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European Journal of Pharmacology 456 (2002) 51–57

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# The 5-$HT_{1A}$ receptor agonist F 13640 attenuates mechanical allodynia in a rat model of trigeminal neuropathic pain

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Received 15 July 2002; received in revised form 16 October 2002; accepted 22 October 2002

**Abstract**

The effects of acute intraperitoneal injections of the 5-$HT_{1A}$ receptor agonists F 13640 [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]-methadone] and F 13714 [3-chloro-4-fluorophenyl-(4-fluoro-4-[[(5-methyl-6-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl-methanone] were studied in comparison with those of baclofen and morphine on responsiveness to von Frey hair stimulation after chronic constriction injury to the rat's infraorbital nerve (IoN-CCI). Following IoN-CCI, an ipsilateral hyperresponsiveness developed that remained stable in control rats throughout the period of drug testing. F 13640, F 13714, baclofen and morphine dose-dependently decreased the hyperresponsiveness; normalization of the response occurred at doses 0.63, 0.04, 5 and 10 mg/kg, respectively. Confirming earlier data, baclofen's effects further validate IoN-CCI as a model of trigeminal neuralgia. The effects of F 13640 and F 13714 are initial evidence that 5-$HT_{1A}$ receptor agonists produce profound analgesia in the IoN-CCI model. The present data extend recent evidence that high-efficacy 5-$HT_{1A}$ receptor activation constitutes a new mechanism of central analgesia the spectrum of which may also encompass trigeminal neuropathic pain.


*Keywords:* Nerve injury, infraorbital; Allodynia, mechanical; F 13640; 5-$HT_{1A}$ receptor; Baclofen; Morphine

## 1. Introduction

High-efficacy 5-$HT_{1A}$ receptor activation was recently proposed (Colpaert et al., 2002) as a new molecular mechanism of central analgesia. F 13640 [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]-methadone], a selective and very-high-efficacy 5-$HT_{1A}$ receptor ligand, produces profound analgesia in models of tonic (i.e., formalin-induced) and chronic nociceptive pain (i.e., in rats with adjuvant arthritis). Remarkably, and in contrast to the tolerance which develops to opioid analgesia, repeated injection or continuous infusion of F 13640 resulted in an increasingly powerful rather than decaying analgesia. Equally remarkably, F 13640 cooperates with nociceptive stimulation in producing analgesia. These findings were anticipated by a theory of signal transduction in nociceptive systems (Colpaert, 1996; Colpaert and Frégnac, 2001). The theory predicts that these novel neuro-adaptive mechanisms (i.e., inverse tolerance, cooperation) should be induced by some principle that mimics the neurophysiological effects of nociceptive stimulation; the data suggest that high-efficacy 5-$HT_{1A}$ receptor stimulation realizes this principle (Colpaert et al., 2002).

Different mechanisms of analgesic drug action are currently used in the treatment of neurogenic pain. The efficacy of tricyclic antidepressants that inhibit noradrenaline and serotonin re-uptake (e.g., imipramine) has been recognized in several neuropathic pain conditions such as postherpetic neuralgia and diabetic neuropathy (Sindrup and Jensen, 1999), but their usefulness is somewhat impaired by side-effects. Selective 5-HT reuptake inhibitors demonstrate some activity in diabetic neuropathy, but are generally less effective than tricyclic antidepressants (Sindrup and Jensen, 1999; Collins et al., 2000; Attal, 2001). Antiepileptic drugs such as carbamazepine are also used in various neuropathic pain syndromes (McQuay et al., 1995). Although approximately 70% of patients suffering from trigeminal neuralgia experience significant pain relief with carbamazepine, loss of efficacy over time and a high incidence of side-effects, including somnolence, vertigo and nausea, are considerable drawbacks. More recently, gabapentin was introduced as an

