Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 83 (2006) 214–220
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Effects of histamine H_1 receptor antagonists on depressive-like behavior in diabetic mice

Shoko Hirano [a], Shigeo Miyata [a], Kenji Onodera [b], Junzo Kamei [a,*]

[a] Department of Pathophysiology and Therapeutics, School of Pharmacy and Pharmaceutical Sciences, Hoshi University, Tokyo 142-8501, Japan
[b] Department of Dental Pharmacology, Okayama University Graduate School of Medicine and Dentistry, Okayama, 700-8525, Japan

Received 24 September 2005; received in revised form 19 January 2006; accepted 1 February 2006
Available online 10 March 2006

Abstract

We previously reported that streptozotocin-induced diabetic mice showed depressive-like behavior in the tail suspension test. It is well known that the central histaminergic system regulates many physiological functions including emotional behaviors. In this study, we examined the role of the central histaminergic system in the diabetes-induced depressive-like behavior in the mouse tail suspension test. The histamine contents in the hypothalamus were significantly higher in diabetic mice than in non-diabetic mice. The histamine H_1 receptor antagonist chlorpheniramine (1–10 mg/kg, s.c.) dose-dependently and significantly reduced the duration of immobility in both non-diabetic and diabetic mice. In contrast, the selective histamine H_1 receptor antagonists epinastine (0.03–0.3 μg/mouse, i.c.v.) and cetirizine (0.01–0.1 μg/mouse, i.c.v.) dose-dependently and significantly suppressed the duration of immobility in diabetic mice, but not in non-diabetic mice. Spontaneous locomotor activity was not affected by histamine H_1 receptor antagonists in either non-diabetic or diabetic mice. In addition, the number and affinity of histamine H_1 receptors in the frontal cortex were not affected by diabetes. In conclusion, we suggest that the altered neuronal system mediated by the activation of histamine H_1 receptors is involved, at least in part, in the depressive-like behavior seen in diabetic mice.

Keywords: Diabetes; Histamine H_1 receptor; Tail suspension test; Depressive-like behavior; Chlorpheniramine; Epinastine; Cetirizine

1. Introduction

It has been recognized that patients with diabetes have a higher prevalence of depression than the general population (Anderson et al., 2001). Diabetic patients with depression also show poor glycemic control (Lin et al., 2004). In addition, psychological troubles are considered to be risk factors for the future development of diabetes-related complications (de Groot et al., 2001). However, little information is available to resolve this problem. In animal studies, streptozotocin-treated rodents are often used as an animal model of type 1 diabetes because streptozotocin induces pancreatic β-cell death and hyperglycemia associated with decreased insulin secretion (Arison et al., 1967; Hohenegger and Rudas, 1971; Tarui et al., 1987). Streptozotocin-induced diabetic rodents show changes in the central nervous system (CNS) as indicated by neurochemical, electrophysiological, morphological and behavioral studies (Hilakivi-Clarke et al., 1990; McCall, 1992; Biessels et al., 1994; Magarinos and McEwen, 2000). We also reported that streptozotocin-induced diabetic mice exhibited depressive-like behavior in the tail suspension test (Kamei et al., 2003), which is often used to screen putative antidepressants (Steru et al., 1985). However, such depressive-like behavior was not observed in mice in the early stage of streptozotocin-induced diabetes or in mice with hyperglycemia induced by glucose injection (Kamei et al., 2003). Since streptozotocin does not cross the blood–brain barrier and has an early excretion rate (Schein, 1969; Karunanayake et al., 1974), we have suggested that the depressive-like behavior in streptozotocin-induced diabetic mice is induced by the diabetic state rather than by streptozotocin itself.

Histamine is regarded as a neurotransmitter in the CNS and regulates neuroendocrine and cardiovascular systems, arousal, circadian rhythms, feeding and drinking behavior, and emotional behaviors (Schwartz et al., 1991; Onodera et al., 1994; Lin et al., 1996). Cell bodies of histaminergic neurons are localized in the tuberomammillary nucleus in the posterior

* Corresponding author. Tel./fax: +81 3 5498 5030.
E-mail address: kamei@hoshi.ac.jp (J. Kamei).

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.02.001

hypothalamus and their fibers are widely distributed throughout the brain, such as in the cerebral cortex and hippocampus (Watanabe et al., 1984; Onodera et al., 1994). It is well known that histaminergic activities are enhanced under stressful conditions. For example, histamine contents in the hypothalamus are increased by a variety of stressors such as restraint (Ito et al., 1999), air blast (Mazurkiewicz-Kwilecki, 1980) and isolation stress (Bugajski et al., 1994). In addition, histamine release and metabolism are also facilitated by stress treatment (Yoshitomi et al., 1986a,b; Westerink et al., 2002). In behavioral studies, it has been suggested that the activation of histamine H_1 receptors induces the anxiety-like behavior in mice (Yuzurihara et al., 2000). In contrast, histamine H_1 receptor-deficient mice show less of a fearful state and decreased aggressive behavior (Yanai et al., 1998a,b). In addition, the histamine H_1 receptor antagonist chlorpheniramine suppresses muricide, which is used for the pharmacological analysis of antidepressants (Onodera, 1987). Based on these findings, it is well accepted that enhancement of histaminergic neurotransmission mediated by histamine H_1 receptors may be associated with psychological problems such as depression.

