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The novel analgesic, F 13640, produces intra- and postoperative analgesia in a rat model of surgical pain

Ivan Kiss [a], Anne-Dominique Degryse [b], Laurent Bardin [b], Ignacio Alvarez Gomez de Segura [c], Francis C. Colpaert [b,*]

[a] *Klinik für Anästhesie, Intensivmedizin und Schmerztherapie, Alfried Krupp Krankenhaus, 45117 Essen, Germany*
[b] *Centre de Recherche Pierre Fabre, 17, Avenue Jean Moulin, 81106 Castres, Cedex, France*
[c] *Department of Experimental Surgery, Hospital Universitario La Paz, Castellana 261, 28046 Madrid, Spain*

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Abstract

F 13640 is a newly discovered high-efficacy 5-HT_{1A} receptor agonist that produces exceptional analgesia in animal models of tonic and chronic, nociceptive and neuropathic pains by novel molecular and neuroadaptive mechanisms. Here we examined the effects of F 13640 and remifentanil (0.63 mg/kg with either compound) when injected i.p. either before or 15 min after rats underwent orthopedic surgery. Surgery consisted of the drilling of a hole in the calcaneus bone and of an incision of the skin, fascia and plantar muscle of one foot. During surgery, the concentration of volatile isoflurane was progressively incremented depending on the animal's response to surgical maneuvers. Other experiments examined the dose-dependent effects of F 13640 (0.04 to 0.63 mg/kg) on surgical pain as well as on the Minimum Alveolar Concentration of isoflurane. Both F 13640 and remifentanil markedly reduced the intra-operative isoflurane requirement. F 13640 also reduced measures of postoperative pain (i.e., paw elevation and flexion). With these postoperative measures, remifentanil produced short-lived analgesia followed by hyperalgesia. F 13640 significantly reduced both surgical pain and the isoflurane Minimum Alveolar Concentration from 0.16 mg/kg onward. F 13640 produced powerful intra- and postoperative analgesia in rats undergoing orthopedic surgery. Unlike the opioid, remifentanil, F 13640 caused no hyperalgesia with ongoing postoperative pain, and should remain effective with protracted postoperative use.
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Keywords: Serotonin; 5-HT_{1A} receptor; Orthopedic surgery; Intra-operative pain; Postoperative pain; Opioid hyperalgesia

1. Introduction

We recently reported on the discovery of the central analgesic, (3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]-methanone (F 13640) that acts by novel molecular and neuroadaptive mechanisms (Colpaert et al., 2002). F 13640 is a new 5-hydroxytryptamine 1A (5-HT_{1A}) receptor ligand that uniquely associates receptor selectivity with the ability to activate 5-HT_{1A} receptors to a very high degree (for structure and receptor binding and efficacy data, see: Colpaert et al., 2002; Wurch et al., 2003). The discovery of F 13640 was guided by a theory of signal transduction in nociceptive systems which specifies that any input to such systems causes not one effect, but two, dual effects that are paradoxical, or opposite in sign (Colpaert, 1996). Thus, opioids produce not only ("1st order") analgesia, but also "2nd order" hyperalgesia. Accounting also for the dynamical, neuroadaptive actions of opioids, the proposed transduction mechanism further explains how, with chronic opioid use, the 2nd order hyperalgesia grows and makes 1st order analgesia decay (i.e., tolerance to opioid analgesia). F 13640 was identified as an agent that should produce the mirror inverse of the effects of opioids. Indeed, in normal rats, F 13640 causes an initial hyperalgesia followed by analgesia. In thus mimicking the effects of nociceptive stimulation (Colpaert et al., 2002; Buritova et al., 2003), F 13640 initiates two remarkable, unprecedented neuroadaptive actions. First, repeated or chronic F 13640 causes an analgesia that grows, rather than decays. Second, F 13640 cooperates with nociceptive stimulation in, paradoxically, causing analgesia. As the result of these actions, the chronic administration of F 13640 causes an analgesia in

* Corresponding author. Tel.: +33 5 34 32 14 24; fax: +33 5 34 32 13 77.
E-mail address: francis.colpaert@pierre-fabre.com (F.C. Colpaert).

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rodent models of chronic nociceptive pain and neuropathic allodynia, that is superior to that, if any, of morphine and of agents exemplifying further central mechanisms of pain relief (Colpaert et al., 2002; Deseure et al., 2003). In the formalin model of tonic nociceptive pain, F 13640 also produces an extent of analgesia that is rivaled only by opioids (Colpaert et al., 2002; Bardin et al., 2003). The possible action of F 13640 on severe, acute nociceptive pain has not been examined so far.