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PII: S0014-2999(02)02640-7

alternative showing less side effects (Sist et al., 1997; Khan, 1998; Solaro et al., 1998; Attal, 2001). The effects of F 13640 were studied in rat models of peripheral (i.e., sciatic nerve ligation; Bennet and Xie, 1988) and central neuropathy (i.e., ischemic spinal cord injury; Xu et al., 1992). The analgesic effects of continuous infusion of F 13640 at 0.63 mg/rat/day in either model surpassed those of both of imipramine at 2.5 mg/rat/day and gabapentin at 10 mg/rat/day (and, also those of morphine at 5 mg/rat/day and of ketamine at 20 mg/rat/day), suggesting that high-efficacy 5-$HT_{1A}$ receptor activation may also offer an efficacious treatment of neuropathic allodynia (Colpaert et al., 2002).

Other than tricyclic antidepressants and gabapentin-like anticonvulsants, the GABA-B receptor agonist baclofen is particularly useful in the treatment of trigeminal neuralgia (Attal, 2001; Sindrup and Jensen, 2002). That is, baclofen produced significant pain relief in 70% of patients suffering from typical trigeminal neuralgia (Fromm et al., 1984), but demonstrated little efficacy in other peripheral neuropathies (Attal, 2001). In a rat model of trigeminal neuropathic pain (Vos et al., 1994), baclofen, but not morphine or tricyclic antidepressants, attenuated the allodynia-like behaviour that is observed following a chronic constriction injury of the infraorbital nerve (IoN-CCI; Idänpään-Heikkilä and Guilbaud, 1999); carbamazepine was only effective at doses that induced marked sedation. Baclofen reduced the hyperresponsiveness to mechanical stimulation at doses that did not impair motor coordination in the rotarod test. The lack of effect of the tricyclic antidepressants clomipramine and amitriptyline against hyperresponsiveness in IoN-CCI rats contrasts with earlier data (Ardid and Guilbaud, 1992) demonstrating efficacy of both compounds in the sciatic nerve CCI model. Idänpään-Heikkilä and Guilbaud (1999) argued that anatomical differences between the trigeminal nerve and the sciatic nerve may account for this discrepancy; unlike the trigeminal nerve, which is purely sensory, the sciatic nerve includes a significant motor component. Also, the trigeminal nerve has no functional overlap in the territory innervated by its branches, whereas the saphenous nerve is believed to be involved in the behavioral effects of sciatic nerve damage (Devor et al., 1979; Ro and Jacobs, 1993).

The present study investigated the effects of F 13640 in the IoN-CCI model, and compared those with baclofen, which available data so far suggest to be exceptionally active in the infraorbital nerve model (Idänpään-Heikkilä and Guilbaud, 1999). To further verify the usefulness of high-efficacy 5-$HT_{1A}$ receptor activation, we also examined the effect of F 13714 [3-chloro-4-fluorophenyl-(4-fluoro-4-[[(5-methyl-6-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl-methanone], another 5-$HT_{1A}$ receptor agonist possessing an intrinsic activity only slightly lower than that of F 13640 (Colpaert et al., 2002). Finally, morphine was also included; unlike Idänpään-Heikkilä and Guilbaud (1999), another study (DeMulder et al., 1994) found that morphine dose-dependently decreased the ipsilateral hyperresponsiveness of IoN-CCI rats.

## 2. Materials and methods

### 2.1. Subjects

Male Sprague–Dawley rats (Charles River, $n = 50$, weighing 220–240 g on arrival) were used. They were housed in solid-bottom polycarbonate cages in a colony room ($21 \pm 1$ °C; R.H. $= 38 \pm 9\%$). Water and food were available ad libitum. Rats were kept under a reversed 12:12 h dark/light cycle (lights on at 20 h) and were allowed to acclimate for 6 days to the housing facilities before pre-operative testing. Animals were treated and cared for according to the guidelines of the Committee for Research and Ethical Issues of IASP (1983). The protocol was approved and carried out in accordance with the institutional Ethical Committee guidelines for animal research.