It has been reported that there is a 35% increase in histamine content of whole brain in diabetic rats compared with control rats (Gill et al., 1988). In addition, it has been reported that histamine levels increase in the brain, excluding the hypothalamus and the cerebellum, of diabetic mice (Nishibori et al., 1989). Furthermore, Nishibori et al. (1989) indicated that diabetic mice showed higher the levels of *tele*-methylhistamine, a major metabolite of brain histamine, in the hypothalamus and the rest of the brain. These reports suggested that the function of central histaminergic neurons might be altered by diabetes. Therefore, we can speculate that an increased function of the central histaminergic system may contribute to changes in emotional behaviors in diabetic mice. In the present study, we examined the involvement of histamine H_1 receptor-mediated neurotransmission in the diabetes-induced depressive-like behavior in the mouse tail suspension test.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science Co., Ltd., Tokyo), 4 weeks of age and weighing approximately 20 g at the beginning of the experiments, were used. They were housed 10 per cage and had free access to food and water. The animal room was maintained at 24 ± 1 °C and 55 ± 5% humidity with a 12-h light–dark cycle (light on at 8:00, light off at 20:00). Animals were rendered diabetic by an injection of streptozotocin (200 mg/kg, i.v.) prepared in citrate buffer at pH 4.5. Age-matched control mice were injected with the vehicle alone. Six-week-old mice (i.e., 14 days after the induction of diabetes) with blood glucose levels above 4000 mg/l were used as diabetic mice. Blood glucose levels were determined using a glucose analyzer (ANTSENSE II, Sankyo Co. Ltd., Tokyo, Japan). All behavioral observations were performed between 11:00 and 17:00 each day. The animals were used only once. This study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the Committee on the Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture.

2.2. Drugs

The drugs used in this study were streptozotocin and the histamine H_1 receptor antagonists (±)-chlorpheniramine maleate, epinastine hydrochloride and cetirizine dihydrochloride. While chlorpheniramine readily penetrates the blood–brain barrier (Nicholson et al., 1991), epinastine and cetirizine penetrate into the brain rather poorly (Chishty et al., 2001). Streptozotocin and chlorpheniramine were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Epinastine and cetirizine were gifts from Boehringer Ingelheim KG (Ingelheim/Rhein, Germany) and UCB Japan (Tokyo, Japan), respectively. Chlorpheniramine, epinastine and cetirizine were dissolved in saline. All drug doses were calculated as the salt weight. Systemic treatments with drugs were given in a volume of 10 ml/kg body weight. I.c.v. treatments with drugs were given in a volume of 5 μl/mouse.

2.3. Histamine contents in the mouse hypothalamus

Diabetic and non-diabetic mice were killed by decapitation under ether anesthesia. Trunk blood was used to measure blood glucose levels. The brains were dissected into the hypothalamus and the frontal cortex on an ice-cold alumina plate. The frontal cortex tissues were used in a [^{3}H]-pyrilamine binding assay. Dissected tissues were stored at −80 °C until homogenization. Hypothalamic tissues were homogenized in 600 μl of phosphate-buffered saline using a Polytron homogenizer (Kinematica, Lucerne, Switzerland). The homogenates were centrifuged at 10,000 ×*g* for 30 min at 4 °C. The supernatants were lyophilized, and then, the lyophilized powders were dissolved in 70 μl of distilled water, and these were used as ELISA samples. Histamine concentrations were determined by a commercially available histamine ELISA kit (Neogen Co., USA) following the manufacturer's directions.

2.4. [^{3}H]-pyrilamine binding assay

Diabetic and non-diabetic mice were killed by decapitation under ether anesthesia. The brains were dissected into the frontal cortex on an ice-cold alumina plate. Dissected tissues were stored at −80 °C until homogenization. Histamine H_1 receptor binding was assayed as described by Tran et al. (1978). In brief, the frontal cortex tissues were homogenized in 30 volumes of assay buffer (50 mM Na^+/K^+ phosphate buffer, pH 7.5) using a Polytron homogenizer (Kinematica). The homogenates were centrifuged at 50,000 ×*g* for 20 min at 4 °C. The membrane pellets were resuspended in the assay buffer and centrifuged at 50,000 ×*g* for 20 min at 4 °C. The final pellets were stored at −80 °C until assay. The membrane preparation was resuspended in the same buffer and incubated with 0.2–10 nM [^{3}H]-

