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European Journal of Pharmacology 478 (2003) 131–137
www.elsevier.com/locate/ejphar

The very-high-efficacy 5-HT_{1A} receptor agonist, F 13640, preempts the development of allodynia-like behaviors in rats with spinal cord injury

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Received 31 March 2003; received in revised form 18 August 2003; accepted 26 August 2003

Abstract

Central neuropathic pain after spinal cord injury (SCI) presents a challenging clinical problem with limited treatment options. [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]]-methadone (F 13640) is a recently discovered very-high-efficacy, selective 5-HT_{1A} receptor agonist that produces a remarkably powerful, central analgesia through unprecedented neuroadaptive mechanisms. In a rat model of spinal cord injury pain, we previously found that chronic infusion of F 13640 alleviated pain-like behaviors. Here, we report that infusion of 0.63 mg/day of F 13640 for 8 weeks starting 24 h before the induction of injury significantly attenuates the development of chronic allodynia-like behavior in rats sustaining a photochemically-induced, ischaemic injury of the dorsal laminae of the L3–L5 segments of the spinal cord. Importantly, the preemptive effect of F 13640 persisted for 2 months after treatment was discontinued. The data warrant the study of the possible effects of the early administration of F 13640 in patients sustaining spinal cord injury.

Keywords: Analgesia; Neuropathic pain; 5-HT_{1A} receptor; Serotonin

1. Introduction

Many patients with spinal cord injury (SCI) suffer chronic debilitating pain (Loeser, 2000) that arises from levels below, at and above the injury (Siddall et al., 2002). The effectiveness, even of opioid analgesics in neuropathic pain, is controversial (Arnér and Meyerson, 1988; Portenoy, 1996). Opioids allegedly exert an only poor effect in most SCI patients (Finnerup et al., 2002); indeed, central neuropathic pain may respond less to opioids than pain after peripheral nerve injury (Rowbotham, 1999).

Guided by a formal theory of signal transduction in pain processing systems (Colpaert, 1978, 1996; Colpaert and Frégnac, 2001), we recently discovered the new centrally acting, broad-spectrum analgesic, F 13640 [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]-methadone] (Colpaert et al., 2002). F 13640 associates selective affinity for 5-HT_{1A} receptors with the ability to activate those receptors to an extent that is unprecedented with other ligands. These unique molecular features make F 13640 induce novel neuroadaptive mechanisms whereby, in rodents, can be achieved an analgesia that grows rather than decays with chronicity and that is enhanced by the presence of nociceptive input. In particular, in a rat model of SCI, the continuous, 2-week infusion of 0.63 mg/day of F 13640 caused a lasting analgesia with each of the three allodynic responses that were examined. At a dose causing analgesia with acute, nociceptive pain, as well as dependence (Bruins Slot et al., 2002), morphine was ineffective in this model; other agents exemplifying non-opioid mechanisms of central analgesia also failed to produce significant effects with any of the allodynic responses (imipramine, ketamine, gabapentin; Colpaert et al., 2002).

Current concepts distinguish between two, overlapping, types of pain (Woolf, 1989; Ji and Woolf, 2001; Coderre et al., 1993). ‘‘Physiological’’ pain refers to transient sensa-

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doi:10.1016/j.ejphar.2003.08.047

tions that occur in response to noxious stimulation; the sensory apparatus bears similarity with other physiological sensations and produces a sensation that has adaptive significance. ''Pathological'' (e.g., neuropathic) pain develops progressively following nerve injury and loss of sensory input (Jensen, 2002); it may persist for a long time and has no apparent adaptive significance. While treatments so far have been considered for their symptomatic effects, the concept of pathological pain raises the question as to whether such pain can be preempted (Ji and Woolf, 2001). Indeed, some treatments administered prior to or immediately following injury may attenuate the development of pathological pain (Katz et al., 1992; Woolf and Chong, 1993).