### 2.2. Surgery

The unilateral ligation of the IoN was performed as described elsewhere (Vos et al., 1994). Rats were anaesthetized with pentobarbital (60 mg/kg, i.p.) and treated with atropine (0.1 mg/kg, i.p.). All surgery was performed under direct visual control using a Zeiss operation microscope (× 10–25). The head of the rat was fixed in a stereotaxic frame and a mid-line scalp incision was made, exposing skull and nasal bone. The infraorbital part of the IoN was exposed using a surgical procedure similar to that described elsewhere (Gregg, 1973; Jacquin and Zeigler, 1983). The edge of the orbit, formed by the maxillary, frontal, lacrimal and zygomatic bones, was dissected free. To give access to the IoN, the orbital contents were gently deflected with a cotton-tipped wooden rod. The IoN was dissected free at its most rostral extent in the orbital cavity, just caudal to the infraorbital foramen. Two chromic catgut ligatures (5–0) were loosely tied around the IoN (2 mm apart). To obtain the desired degree of constriction, a criterion proposed by Bennet and Xie (1988) was applied: the ligatures reduced the diameter of the nerve by a just noticeable amount and retarded, but did not interrupt the circulation through the superficial vasculature. The scalp incision was closed using polyester sutures (4–0).

### 2.3. Behavioral testing

Rats were habituated to the test procedure on pre-operative days −4 and −3. Habituation and testing were conducted in a darkened room (light provided by a 60-W red light bulb suspended 1 m above the test area) with a 45-dB background noise. Rats were tested 1 day before surgery and subsequently on post-operative days +24 to +29. As elsewhere (Vos et al., 1994), a graded series of five von Frey hairs (Pressure Aesthesiometer®, Stoelting, Chicago, IL) were used. The force required to bend the filaments was 0.015, 0.127, 0.217, 0.745 and 2.150 g, respectively. The stimuli were applied within the IoN territory, near the center of the vibrissal pad, on

the hairy skin surrounding the mystacial vibrissae. This area was stimulated unilaterally before surgery, and on both sides of the face after surgery, i.e., ipsilateral and contralateral to the side where surgery had been performed. Stimuli were applied in an ascending order of intensity. The ipsilateral and contralateral sides were stimulated in a randomized order for each stimulus intensity within each subject. The scoring system described by Vos et al. (1994) was used to evaluate the response of the rats to the stimulation. The response was observed to belong to one of the following response categories: (score 0) *no response*; (score 1) *detection* = the rat turns the head toward the stimulating object and the stimulus object is then explored; (score 2) *withdrawal reaction* = the rat turns the head slowly away or moves it briskly backward when the stimulation is applied, and sometimes a single face wipe ipsilateral to the stimulated area occurs; (score 3) *escape/attack* = the rat avoids further contact with the stimulus object, either passively by moving its body away from the stimulating object to assume a crouching position against the cage wall, or actively by attacking the stimulus object, making biting and grabbing movements; (score 4) *asymmetric face grooming* = the rat displays an uninterrupted series of at least three face-wash strokes directed toward the stimulated facial area.

Drug effects on the surgery-induced hyperresponsiveness to mechanical stimulation were examined as follows. Each drug was tested in a separate group of animals ($n = 10$ per group). Injections were given i.p. (injection volume: 10 ml/kg), 30 min before the start of behavioral testing. During five consecutive days (i.e. post-operative days +25 to +29), each animal in a group was injected with either vehicle or one of four different doses of the test drug. The order in which these five different treatments were tested differed among animals; a Latin square design was used to ensure that each day all five treatments were tested. An additional group of animals ($n = 10$) received only saline injections during post-operative days +25 to +29.

### 2.4. Drugs and doses

The following drugs were used: F 13714 (0.01, 0.04, 0.16 and 0.63 mg/kg) and F 13640 (0.04, 0.16, 0.63 and 2.5 mg/kg) (Centre de Recherche Pierre Fabre, Castres, France), morphine hydrochloride (0.16, 0.63, 2.5 and 10 mg/kg) (Belgapio, Louvain-La-Neuve, Belgium) and baclofen (0.31, 1.25, 5 and 20 mg/kg) (Sigma, St. Louis, MO). All drugs were dissolved in sterile water within 2 h before administration. Doses refer to the free base weight.

