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Antidepressant-like effects of endogenous histamine and of two histamine H_1 receptor agonists in the mouse forced swim test

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1 Effects of substances which are able to alter brain histamine levels and two histamine H_1 receptor agonists were investigated in mice by means of an animal model of depression, the forced swim test.

2 Imipramine (10 and 30 mg kg^{-1}, i.p.) and amitriptyline (5 and 15 mg kg^{-1}, i.p.) were used as positive controls. Their effects were not affected by pretreatment with the histamine H_3 receptor agonist, (**R**)-α-methylhistamine, at a dose (10 mg kg^{-1}, i.p.) which did not modify the cumulative time of immobility.

3 The histamine H_3 receptor antagonist, thioperamide (2–20 mg kg^{-1}, s.c.), showed an antidepressant-like effect, with a maximum at the dose of 5 mg kg^{-1}, which was completely prevented by (**R**)-α-methylhistamine.

4 The histamine-*N*-methyltransferase inhibitor, metoprine (2–20 mg kg^{-1}, s.c.), was effective with an ED_{50} of 4.02 (2.71–5.96) mg kg^{-1}; its effect was prevented by (**R**)-α-methylhistamine.

5 The histamine precursor, L-histidine (100–1000 mg kg^{-1}, i.p.), dose-dependently decreased the time of immobility [ED_{30} 587 (499–712) mg kg^{-1}]. The effect of 500 mg kg^{-1} L-histidine was completely prevented by the selective histidine decarboxylase inhibitor, (**S**)-α-fluoromethylhistidine (50 mg kg^{-1}, i.p.), administered 15 h before.

6 The highly selective histamine H_1 receptor agonist, 2-(3-trifluoromethylphenyl)histamine (0.3–6.5 μg per mouse, i.c.v.), and the better known H_1 agonist, 2-thiazolylethylamine (0.1–1 μg per mouse, i.c.v.), were both dose-dependently effective in decreasing the time of immobility [ED_{50} 3.6 (1.53–8.48) and 1.34 (0.084–21.5) μg per mouse, respectively].

7 None of the substances tested affected mouse performance in the rota rod test at the doses used in the forced swim test.

8 It was concluded that endogenous histamine reduces the time of immobility in this test, suggesting an antidepressant-like effect, via activation of H_1 receptors.

Keywords: Forced swim test; depression; L-histidine; (**S**)-α-fluoromethylhistidine; (**R**)-α-methylhistamine; thioperamide; metoprine; histamine H_1 receptors; 2-(3-trifluoromethylphenyl)histamine; 2-thiazolyethylamine

Introduction

In the aetiology of affective disorders in general, and more specifically in depression, a dysfunction of the monoaminergic (5-hydroxytryptamine, noradrenaline and dopamine) neuronal systems is commonly accepted. Nevertheless, about 7% of treated patients remains chronically depressed even after ten years of therapy (Esposito & Liguori, 1996). Despite another monoaminergic system, the histaminergic system, has been anatomically and functionally defined (Panula *et al*., 1989; Wada *et al*., 1991), its role in the control of depressive states has been poorly studied up to now. Papers have been published on the effects of histamine H_1 and H_2 receptor antagonists in various animals models of depression since the 60s (Horovitz *et al*., 1966; Barnett *et al*., 1969a,b; Wallach & Hedley, 1979; Onodera & Ogura, 1984; Delini-Stula *et al*., 1988; Noguchi *et al*., 1992; O'Neill & Gertner, 1986), often regarded as false positives in these tests (Barnett *et al*., 1969a,b; Katz & Sibel, 1982; Willner, 1984; Borsini & Meli, 1988; Sunal *et al*., 1994), while the effect of relatively high doses of histamine itself in the forced swim test has been investigated in only one study (Nath *et al*., 1988).

In the present work, a different approach to the study of the possible implication of the histaminergic system in depressive-like states was adopted, by investigating the effects of endogenous brain histamine in the mouse forced swim (Porsolt) test. Different substances such as the histamine precursor, L-histidine, the histidine decarboxylase [EC 4.1.1.22] (HDC) inhibitor, (**S**)-α-fluoromethylhistidine (FMH) (Kollonitsch *et al*., 1978) and the histamine-*N*-methyltransferase [EC 2.1.1.8] (HMT) inhibitor, metoprine (Duch *et al*., 1978), have been described as able to alter selectively histamine brain levels. Similarly, the selective histamine H_3 receptor agonist, (**R**)-α-methylhistamine (RAMH), and antagonist, thioperamide, have been shown to inhibit and stimulate histamine release and synthesis, respectively (Arrang *et al*., 1987; Garbarg *et al*., 1989). Therefore, all these substances were used in the present study. To investigate further this topic we thought it worthwhile to test also the two most selective H_1 receptor agonists, 2-(3-trifluoromethylphenyl)histamine (FMPH) (Leschke *et al*., 1995) and 2-thiazolylethylamine (2-TEA) (Ganellin, 1982).

