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European Journal of Pharmacology 395 (2000) 113–119

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An acute i.c.v. infusion of leptin has no effect on hypothalamic histamine and *tele*-methylhistamine contents in Wistar rats

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Received 20 December 1999; received in revised form 2 March 2000; accepted 28 March 2000

Abstract

The actions of intracerebroventricularly (i.c.v.) infused leptin on food intake, body weight and hypothalamic contents of histamine and *tele*-methylhistamine, the main histamine metabolite in the mammalian brain, were studied in male Wistar rats. The effect of the histamine H_1 receptor blockade on leptin-induced anorexia was also examined. It was found that leptin at the dose of 10 μg i.c.v. reduced 24-h food intake by 48% as compared with the controls ($P < 0.01$). This leptin dose reduced feeding during 2–4 consecutive days. In spite of the marked changes in food consumption and body weight gain, leptin did not alter the hypothalamic contents of histamine and *tele*-methylhistamine. Furthermore, the blockade of histamine H_1 receptors by mepyramine did not attenuate the effect of leptin on feeding and body weight. The findings indicate that centrally administered leptin suppresses feeding and promotes weight loss through mechanisms that do not require the direct participation of the brain histaminergic neuron system.

Keywords: Food intake; Histamine; Hypothalamus; (Intracereboventricular infusion); Leptin; *Tele*-methylhistamine

1. Introduction

Leptin, a product of the *ob* gene (Zhang et al., 1994), is secreted by the adipose tissue. It conveys information on the size of energy stores to the brain and activates hypothalamic centers that regulate energy intake and expenditure. Leptin regulates feeding behaviour by reducing food consumption (Schwartz et al., 1996). The majority of studies investigating leptin-sensitive control of food intake have focused on neuropeptide Y, a powerful appetite stimulator (Sahu, 1998). The concentration of neuropeptide Y is elevated in the hypothalamus of genetically obese rats and mice, and its synthesis and release are decreased by leptin (Stephens et al., 1995; Schwartz et al., 1996). However, neuropeptide Y knockout mice are responsive to leptin (Erickson et al., 1996), indicating that neuropeptide Y is not the only neurotransmitter that mediates the effects of leptin on food intake. Furthermore, it has recently been reported that the short-term anorectic effect of leptin is not directly related to neuropeptide Y release (Beck et al., 1998). The present data suggest that the melanocortin system (Seeley et al. 1997; Kask et al. 1998) and corticotropin releasing hormone (Uehara et al. 1998) may be involved in the anorexigenic effect of leptin. In addition to neuropeptides, many biogenic amines, such as histamine, participate the control of food intake, but the relationship between leptin and the various biogenic amines is poorly understood.

Intracerebroventricular (i.c.v.) injection of histamine has been shown to suppress food consumption in rats (Machidori et al., 1992; Lecklin et al., 1998), cats (Clineschmidt and Lotti, 1973) and goats (Tuomisto and Eriksson, 1979). Inhibition of histamine catabolism by metoprine can also reduce food intake (Lecklin and Tuomisto, 1998). Brain histamine appears to modulate feeding via the histamine H_1 receptors. A centrally administered histamine H_1 receptor agonist suppressed food consumption in rats, whereas an i.c.v. infusion of a histamine H_2 receptor agonist had no effect (Lecklin et al., 1998). Pretreatment with histamine H_1 receptor blockers antagonized the effects of

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00266-1

both histamine and the histamine H_1 receptor agonist on food intake (Lecklin et al., 1998). The histamine H_3 receptor is a presynaptic autoreceptor that modulates the release and synthesis of histamine (Arrang et al. 1983). Thus, thioperamide, a selective H_3 antagonist, suppressed food intake by enhancing the release of histamine. Its effect on feeding was abolished by pretreatment with a histamine H_1 receptor blocker (Sakata et al. 1990). An increase in the extracellular histamine level in rat hypothalamus after a meal has been demonstrated (Itoh et al., 1991), which is evidence that histaminergic neurons alter their activity in response to feeding.

Here we have studied the relationship between leptin and histaminergic systems by evaluating the effects of central administration of leptin on food intake, body weight and hypothalamic contents of histamine and *tele*-methylhistamine, which is the main metabolite of histamine in the mammalian brain (Schwartz et al., 1971). The effect of histamine H_1 receptor blockade on leptin-induced suppression in food consumption was also studied.