As the infusion of 0.63 mg/day of F 13640 causes a comparatively large analgesia in rats with SCI (Colpaert et al., 2002), we here determined whether it may also exert a preemptive action. In this model, rats sustain a lesion of the dorsal laminae of spinal cord segments L3–L5. Over the following months, many animals develop allodynic responses to cutaneous stimulations such as a gentle brush, a cold spray, or von Frey filament application (Hao et al., 1991, 1992; Xu et al., 1992, 2002; Wiesenfeld-Hallin et al., 1996). A similar variability in the delay and extent of allodynia occurs among SCI patients (e.g., Bonica, 1991; Siddall et al., 2002). To minimize variability, in our previous study, we used rats in which, at least 3 months after the injury, allodynia had developed to a marked and stable extent (Colpaert et al., 2002). As such a selection was not possible for the present study, rats here were infused either F 13640 or saline in the first 2 months after injury, and observations were continued for another 2 months thereafter. We hypothesized that although variability might confound the drug's effects during the first 2 months, there might be a better possibility to reveal a drug effect in the further 2 months, and this in spite of the treatment having then been discontinued.

2. Materials and methods

2.1. Photochemically induced ischemic spinal cord injury

Female Sprague–Dawley rats (B&K Universal, Sollentuna, Sweden) weighing 180–210 g at the time of spinal cord injury were used. The experiments were carried out according to the Ethical Guidelines of the International Association for the study of Pain and were approved by the institutional Research Ethics Committee. Ischaemic spinal cord injury was produced as described previously (Hao and Xu, 1996). Briefly, the rats were anesthetized with chloral hydrate (Sigma, 300 mg/kg, i.p.) and one jugular vein was cannulated. Vertebrae T12-L1 were exposed after a midline incision of the skin on the back. The animals were positioned beneath a tuneable argon ion laser (Innova, Model 70, Coherent Laser Products Division) and irradiated with a knife edge beam, which was used to cover the single T13 vertebra; average power was 0.16 W for 10 min. Immediately before the irradiation, Erythrosin B (Red No. 3, Aldrich-Chemie) was injected intravenously in 0.9% saline at a dose of 32.5 mg/kg. Since Erythrosin B is rapidly metabolized, the injection at this dose was repeated at 5-min intervals during the irradiation in order to maintain an adequate concentration. With sham-injured rats, the surgical procedure was performed and the spinal cord irradiation carried out without administration of erythrosine B. (This photosensitizing dye has an optimal absorption wave-length similar to that of the laser light. When it receives this light, a photochemical reaction occurs inside the spinal cord blood vessel where the laser is aimed. One of the reaction products, singlet oxygen, accumulates in the vessel, injuring its endothelial layer and causing platelet release and coagulation and, thus, ischemia.)

2.2. Behavioral testing

A set of calibrated von Frey hairs was used to determine the vocalization threshold to graded mechanical touch/pressure ranging from 0.021 to 410 g. During testing, the rats was gently restrained in a standing position and the von Frey hair was pushed onto the skin until the filament bent. The frequency of the stimulation was about 1 Hz and at each intensity, the stimuli were applied 5–10 times. The intensity of the stimulation that induced consistent vocalization (>75% response rate) was considered as the pain threshold. Although a number of reactions were noted in response to light mechanical stimulation in allodynic rats after spinal cord lesion (e.g., biting, escaping and hindlimb flexion), vocalization was chosen to represent the pain-like response as it was most consistent and easiest to characterize.

The response to brushing was determined by having the blunt point of a pencil gently brushing the rat's skin in a rostral–caudal direction. The frequency of the stimulation was about 1 Hz; responses were graded with a score of 0: no observable response; 1: transient vocalization and moderate effort to avoid the probe, 2: consistent vocalization and aversive reactions and 3: sustained and prolonged vocalizations, aggressive behaviors. Healthy rats exhibit little of no reactions (score 0, sometimes 1).

The response to cold was determinated by spraying ethyl chloride (Medikema, Perstorp, Sweden) on the shaved skin area exhibiting mechanical allodynia. The response was graded with a score of 0: no observable response; 1: localized response (skin twitch and contraction), no vocalization; 2: transient vocalization, moderate struggle and 3: sustained vocalization and aversive reactions. Healthy rats typically obtain a score of 0 or 1.

As elsewhere (Hao and Xu, 1996), the areas being examined with these challenges were the flank, hip, and back, but not the area surrounding the pump.