Preliminary results were presented at the XXVth and XXVIth Annual Meetings of the European Histamine Research Society (Lamberti *et al*., 1996; 1997).

Methods

Male Swiss albino mice (22–28 g) were used. Twelve mice were housed per cage and fed a standard laboratory diet and

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tap water *ad libitum* during 12 h/12 h light/dark cycles (lights on between 7 h 00 min and 19 h 00 min). The cages were brought into the experimental room the day before the experiment for acclimatization. All experiments were performed between 10 h 00 min and 17 h 00 min.

Forced swim (behavioural despair) test

The forced swim test was performed according to Porsolt *et al.* (1977). The apparatus consisted of two plexiglass cylinders (diameter 10 cm; height 25 cm) vertically placed in a transparent animal cage ($21 \times 16 \times 12$ cm) containing 6 cm of water at 22–23°C. Two mice, each of them having received a different treatment, were tested simultaneously by being dropped into the cylinders and left there for 6 min. The duration of immobility was measured with two stop-watches during the last 4 min. A decrease in the duration of immobility is indicative of an antidepressant-like effect.

Rota rod test

The integrity of motor coordination was assessed with a rota rod apparatus (Ugo Basile, Varese, Italy) at a rotating speed of 24 r.p.m., immediately before each swim trial, by counting the number of falls from the rod in 30 s (Vaught *et al.*, 1985).

Drugs

The following drugs were used: amitriptyline HCl (Aldrich), imipramine HCl (Sigma), (**R**)-α-methylhistamine 2HCl (RBI), thioperamide maleate (RBI), metoprine (Burroughs Wellcome Co), L-histidine HCl (Sigma) and (**S**)-α-fluoromethylhistidine HCl (FMH; Merck Sharp & Dohme Research Lab.), 2-(3-trifluoromethylphenyl)histamine (Institute of Pharmacy I, Freie Universität Berlin), 2-thiazolylethylamine 2HCl (SmithKline Beecham). All drugs except metoprine were dissolved in isotonic (NaCl 0.9%) saline solution immediately before use. Metoprine was dissolved in 10% aqueous lactic acid and then diluted with saline (1:30).

Drug concentrations were prepared in such a way that the necessary dose could be injected in a volume of 10 ml kg^{-1} by both s.c. and i.p. routes. For i.c.v. administration a short ether anaesthesia was adopted. Substances were injected in the necessary dose dissolved in 5 μl per mouse according to the method described by Haley & McCormick (1957). To ascertain the exact site of i.c.v. injection, some mice were injected i.c.v. with 5 μl of 1:10 diluted India ink and their brains were examined macroscopically after sectioning.

Statistical analysis

Results are presented as the mean ± s.e. Statistical analysis was performed by means of ANOVA followed by Scheffe's test. P values of less than 0.05 were considered significant. Data were analysed with a computer programme (Number Cruncher Statistical System, Version 5.03 9/92). ED_{50} and ED_{30} values are the doses which produced, respectively, the 50% and 30% of the maximum possible effect, with 95% confidence limits. Both percentages were calculated according to Tallarida & Murray (1984).

Results

Imipramine (10 and 30 mg kg^{-1}, i.p.) and amitriptyline (5 and 15 mg kg^{-1}, i.p.) were used as reference molecules. Both drugs, administered (i.p.) 30 min before the test, were dose-dependently effective, and RAMH did not affect the reduced duration of immobility induced by these antidepressants (Figure 1).

Thioperamide, injected (s.c.) 15 min before the test, reduced the cumulative time of immobility, with a maximum effect at a dose of 5 mg kg^{-1} (Figure 2). Mice treated with RAMH, 10 mg kg^{-1} (i.p.), showed no statistically significant differences in the cumulative time of immobility with respect to controls. Conversely, when RAMH was administered 15 min before thioperamide (5 mg kg^{-1}) treatment, it was able to antagonize completely the antidepressant-like effect of the latter.

Similarly to thioperamide, metoprine, administered 30 min before the test, reduced dose-dependently the time of immobility (Figure 3). Such a reduction was statistically significant at all three doses used (2, 7 and 20 mg kg^{-1}, s.c.), with an ED_{50} of 4.02 (2.71–5.96) mg kg^{-1}. When histamine release was inhibited by pretreatment with RAMH, administered 15 min before, the metoprine (2 mg kg^{-1}) effect was completely reversed.