2. Materials and methods

2.1. Animals

In this study, 75 male Han:Wistar rats, weighing 274 ± 34 g (mean ± S.D.) at the start of experiment, were used. The rats were adapted to a 12 h/12 h reversed light–dark cycle (lights off from 8.30 a.m. to 8.30 p.m.) for two weeks before surgical operations. The animals were housed in stainless steel wire mesh cages in a temperature-controlled room (20 ± 1°C) with relative air humidity 40–60%. During the experiment, the rats were kept in plastic metabolic cages (Tecniplast® 3700 or 3701) and unless otherwise specified, they had free access to tap water and R36 rat feed (Lactamin, Södertälje, Sweden). In the metabolic cages, the feed was given in a powdered form. The study was approved by the Kuopio provincial government.

2.2. Chemicals

Recombinant mouse leptin was a gift from Eli Lilly and Co. (Lilly Corporate Center, Indianapolis, IN, USA). Leptin was dissolved in saline for i.c.v. infusions. Pargyline hydrochloride (Sigma, St. Louis, MO) and mepyramine maleate (Sigma) were also dissolved in saline. Pargyline was administered intraperitoneally (i.p. at the volume of 1 ml/kg). Mepyramine was delivered with osmotic minipumps (ALZA Pharmaceuticals, Palo Alto, CA).

2.3. Surgical procedure

Rats were anaesthetized with chloral hydrate (350 mg/kg i.p.). A stainless steel cannula (22-gauge) was implanted above the third ventricle to the depth of 2.5 mm from the cortical surface at a point on the midline 4.3 mm posterior to the bregma, according to the atlas of Paxinos and Watson (1986). The guide cannula was fixed to the skull with screws and dental acrylic cement (De Trey Dentsply, UK). A stainless wire stylet was placed in the guide cannula. The skin around the cannula was sutured and the rats were allowed to recover for 1 week before the experiments began. During this period, the animals were accustomed to the metabolic cages where food consumption could be measured.

2.4. Experimental procedures

In the first part of the experiment, the effects of leptin on food consumption and body weight were studied with 21 rats (7 rats/group). In the morning of the test day (just before the dark onset), leptin (5 or 10 μg/rat) was infused into the third ventricle at a rate of 5 μl/min. The infusion volume was 5 or 10 μl, and the control animals received saline. Immediately after the drug administration, the rats were returned to their home cages and food consumption was measured 1, 2, 3, 4, 6, 8, 12 and 24 h after the drug administration. The food intake and body weights were then measured every morning for four consecutive days. After the experiment, dye (Cresyl violet) was infused through the cannula to verify the position of the infusion cannula. Subsequent histological analysis revealed the correct position of the infusion cannula in all rats tested.

In the second part of the study, the animals were kept without food but they had free access to water. The effect of leptin on histamine turnover was determined from *tele*-methylhistamine accumulation after injection of pargyline, an inhibitor of monoamine oxidase B. Rats were assigned to four groups (10 rats /group): (1) pargyline (i.p) + saline (i.c.v.), (2) pargyline (i.p.) + leptin (i.c.v.), (3) saline (i.p.) + saline (i.c.v.), (4) saline (i.p.) + leptin (i.c.v.). In the morning of the test day, pargyline at the dose of 70 mg/kg or saline was injected i.p. to rats 30 min before the i.c.v. infusion of leptin (10 μg/rat) or saline. Half of the rats in all experimental groups were decapitated 3 h after the pargyline/saline administration. The remainder of the animals were given another dose of pargyline (50 mg/kg i.p.)/saline 5 h after the first one. These rats were killed 10 h after the first injections. After decapitation, the skulls were cooled in liquid nitrogen. Hypothalami were dissected on ice according to Glowinski and Iversen (1966), and the brain samples were frozen in liquid nitrogen and stored at −70°C until histamine and *tele*-methylhistamine assays.