2.3. Experimental design

Thirty rats were randomly divided into three groups ($n = 10$ per group). Spinal cord injury was produced in two groups and the sham procedure in the remaining group. An osmotic minipump (Alzet 2ML4 releasing a nominal volume of 2.5 μl/h for 28 days) was implanted subcutaneously under the right shoulder blade under chloral hydrate anesthesia. The pump released either 0.63 mg/day of F 13640 (group 1) or saline (groups 2 and 3). On day 28 after their implantation, the pumps were replaced with new 28-day pumps releasing the same solutions. Thus, the total time of pharmacological treatment was 56 days.

Pump implantation occurred prior to the injury. This was because, like other 5-HT_{1A} receptor agonists (De Vry, 1995), F 13640 induces a hypothermia (Bruins Slot et al., 2003) which may perhaps exert unspecific neuroprotective effects (Kline et al., 2001), protecting the animals from injury-induced tissue damage. As with other 5-HT_{1A} receptor agonists, however (De Vry, 1995), F 13640s hypothermic action is transient; in rats, hypothermia does occur upon the implantation of a pump releasing 0.63 mg/day of F 13640, but body temperature then normalizes within 4 h and remains at that level thereafter (Deseure et al., 2003). For this reason, in the present study, rats were implanted with osmotic pumps 24 h prior to surgery, thus leaving ample time for the hypothermia to dissipate before the injury was implemented and its sequellae could develop. Equally, this 24-h period as well as the further 3-day delay before observations were made, allowed for tachyphylaxis to develop to F 13640's motor effects (i.e., signs of the 5-HT syndrome; Bruins Slot et al., 2003).

Beginning on day 3 after surgery, behavioral testing was conducted twice weekly for up till day 110 after surgery. The tests were spaced by at least 2 days and conducted in a blind fashion.

2.4. Further assessments

Motor function during the time of saline or drug treatment was evaluated using a combined motor score described elsewhere (Hao and Xu, 1996).

Also, after the 110-day period of behavioral assessments, five saline- and five F 13640-treated rats were euthanized, and the spinal cord segments containing the lesion as well as two segments above and below the lesion site were dissected out. Fourteen-micrometer sections were cut, stained with cresyl violet, and microscopically examined to assess the rostro-caudal and dorso-ventral extent of the lesion.

Neither the motor nor the microscopic assessments revealed any apparent drug effect, and the data are not reported.

2.5. Statistics

Data are presented (Figs. 1–3) as mean ± S.E.M. and were analysed by means of two-factor analysis of variance (ANOVA) with treatment groups as between-subjects factor and days as within-subjects factor. ANOVAs were performed separately on data obtained while pumps were implanted (i.e., the treatment period; days 3 to 55) and on data obtained after pumps had been removed (i.e., the post-treatment period; days 60–110). As each treatment group was compared with the other groups, the Newman–Keuls test was used for multiple post-hoc comparisons. $P < 0.05$ was considered statistically significant.

3. Results

Inspection of the von Frey (Fig. 1), brush (Fig. 2) and cold challenge (Fig. 3) data reveals that the saline control animals displayed marked pain behaviors (as compared to sham-lesioned rats), and that F 13640 consistently attenuated these. Most importantly, pump-removal failed to make the pain behaviors in formerly F 13640-treated rats develop to an extent comparable to that in saline controls.

3.1. von Frey threshold

ANOVA of data obtained during the treatment period revealed a significant main effect of time ($F[14,378] = 5.82$; $P < 0.001$), but not of group ($F[2,27] = 0.66$; $P = 0.52$); the