Also L-histidine showed a dose-dependent antidepressant-like effect when administered at 100, 250, 500 and 1000 mg kg^{-1} (i.p.) 2 h before the test, with an EC_{30} of 587 (499–712) mg kg^{-1} (Figure 4). This effect was statistically significant for the two higher doses tested. Mice pretreated with FMH administered at a dose of 50 mg kg^{-1} (i.p.) 4 or 15 h before saline treatment were not significantly different from controls. In contrast, when FMH was administered 4 h before treatment with 500 mg kg^{-1} L-histidine, the effect of the latter was slightly reduced. This reduction was stronger and statistically significant when FMH was administered 15 h before L-histidine (Figure 4).

Due to their inability to cross the blood brain barrier, both FMPH and 2-TEA were administered i.c.v. 15 min before the

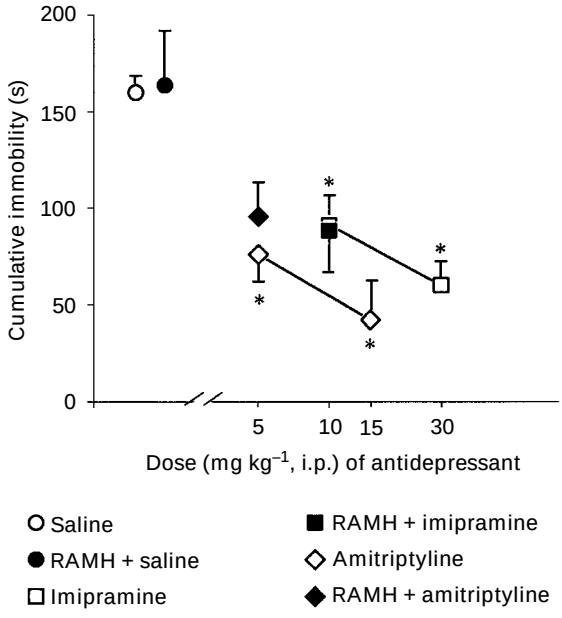

Figure 1 Effects of the tricyclic antidepressants imipramine HCl and amitriptyline HCl alone and in combination with (**R**)-α-methylhistamine 2HCl (RAMH) in the mouse forced swim test. RAMH (10 mg kg^{-1}, i.p.) was administered 15 min before saline or antidepressant treatment, which were injected i.p. 30 min before the test. *$P < 0.001$ versus saline controls (ANOVA followed by Scheffe's test). Each point represents the mean (with s.e.mean shown by vertical lines) of 10–50 mice.

test. Both FMPH and 2-TEA were dose-dependently effective in reducing the time of immobility. FMPH, administered in four different doses (0.3, 1, 2.65 and 6.5 μg per mouse), had a statistically significant effect at the highest dose (Figure 5) and an ED_{50} of 3.6 (1.53–8.48) μg per mouse, while 2-TEA proved to be significantly effective at all three doses tested (0.1, 0.3 and 1 μg per mouse) (Figure 5), with an ED_{50} of 1.34 (0.084–21.5) μg per mouse.

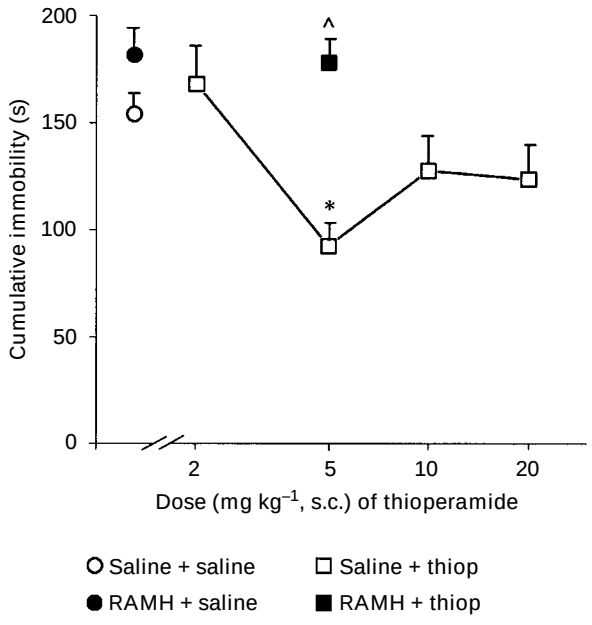

Figure 2 Antidepressant-like effect of thioperamide maleate (Thiop) and its antagonism by (**R**)-α-methylhistamine 2HCl (RAMH) in the mouse forced swim test. RAMH (10 mg kg^{-1}, i.p.) was administered 15 min before saline or thioperamide treatment, which was injected s.c. 15 min before the test. $^*P<0.05$ versus saline controls; $\hat{}P<0.001$ versus thioperamide (5 mg kg^{-1})-treated mice (ANOVA followed by Scheffe's test). Each point represents the mean (with s.e.mean shown by vertical lines) of 11–26 mice.