### 2.5. Statistical analysis

The response scores that were obtained here constitute an ordinal variable; therefore median scores for the five von Frey hairs were determined for each rat and at every designated time, and analyzed non-parametrically. Post-operative changes of baseline values before drug treatment were analyzed using the (non-parametric) Wilcoxon signed-rank test. Mechanical stimulation data obtained in animals repeatedly tested with saline during post-operative days +25 to +29 were analyzed by means of the Friedman test. These analyses and those described hereafter were performed separately on data obtained after ipsilateral and after contralateral stimulation. Data obtained in drug-treated groups were also analyzed by means of the Friedman test, followed by the Wilcoxon signed-rank test. However, and perhaps due to the limited variation in score that was allowed (i.e., from 0 to 4), graphic representation of the data using median scores quite poorly reflected the results obtained from the above statistical analyses.

In an attempt to obtain a better coherence between the data's statistical analysis and their graphic representation, mean scores were calculated for each rat at every designated time, and parametric analyses were performed on these means. Post-operative changes of baseline values before drug treatment were analyzed using parametric paired *t*-tests. Mechanical stimulation data obtained in animals repeatedly tested with saline during post-operative days +25 to +29 were analyzed by means of a parametric repeated measures analysis of variance (ANOVA) with days as within-subjects factor. Mechanical stimulation data obtained in drug-treated groups were analyzed using a Latin-square ANOVA with dose (i.e., four different doses of each drug and its vehicle) and day (rats were treated with each of the four different drug doses and with the vehicle on five consecutive days) as within-subjects factors, and sequence (different doses and vehicle were administered in a different order) as between-subjects factor (Winer et al., 1991). Post-hoc comparisons were carried out using Dunnett's test for comparing means with a control mean.

While the non-parametric and parametric analyses yielded essentially identical results, the parametric approach offered a more satisfactory coherence between the analysis

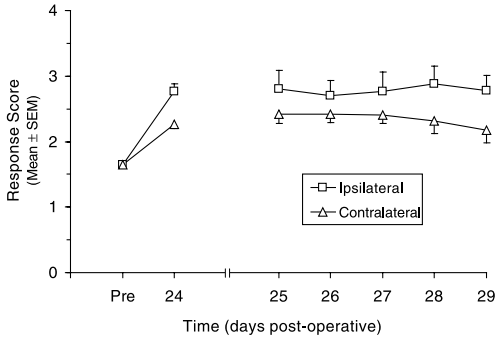


Fig. 1. Time course of the effects of IoN-CCI ligation on responsiveness to mechanical stimulation. Data points represent the mean (± S.E.M.) response score to von Frey hair stimulation of the territory of the ligated nerve (squares: ipsilateral) and of the contralateral side (triangles). The left panel reports the data obtained one day before (pre) and 24 days after surgery from all rats ($n = 50$) that took part in the study. The right panel reports the data obtained on days 25–29 in rats ($n = 10$) that received a daily injection of saline during this time.