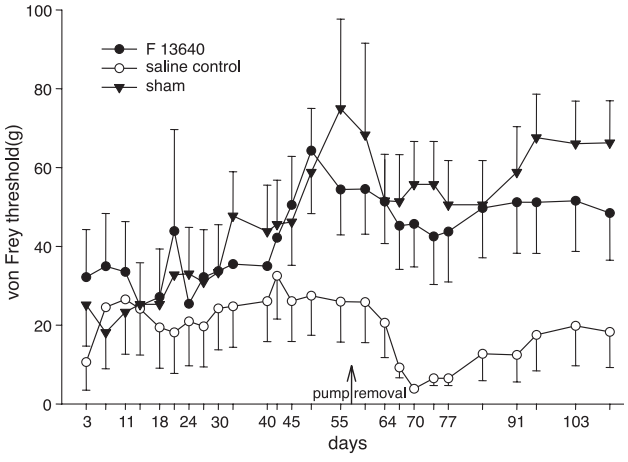

Fig. 1. Effects of F 13640 on the vocalization threshold to stimulation with von Frey hairs in spinally injured rats. Rats were implanted with osmotic pumps releasing either 0.63 mg/day of F 13640 or saline ($n = 10$ per group) and received a photochemically induced ischaemic lesion of the dorsal spinal cord. Treatments continued for in all 56 days, after which pumps were removed. An additional group ($n = 10$) was similarly implanted with a saline pump and underwent a sham procedure. Abscissa: days after injury; ordinate: von Frey threshold (in g). Upon pump removal, the main effects of group and of time were significant ($P < 0.01$), but not the time × group interaction ($P > 0.05$); F 13640 differed from saline ($P < 0.05$), but not from sham. Data points are mean ± 1 S.E.M.

time × group interaction fell narrowly short of significance ($F[28,378]=1.48$; $P=0.058$). Upon pump removal, the main effect of group was significant ($F[2,17]=5.94$; $P<0.01$). *Post hoc* comparisons revealed the F 13640 group to differ ($P<0.05$) from vehicle controls, but not ($P>0.05$) from sham-lesioned animals, while there was also a significant difference ($P<0.05$) between the vehicle control and sham groups. During the post-treatment period, the main effect of time persisted ($F[10,270]=2.85$; $P<0.01$) but, importantly, the time × group interaction was not significant ($F[20,270]=0.48$; $P=0.30$).

The area-under-the-curve (AUC) that was circumscribed by the average data points found after pump removal, amounted to 572,508 and 120 arbitrary units (AUs) in the sham, F 13640-treated/lesioned and saline-treated/lesioned groups, respectively. Thus, at this time, the lesion had reduced the von Frey threshold by 79% in formerly saline-treated, but only by 13% in formerly F 13640-treated animals.

3.2. Brush

During the treatment period, the main effect of both time ($F[14,378]=2.02$; $P<0.025$) and group ($F[2,27]=5.18$; $P<0.025$) was significant. Post hoc analysis revealed a significant ($P<0.05$) difference between the control and sham groups, but not in any other comparison. The time × group interaction was not significant ($F[28,378]=1.21$; $P=0.22$).

During the post-treatment period, the main effect of time ($F[10,270]=2.53$; $P<0.01$) and group ($F[2,27]=18.45$; $P<0.001$) was again significant, and all three groups differed from each other ($P<0.05$). There again was no time × group interaction ($F[20,270]=0.79$; $P=0.072$).

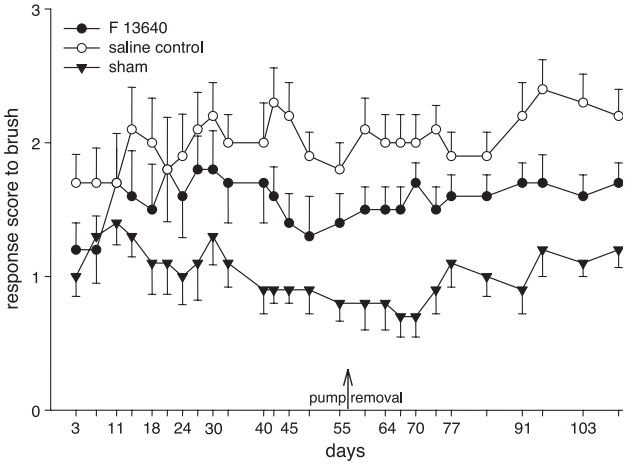

Fig. 2. Effects of F 13640 on the pain-like response induced by tactile stimulation (brush) in spinally injured rats. Ordinate: response score; scores varied from 0 to 3. Upon pump removal, the main effects of group ($P<0.001$) and of time ($P<0.01$) were significant but not the time × group interaction ($P>0.05$); F 13640 differed from both saline and sham ($P<0.05$). See also legend to Fig. 1.