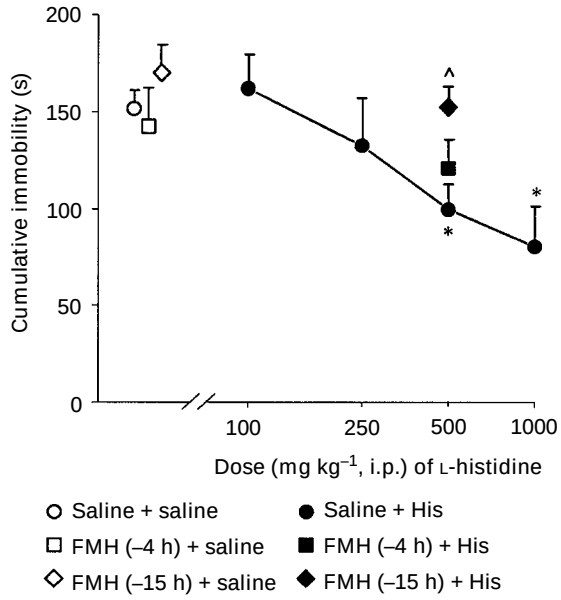

Figure 4 Antidepressant-like effect of L-histidine (His) and its antagonism by (**S**)-α-fluoromethylhistidine HCl (FMH) in the mouse forced swim test. FMH (50 mg kg^{-1}, i.p.) was administered 4 or 15 h before saline or His treatment, which were injected (i.p.) 2 h before the test. $^*P<0.05$ versus saline controls; $\hat{}P<0.05$ versus His (500 mg kg^{-1})-treated mice (ANOVA followed by Scheffe's test). Each point represents the mean (with s.e.mean shown by vertical lines) of 10–36 mice.

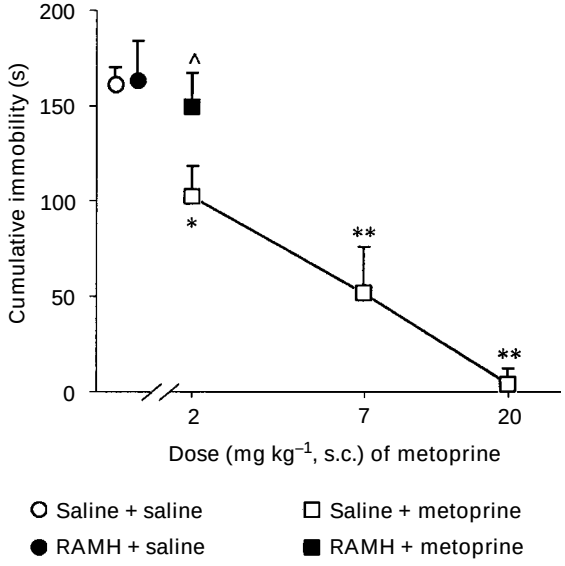

Figure 3 Antidepressant-like effect of metoprine and its antagonism by (**R**)-α-methylhistamine 2HCl (RAMH) in the mouse forced swim test. RAMH (10 mg kg^{-1}, i.p.) was administered 15 min before saline or metoprine treatment, which were injected s.c. 30 min before the test. $^*P<0.05$, $^{**}P<0.001$ versus saline controls; $\hat{}P<0.05$ versus metoprine (2 mg kg^{-1})-treated mice (ANOVA followed by Scheffe's test). Each point represents the mean (with s.e.mean shown by vertical lines) of 11–28 mice.

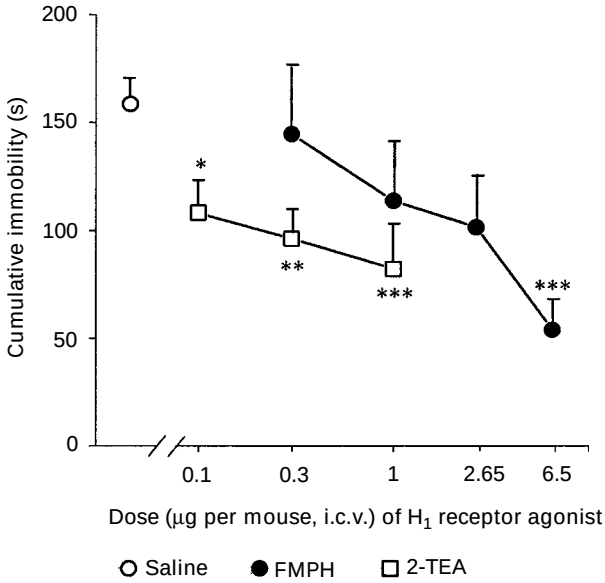

Figure 5 Antidepressant-like effects of 2-(3-trifluoromethylphenyl)-histamine dihydrogenmaleate (FMPH) and 2-thiazolylethylamine 2HCl (2-TEA) in the mouse forced swim test. The test was performed 15 min after treatment with either FMPH or 2-TEA. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ versus saline (i.c.v.-treated) controls (ANOVA followed by Scheffe's test). Each point represents the mean (with s.e.mean shown by vertical lines) of 10–32 mice.