In the third part of the study, the effect of the H_1 receptor blockade on leptin-induced anorexia was assessed. The histamine H_1 receptor blocker, mepyramine, has a relatively short duration of action compared that of leptin (Babe and Serafin, 1996). Therefore, mepyramine was delivered with osmotic minipumps. The minipumps had

200-μl reservoir (Model 2002), designed to provide continuous infusion for 14 days at a rate of 0.5 μl/h. Rats received mepyramine at a daily dose of 5 mg/kg or saline as a subcutaneous infusion ($n = 5–6$ rats/group). To avoid another anesthesia during the experiment, the minipumps were implanted at the same time as the i.c.v. guide cannula. After one week, leptin (10 μg/rat) or saline was infused into the third ventricle and food consumption was measured 1, 2, 3, 4, 6, 8, 12 and 24 h postinfusion. The food intake and body weights were then measured every morning for four consecutive days. After the experiment, dye was infused through the cannula to verify the correct position of the infusion cannula. The histological analysis confirmed later that the infusion cannula had been correctly implanted in all rats.

2.5. Histamine and tele-methylhistamine assays

Hypothalami were homogenized by sonication (Soniprep 150 ultrasonic disintegrator) in 1.0 ml of 0.4 N perchloric acid containing 5 mM EDTA. The homogenate was centrifuged at $100\,000 \times g$ for 40 min at +4°C and the supernatant was used for the assays. Histamine was measured by high performance liquid chromatography utilizing ion exchange separation, post column derivatization and fluorescence detection (Yamatodani, 1991). *tele*-Methylhistamine was determined by gas chromatography-mass spectrometry (Hough et al., 1981) with some modifications (Tuomisto et al., 1996).

2.6. Open-field test

Increased drowsiness is a common side effect of the first generation histamine H_1 receptor blockers (Babe and Serafin, 1996). Since drowsiness may interfere with feeding studies, the possible sedative effect of the mepyramine treatment was estimated by measuring the locomotor activity of rats in an open-field. This is a white circular arena (inside diameter 83 cm, divided into 19 equal areas, with 40 cm high walls). The frequency of ambulation and rearings were manually recorded. Each rat was tested twice for 5 min. The first test was performed one day before the leptin infusion. The test was performed at the end of dark phase (between 7 and 8 p.m.). The second test was performed at the end of light phase (between 7 and 8 a.m.) just before the i.c.v. infusions of leptin.

2.7. Data analysis

The data are presented as the mean ± S.E.M. Data were analyzed by repeated measures analysis of variance. Then the statistical differences between groups were analyzed by one-way analysis of variance followed by the post hoc comparisons with the test of Scheffe. When the presumptions of the one-way analysis of variance were not fulfilled, the non-parametric Kruskal–Wallis test, followed by Mann–Whitney *U*-test, was used.

3. Results

3.1. Food intake and body weights after leptin treatment

Fig. 1 shows cumulative 24-h food intakes in the leptin and saline treated groups. Leptin at the dose of 10 μg decreased feeding already 2 h after its i.c.v. infusion (Fig 1). It suppressed food intake during the first postinfusion day by 48% ($P < 0.01$) in comparison to the saline treated controls. This leptin dose markedly reduced feeding for four consecutive postinfusion days (Fig. 2A). A significant reduction in body weight was also observed in rats receiving 10μg leptin (Fig. 2B). The lower leptin dose (5 μg i.c.v.) had less pronounced effects. It significantly reduced food consumption during the second postinfusion day ($P < 0.01$) (Fig. 2A), but food intake during the first day was 86% (n.s.) of that of the controls (Fig. 1). This leptin dose had no effect on body weight (Fig. 2B).

3.2. Hypothalamic contents of histamine and tele-methylhistamine

In the control animals, the hypothalamic contents of histamine and *tele*-methylhistamine are in agreement with previous reports (Oishi et al., 1983; Sakata et al., 1994; Tuomisto et al., 1996). Inhibition of monoamine oxidase B