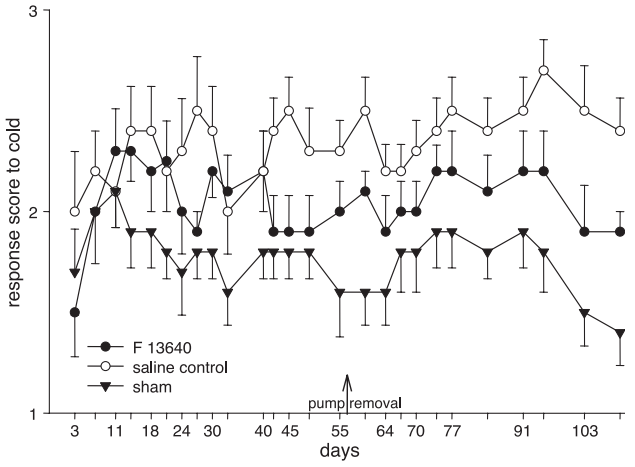

Fig. 3. Effects of F 13640 on the pain-like response induced by cold stimulation in spinally injured rats. Upon pump removal, the main effects of group ($P<0.01$) and of time ($P<0.01$) were significant but not the time × group interaction ($P>0.05$); F 13640 differed from neither saline nor sham ($P>0.05$). See also legend to Figs. 1 and 2.

The AUC after pump removal amounted to 91,162 and 215 AUs in the sham, F 13640-treated/lesioned and saline-treated/lesioned groups, respectively. Thus, the lesion by this time had increased the response to brush to 236% in formerly saline-treated, but only to 178% in formerly F 13640-treated animals.

3.3. Cold challenge

During both the treatment and the post-treatment periods, the main effect of time ($F[14,378]=1.88$; $P<0.05$ and $F[10,270]=2.84$; $P<0.0025$, respectively) and of group ($F[2,27]=3.55$; $P<0.05$ and $F[2,27]=7.92$; $P<0.0025$, respectively) was significant, but not the time × group interaction ($F[28,378]=1.08$ and $F[20,270]=0.80$; $P=0.35$ and $P=0.71$, respectively). During both periods, there was a significant ($P<0.05$) difference between the vehicle control and sham groups, but not in any other comparison.

The AUC after pump removal amounted to 180,215 and 243 AUs in the sham, F 13640-treated/lesioned and saline-treated/lesioned groups, respectively. Thus, the lesion by this time had increased the response to cold to 135% in formerly saline-treated, and to 119% in formerly F 13640-treated animals.

4. Discussion

The data indicate that F 13640 produces preemptive analgesia with some allodynia-like behaviors that develop upon SCI in the rat. Animals were treated with 0.63 mg/day of F 13640 for 56 days, a period that covers much of the post-injury time that is required in this model for allodynia-like behaviors to develop and stabilize at a long-lasting,

perhaps permanent asymptote (Hao et al., 1991; Xu et al., 1992; Wiesenfeld-Hallin et al., 1996). Upon the discontinuation of F 13640 treatment, pain behaviors (i.e., the threshold to von Frey—and the response to brush stimulation; Figs. 1 and 2) were attenuated. Upon this discontinuation, the responses also failed to amplify for up to 2 months, i.e., a length of time that is required for these behaviors to otherwise develop early upon the injury. Specifically, after pump removal, none of the three parameters demonstrated a significant time × treatment interaction, implying that formerly F 13640-treated animals failed to then further develop a pain behavior in any manner different from formerly saline-treated and, also, sham animals. These data indicate that F 13640's preemptive action is long-lasting.

It is useful to note that relative to sham animals, the 0.63 mg/day dose of F 13640 did not fully restore responsiveness, at least to the brush and cold challenges. However, F 13640's effects are dose-dependent, typically achieving full analgesia at appropriate doses (Colpaert et al., 2002; Deseure et al., 2002). Thus, it is likely that a higher dose would have produced an equally full effect in the present conditions.

F 13640's preemptive action was such that the compound's effects (von Frey and brush, not cold) were significant for the 2-month period that followed the discontinuation of treatment, but not while the treatment was implemented. As pointed out above (Introduction), this can be understood from the fact that the previous study in which F 13640 inhibited all three parameters was conducted in selected animals in which, 3 months after the injury, a little-variable and large allodynia had developed (Colpaert et al., 2002). The necessarily larger variability in the present data also accounts for the absence of a significant difference with the cold challenge between saline and F 13640 in the post-treatment period; this is in spite of each of the 11 post-drug data points being lower than the corresponding post-saline points (Fig. 3).