pyrilamine (33.0 Ci/mM; Amersham Biosciences, Tokyo, Japan) in the absence (to measure total binding) or the presence (to measure non-specific binding) of unlabeled 1 μM triprolidine (Sigma Chemical Co). The reaction mixture (total volume, 500 μl) was incubated at 25 °C for 20 min. Following incubation, membrane-bound radioligand was separated from free radioligand by rapid vacuum filtration over a Whatman GF/B glass microfiber filter (Whatman, Maidstone, UK) presoaked with the assay buffer and washed through with three 4-ml volumes of ice-cold assay buffer. Filter-bound radioactivity was transferred to scintillation vials containing 10 ml Aquasol-2 scintillation cocktail and counted by a liquid scintillation counter. Specific binding was calculated as the difference between total and non-specific binding. Protein content was determined by the Bio-Rad method (Bio-Rad Laboratories Ltd, Hemel Hempstead, Hertfordshire, UK). Assays of [^{3}H]-pyrilamine binding were performed in duplicate. The number of binding sites (B_{max}) and the binding affinity (K_d) were calculated separately for each sample using a Scatchard analysis.

2.5. Tail suspension test

The procedure was according to our previous report (Kamei et al., 2003). The tail suspension apparatus consisted of a white translucent plastic box (30 × 30 × 30 cm) with a hook in the middle of the ceiling from which to suspend the mouse. Mice were suspended by the tail using adhesive Scotch tape affixed to the hook, which was connected to a strain gauge (TAIL SUSPENSION AMP, Neuroscience Inc., Tokyo, Japan) that picked up all movements of the mouse and transmitted them to a central processing unit which calculated the total duration of immobility and the strength of movements during the 10 min of the test. Each mouse was suspended individually. The movements of the mice were digitized and processed by a Super Scope II (GWI; Somerville, MA, USA). The threshold level was set to exclude respiration movement. The duration of immobility was defined as the total amount of time that the animal showed no movement. Chlorpheniramine was injected subcutaneously (s.c.) 60 min before testing. Epinastine and cetirizine were injected i.c.v. 30 min before testing. The dose ranges of chlorpheniramine, epinastine and cetirizine were based on our previous reports (Onodera, 1987; Kamei et al., 2005).

2.6. Locomotor activity

Spontaneous locomotor activity of mice was measured by a digital counter with an infrared sensor (NS-AS01, Neuroscience Inc., Tokyo, Japan). Mice were placed individually in a transparent plastic cage (27 × 17 × 13 cm), a transparent plastic ceiling was installed, and an infrared sensor was placed at the center of the ceiling. Total activity counts were automatically recorded for 10 min according to the measurement period in the tail suspension test. Chlorpheniramine was injected s.c. 60 min before testing. Epinastine and cetirizine were injected i.c.v. 30 min before testing.

Table 1
Effects of diabetes on body weight, blood glucose level and histamine content in the hypothalamus in mice

	Non-diabetic mice	Diabetic mice
Body weights (g)	35.3 ± 1.0	24.3 ± 0.8***
Blood glucose levels (mg/l)	1672.2 ± 74.1	7665.0 ± 209.0***
Histamine levels (ng/mg tissue)	1.087 ± 0.057	1.270 ± 0.061*

Data represent the mean ± SE of 9 mice. *$p<0.05$ and ***$p<0.001$ vs. respective values in non-diabetic mice (Student's t-test or Aspin–Welch's t-test).

Table 2
Effect of diabetes on the specific binding of [^{3}H]-pyrilamine to mouse frontal cortex membranes

	K_d (pM)	B_{max} (fmol/mg protein)
Non-diabetic mice	680.9 ± 117.9	19 ± 0.4
Diabetic mice	723.4 ± 98.6	25 ± 2.0

The maximal number of binding sites (B_{max}) and the binding affinity constant (K_d) were calculated separately for each sample by a Scatchard analysis. Each value represents the mean ± SE of 3–4 samples.

2.7. I.c.v. injection

One day before beginning i.c.v. injections, mice were anesthetized with ether and a 3-mm double-needle (tip: 28 gauge × 3 mm and base: 22 gauge × 5 mm; Natsume Seisakusho Co., Ltd., Tokyo, Japan) attached to a 25-μl Hamilton microsyringe was advanced to a unilateral injection site to make a hole. The unilateral injection site was 2 mm from either side of the midline between the anterior roots of the ears. On the day for i.c.v. injection, the head of the mouse was held against a V-shaped holder without any anesthetics, and the drugs were injected into the hole. The site of administration was checked by injecting dye solution in preliminary experiments. The placement of the injection was confirmed by the injection of dye solution after all experiments. This procedure was described previously (Aoki et al., 2003; Kamei et al., 2005).