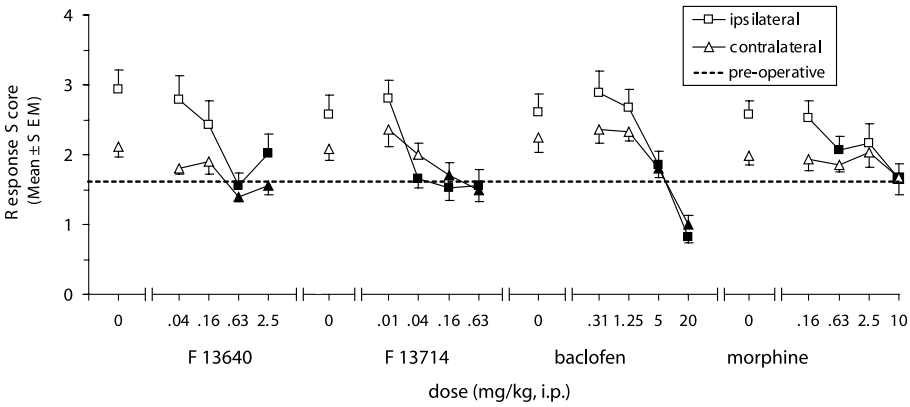


Fig. 2. Effect of F 13640, F 13714, baclofen and morphine on hyper-responsiveness to mechanical stimulation induced by IoN-CCI ligation. Data points represent the mean ($n = 10$ per dose level) (± S.E.M.) response score to von Frey hair stimulation (ordinate) of the territory of the ligated nerve (squares) and of the contralateral side (triangles) as a function of dose (abscissa); the pre-operative responsiveness is represented by the dashed line. Doses at which data were significantly different (Dunnett's test, $P < 0.05$) from the 0-dose (i.e., saline; specified for each drug and each side) are indicated by a closed symbol.

and graphical representation of the data. For this reason, the parametric analysis is detailed below, and the central tendency of the data represented accordingly by means (Figs. 1 and 2). The results of the non-parametric analysis are also provided briefly in the text.

## 3. Results

As indicated in Section 2, the following two paragraphs refer to the results of parametric analysis. Thereafter are reported the results of non-parametric analysis as well as any discrepancies between the two analyses.

Compared with pre-operative values, the IoN injured rats showed a marked increase on post-operative day +24 of responsiveness to ipsilateral mechanical stimulation of the territory of the ligated IoN [$t = 9.03$, $df = 49$, $P < 0.001$] (Fig. 1). The animals also showed increased responsiveness to mechanical stimulation of the territory of the non-ligated, contralateral IoN [$t = 7.61$, $df = 49$, $P < 0.001$]. Difference scores (not shown) between day +24 and pre-operative values, however, were significantly larger for the ipsilateral than for the contralateral side [$t = 4.78$, $df = 49$, $P < 0.001$]. In animals receiving a daily injection of saline, this hyperresponsiveness was stable during the following 5 days (post-operative days +25 to +29); during this period, no significant effect of days was observed either at the ipsilateral [$F(4,36) = 0.26$, NS] nor at the contralateral side [$F(4,36) = 1.16$, NS].

F 13640, F 13714, baclofen and morphine each dose-dependently decreased the hyperresponsiveness to ipsilateral [$F(4,20) \geq 7.33$, $P < 0.001$] and contralateral [$F(4,20) \geq 6.48$, $P < 0.01$] stimulation of the IoN territory, except for morphine at the contralateral side [$F(4,20) = 1.53$, NS] (Fig. 2). All drugs decreased the hyperresponsiveness to the pre-operative level.

Non-parametric analysis similarly showed a significant increase on post-operative day +24 of responsiveness to mechanical stimulation of the territory of both the ligated IoN [$P < 0.001$] and the non-ligated contralateral IoN [$P < 0.001$]. Again similarly to the parametric analysis, post-operative responsiveness to mechanical stimulation was significantly higher at the ipsilateral side than at the contralateral side [$P < 0.001$]. Equally, this hyperresponsiveness was stable in saline-treated animals during the following five days (post-operative days +25 to +29); during this period, no significant effect of days was observed either at the ipsilateral [$P = 0.76$] or at the contralateral side [$P = 0.36$].

F 13640, F 13714, baclofen and morphine each dose-dependently decreased the hyperresponsiveness to ipsilateral [$P < 0.01$] and contralateral [$P < 0.05$] stimulation of the IoN territory, except for morphine at the contralateral side [$P = 0.36$]. These results of non-parametric analysis demonstrate an identical pattern of significance (significance level: 0.05) compared with the results obtained from the parametric analyses. Furthermore, post hoc comparisons using non-parametric Wilcoxon signed rank tests also showed a strikingly similar pattern of significant doses compared with the parametric Dunnett's tests. In fact, at the ipsilateral side, all doses found to be significantly different from saline using non-parametric tests were also found to be significantly different using parametric tests. At the contralateral side, this was also the case except for two doses, i.e., F 13714 at 0.16 mg/kg, and baclofen at 5 mg/kg. The latter were not significantly different from saline according to the non-parametric tests (respectively, $P = 0.057$ and $P = 0.28$), this in contrast to parametric analysis ($P < 0.05$). Thus, only 2 out of 32 post hoc comparisons led to a different result, none of which at the ipsilateral side.

