggest that this effect is due to peripheral action. This property may be beneficial during therapeutic use in oncology especially if BIM-46187 is associated with other anticancer agents inducing neuropathy.

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INVOLVEMENT OF CONNECTIONS BETWEEN THE ANTERIOR PRETECTAL NUCLEUS AND THE DEEP LAYERS OF THE SUPERIOR COLLICULUS IN ANTINOCICEPTIVE PROCESSES

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The aim of this work was to study the physiological role of anterior pretectal nucleus (APtN) and the superior colliculus (SC) neural connections in the antinociception evoked by APtN electrical stimulation. Wistar rats (n-8, per group), weighing 200–250 g, were anaesthetized with sodium pentobarbital (45 mg/kg, IP) and submitted to a stereotaxic surgery for the introduction of guide-cannula glued to a brain electrode aiming at the NPtA and a guide-cannula aiming at the SC. After 5 days of post-operative recovery, the tail-flick baseline was recorded, and the tail-withdrawal latency (TFL) was measured again at 0, 15, 30, 45 e 60 min after the electrical stimulation (100 muA; 15 s) of the APtN. After 24 h, 5.0mug/0.5muL of methysergide, naloxonazine or physiological saline, or ibotenc acid (1.0mug/0.5muL; under anesthesia) were microinjected into the SC, in independent groups of animals and, 10 min after the pharmacological antagonism with methysergide, 24h after naloxonazine administration or 5 days after the neurochemical damage in the SC, the APtN was electrically stimulated, following the TFL recording. The electrical stimulation of APtN caused a statistically significant antinociception with 60 min of duration. This antinociceptive phenomenon decreased after the neurochemical damage of the CS. Both methysergide and naloxonazine microinjected into the intermediate and deep layers of the superior colliculus antagonized the APtN-electric stimulation-induced antinociception. These findings suggest that SC neural substrates, as well as mu1-opioid receptor and serotonergic receptors exert a key-role in the APtN-electric stimulation-induced antinociception.
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PLACEBO EFFECTS IN LASER-EVOKED PAIN POTENTIALS

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Background and Aims: Placebo treatment may affect multiple components of pain, including inhibition of nociceptive input, automatic or deliberative appraisal of pain, or cognitive judgments involved in pain reporting. If placebo analgesia is due in part to an attenuation of early nociceptive processing, then pain-evoked event-related potentials (ERPs) should be reduced with placebo. In this study we tested for placebo effects in P2 laser-evoked potentials at midline scalp electrodes.
Methods: Twenty-four subjects participated in the study. Subjects received painful laser stimuli (1-ms; Thulium YAG infrared laser) on the volar forearm. ERPs were recorded from midline electrodes (FCz, Cz, CPz, Pz). The amplitude of the first major negative (N2) and positive (P2) component was extracted and compared between areas treated with a placebo analgesic cream and a control cream. In reality both creams were ineffective. The treatments differed only in the instructions about expected analgesia given to participants.
Results: We found that placebo treatment produced significant decreases in P2 amplitude, and that P2 placebo responses were large enough to reflect a meaningful difference in nociceptive processing. However, we also found evidence that the very robust placebo-induced decreases in reported pain are not solely explained by early reductions in P2. N2 amplitude was affected by neither placebo nor reduction of laser intensity.
Conclusions: These results suggest that placebo treatment affects early nociceptive processing, but that another component of placebo effects in reported pain occurs later, either in retrospective evaluation of pain or cognitive judgments about pain reports.