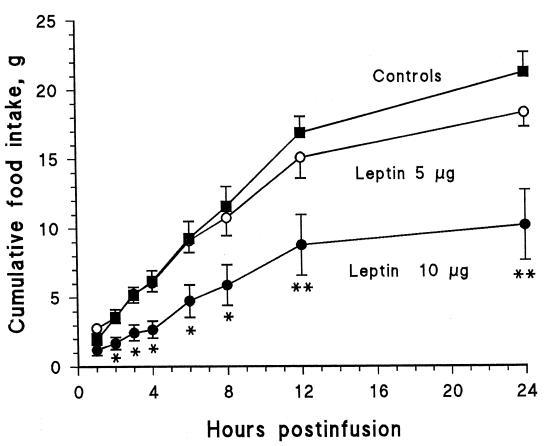

Fig. 1. Cumulative food consumption during the 24-h period after a single i.c.v. infusion of either recombinant mouse leptin (5 and 10 μg/rat) or saline (controls) in male Wistar rats. Each point represents the mean ± S.E.M. ($n = 7$). Repeated measures analysis of variance indicated a significant group effect ($P < 0.001$) in food intake. Significantly different from the control group: $^{*}P < 0.05$, $^{**}P < 0.01$ (Scheffe's test).

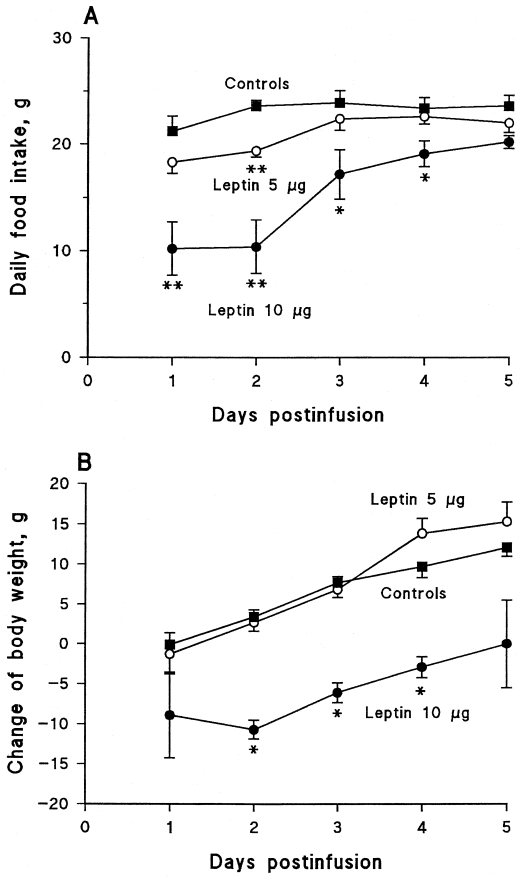

Fig. 2. (A) Daily food consumptions and (B) changes in body weight in rats treated with a single i.c.v. infusion of recombinant mouse leptin (5 and 10 μg/rat) or saline (controls). Each point indicates the mean ± S.E.M. ($n = 7$). Repeated measures analysis of variance indicated a significant group effect in food intake ($P < 0.001$) and body weight ($P < 0.01$). Significantly different from the control group: $^{*}P < 0.05$, $^{**}P < 0.01$ (Mann–Whitney's U-test). The control values for the daily food intake in saline, 5 or 10 μg leptin treated groups were 21.4 ± 1.4, 20.2 ± 0.7 and 22.0 ± 1.0 g, and for the body weights 298 ± 16, 248 ± 41 and 269 ± 31 g, respectively.