The highest doses of F 13640 and F 13714 induced signs of the so-called 5-HT syndrome (i.e., flat body posture and forepaw treading) and lower lip retraction in all rats tested. Baclofen, at 5 and 20 mg/kg, induced immobility in 3 and 8 out of 10 rats. And morphine, at 10 mg/kg, induced akinesia in all rats.

## 4. Discussion

Confirming previous data (e.g., Vos et al., 1994), loose ligation of the infraorbital nerve induced clear mechanical hypersensitivity in the IoN territory of the rat (Fig. 1); the hyperresponsive state persisted throughout the observation period of 29 days after IoN-CCI surgery. At the contralateral, non-operated side, some degree of hypersensitivity developed as well, but it was less pronounced than that at the ipsilateral side. Vos et al. (2000) have also reported bilateral changes in neuronal activities in the two ventral posterior medial nuclei of the thalamus in the IoN-CCI model, suggesting the involvement of central processing of sensory information. Furthermore, studying the induction of Fos protein-like immunoreactivity in the trigeminal spinal nucleus caudalis following noxious and non-noxious stimulation of the snout of rats with an inferior alveolar nerve transection, Nomura et al. (2002) found that Fos protein-like immunoreactive cells were expressed bilaterally, but were more numerous on the side ipsilateral to transection than on the contralateral side.

In agreement with a previous study (Idänpään-Heikkilä and Guilbaud, 1999), hyperresponsiveness to ipsilateral mechanical stimulation was significantly reduced after a single i.p. injection of baclofen at 5 mg/kg. Since baclofen demonstrates clinical efficacy in patients suffering from trigeminal neuralgia (Fromm et al., 1984; Fromm and Terrence, 1987), this finding further supports IoN ligation as a model of trigeminal neuropathic pain with possible relevance to trigeminal neuralgia. Considering the position and extent of the lesion, and also the apparent differences in symptomatology, the face validity of chronic constriction to the infraorbital nerve as a model of typical trigeminal neuralgia is questionable. In patients suffering from trigeminal neuralgia, the most important etiologic factor seems to be a localized irritation or compression at the level of the posterior root (Fromm and Sessle, 1991) or the ganglion, while in the IoN-CCI model, nerve damage is localized in the infraorbital branch of the trigeminal nerve. However, this does not discard the model's validity as a tool to evaluate potential analgesic drugs for this type of neurogenic pain. Indeed, trigeminal neuralgia-like symptoms, such as allodynia to light tactile stimulation, have been described after distal nerve injury in man (Gregg, 1990a,b); also, several authors (Kerr, 1967; Fromm and Sessle, 1991; Rappaport and Devor, 1990) agree that the key feature of the pathology is a focal lesion resulting from a chronic irritation of the nerve, at any location.

Some differences are apparent between the present study and that by Idänpään-Heikkilä and Guilbaud (1999). In the present study, increases in responsiveness to mechanical stimulation after IoN-CCI were significantly smaller on the contralateral than on the ipsilateral side; Idänpään-Heikkilä and Guilbaud (1999) found no such difference. Also, in the present study, baclofen significantly decreased hyperresponsiveness on both the ipsilateral and the contralateral side; Idänpään-Heikkilä and Guilbaud (1999) observed an effect only on the ipsilateral side. Finally, in the present study—and in agreement with DeMulder et al. (1994)—a significant effect was found for morphine (0.63 and 10 mg/kg, i.p.). Administration of morphine, i.v. at 1 mg/kg produced no significant effect in the study by Idänpään-Heikkilä and Guilbaud (1999).