In the rota rod test none of the substances at the doses used altered mouse performance in comparison to one group of 16 controls, which scored 0.47 ± 0.19 falls from the rod in 30 s.

Discussion

The present results suggest an involvement of the histaminergic system in the modulation of depressive states as evidenced by the forced swim test. In fact, substances able to enhance histaminergic transmission reduced the duration of immobility, indicating a possible antidepressant effect. This antidepressant-like effect might be due to activation of histamine H_1 receptors, since two selective H_1 agonists caused reduced immobility as well.

The two reference molecules used, the tricyclic antidepressants, imipramine and amitriptyline, were tested as positive controls in our condition. Thioperamide showed a statistically significant antidepressant-like effect at a dose of 5 mg kg^{-1}. Since thioperamide was described as a selective antagonist for histamine H_3 presynaptic autoreceptors (Arrang *et al*., 1987), the reduced duration of immobility may be due to enhanced histamine release from the synaptic terminals. The antagonism of thioperamide effect by the H_3 receptor agonist, RAMH, administered at a dose ineffective *per se* on the duration of immobility, is not likely to be aspecific, since RAMH did not affect the behaviour of mice treated with the classical antidepressants. Furthermore, studies have demonstrated that several antidepressant drugs, including amitriptyline, exhibit low or negligible affinities for the histamine H_3 receptor (Kathmann *et al*., 1994).

Interestingly, at higher thioperamide doses, 10 and 20 mg kg^{-1}, a less pronounced effect was observed. Since thioperamide has been shown to have a K_i of 4 nM on the H_3 and >10,000 nM on the H_1 or H_2 receptors (Schwartz *et al*., 1990), the hypothesis of a postsynaptic antagonism can be ruled out. Instead, the less pronounced effect is probably due to competition between thioperamide and the endogenous histamine released on the H_3 receptor. Such a partial reversal of thioperamide effect with increasing doses was also observed while tests were being performed for antinociception (Malmberg-Aiello *et al*., 1994) and locomotor activity (Sakai *et al*., 1991).

A further approach to study the effects of endogenous histamine was to inhibit its catabolism or enhance its synthesis. The dose-dependence of the decrease in immobility induced by the HMT inhibitor, metoprine, reflects the degree of inhibition of the enzyme, since, as demonstrated by Hough *et al*. (1986), 5 mg kg^{-1} (i.p.) metoprine reduced whole brain HMT activity by 70%, while a 90% reduction could be obtained with 20–30 mg kg^{-1} (i.p.). The complete antagonism of such a decrease in immobility by pretreatment with RAMH, due to inhibition of histamine release, demonstrates that metoprine activity is due to released histamine which has not been catabolized.

Histamine synthesis can be enhanced by systemic administration of the precursor, L-histidine, since the enzyme HDC is not saturated in physiological conditions (Schwartz *et al*., 1972; Abou *et al*., 1973). Furthermore, histidine loads (1000 mg kg^{-1}) in mice produce a rise in histamine whole brain levels with a maximum occurring 1 h after treatment, and a slowly decreasing plateau thereafter (Taylor & Snyder, 1972). In our experience, antinociception following administration of 50 or 1000 mg kg^{-1} (i.p.) reached a maximum effect 2 h after treatment in the mouse abdominal constriction test (Malmberg-Aiello *et al*., 1994). Therefore, in the present study we treated mice with L-histidine 2 h before the test. To demonstrate that L-histidine activity was actually due to its conversion into histamine, mice were also pretreated with FMH, a highly selective irreversible HDC inhibitor which has been demonstrated to halve brain histamine levels in mice within 2 h up to 48 h, at the dose of 25 mg kg^{-1} (i.p.) (Maeyama *et al*., 1982). Antagonism by FMH was complete when the substance was administered 15 h before L-histidine.