2.8. Statistics

Data were expressed as the means with SE. The statistical significance of differences between groups was assessed by one-way and two-way analysis of variance (ANOVA) for factorial comparisons and by the Bonferroni test for multiple comparisons. Student's t-test or Aspin–Welch's t-test was used to evaluate differences between two groups. Significance was accepted at $p<0.05$.

3. Results

3.1. Effects of diabetes on body weight, blood glucose level and histamine content in the hypothalamus in mice

As shown in Table 1, body weights were significantly decreased in diabetic mice compared to non-diabetic mice. Blood glucose levels were significantly increased in diabetic mice. The histamine levels in the hypothalamus were significantly higher in diabetic mice than in non-diabetic mice.

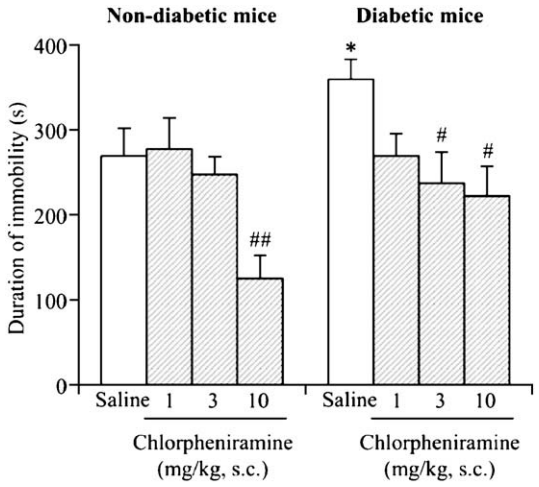

Fig. 1. Effect of chlorpheniramine on the duration of immobility in the tail suspension test in non-diabetic and diabetic mice. Each column represents the mean±SE of 9–10 mice. *$p<0.05$ vs. saline-treated non-diabetic mice (Student's t-test). $^{\#}p<0.05$ and $^{\#\#}p<0.01$ vs. respective saline-treated mice (Bonferroni test). A two-way ANOVA revealed that the duration of immobility was significantly affected by diabetes [$F(1,70)=5.387$, $p<0.05$] and drugs [$F(3,70)=7.826, p<0.001$], but not their interaction [$F(3,70)=1.665, p=0.1824$].

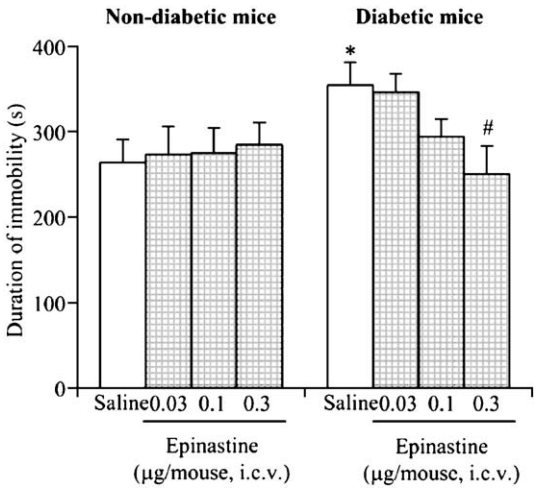

Fig. 2. Effect of epinastine on the duration of immobility in non-diabetic and diabetic mice. Each column represents the mean±SE of 9–10 mice. *$p<0.05$ vs. saline-treated non-diabetic mice (Student's t-test). $^{\#}p<0.05$ vs. respective saline-treated mice (Bonferroni test). A two-way ANOVA revealed that the duration of immobility was significantly affected by diabetes [$F(1,69)=4.445$, $p<0.05$], but not drugs [$F(3,69)=1.338, p=0.2690$] or their interaction [$F(3,69)=2.502$, $p=0.0665$].

3.2. Effect of diabetes on the specific binding of [^{3}H]-pyrilamine to mouse frontal cortex membranes

As shown in Table 2, diabetes had no significant effect on B_{max} values or K_d values of [^{3}H]-pyrilamine binding in the mouse frontal cortex.

3.3. Effects of chlorpheniramine on the duration of immobility in the tail suspension test and spontaneous locomotor activity in non-diabetic and diabetic mice

Diabetic mice showed a marked prolongation of immobility compared to non-diabetic mice (Fig. 1) without any difference in spontaneous locomotor activity (Table 3). Chlorpheniramine (1–10 mg/kg, s.c.) dose-dependently and significantly reduced the duration of immobility in both non-diabetic and diabetic mice (Fig. 1). The reduction in the duration of immobility in diabetic mice was statistically significant at doses of 3 and 10 mg/kg. However, the reduction in the duration of immobility in non-diabetic mice was only significant at a dose of 10 mg/kg.