Some of these discrepancies are perhaps related to procedural differences. Whereas in the present study, responses to mechanical stimulation were quantified using the graded scoring system described by Vos et al. (1994), Idänpään-Heikkilä and Guilbaud (1999) used a threshold to quantify the responses. A specific intensity of stimulation was considered as the mechanical response threshold when the rat performed a brisk withdrawal reaction, an escape/attack reaction or asymmetric face grooming. Although these responses represent the highest scores in the graded scoring system by Vos et al. (1994), in the threshold scoring system, these responses are all considered as nociceptive behaviour and result in the same threshold. In contrast, in the graded scoring system, they are assigned different response scores. As a consequence, if for example an animal displays an escape/attack reaction in response to contralateral stimulation, and asymmetric face grooming in response to ipsilateral stimulation, then using the threshold model, this animal would have equal thresholds for both sides, but different response scores using the response scoring system. Observations from other studies corroborate this viewpoint. Concerning the discrepancy in the responsiveness to contralateral mechanical stimulation, Christensen et al. (1999, 2001) obtained results similar to those of Idänpään-Heikkilä and Guilbaud (1999) using the threshold model. In contrast, Vos et al. (1994) and Vos and Strassman (1995) found similar results as reported in the present study, using the response categories.

Most importantly, the present data offer unprecedented evidence that 5-$HT_{1A}$ receptor activation produces marked analgesia in the IoN-CCI model. Both of the two high-efficacy receptor agonists F 13640 and F 13714, at doses of 0.63 and 0.04 mg/kg onward, respectively, reduced the mechanical hyperresponsiveness to the pre-operative level (Fig. 2). The magnitude of this effect was comparable to that achieved with 5 mg/kg of baclofen and 10 mg/kg of morphine. Like those of morphine, the effects of F 13640 and F 13714 were specific in that neither compound decreased responsiveness to a level lower than that observed pre-operatively. Non-specific effects were only found with baclofen at a dose (i.e., 20 mg/kg) at which it also rendered the animals immobile. The 5-$HT_{1A}$ receptor agonists and morphine also produced behavioral effects, but it is unclear to what extent, if any, these effects influenced the mechanical responsiveness. Repeated injection of the other 5-$HT_{1A}$ receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), induced tachyphilaxis to its ability to induce the 5-HT syndrome, while continuing to inhibit formalin-induced pain behaviors (Bardin et al., 2001).

While the present data are in keeping with F 13640's uniquely powerful effects in rat models of other neuropathic pains (Colpaert et al., 2002), studies implementing chronic drug administration are required to further assess the compound's relative activity in the IoN-CCI model of trigeminal neuropathic pain. Trigeminal neuralgia necessitating chronic treatment, and response normalization in the IoN-CCI model requiring as high a morphine dose as 10 mg/kg (Fig. 2), it is quite conceivable that tolerance may develop to the opioid's ability to alleviate the mechanical hyperresponsiveness. In contrast, the magnitude of the analgesia produced by 5-$HT_{1A}$ receptor activation must be expected to, if anything, increase with chronicity. Large-amplitude 5-$HT_{1A}$ receptor activation presumably (Colpaert et al., 2002) mimics the effects of nociceptive stimulation, and a theory (Colpaert, 1996) of nociceptive signal transduction predicts such activation to induce two remarkable neuro-adaptive mechanisms. That is, inverse tolerance should develop to the analgesia produced by 5-$HT_{1A}$ receptor agonists, and the latter's effects should cooperate with those of nociceptive stimulation in inducing analgesia. This has been observed, for example, in a model of neuropathic pain induced by ischemic injury of the spinal cord, where continuous infusion of F 13640 over two weeks induced an increasingly large analgesia (Colpaert et al., 2002).

In conclusion, the data presented here, to our knowledge, provide the first evidence that 5-$HT_{1A}$ receptor activation produces analgesia in the IoN-CCI model of trigeminal neuropathic pain. Further work is required to assess the usefulness of this novel molecular mechanism in trigeminal neuropathic pain in chronic treatment conditions.

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