It is unlikely that F 13640's preemptive effect is due to the drug's persisting presence; circulating plasma levels of F 13640 in rats similarly implanted with a pump releasing 0.63 mg/day, reach asymptote some 24 h after pump implantation, and then remain stable (at about 80 ng/ml). Upon pump ex-plantation, the plasma level drops below the 0.1 ng/ml detection limit within 3 days (unpublished observations).

It is also unlikely that the preemptive effect was due to a possible, unselective, neuroprotective action of F 13640. As indicated above (Materials and methods), the study design avoided that the F 13640 produced its transient hypothermic action at the time that the injury was implemented and, thereby, avoided the neuroprotection which hypothermia can provide (Corbett and Thornhill, 2000). Also, evaluations of the motor function that is impaired in thus injured rats (Hao and Xu, 1996) and microscopic determination of the volume of tissue damage failed to reveal any difference between saline- and F 13640-treated rats (not shown). This is consistent with findings that the development of allodynia in this model does not correlate with lesion size (Xu et al., 1992). The above finding does not exclude the possibility that some selective, unidentified neuroprotective action did occur with F 13640. Such an action has been observed with 5-HT_{1A} receptor agonists in other experimental conditions, though it is uncertain to what extent hypothermia might have been involved (Kline et al., 2001).

Such manipulations as spinal disinhibition, local nerve anesthesia, the blockade of NMDA receptors and the activation of α_2-adrenoceptors and opioid receptors have previously been found to exert preemptive actions in models of peripheral neuropathic pain (Seltzer et al., 1991; Mao et al., 1992; Puke and Wiesenfeld-Hallin, 1993; Smith et al., 1993). The present data to our knowledge constitute the first evidence, however, of a preemptive action in a pain model of SCI-induced pain. The data are reminiscent, though, of findings in a model of trigeminal neuropathic pain. There, rats sustained a constriction of the infraorbital nerve and were implanted with a pump releasing 0.63 mg/day of the compound. During the following 2-week period, F 13640 inhibited allodynia-like behavior; the effect persisted 6 days after pump removal (Deseure et al., 2003).

The cellular and neurophysiological mechanisms and pathways whereby F 13640 exerts its pre-emptive action remain to be identified. It is thought that several plastic changes occur during the development of SCI pain (Yezierski, 2002). The hypersensitivity that develops early after even minor injury (Hao et al., 1991, Wiesenfeld-Hallin et al., 1996) may involve the loss of inhibition exerted by spinal gamma-amino butyric acid (GABAergic) neurons (Hao et al., 1991, 1992; Zhang et al., 1994) that are susceptible to ischaemia (Sloper et al., 1980; Zhang et al., 1994); it is unclear, however, how 5-HT_{1A} receptor stimulation may interfere with these GABAergic neurons. SCI also reduces 5-HT immunoreactivity in dorsal and ventral spinal cord (Faden et al., 1988); conceivably therefore, F 13640 compensates for a possible loss of serotonergic tone at 5-HT_{1A} receptors. Indeed, Jensen (2002) points out that the development of neuropathic allodynia is preceeded by a loss of sensory input. Behavioral evidence indicates that 5-HT_{1A} receptor activation in normal animals causes hyperalgesia (Millan et al., 1989, 1991; Colpaert et al., 2002), and F 13640 has been shown to exert the several, intricate effects that are to be expected (Colpaert, 1996) from an agent that presumably mimics the central effects of nociceptive stimulation. Thus, conceivably, the development of neuropathic allodynia is not only preceeded, but perhaps also caused by an injury-induced loss of sensory input that can possibly be compensated for by 5-HT_{1A} receptor stimulation (i.e., by a loss for which this stimulation would substitute).

In conclusion, the present data indicate that infusion of F 13640 preempts the development of chronic allodynia-like behaviors in spinally injured rats. Further research is re-

quired to identify the cellular and neurophysiological mechanisms of this preemptive action.

Acknowledgements

This study was supported by the Centre de Recherche Pierre Fabre, the Swedish Science Council, the Clinical Research Center of Huddinge University Hospital and the Research Fund of the Karolinska Institutet.

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