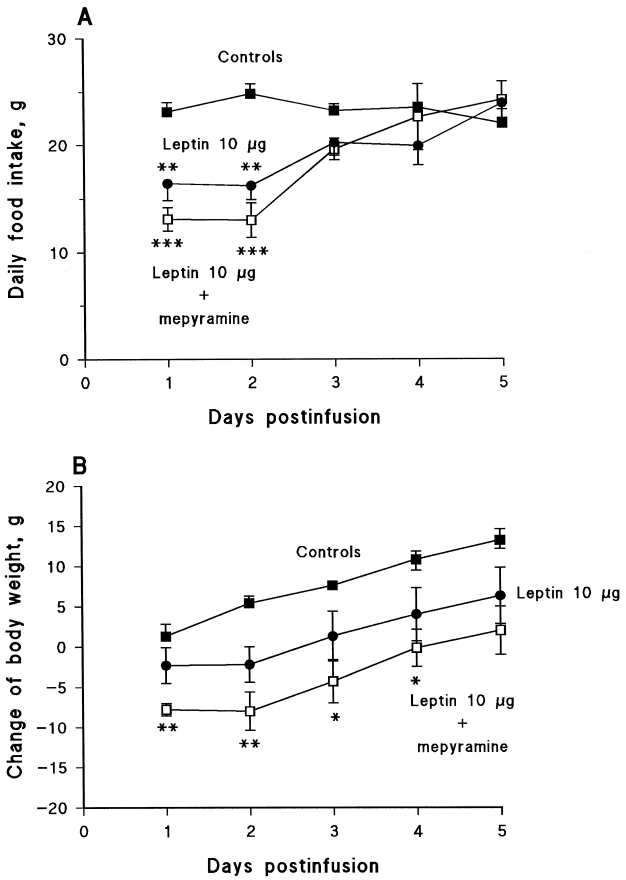

Fig. 3. (A) Daily food consumptions and (B) changes in body weight in saline or mepyramine (5 mg/kg per day in osmotic minipumps) pretreated rats after a single i.c.v. infusion of recombinant mouse leptin (10 μg/rat) or saline (controls). Each point indicates the mean ± S.E.M. ($n = 5$–6). Repeated measures analysis of variance indicated a significant group effect in food intake ($P < 0.01$) and body weight ($P < 0.01$). Significantly different from the control group: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Scheffe's test). The control values for the daily food intake in saline, leptin and mepyramine + leptin treated groups were 22.0 ± 2.9, 23.9 ± 4.0 and 24.1 ± 3.9 g, and for the body weights 309 ± 17, 305 ± 26 and 300 ± 18 g, respectively.

by pargyline produced significant increases in the hypothalamic *tele*-methylhistamine content measured 3 and 10 h after pargyline injection (Table 1). Inhibition of the activity of monoamine oxidase B had no effect on the hypothalamic content of histamine (Table 1). In spite of the

Table 1
Hypothalamic contents of histamine and *tele*-methylhistamine after i.c.v. administration of leptin (10 mg) in saline and pargyline pretreated rats 3 and 10 h after pargyline administration
Values are mean ± S.E.M. ($n = 5$). Values marked with superscript 'a' differ significantly from the control group $P < 0.001$. Values marked with superscript 'b' differ from the leptin treated group ($P < 0.001$) and those marked with superscript 'c' differ from the respective values 3 h after pargyline administration $P < 0.01$ (Scheffe's test).

	3 h		10 h	
	Histamine (nmol/g)	*tele*-Methylhistamine (nmol/g)	Histamine (nmol/g)	*tele*-Methylhistamine (nmol/g)
Controls	3.70 ± 0.46	0.65 ± 0.06	3.95 ± 0.45	0.75 ± 0.10
Leptin	3.74 ± 0.54	0.64 ± 0.08	4.53 ± 0.32	0.68 ± 0.10
Pargyline + saline	4.49 ± 0.44	1.76 ± 0.05[a]	4.82 ± 0.39	2.53 ± 0.09[a,c]
Pargyline + leptin	3.94 ± 0.32	1.71 ± 0.04[a,b]	4.42 ± 0.34	2.49 ± 0.19[a,b,c]

Table 2
Five min rearings and ambulation in rats treated with saline or mepyramine (5 mg/kg per day) before i.c.v. administration of leptin (10 μg) Values are mean ± S.E.M. ($n = 6$).

	Dark phase (7–8 p.m.)		Light phase (7–8 a.m.)	
	Rearings	Ambulation	Rearings	Ambulation
Saline	39 ± 3	88 ± 6	27 ± 4	64 ± 9
Mepyramine 5 mg/kg per day	33 ± 5	92 ± 8	22 ± 3	77 ± 8

marked changes in food consumption, i.c.v. administration of 10 μg leptin caused no change in the hypothalamic contents of histamine and *tele*-methylhistamine when compared with those in saline treated groups (Table 1).

3.3. The effect of the H_1 receptor blockade on leptin-induced anorexia

There was no difference between mepyramine and saline treated rats in the food consumption measured one day before i.c.v. infusion of leptin. The leptin-induced decrease in food consumption was not attenuated by the blockade of histamine H_1 receptors by mepyramine. Mepyramine rather tended to supplement the food intake and body weight suppressive effects of leptin, although this effect was not statistically significant (Fig. 3A and B).