Thus, in the present study three approaches were adopted to investigate the effects of endogenous histamine, and the results obtained with all of them suggest a possible positive control by the histaminergic system in depressive-like states. A further indication for the involvement of the histaminergic system in the control of depressive states is given by the effects of electroconvulsive shocks (ECS). ECS was shown to reduce the time of immobility in the rat forced swim test (Porsolt *et al*., 1978), and at present is one of the therapeutic strategies adopted in some cases of depression, such as when patients respond poorly to medication (Weiner & Krystal, 1994). It has been demonstrated that histamine levels in rat cerebral cortex are significantly decreased 24 h after a single ECS, indicating that histamine release had occurred, while HDC activity was increased both 24 h after a single shock and 1 and 24 h after repeated ECS (Zawilska & Nowak, 1985). All this seems to be in contrast with the work by Nath *et al*. (1988), who found an increase in the duration of immobility in the mouse forced swim test following intracerebral administration of histamine. On the other hand, the histamine doses at which such an increase was observed (50, 100 and 200 μg per mouse) were rather high, since 100 μg per mouse (i.c.v) were shown to induce facial convulsions (Malmberg-Aiello *et al*., 1994), and 200–400 μg per rat to produce catalepsy (Glick & Crane, 1978). For this reason, all the substances used in the present work were also tested by means of a rota rod apparatus before the forced swimming test was performed, to make sure that they did not influence the normal motor activity of the mice. Since ataxic mice are not able to coordinate movements and fall from the rotating rod, while excited animals tend to jump off the rod, the good performance on the rod by mice in the present study indicates the results obtained with the forced swim test are not due to altered motor activity induced by the substances at the doses used. Furthermore, drugs which have a known psychostimulant effect, like (+)-amphetamine and caffeine, at the same doses at which they are able to decrease the time of immobility in the rat forced swim test, also show a significantly increased motor activity in an open field (Porsolt *et al*., 1978).

After the effects of endogenous histamine had been studied, it seemed worthwhile to investigate the consequences of H_1 receptor activation. This was possible thanks to the recent development of a potent and selective H_1 receptor agonist, FMPH. The molecule is 2138 fold more selective on H_1 than on H_2 receptors, and discriminates between H_1 and other receptors by >64 (H_1:H_3), 1000 (H_1:M_3), 105 (H_1: α_1), 708 (H_1:β_1) and 71 (H_1:5-HT_{2A}) (Leschke *et al*., 1995). For comparison, the better known H_1 receptor agonist, 2-TEA, was studied, although it does not discriminate between H_1 and H_2 receptors on a wide range, its relative potency on H_1:H_2 receptors being about 12:1 (Ganellin, 1982). Both FMPH and 2-TEA were administered in doses which completely prevented the antinociception induced by the H_1-antagonist, pyrilamine, in our nociception tests (Malmberg-Aiello *et al*., unpublished observation). The dose-dependent efficacy of the two H_1 agonists in reducing the time of immobility strongly suggests a role for the H_1 receptor in mediating the responses of the mice in the forced swim test following histaminergic system activation. It is interesting to note that the two substances were

equipotent in producing their effects, considering that FMPH has a 2.5 fold higher molecular weight than 2-TEA, and the same 2.5 fold difference was evident when their ED_{50} values were compared.

The antidepressant-like effect of H_1 receptor agonists is not surprising. In fact, FMPH was shown to increase waking in rats (Monti *et al*., 1994), and the role of the histaminergic system in waking states has been variously demonstrated (Kalivas, 1982; Monti, 1993; Lin *et al*., 1994). On the other hand, the antidepressant effect of a one-night sleep deprivation, which produces an immediate and short-lasting therapeutic effect in about 60% of depressed patients, has also been described (Gillin, 1983). Therefore, it can be speculated that the therapeutic effect of sleep deprivation, the waking role of the histaminergic system (via H_1 receptors) and the antidepressant-like effects evidenced in the present study are somehow related to each other. Furthermore, the immediate beneficial effect of sleep deprivation might also explain the effects observed with acute administration of the substances used in the present study.

In conclusion, the present work suggests a possible importance of the histaminergic system in the control of depressive states, as indicated by the positive role of endogenous histamine in the forced swim test. A role for H_1 receptors has been defined by the use of H_1 receptor agonists, while the eventual implication of H_2 receptors still remains to be thoroughly investigated, mainly due to the lack of really selective H_2 agonists. It is speculated that a further study on the central histaminergic system might provide new therapeutic possibilities for the treatment of depression.

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References

ABOU, Y.Z., ADAM, H.M. & STEPHEN, W.R.G. (1973). Concentration of histamine in different parts of the brain and hypophysis of rabbit: effect of treatment with histidine, certain other amino acids and histamine. *Br. J. Pharmacol.,* **48,** 577–589.

ARRANG, J.-M., GARBARG, M., LANCELOT, J.C., LECOMTE, J.M., POLLARD, H., ROBBA, M., SCHUNACK, W. & SCHWARTZ, J.-C. (1987). Highly potent and selective ligands for histamine H_3-receptors. *Nature,* **327,** 117–123.

BARNETT, A., TABER, R.I. & GREENHOUSE, D.D. (1969a). Mechanism of action of antihistamines in laboratory antidepressant tests. *Int. J. Neuropharmacol.,* **8,** 353–360.

BARNETT, A., TABER, R.I. & ROTH, F.E. (1969b). Activity of antihistamines in laboratory antidepressant tests. *Int. J. Neuropharmacol.,* **8,** 73–79.