Table 3
Effects of histamine H_1 receptor antagonists on spontaneous locomotor activity in non-diabetic and diabetic mice

Drugs	Total activity (counts/10 min)	
	Non-diabetic mice	Diabetic mice
Saline (s.c.)	359.5±16.3	374.0±22.2
Chlorpheniramine		
(3 mg/kg, s.c.)	–	391.8±18.2
(10 mg/kg, s.c.)	362.5±13.7	–
Saline (i.c.v.)	338.4±33.7	326.2±19.7
Epinastine (0.3 μg/mouse, i.c.v.)	321.4±18.5	312.6±23.7
Cetirizine (0.1 μg/mouse, i.c.v.)	354.3±11.8	323.6±26.3

Data represent the mean locomotor activity counts±SE of 10 mice. Each drug was administered at the effective or maximal doses using the tail suspension test.

Chlorpheniramine had no significant effect on spontaneous locomotor activity in either non-diabetic or diabetic mice (Table 3).

3.4. Effects of epinastine and cetirizine on the duration of immobility in the tail suspension test and spontaneous locomotor activity in non-diabetic and diabetic mice

Epinastine (0.03–0.3 μg/mouse, i.c.v.) and cetirizine (0.01–0.1 μg/mouse, i.c.v.) had no significant effect on the duration of

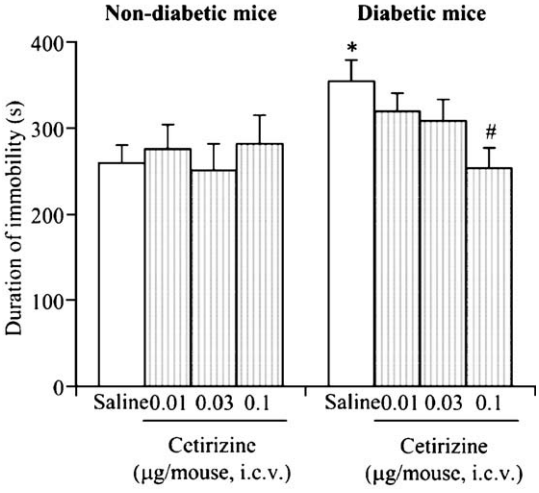

Fig. 3. Effect of cetirizine on the duration of immobility in non-diabetic and diabetic mice. Each column represents the mean±SE of 8–10 mice. *$p<0.05$ vs. saline-treated non-diabetic mice (Student's t-test). $^{\#}p<0.05$ vs. respective saline-treated mice (Bonferroni test). A two-way ANOVA revealed that the duration of immobility was significantly affected by diabetes [$F(1,66)=5.107$, $p<0.05$], but not drugs [$F(3,66)=0.885, p=0.4535$] or their interaction [$F(3,66)=1.845$, $p=0.1477$].

immobility in non-diabetic mice (Figs. 2 and 3). In contrast, epinastine (0.03–0.3 μg/mouse, i.c.v.) and cetirizine (0.01–0.1 μg/mouse, i.c.v.) dose-dependently and significantly decreased the duration of immobility in diabetic mice to the same levels as in non-diabetic mice (Figs. 2 and 3).

Epinastine (0.3 μg/mouse, i.c.v.) and cetirizine (0.1 μg/mouse, i.c.v.) had no significant effect on spontaneous locomotor activity in non-diabetic mice (Table 3).

4. Discussion

Histamine H_1 receptor-mediated neurotransmission participates in the regulation of emotional behaviors (Onodera, 1987; Yuzurihara et al., 2000). We previously reported that diabetic mice showed the prolonged immobility in the tail suspension test without any change in spontaneous locomotor activity (Kamei et al., 2003; Miyata et al., 2004). In addition, we also reported that there is no correlation between the duration of immobility and body weight (Kamei et al., 2003). In this study, the prolongation of immobility in diabetic mice was suppressed by the selective histamine H_1 receptor antagonists epinastine and cetirizine. On the other hand, these drugs had no significant effect on the duration of immobility in non-diabetic mice. Therefore, we suggest that histamine H_1 receptor-mediated neurotransmission may play an important role in depressive-like behavior seen in diabetic mice in the tail suspension test. In contrast, chlorpheniramine had an anti-immobility effect in both non-diabetic and diabetic mice, although a high dose of chlorpheniramine was required to reduce the duration of immobility in non-diabetic mice. It has been reported that chlorpheniramine also inhibits the reuptake of dopamine, noradrenaline and serotonin (Lidbrink et al., 1971; Shishido et al., 1991; Tatsumi et al., 1997; Suzuki et al., 1999). Therefore, we can speculate that the antidepressant-like effect of chlorpheniramine in the tail suspension test may be partly related to its inhibitory effect on monoamine reuptake sites. On the other hand, it has been reported that epinastine has no inhibitory effects on monoamine reuptake sites (Fugner et al., 1988). Furthermore, cetirizine shows selective affinity to histamine H_1 receptors (Kato et al., 1997). These reports strongly support our idea that the anti-immobility effects of epinastine and cetirizine in diabetic mice were induced by the selective inhibition of histamine H_1 receptors.