3.4. The effect of H_1 receptor blockade on the locomotor activity in the open field test

There were no differences in ambulation and rearings between mepyramine (5 mg/kg per day) and saline treated rats in the open field test (Table 2).

4. Discussion

The present study shows that an infusion of leptin into the third cerebroventricle potently suppresses food intake and body weight in ad libitum fed rats. Such an acute leptin infusion resulted in a decrease in food intake and body weight that persisted for 2–4 days. The finding is in agreement with the previous observations (Schwartz et al., 1996; Mistry et al., 1997).

Genetically obese Zucker (*fa/fa*) rats, which have a point mutation in the gene encoding the leptin receptor (Takaya et al., 1996) and are therefore resistant to the actions of leptin (Cusin et al., 1996), have a defect also in the hypothalamic histamine formation (Machidori et al., 1992). Histamine administration does not reduce food intake in this genetically obese rat strain as it does in their lean littermates (Machidori et al., 1992), suggesting that there could be an interaction between the histaminergic neuron system and leptin. Although brain histamine seems to be one of the many transmitters involved in the control of food intake, its importance in the regulation of feeding has not been clarified. It has previously been shown that the blockade of histamine H_1 receptors elicits a transient feeding response by abolishing the inhibitory action of endogenous histamine on feeding (Ookuma et al., 1989). Therefore, a role for histamine as a satiety agent, similarly to that of leptin, has been proposed (Ookuma et al., 1989). Since histamine is involved in the control of circadian rhythms (Schwartz et al., 1991), this amine may also influence food intake by modifying the circadian rhythms of feeding (Doi et al., 1994; Lozeva et al., 2000).

The present study suggests, that the effect of leptin to suppress feeding after its i.c.v. administration does not directly involve brain histaminergic mechanisms. There was no change in the hypothalamic histamine and *tele*-methylhistamine levels determined 2.5 and 9.5 h after i.c.v. infusion of leptin (i.e. 3 and 10 h after administration of pargyline). However, a contradictory result has recently been published. In the study of Yoshimatsu et al. (1999), the hypothalamic levels of *tele*-methylhistamine in rats were found to be increased 1 h after central administration of leptin. It is therefore possible that the effect of leptin on histamine turnover is short-lived. In that case, the physiological relevance of such a short response may be doubtful, because the anorexigenic effect of leptin is long. In addition to the different time schedule, also study designs in these two experiments were different. Our rats had no food available during the turnover study, whereas in the study of Yoshimatsu et al. (1999) the rats were allowed to eat. This difference might explain the higher baseline in the hypothalamic *tele*-methylhistamine content observed in the latter study. Nevertheless, if hypothalamic histamine act as a mediator of the anorexigenic effect of leptin, the blockade of histamine H_1 receptors should attenuate the response to leptin administration. The present results show that the effect of leptin on food intake and body weight was not antagonized by mepyramine treatment. This finding confirms our view that activation of central histamine H_1 receptors is not responsible for leptin-induced anorexia and weight loss. As leptin has lost its activity in mice lacking histamine H_1 receptors (Morimoto et al., 1999), we cannot fully exclude the importance of the histaminergic system in the mechanism of action of leptin in this species.

In the present study, mepyramine tended to supplement rather than to antagonize the suppressive effect of leptin on food intake and body weight. Since mepyramine at a dose of three times higher than the one used here has been found to abolish circadian rhythmicity of spontaneous locomotor activity and suppress daily food intake in rats (Lozeva et al., 2000), the locomotor activity of rats receiving mepyramine 5 mg/kg per day was studied. There was no sedative effects seen in mepyramine treated rats in the open field test, which suggests that a tendency to reduced

food intake was not due to increased drowsiness after the blockade of H_1 receptors in the brain.

In conclusion, the present study provides evidence that central administration of leptin can suppress feeding and promote weight loss via mechanisms that do not directly involve brain histaminergic mechanisms.

Acknowledgements

We thank Mrs. Hannele Jaatinen and Dr. Leena Tuomisto for aid in the *tele*-methylhistamine assay and Mrs. Sirkka Tsavaris for technical assistance. We also want to thank Dr. Ewen MacDonald for advice on the text. This study was supported by the Finnish Pharmaceutical Association.

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