BORSINI, F. & MELI, A. (1988). Is the forced swimming test a suitable model for revealing antidepressant activity? *Psychopharmacology,* **94,** 147–160.

DELINI-STULA, A., RADEKE, E. & VAN RIEZEN, H. (1988). Enhanced functional responsiveness of the dopaminergic system – the mechanism of anti-immobility effects of antidepressants in the behavioural despair test in the rat. *Neuropharmacology,* **27,** 943–947.

DUCH, D.S., BOWERS, S.W. & NICHOL, C.A. (1978). Elevation of brain histamine levels of diaminopyrimidine inhibitors of histamine *N*-methyltransferase. *Biochem. Pharmacol.,* **27,** 1507–1509.

ESPOSITO, E. & LIGUORI, P. (1996). Le basi neurobiologiche della depressione. *Le Scienze,* **330,** 40–49.

GANELLIN, C.R. (1982). Chemistry and structure-activity relationship of drugs acting at histamine receptors. In *Pharmacology of Histamine Receptors*. ed. Ganellin, C.R. & Parsons, M.E. pp. 10–102. Bristol: Wright.

GARBARG, M., TRUNG TUONG, M.D., GROS, C. & SCHWARTZ, J.-C. (1989). Effects of histamine H_3-receptor ligands on various biochemical indices of histaminergic neuron activity in the rat brain. *Eur. J. Pharmacol.,* **164,** 1–11.

GILLIN, J.C. (1983). The sleep therapies of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **7,** 351–364.

GLICK, S.D. & CRANE, L.A. (1978). Opiate-like and abstinence-like effects of intracerebral histamine administration in rats. *Nature,* **273,** 547–549.

HALEY, T.J. & MCCORMICK, W.G. (1957). Pharmacological effects produced by intracerebral injections of drugs in the conscious mouse. *Br. J. Pharmacol. Chemother.,* **12,** 12–15.

HOROVITZ, Z.P., PIALA, J.J., HIGH, J.P., BURKE, J.C. & LEAF, R.C. (1966). Effects of drugs on the mouse-killing (muricide) test and its relationship to amigdaloid function. *Int. J. Neuropharmacol.,* **5,** 405–411.

HOUGH, L.B., KHANDELWAL, J.K. & GREEN, J.P. (1986). Inhibition of brain histamine metabolism by metoprine. *Biochem. Pharmacol.,* **35,** 307–310.

KALIVAS, P.W. (1982). Histamine-induced arousal in the conscious and pentobarbital-pretreated rats. *J. Pharmacol. Exp. Ther.,* **222,** 37–42.

KATHMANN, M., SCHLICKER, E. & GÖTHERT, M. (1994). Intermediate affinity and potency of clozapine and low affinity of other neuroleptics and of antidepressants at H_3 receptors. *Psychopharmacology,* **116,** 464–468.

KATZ, R.J. & SIBEL, M. (1982). Further analysis of the specificity of a novel animal model of depression – effects of an antihistaminic, antipsychotic and anxiolytic compound. *Pharmacol. Biochem. Behav.,* **16,** 979–982.

KOLLONITSCH, J., PERKINS, L.M., PATCHETT, A.A., DOLDOURAS, G.A., MARBURG, S., DUGGAN, D.E., MAYCOCK, A.L. & ASTER, S.D. (1978). Selective inhibitors of biosynthesis of aminergic neurotransmitters. *Nature,* **274,** 906–908.

LAMBERTI, C., IPPONI, A., BARTOLINI, A. & MALMBERG-AIELLO, P. (1996). Antidepressant-like effects of substances which enhance histamine brain levels in mice. *Eur. Histamine Res. Soc., XXVth Annual Meeting*, Antwerp, Belgium, 22–25 May, 1996, Abstr. p. 39.

LAMBERTI, C., IPPONI, A. BARTOLINI, A., SCHUNACK, W. & MALMBERG-AIELLO, P. (1997). Antidepressant-like effects of two H_1-receptor agonists in the mouse forced swim test. *Eur. Histamine Res. Soc. XXVIth Annual Meeting*, Seville, Spain, May 14–17, Abstr. p. 111.

LESCHKE, C., ELZ, S., GARBARG, M. & SCHUNACK, W. (1995). Synthesis and histamine H_1 receptor agonist activity of a series of 2-phenylhistamines, 2-heteroarylhistamines and analogues. *J. Med. Chem.,* **38,** 1287–1294.

LIN, J.S., SAKAI, K. & JOUVET, M. (1994). Hypothalamo-preoptic histaminergic projections in sleep-wake control in the cat. *Eur. J. Neurosci.,* **6,** 618–625.