There are several lines of evidence which indicate that diabetes affects central histaminergic activities. Gill et al. (1988) and Nishibori et al. (1989) suggested that the contents of histamine and its metabolite are increased in the brains of diabetic rodents. Consistent with these reports, we also found that histamine levels in the hypothalamus, which is the major region for the synthesis of histamine in the central nervous system, were significantly higher in diabetic mice than in non-diabetic mice (Watanabe et al., 1984; Onodera et al., 1994). Although histamine levels were increased in diabetic mice, there was no significant change in the number or affinity of histamine H_1 receptors in the frontal cortex, which is a terminal region of histamine neurons (Watanabe et al., 1984; Onodera et al., 1994) and is rich in histamine H_1 receptors (Martinez-Mir et al., 1990; Yanai et al., 1992). It is still unclear whether our results are consistent with the condition in diabetic patients, since there is no clinical report on the effect of diabetes on central histaminergic systems. In patients with depression, it has been reported that the densities of histamine H_1 receptors were decreased in the frontal and cingulate cortices. In addition, these binding potential values are negatively correlated with the severity of disease (Kano et al., 2004). In that report, Kano and co-researchers suggested that prolonged histamine release and histamine turnover under repetitive stress conditions may lead to the down-regulation of histamine H_1 receptors. In this study, we detected that the blockade of histamine H_1 receptors suppressed the depressive-like behavior of diabetic mice. Therefore, we can speculate that diabetes alters the neuronal activities triggered by the activation of histamine H_1 receptors, and this alteration may underlie, at least in part, the depressive-like behavior of diabetic mice in the tail suspension test. Further studies are necessary to resolve whether this altered neuronal system is related to the hyperactivation of histamine neurons.

There are several reports investigating the role of histamine H_1 receptors on the behavioral despair in the forced swimming test. Noguchi et al. (1992) revealed that the histamine H_1 receptor antagonists levoprotiline and mepyramine had the antidepressant-like effect in the mouse forced swimming test when mice were repeatedly treated with these drugs (twice a day for 7 days). In contrast, Lamberti et al. (1998) reported that the histamine H_1 receptor agonist had the antidepressant-like effect in the mouse forced swimming test. Yanai et al. (1998b) suggested that histamine H_1 receptor deficiency did not affect significantly the duration of immobility in the mouse forced swimming test. This discrepancy may be related to the differences in the experimental procedures or used drugs. In this study, we observed that epinastine and cetirizine had no significant effect in non-diabetic (normal) mice. Therefore, our findings were consistent with Yanai's suggestion (1998b) because epinastine and cetirizine are the highly selective histamine H_1 receptor antagonists (Fugner et al., 1988; Kato et al., 1997).

Several lines of evidence indicate that central histaminergic activity is regulated by monoaminergic system such as serotonin, noradrenaline and dopamine. Local perfusion of serotonin increases histamine release from the hypothalamus (Laitinen et al., 1995). In addition, the activation of α_2 adrenoceptors significantly suppresses histamine release from the cortex (Hill and Straw, 1988; Gulat-Marnay et al., 1989) and hypothalamus (Prast et al., 1991). Furthermore, the dopaminergic stimulation in the hypothalamus enhances histamine release via dopamine D_2 receptors but suppresses via dopamine D_3 receptors (Prast et al., 1993). It is well known that these monoaminergic activities are altered by diabetes. In the microdialysis studies, the extracellular levels of serotonin and noradrenaline in the hypothalamus are decreased in streptozotocin-induced diabetic rats (Shimizu, 1991; Ohtani et al., 1997). In addition, the extracellular dopamine levels are unaltered or increased in streptozotocin-induced diabetic rats (Shimizu, 1991; Ohtani et al., 1997). Therefore, these alterations of

monoaminergic system may affect the histaminergic neuronal activity and histamine-related behaviors. Further studies are needed to elucidate this problem.

In conclusion, we suggest that the alteration of neuronal system mediated by the activation of histamine H_1 receptors may be involved in the depressive-like behavior seen in diabetic mice in the tail suspension test.

Acknowledgements

We are grateful to Boehringer Ingelheim KG and UCB Japan for their gifts of epinastine and cetirizine, respectively. We thank Ms. M. Atsumi, Mr. S. Narushima and Ms. N. Aono for their excellent technical assistance.

References

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes. A meta-analysis. Diabetes Care 2001;24:1069–78.

Aoki T, Narita M, Ohnishi O, Mizuo K, Narita M, Yajima Y, et al. Disruption of the type 1 inositol 1,4,5-trisphosphate receptor gene suppresses the morphine-induced antinociception in the mouse. Neurosci Lett 2003;350:69–72.

Arison RN, Ciaccio EI, Glitzer MS, Cassaro JA, Pruss MP. Light and electron microscopy of lesions in rats rendered diabetic with streptozotocin. Diabetes 1967;16:51–6.

Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW, Gispen WH. Cerebral function in diabetes mellitus. Diabetologia 1994;37:643–50.

Bugajski AJ, Chlap Z, Gadek-Michalska, Bugajski J. Effect of isolation stress on brain mast cells and brain histamine levels in rats. Agents Actions 1994;41: C75–6.

Chishty M, Reichel A, Siva J, Abbott NJ, Begley DJ. Affinity for the P-glycoprotein efflux pump at the blood–brain barrier may explain the lack of CNS side-effects of modern antihistamines. J Drug Target 2001;9:223–8.

de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–30.

Fugner A, Bechtel WD, Kuhn FJ, Mierau J. In vitro and in vivo studies of the non-sedating antihistamine epinastine. Arzneimittelforschung 1988;38: 1446–53.

Gill DS, Thompson CS, Dandona P. Increased histamine in plasma and tissues diabetic rats. Diabetes Res 1988;7:31–4.

Gulat-Marnay C, Lafitte A, Arrang JM, Schwartz JC. Modulation of histamine release and synthesis in the brain mediated by alpha 2-adrenoceptors. J Neurochem 1989;53:513–8.

Hilakivi-Clarke LA, Wozniak KM, Durcan MJ, Linnoila M. Behavior of streptozotocin-diabetic mice in tests of exploration, locomotion, anxiety, depression and aggression. Physiol Behav 1990;48:429–33.

Hill SJ, Straw RM. Alpha 2-adrenoceptor-mediated inhibition of histamine release from rat cerebral cortical slices. Br J Pharmacol 1988;95:1213–9.

Hohenegger M, Rudas B. Kidney function in experimental diabetic ketosis. Diabetologia 1971;7:334–8.

Ito C, Shen H, Toyota H, Kubota Y, Sakurai E, Watanabe T, et al. Effects of the acute and chronic restraint stresses on the central histaminergic neuron system of Fischer rat. Neurosci Lett 1999;262:143–5.

Kamei J, Miyata S, Morita K, Saitoh A, Takeda H. Effects of selective serotonin reuptake inhibitors on immobility time in the tail suspension test in streptozotocin-induced diabetic mice. Pharmacol Biochem Behav 2003;75: 247–54.

Kamei J, Hirano S, Miyata S, Saitoh A, Onodera K. Effects of first- and second-generation histamine-H_1-receptor antagonists on the pentobarbital-induced loss of the righting reflex in streptozotocin-induced diabetic mice. J Pharmacol Sci 2005;97:266–72.

Kano M, Fukudo S, Tashiro A, Utsumi A, Tamura D, Itoh M, et al. Decreased histamine H_1 receptor binding in the brain of depressed patients. Eur J Neurosci 2004;20:803–10.

Karunanayake EH, Hearse DJ, Mellows G. The synthesis of [^{14}C] streptozotocin and its distribution and excretion in the rat. Biochem J 1974;142:673–83.

Kato M, Nishida A, Aga Y, Kita J, Kudo Y, Narita H, et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. Arzneimittelforschung 1997;47:1116–24.

Laitinen KS, Tuomisto L, Laitinen JT. Endogenous serotonin modulates histamine release in the rat hypothalamus as measured by in vivo microdialysis. Eur J Pharmacol 1995;285:159–64.

Lamberti C, Ipponi A, Bartolini A, Schunack W, Malmberg-Aiello P. Antidepressant-like effects of endogenous histamine and of two histamine H_1 receptor agonists in the mouse forced swim test. Br J Pharmacol 1998; 123:1331–6.

Lidbrink P, Jonsson G, Fuxe K. The effect of imipramine-like drugs and antihistamine drugs on uptake mechanisms in the central noradrenaline and 5-hydroxytryptamine neurons. Neuropharmacology 1971;10:521–36.

Lin JS, Hou Y, Sakai K, Jouvet M. Histaminergic descending inputs to the mesopontine tegmentum and their role in the control of cortical activation and wakefulness in the cat. J Neurosci 1996;16:1523–37.

Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 2004;27:2154–60.

Magarinos AM, McEwen BS. Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. Proc Natl Acad Sci U S A 2000;97:11056–61.

Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, Traiffort E, et al. Three histamine receptors (H_1, H_2 and H_3) visualized in the brain of human and non-human primates. Brain Res 1990;526:322–7.

Mazurkiewicz-Kwilecki IM. Single and repeated air blast stress and brain histamine. Pharmacol Biochem Behav 1980;12:35–9.

McCall AL. The impact of diabetes on the CNS. Diabetes 1992;41:557–70.

Miyata S, Hirano S, Kamei J. Diabetes attenuates the antidepressant-like effect mediated by the activation of 5-HT_{1A} receptor in the mouse tail suspension test. Neuropsychopharmacology 2004;29:461–9.