The research presented here was aimed at investigating F 13640's effects on both the intra- and the postoperative pain that is associated with surgery in the rat. To this end, rats underwent a combination of two surgical interventions that have been described earlier (i.e., incision of skin, fascia and plantar muscle of the foot and drilling of a hole in the calcaneus; Brennan et al., 1996; Houghton et al., 1997). The esterase-metabolised, short-acting μ-opioid remifentanil was also studied, as it is often implemented in human anesthesia (Bürkle et al., 1996; Glass et al., 1999). The experiments thus examined the effects of F 13640 and of remifentanil as the agents were administered either pre- or postoperatively. A further experiment determined F 13640's effects on the Minimum Alveolar Concentration of isoflurane in rats exposed to a standardized nociceptive stimulation.

2. Methods

2.1. Experimental animals

Male Sprague–Dawley rats (Iffa Credo, Lyon, France) weighing 180–200 g on arrival were used after a 4–5 day quarantine period; they were housed individually in wire bottom cages measuring 18×31×18 cm (ambient temperature 21±1 °C; relative humidity 55±5%; reversed 12:12 h dark–light cycle, lights on at 6 a.m.). The European Community guidelines for the use of experimental animals were adhered to; the protocol complies with these guidelines and was approved by the institutional Ethical Committee (n° 246). Throughout, experimenters were blinded to the independent variables.

2.2. Vocalization threshold: dose- and time-effect experiments

These two experiments were conducted to define the dose and the time at which F 13640 and remifentanil were to be implemented in the studies of surgical pain. To this end, the Randall and Selitto (Randall and Selitto, 1957) technique was used, as it can express the in vivo pharmacodynamic actions both of F 13640 (which can produce hyperalgesia in this assay; Colpaert et al., 2002) and of opioids (which can produce analgesia; Zhou et al., 1998). The technique determines the vocalization threshold to acute mechanical stimulation; using a Ugo Basile analgesia-meter (Apelex®; probe tip diameter: 1 mm; weight: 20 g; cut-off pressure: 600 *g*), progressively increasing pressure was applied to the left hind paw until a squeak (vocalization threshold, in g) was obtained.

In one experiment, rats (n=7/group) received an intraperitoneal (i.p.) injection of either saline or one of different doses of remifentanil (0.16, 0.31, 0.63, 2.5 and 10 mg/kg), and the vocalization threshold was determined immediately before as well as at stated intervals (Fig. 1A) for up to 60 min after the injection. In a second experiment, rats (n=6/group) received an i.p. injection of either saline or one of different doses of F 13640 (0.04, 0.16 and 0.63 mg/kg), and the threshold was determined before as well as at stated intervals (Fig. 1B) for up to 4 h after the injection.

2.3. Intra- and postoperative pain

2.3.1. Anesthesia and surgery

Anesthesia was induced by isoflurane 2 vol.% in 2 l/min oxygen delivered in a closed induction box. After 3 min, anesthesia was continued by isoflurane 1.5 vol.% provided via a facemask. At this point, surgery was started. In the case the animal made any movement on surgical stimulation, surgery was stopped, the concentration of isoflurane was increased by 0.5 vol.%, and, after 30 s, surgery was resumed whilst maintaining the rats under this new level of anesthesia. The same procedure was repeated and the anesthesia further increased every time a movement occurred. Note that this fixed, 30 s duration of exposure does not guarantee that equilibrium be

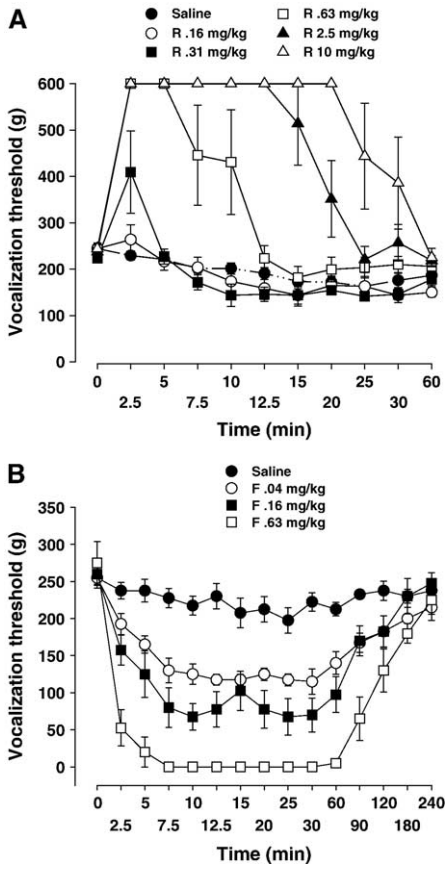

Fig. 1. Dose- and time-dependence of the effects of remifentanil and F 13640 on the mechanical threshold to induce vocalization in rats. In two separate experiments, animals received an i.p. injection of either saline, remifentanil (R; n=7/dose; A) or F 13640 (F; n=6/dose; B), and the threshold for mechanical stimulation (ordinate, in g) to induce vocalization was determined immediately before as well as at stated intervals after the injection. Data are mean±S.E.M.

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