MAEYAMA, K., WATANABE, T., TAGUCHI, Y., YAMATODANI, A. & WADA, H. (1982). Effects of α-fluoromethylhistidine, a suicide inhibitor of histidine decarboxylase, on histamine levels in mouse tissues. *Biochem. Pharmacol.,* **31,** 2367–2370.

MALMBERG-AIELLO, P., LAMBERTI, C., GHELARDINI, C., GIOTTI, A. & BARTOLINI, A. (1994). Role of histamine in rodent antinociception. *Br. J. Pharmacol.,* **111,** 1269–1279.

MONTI, J.M., JANTOS, H., LESCHKE, C., ELZ, S. & SCHUNACK, W. (1994). The selective histamine H_1-receptor agonist 2-(3-trifluoromethylphenyl)histamine increases waking in the rat. *Eur. Neuropsychopharmacol.,* **4,** 459–462.

MONTI, J.M. (1993). Involvement of histamine in the control of the waking state. *Life Sci.,* **53,** 1331–1338.

NATH, C., GULATI, A., DHAWAN, K.N. & GUPTA, G.P. (1988). Role of central histaminergic mechanism in behavioural depression (swimming despair) in mice. *Life Sci.,* **42,** 2413–2417.

NOGUCHI, S., INUKAI, T., KUNO, T. & TANAKA, C. (1992). The suppression of olfactory bulbectomy-induced muricide by antidepressants and antihistamines via histamine H_1 receptor blocking. *Physiol. Behav.,* **51,** 1123–1127.

O'NEILL, K.A. & GERTNER, S.B. (1986). Effect of centrally administered H_2 antagonists in the behavioural despair test. *Psychopharmacology,* **90,** 190–192.

ONODERA, K. & OGURA, Y. (1984). Effects of histaminergic drugs on muricide induced by thiamine deficiency. *Jpn. J. Pharmacol.,* **34,** 15–21.

PANULA, P., PIRVOLA, U., AUVINEN, S. & AIRAKSINEN, M.S. (1989). Histamine-immunoreactive nerve fibres in the rat brain. *Neuroscience,* **28,** 585–610.

PORSOLT, R.D., ANTON, G., BLAVET, N. & JALFRE, M. (1978). Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.,* **47,** 379–391.

PORSOLT, R.D., BERTIN, A. & JALFRE, M. (1977). Behavioural despair in mice: a primary screening test for antidepressants. *Arch. Int. Pharmacodyn.,* **229,** 327–336.

SAKAI, N., ONODERA, K., MAEYAMA, K., YANAI, K. & WATANABE, T. (1991). Effects of thioperamide, a histamine H_3 receptor antagonist, on locomotor activity and brain histamine content in mast cell-deficient W/W^v mice. *Life Sci.,* **48,** 2397–2404.

SCHWARTZ, J.-C., LAMPART, C. & ROSE, C. (1972). Histamine formation in rat brain in vivo: effects of histidine loads. *J. Neurochem.,* **19,** 801–810.

SCHWARTZ, J.-C., ARRANG, J.-M., GARBARG, M. & POLLARD, H. (1990). A third histamine receptor subtype: characterization, localisation and function of the H_3-receptor. *Agents Actions,* **30,** 13–23.

SUNAL, R., GÜMÜSEL, B. & KAYAALP, S.O. (1994). Effect of changes in swimming area on results of ''behavioral despair test'' *Pharmacol. Biochem. Behav.,* **49,** 891–896.

TALLARIDA, R.J. & MURRAY, R.B. (1984). *Manual of Pharmacological Calculations with Computer Programmes.* Second edition. New York: Springer-Verlag.

TAYLOR, K.M. & SNYDER, S.H. (1972). Dynamics of the regulation of histamine levels in mouse brain. *J. Neurochem.,* **19,** 341–354.

VAUGHT, J.L., PELLEY, K., COSTA, L.G., SETLER, P. & ENNA, S.J. (1985). A comparison of the antinociceptive responses to the GABA-receptor agonists THIP and baclofen. *Neuropharmacology,* **24,** 211–216.

WADA, H., INAGAKI, N., ITOWI, N. & YAMATODANI, A. (1991). Histaminergic neuron system in the brain: distribution and possible functions. *Brain Res. Bull.,* **27,** 367–370.

WALLACH, M.B. & HEDLEY, L.R. (1979). The effects of antihistamines in a modified behavioural despair test. *Commun. Psychopharmacol.,* **3,** 35–39.

WEINER, R.D. & KRYSTAL, A.D. (1994). The present use of electroconvulsive therapy. *Annu. Rev. Med.,* **45,** 273–281.

WILLNER, P. (1984). The validity of animal models of depression. *Psychopharmacology,* **83,** 1–16.

ZAWILSKA, J. & NOWAK, J.Z. (1985). Alteration of histamine metabolism in the rat brain under influence of various antidepressive treatments. *Agents Actions,* **16,** 105–108.

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