Nicholson AN, Pascoe PA, Turner C, Ganellin CR, Greengrass PM, Casy AF, et al. Sedation and histamine H_1-receptor antagonism: studies in man with the enantiomers of chlorpheniramine and dimethindene. Br J Pharmacol 1991;104:270–6.

Nishibori M, Oishi R, Itoh Y, Saeki K. Changes in histamine metabolism in the brains of mice with streptozotocin-induced diabetes. J Neurochem 1989;52:1375–81.

Noguchi S, Fukuda Y, Inukai T. Possible contributory role of the central histaminergic system in the forced swimming model. Arzneimittelforschung 1992;42:611–3.

Ohtani N, Ohta M, Sugano T. Microdialysis study of modification of hypothalamic neurotransmitters in streptozotocin-diabetic rats. J Neurochem 1997;69:1622–8.

Onodera K. Muricidal suppression by chlorpheniramine and changes in brain levels following dietary-induced thiamine deficiency in rats. Physiol Behav 1987;41:71–8.

Onodera K, Yamatodani A, Watanabe T, Wada H. Neuropharmacology of the histaminergic neuron system in the brain and its relationship with behavioral disorders. Prog Neurobiol 1994;42:685–702.

Prast H, Heistracher M, Philippu A. In vivo modulation of the histamine release in the hypothalamus by adrenoreceptor agonists and antagonists. Naunyn-Schmiedebergs Arch Pharmacol 1991;344:183–6.

Prast H, Heistracher M, Philippu A. Modulation by dopamine receptors of the histamine release in the rat hypothalamus. Naunyn-Schmiedebergs Arch Pharmacol 1993;347:301–5.

Schein PS. 1-Methyl-1-nitrosourea depression of brain nicotinamide adenine dinucleotide in the production of neurologic toxicity. Proc Soc Exp Biol Med 1969;131:517–20.

Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. Histaminergic transmission in the mammalian brain. Physiol Rev 1991;71:1-51.

Shimizu H. Alteration in hypothalamic monoamine metabolism of freely moving diabetic rat. Neurosci Lett 1991;131:225–7.

Shishido S, Oishi R, Saeki K. In vivo effects of some histamine H_1-receptor antagonists on monoamine metabolism in the mouse brain. Naunyn-Schmiedebergs Arch Pharmacol 1991;343:185–9.

Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 1985;85: 367–70.

Suzuki T, Mori T, Tsuji M, Nomura M, Misawa M, Onodera K. Evaluation of the histamine H_1-antagonist-induced place preference in rats. Jpn J Pharmacol 1999;81:332–8.

Tarui S, Yamada K, Hanafusa T. Animal models utilized in the research of diabetes mellitus-with special reference to insulitis-associated diabetes. Prog Clin Biol Res 1987;229:211–23.

Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340:249–58.

Tran VT, Chang RS, Snyder SH. Histamine H_1 receptors identified in mammalian brain membranes with [^{3}H] mepyramine. Proc Natl Acad Sci U S A 1978;75:6290–4.

Watanabe T, Taguchi Y, Shiosaka S, Tanaka J, Kubota H, Terano Y, et al. Distribution of the histaminergic neuron system in the central nervous system of rats; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res 1984;295:13–25.

Westerink BH, Cremers TI, De Vries JB, Liefers H, Tran N, De Boer P. Evidence for activation of histamine H_3 autoreceptors during handling stress in the prefrontal cortex of the rat. Synapse 2002;43:238–43.

Yanai K, Watanabe T, Yokoyama H, Meguro K, Hatazawa J, Itoh M, et al. Histamine H_1 receptors in human brain visualized in vivo by [^{11}C]doxepin and positron emission tomography. Neurosci Lett 1992;137:145–8.

Yanai K, Son LZ, Endou M, Sakurai E, Watanabe T. Targeting disruption of histamine H_1 receptors in mice: behavioral and neurochemical characterization. Life Sci 1998a;62:1607–10.

Yanai K, Son LZ, Endou M, Sakurai E, Nakagawasai O, Tadano T, et al. Behavioural characterization and amounts of brain monoamines and their metabolites in mice lacking histamine H_1 receptors. Neuroscience 1998b;87:479–87.

Yoshitomi I, Itoh Y, Oishi R, Saeki K. Brain histamine turnover enhanced by footshock. Brain Res 1986a;362:195–8.

Yoshitomi I, Oishi R, Saeki K. Involvement of opioid and non-opioid mechanisms in footshock-induced enhancement of brain histamine turnover in mice. Brain Res 1986b;398:57–62.

Yuzurihara M, Ikarashi Y, Ishige A, Sasaki H, Kuribara H, Maruyama Y. Effects of drugs acting as histamine releasers or histamine receptor blockers on an experimental anxiety model in mice. Pharmacol Biochem Behav 2000;67: 145–50.